The First Synthesis of a Three-Dimensional Acetylenic Scaffold with Platonic Symmetry: An Expanded Cubane

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Ai miei genitori e

a Ju-Ping

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Publications and Presentations

Publication:

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Abbreviations

Å	Angstrom (1 Å = 10^{-10} m)
AcOH	acetic acid
anal.	elemental analysis
aq.	aqueous
br.	broad (IR)
B.C.	Before Christ
Bu$_4$NF	tetrabutylammonium fluoride
n-BuLi	*n*-butyllithium
c.	circa
°C	degree centigrade (0 °C = 273.15 K)
cal	calorie (1 cal = 4.184 J)
calc.	calculated
CAN	cerium(IV) ammonium nitrate
CDI	carbonyldiimidazole
CDCl$_3$	*d*-chloroform
conc.	concentrated
δ	chemical shift (NMR)
d	doublet (NMR)
d	day
D	Debye
DCC	*N,N'*-dicyclohexylcarbodiimide
DCTB	*trans*-2-[3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
d.e.	diastereomeric excess
DEE	(*E*)-1,2-diethynylethene ((*E*)-hex-3-ene-1,5-diyne)
DHB	2,5-dihydroxybenzoic acid
DHP	3,4-dihydro-2H-pyran
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	*Dess-Martin* periodinane

DPTC	*O,O'*-di(2-pyridyl)thiocarbonate
d.r.	diastereomeric ratio
ΔH_f	heat of formation
ε	extinction coefficient
E	energy, potential (electrochemistry)
E_g	energy (optical gap)
e.e.	enantiomeric excess
ECL	effective conjugation length
e.g.	for example
equiv.	equivalent
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
eV	electronvolt ($1eV = 1.602 \times 10^{-19}$ J)
exp.	experimental
Fc	Ferrocene
Fc^+	Ferricinium
FT-MALDI	fourier transform matrix assisted laser desorption-ionization
g	gram
GPC	gel permeation chromatography
h	hour
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HR	high resolution
Hz	Hertz (s^{-1})
ICR	ion-cyclotron-resonance
Ind	indane
IR	infrared (spectroscopy)
J	Joule
J	coupling constant (NMR)
k	kilo (10^3)
λ	wavelength
λ_{end}	end-absorption (UV/Vis)
λ_{max}	longest wavelength maxima (UV/Vis)

L	liter
LD	laser desorption
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
μ	micro (10^{-6})
m	milli (10^{-3})
m	medium (IR), multiplet (NMR)
M	molarity [mol l^{-1}]
M	metal
MALDI-TOF	matrix assisted laser desorption-ionization time-of-flight
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute
M_n	number-averaged molecular
MO	molecular orbital
mol	mole
M.p.	melting point
MS	mass spectrometry
(*R*)-MTPACl	α-methoxy-α-trifluoromethylphenylacetyl chloride
NBS	*N*-bromosuccinimide
NLO	nonlinear optics
nm	nanometer
NMR	nuclear magnetic resonance (spectroscopy)
PA	polyacetylene
PCC	pyridinium chlorochromate
PDA	poly(diacetylene)
PG	protecting group
PHA	polycyclic aromatic hydrocarbon
PM3	parameter model 3
PMB	*p*-methoxybenzyl chloride
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

^{i}Pr	isopropyl
PTA	poly(triacetylene)
q	quartet (NMR)
R_f	retention factor
r.t.	room temperature
s	strong (IR), singlet (NMR)
s	second
sat.	saturated
SiEt$_3$	triethylsilyl
SiMe$_3$	trimethylsilyl
SiO$_2$	silica gel
Si^{i}Pr$_3$	triisopropylsilyl
t	triplet (NMR)
TEE	tetraethynylethene (3,4-diethynylhex-3-ene-1,5-diyne)
TfOH	trifluoromethanesulfonic acid.
THF	tetrahydrofuran
THP	tetrahydopyran
TLC	thin layer chromatography
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TsOH	*p*-toluenesulfonic acid
UV	ultra-violet
V	Volt
Vis	visible
vs.	versus
w	weak (IR)
X_n	degree of oligomerization

Summary

Acetylenic molecular scaffolding has emerged as a major area of research over the past decade. Series of acetylenic expanded structures have been developed with the intention of investigating the properties arising from the insertion of rigid alkyne units into linear and macrocyclic frameworks. Geometrically defined expansion of linear molecules such as polyacetylenes and dendralenes by introduction of buta-1,3-diyne-1,4-diyl fragments ($-C\equiv C-C\equiv C-$) has allowed access to new chromophores such as poly(triacetylene)s and expanded dendralenes. These new compounds show interesting optoelectronic properties, particularly with respect to their potential applications in material science. The application of this general concept to two-dimensional structures has provided other novel carbon-rich macrocycles, such as dehydro[n]annulenes and expanded radialenes, which also exhibit attractive physicochemical properties. The extension of this concept to three-dimensional structures begins with this doctoral thesis.

In the first part of Chapter 1, the reader is introduced to selected examples of expanded linear and two-dimensional systems, describing their development with a particular regard to properties. The poly(triacetylene)s and the expanded dendralenes are presented, followed by a description of a series of acetylenic expanded macrocycles such as the perethynylated dehydroannulenes, the perethynylated expanded radialenes, the peralkynylated radiaannulenes, and the expanded pericyclynes. In the second part, examples of three-dimensional acetylenic scaffolds (cage polyynes) capable of rearrangement into fullerene C_{60} under *flash vacuum pyrolytic* conditions are reported. Lastly, a short introduction to the geometric Platonic solids is given.

The first part of the presented doctoral work is described in Chapter 2, where the synthesis of the expanded cubane **44** with a C_{56} core is reported. Formally derived by

MeO 44 OMe
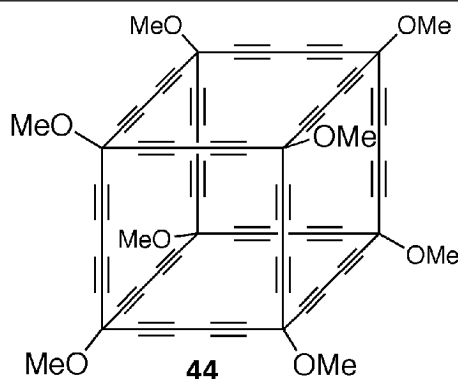
corners, edges, and faces as key building blocks and intermediates. Expanded cubane **44** is obtained after eleven synthetic steps, principally based on the iterative alkyne deprotection and oxidative acetylenic Hay *homo*-coupling of the respective building blocks. Evidence for the successful synthesis of **44** was given by ^{1}H- and ^{13}C-NMR spectroscopy demonstrating its O_{h} symmetry. Further confirmation was obtained by matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) experiments in the negative ion mode, where the peak corresponding to $[M - OMe]^{-}$ was the only peak revealed in the entire spectrum. The target compound was quite unstable and exploded upon scraping, yielding a cloud of black soot. Such a high-energy compound (estimated heat of formation of 1023 kcal/mol) could rearrange into fullerenes under specific mass spectrometric conditions with the loss of all methoxy groups. In particular, under conditions of Fourier-transform ion cyclotron resonance mass spectrometry in the negative ion mode it rearranged into fullerenes anions C_{54}^{-}, C_{52}^{-}, and C_{50}^{-}. In the positive ion mode it underwent fullerene coalescence reactions providing a pattern of higher fullerenes.

The attempted synthesis of more strained molecules such as expanded tetrahedrane **79** and expanded prismane **80** are presented in Chapter 3. These target compounds have an identical triangular base (**85**), therefore the synthesis first targeted the preparation of this essential building block. Unfortunately macrocyclization of the trimeric precursor **84** by intramolecular oxidative *homo*-coupling did not provide the base module **85**, likely indicating the high instability of the product that is possibly enhanced by the methoxy groups.

OMe

79

OMe

MeO OMe

OMe

MeO OMe

80
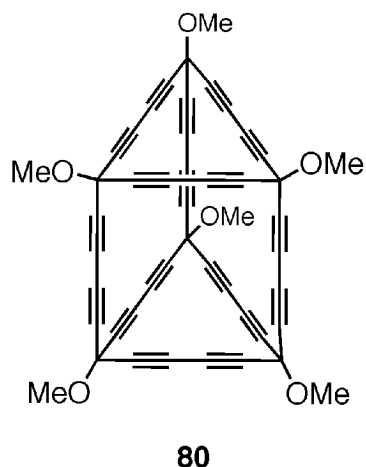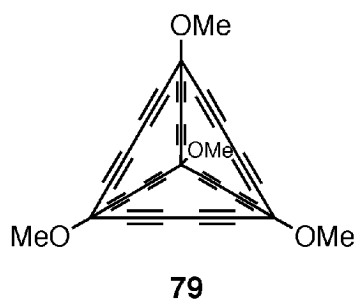
The last part of this work is reported in Chapter 4, and consists of the development of a new strategy in order to improve the synthesis of the expanded cubane **44**. In the prior synthesis (Chapter 2), the preparation of this expanded Platonic molecule was hampered by the formation of unnecessary stereoisomeric side products, which caused a great loss of material. As an alternative, a stereoselective synthesis of the edge building block *meso*-**61** was planned that relied on the *hetero*-coupling of two enantiomeric, optically pure corner modules. The development of this project is still ongoing. In this Section the construction of one optically active corner module, by enantiomer (+)-(*R*)-**114**, is described. This key building block was obtained *via* a diastereoselective pathway composed of eight synthetic steps. In an earlier approach, the resolution of the corner module (±)-**49** was attempted using a chiral auxiliary, but unsatisfactory results were obtained.

Riassunto

Negli ultimi dieci anni, strutture molecolari caratterizzate dall'avere acetileni come unitá base hanno rappresentato un'area di ricerca di crescente interesse. Diverse strutture acetileniche espanse sono state sviluppate al fine di investigare le proprietá che scaturiscono dalla inserzione di un'unitá alchinica rigida all'interno di una struttura lineare o macrociclica. L'introduzione del frammento buta 1,3-diino-1,4-diile ($-C\equiv C-C\equiv C-$) in strutture lineari come i poliacetileni e i dendraleni, ha permesso l'ottenimento di nuovi cromofori, quali i poli(triacetileni) e i dendraleni espansi. Queste nuove strutture complesse hanno evidenziato peculiari proprietá ottico-elettroniche che le rendono interessanti, da un punto di vista applicativo, nella scienza dei materiali. L'estensione di questo concetto a strutture bidimensionali ha permesso la creazione di nuovi macrocicli come i diidro-anuleni e i radialeni espansi, i quali hanno mostrato affascinanti proprietá chimico-fisiche. L'ulteriore estensione a strutture tridimensionali è il soggetto di questa tesi di dottorato.

La prima parte del Capitolo 1 consiste nella descrizione dello sviluppo, con particolare riguardo alle loro proprietá, di selezionate strutture lineari espanse (poli(triacetileni) e dendraleni espansi) e acetileni macrocicli espansi (diidroanuleni peretinilati, radialeni espansi peretinilati, radiaanuleni peralchinilati ed periciclini espansi). La seconda parte descrive esempi di strutture acetileniche tridimensionali (gabbie poliiniche) le quali, in particolari condizioni pirolitiche (*flash vacuum*), subiscono un riarrangiamento dando luogo alla formazione del fullerene C_{60}. L'ultima parte di questo capitolo presenta una piccola introduzione alle figure solide platoniche.
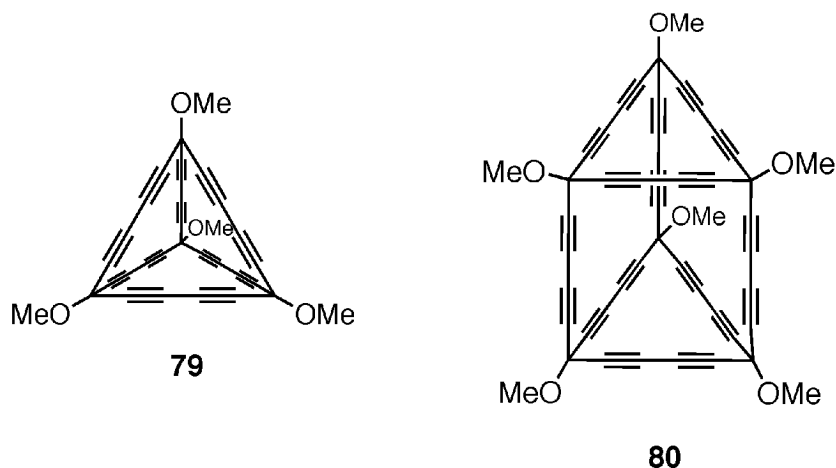
Il Capitolo 2 rappresenta il cuore di questo lavoro di dottorato. Consiste nella descrizione della via sintetica ideata per ottenere il cubano espanso **44**, una struttura con un nucleo a 56 atomi di carbonio.
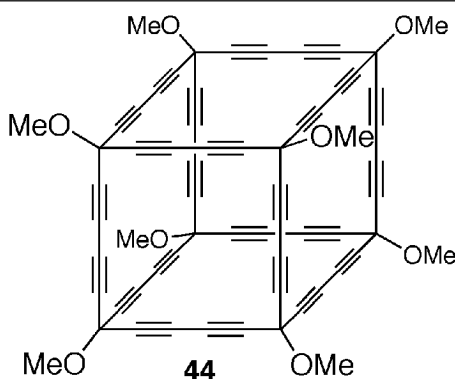
La sintesi di questa molecola, che formalmente deriva dalla inserzione di un'unitá di buta-1,3-diino-1,4-diile in tutti i 12 legami singoli C–C dell'ottametossicubano ($C_8(OMe)_8$), consiste nella formazione di elementi chiave base (angoli, lati e facce del cubo) e di intermedi. La molecola **44** è stata ottenuta seguendo un persorso sintetico di undici passaggi, basati sulla reiterata deprotezione dell'alchino e sull'omo-accoppiamento ossidativo di tipo Hay tra gli acetileni dei diversi elementi base. Le caratterizzazioni spettroscopiche (^{1}H- e ^{13}C-NMR) hanno confermato la perfetta riuscita della sintesi ed hanno dimostrato la simmetria O_h del cubano **44**. Ulteriori conferme sono state date dagli esperimenti di MALDI-TOF (matrix-assisted laser desorption-ionization time-of-flight) in negative ion mode, che hanno rivelato, nell'intero spettro, la presenza di un solo picco corrispondente a $[M - OMe]^-$. La molecola finale è caratterizzata da una forte instabilitá e da una tendenza all'esplosione se sottoposta a sforzo meccanico, con conseguente formazione di una nuvola di fuliggine nera. È stato evidenziato che un composto di così alta energia (la stima per il calore di formazione è di 1023 kcal mol^{-1}), se sottoposto a specifiche condizioni spettrometriche di massa, può subire un riarrangiamento e dar luogo a una serie di fullereni con conseguente perdita di tutti i gruppi metossi. In particolare è stato osservato che, in condizioni di Fourier-transform ion cyclotron resonance di spettrometria di massa in negative ion mode, il cubano **44** riarrangia dando luogo agli anioni dei fullereni C_{54}^-, C_{52}^-, C_{50}^-. Nelle stesse condizioni, condotte però in positive ion mode, il composto subisce riarrangiamenti tali da ottenere una serie di fullereni a numero di carboni più elevato.

Nel Capitolo 3 sono descritti i diversi tentativi di sintesi effettuati allo scopo di ottenere molecole a maggiore tensione interna, come il tetraedrano espanso **79** e il prismano espanso **80**. Per entrambe le molecole, caratterizzate da una identica base triangolare (**85**), lo stadio chiave della sintesi consiste nella preparazione dello stesso elemento base. Sfortunatamente la macrociclizzazione del trimero precursore **84**, la quale

consiste in un omo-accoppiamento ossidativo, non ha portato alla formazione del modulo base **85**, mettendo in evidenza un'alta instabilitá del prodotto, aggravata dalla presenza dei gruppi metossi.

L'ultima parte di questo lavoro, rappresentata dal Capitolo 4, consiste nel concepimento di una nuova strategia, atta a migliorare il percorso sintetico del cubano espanso **44**. Il limite della via sintetica descritta nel Capitolo 2, consiste nella presenza di stereoisomeri indesiderati, la formazione dei quali causa la perdita di una grande quantitá di materiale, rendendo difficile l'intero percorso sintetico. Un'alternativa consiste nell'ideazione di una sintesi stereoselettiva dell'elemento base *meso*-**61** ottenuto da un etero-accoppiamento di due angoli enantiomerici otticamente attivi. Lo sviluppo di questa innovativa strategia sintetica è in corso. In questa sezione è descritta la sintesi di un angolo del cubano **44** otticamente attivo, l'enantiomero (+)-(*R*)-**114**. Questo elemento base è stato ottenuto attraverso un percorso di sintesi diastereoselettiva composto da otto passaggi. Un primissimo tentativo di risoluzione dell'angolo (±)-**49**, consistente nell'uso di un ausiliare chirale, ha dato purtroppo risultati non soddisfacenti.

1 Introduction

Carbon is the fourteenth-most abundant element on earth and its importance in Nature is fundamental. On earth, two natural allotropes of carbon, *graphite* and *diamond*, are found (*Figure 1.1*). Their availability in large quantities combined with their amazing properties make them useful in many technological applications [1]. Diamond is a three-dimensional network made of covalent bonds between sp^3 carbon atoms. It is the hardest, electrically most insulating, albeit most heat-conductive substance known to man. The different hybridization in graphite (sp^2) leads to two-dimensional planar networks with "infinitely" linearly conjugated double bonds, and these networks are aligned in parallel stacks. It is very soft, and finds its major technological applications as an electrode component, due to its conducting properties, and as a solid lubricant. Another carbon allotrope was experimetally observed and reported in 1985 by *Kroto*, *Smalley*, *Curl*, and co-workers during experiments aimed at understanding the mechanisms by which long-chain carbon molecules are formed in interstellar space [2]. They vaporized graphite by laser irradiation producing predominantly carbon clusters of masses 720 and 840, corresponding to 60 and 70 carbon atoms, respectively. The most abundant species, C_{60}, is composed of sp^2 hybridized atoms, organized in a spheroidal shape (as a football) with I_h symmetry and was named buckminsterfullerene in honor of the architect *Richard Buckminster Fuller*, whose geodesic domes conform to similar geometrical rules (*Figure 1.1*). For this work the three seniors scientists were awarded the Nobel Prize for Chemistry in 1996.
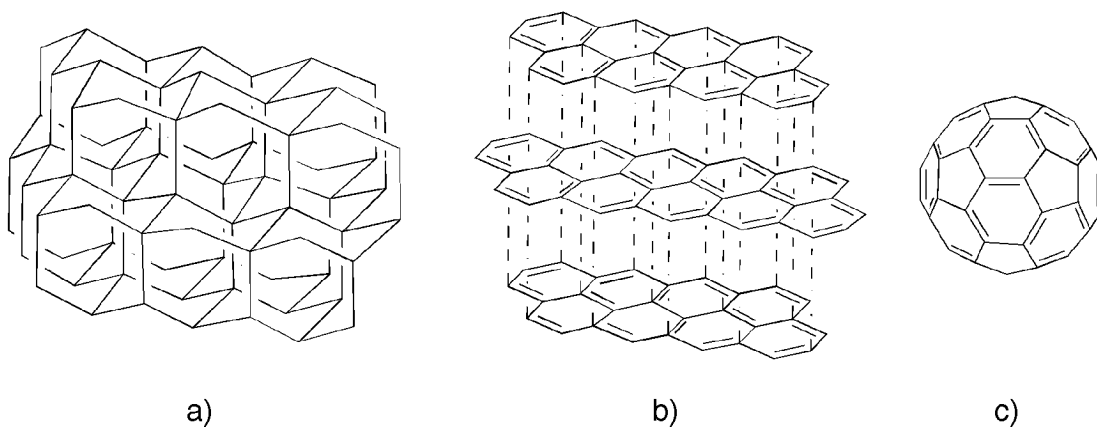

a)   b)   c)

Figure 1.1: Allotropic forms of carbon: a) diamond, b) graphite, and c) buckminsterfullerene C_{60}.

Buckminsterfullerene was made accessible in bulk quantities for the first time a few years after its discovery, when *Krätschmer* and *Huffman* evaporated graphite in an electrical arc under an inert atmosphere of helium [3].

Owing to the ability of carbon atoms to adopt three different hybridization states (sp^3, sp^2, and sp), there are numerous combinations by which atoms of this exceptional element can be bonded to each other, and therefore a huge number of all-carbon and carbon-rich compounds can be imagined. A common feature in the efforts directed toward the construction of such composites is the use of the $C \equiv C$ bond as a functional group and linking unit. The alkynyl group is a readily accessible all-carbon building block, and terminal acetylene functions can be linked to $C(sp^2)$ and $C(sp)$ centers by cross-coupling [4] and by copper-catalyzed oxidative coupling [5], respectively. In addition, the relative rigidity and linearity of the $C \equiv C$ fragment seems to be appropriate for the synthesis of rigid and uniformly shaped structures, and the characteristics of the π-bond may provide compounds with interesting properties [6]. For instance, novel fascinating topologies have been proposed based on the expansion of the two most common carbon allotropes by insertion of alkyne units. Graphite may be enlarged into the novel structure **1** termed *graphdiyne* (*Figure 1.2*), which should exhibit attractive properties such as third-order nonlinear optical susceptibility, an enhanced redox activity, and conductivity or superconductivity when doped with alkali metals incorporated into the pores (about 2.5 Å) within its dehydro[18]annulene units [7, 8]. Similar expansion of the $C(sp^3)$–$C(sp^3)$ bonds of diamond would provide the three-dimensional lattice **2**, called *superdiamond* (*Figure 1.2*), which is expected to be quite stable because of its lack of extended acetylenic π conjugation [9-11].
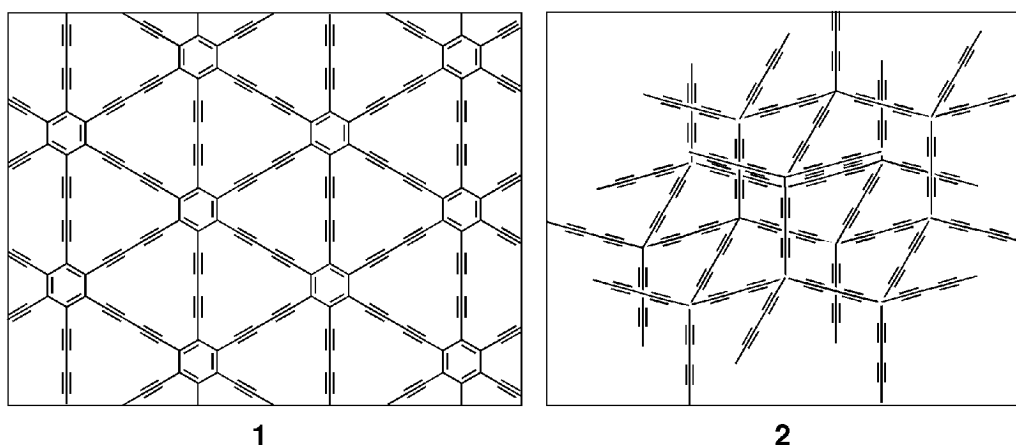

1   **2**

Figure 1.2: Proposal of new carbon allotropes: graphdiyne (**1**) and superdiamond (**2**).

Continuous research in the construction of carbon networks has furnished a tremendous number of new acetylenic scaffolds with exceptional molecular architecture in one, two, and three dimensions [12-15]. Since the early 1990s, the *Diederich* Group has been interested in the geometrically defined expansion of molecules by the introduction of buta-1,3-diyne-1,4-diyl fragments between all C–C single bonds, thereby enhancing both the carbon atom content and the optoelectronic properties of the resulting chromophores. Thus, linear sytems such as polyacetylenes and dendralenes gave poly(triacetylenes) and expanded dendralenes, respectively. Extention of this general concept to two-dimensional structures led to novel macrocyclic systems such as dehydro[*n*]annulenes, expanded radialenes, radiaannulenes, and "exploded" pericyclynes.

1.1 Linear Systems

1.1.1 Poly(triacetylene)s

Poly(triacetylene)s (PTAs) are linearly π-conjugated polymers with a nonaromatic all-carbon backbone. They are the third member of a series that starts with polyacetylene (PA), followed by poly(diacetylene) (PDA), and progresses up to carbyne (*Figure 1.3*) [16]. The additional alkyne unit per monomer in PTA increases the spacing between laterally appended side chains, which has the advantage of remarkably reducing or even canceling the intramolecular steric repulsions that distort the linear chain in polyacetylenes and also poly(diacetylene)s from planarity, affecting the π-conjugation.

poly(acetylene) poly(diacetylene) poly(triacetylene) carbyne
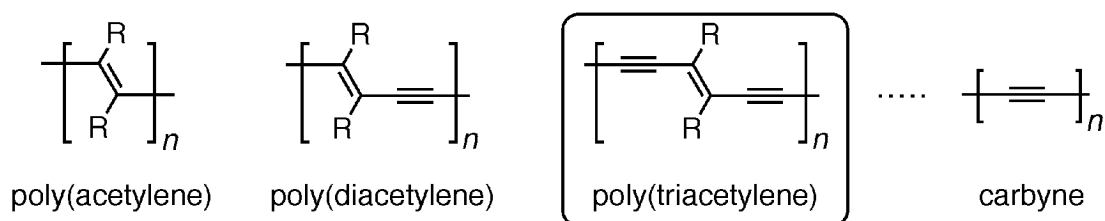
Figure 1.3: Progression of linearly π-conjugated all-carbon backbones from polyacetylene (PA) *via* poly(diacetylene) (PDA) and poly(triacetylene) (PTA) to carbyne.

The synthesis of a "molecular construction kits" consisting of tetraethynylethene (TEE, 3,4-diethynylhex-3-ene-1,5-diyne) and (*E*)-1,2-diethynylethene (DEE, (*E*)-hex-3-ene-1,5-diyne) derivatives provided suitable PTA monomers [17, 18]. Generally, PTAs are prepared by oxidative coupling of the monomer in the presence of an end-capping

reagent and some examples are illustrated in *Figures 1.4* and *1.5*. Longer-chain PTA polymers end-capped by 3,5-bis(*tert*-butyl)phenylacetylene such as **3-5** show high thermal and kinetic stability and a large third-order nonlinear optical (NLO) response [19, 20]. Polymer **3** is soluble only in hot chlorinated solvents, but solubility at r.t. could be obtained with the preparation of the PTA **5** which has pendant (*tert*-butyldimethylsilyl)oxymethylene groups. The optical gap of **3** (E_g = 2.0 eV) is in the range of the values determined for many PDAs (E_g = 2.1 eV) [16], and is lower than that determined for **5** (E_g = 2.4 eV), due to the cross-conjugation with the lateral alkynyl groups. Furthermore, in comparison to **3**, the substitution of the Si^{i}Pr$_3$ groups by the electron-donating *p*-(didodecylamino)phenyl group significantly lowers the optical gap in **4** (E_g = 1.6 eV).
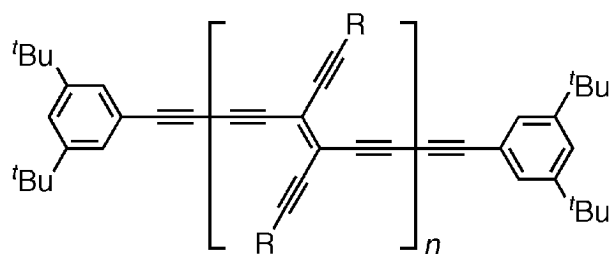
3 R = Si^{i}Pr$_3$, M_n = 9600, X_n = 22
4 R = *p*-C$_6$H$_4$N(C$_{12}$H$_{25}$)$_2$, M_n = 16800, X_n = 17
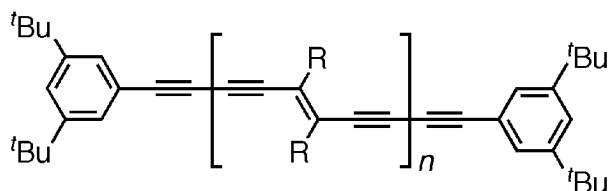
5 R = CH$_2$OSi^{t}BuMe$_2$, M_n = 11300, X_n = 31

Figure 1.4: Poly(triacetylene) polymers **3-5** prepared by oxidative coupling under end-capping conditions. M_n = number-averaged molecular weight, X_n = degree of oligomerization.

The fact that extensive linearly π-conjugated polymers exhibit saturation of properties, and therefore an *effective conjugation length* (ECL), may arise from the distortions from planarity of the linear backbone in solution, resulting in reduced p-orbital overlap and a concomitant decrease of the π-conjugation. The ECL defines the number of repeat or monomer units in a π-conjugated polymer at which the saturation of properties occurs. It can be quantified by extrapolation of measured optical (absorption, emission, NLO,

Raman spectroscopy) and electrochemical (cyclic voltammetry and differential pulse voltammetry) properties of monodisperse oligomeric series [16]. Thus, monodisperse oligomers can be employed as models in order to estimate the properties of infinite-chain PTA polymers and to predict at which monomeric repeat unit saturation of the properties occurs. This has the considerable advantage of providing physicochemical information for long PTA polymers without the need to synthesize them. Therefore, the first series of PTA oligomers **6a-e**, end-capped by phenylacetylene and with appended peripheral bulky Si^{i}Pr$_3$ groups in order to protect the backbone and enhance the solubility, was prepared [21]. These oligomers are highly colored compounds (from yellow to dark red), and this is reflected in their electronic absorption spectra, which reveal a bathochromic shift toward longer wavelength with increasing rod length. The optical gap for the series **6a-e** extrapolated to an infinite polymer was estimated to be E_g = 2.3 eV. Furthermore, the electrochemical analysis revealed that the rods are difficult to oxidize (no oxidation occurred below +1.0 V *vs.* Fc/Fc$^+$), but undergo facile one-electron reduction, which becomes easier when the number of the monomer units present in the chain increases. In fact, the first reductions of **6a** and **6e** occurred at E = −1.57 V and E = −1.07 V, respectively, demonstrating the effect of extended π-conjugation [22].

Others series of oligomers based on DEE repeat units, which confer higher solubility in comparison to **6a-e**, have recently been prepared in the group of *Diederich* [23, 24]. Thus, oligomer series **7a-f** and **8a-k** bearing the end-capping SiMe$_3$ and SiEt$_3$ groups, respectively, were isolated and analyzed. Similar to the TEE-based oligomers they show high stability and can be stored on the laboratory bench for months. Estimation of the ECL of compounds **7a-f** by UV/Vis and nonlinear optical methods was found to be in the range of 7–10 monomer units [25]. The longer oligomers **8a-k**, which extend up to the 17.8 nm-long 24-mer, could give more accurate information. Indeed, evaluation of the ECL by linear and nonlinear optical properties, as well as electrochemical properties, occurred at about n = 10 monomeric units, which is in good agreement with the results obtained for the previous oligomeric series **7a-f** [26-28]. The planar s-*trans* conformation of the olefinic moieties in the oligomer backbone with respect to the connecting buta-1,3-diyne-1,4-diyl fragments was confirmed by X-ray crystal structure analysis of a 3.2 nm-long 4-mer **8d** [29]. Substitution of the end-capping group by a donor moiety such as 4-(dimethylamino)phenyl led to the donor-donor end-functionalized oligomer series **9a-f**, which already shows a saturation of the linear optical properties at n = 4. In the case of the acceptor-acceptor PTA oligomers represented by **10a-f**, the properties resemble much

more those of the previous $SiMe_3$- and $SiEt_3$-end-capped PTA oligomers [30]. Interesting results were obtained with PTA oligomers encapsulated into shells of *Fréchet*-type dendrimers from first to third generation (**11a-e**, **12a-c**, and **13a,b**). UV/Vis studies evidenced no alteration of the electronic characteristics of the PTA backbone, independent of the dendritic generation number [31, 32].
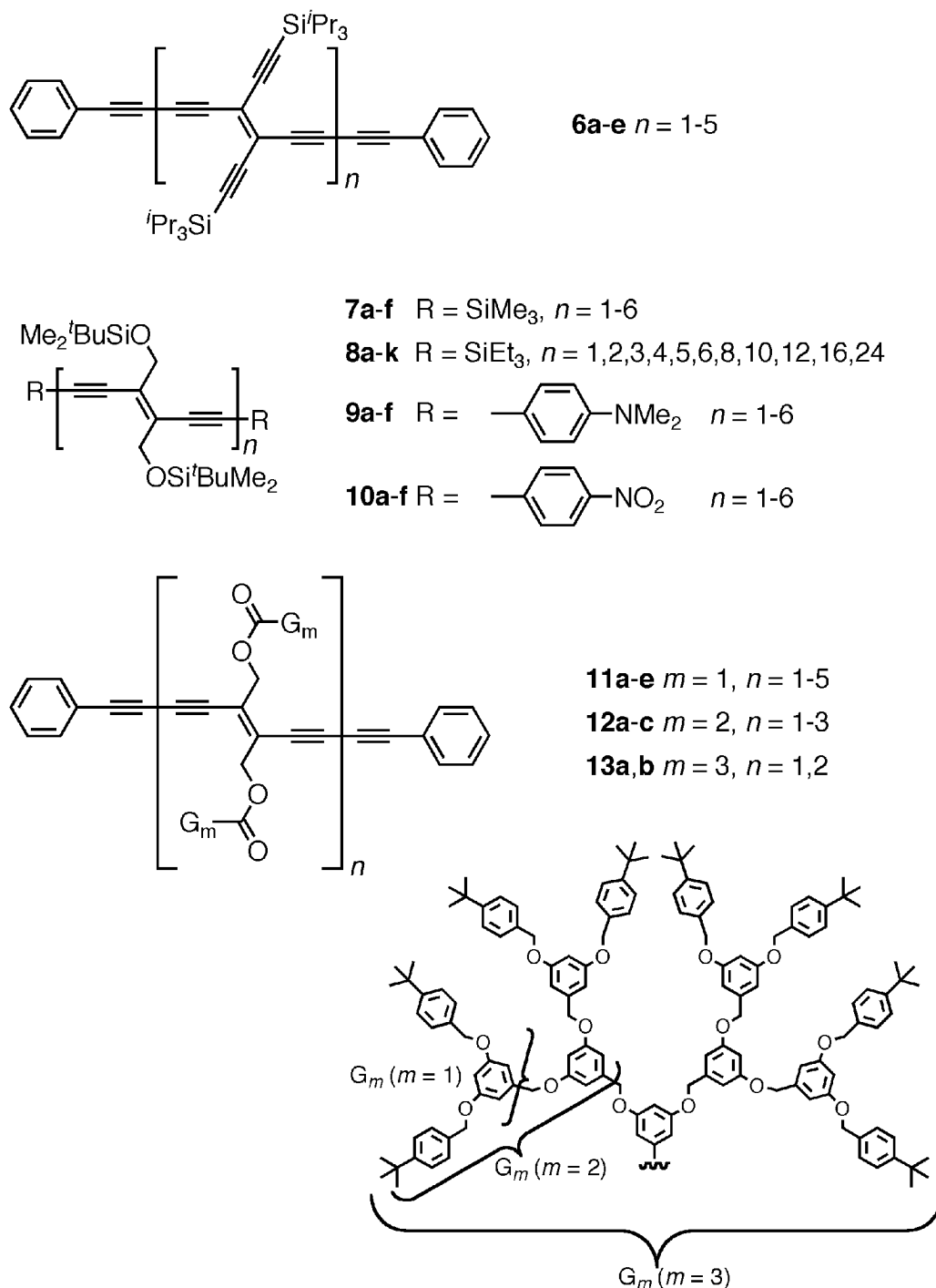

Figure 1.5: PTA-oligomers **6-13**, prepared by oxidative acetylenic coupling.

The bulky dendrimers minimally changed the longest-wavelength absorption maxima λ_{max}, indicating that π-electron conjugation along the backbone is not affected by distortion from planarity due to steric hindrance. Such observations suggest that the π-conjugation of the acetylene units is best described as being cylindrical and is maintained upon rotation about $C(sp)$–$C(sp^2)$ and $C(sp)$–$C(sp)$ single bonds.

1.1.2 Expanded Dendralenes with an *iso*-Poly(triacetylene) Backbone

Besides the linearly π-conjugated PTA oligomers, cross-conjugated isomeric counterparts named *iso*-poly(triacetylene)s have been investigated. Similar to the poly(*n*-acetylenic) series, *iso*-poly(triacetylene)s are the third member of a series which starts from dendralenes (*Figure 1.6*) [33, 34]. In order to obtain a cross-conjugated [35] arrangement, at least three C=C bonds are required in these polyene hydrocarbons. Insertion of an acetylene unit between the C=C bonds gives the *iso*-poly(diacetylene)s [36-38], and of a buta-1,3-diyne-1,4-diyl moiety affords the *iso*-poly(triacetylene)s. The continuous elongation of the skeleton by alkyne fragments leads to conjugated systems approaching ultimately the carbon allotrope carbyne.

R R
[ ]n
n ≥ 3
dendralene

R R
[ ]n
iso-polydiacetylene

R R
[ ]n
iso-polytriacetylene

[ ]n
carbyne
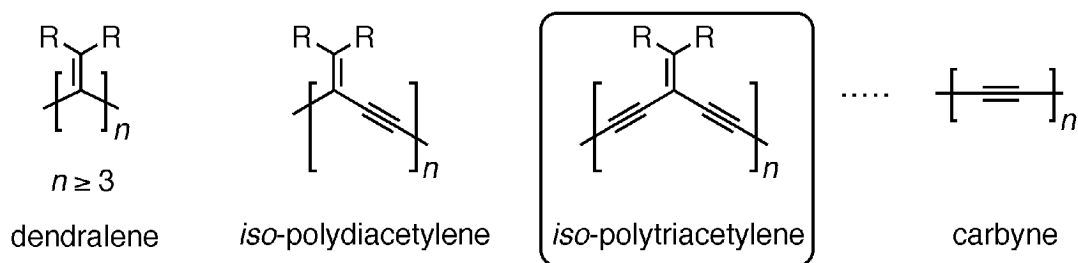
Figure 1.6: Series of cross-conjugated polymers from dendralene to carbyne.

The first expanded dendralenes **14a,b** and **15** were synthesized by *Diederich* and co-workers in 1995, by oxidative coupling of the appropriate desilylated tetraethynylethenes (TEE) (*Figure 1.7*) [22]. The electronic absorption spectra of **14a,b** displayed no bathochromic shift with increasing π-system, revealing an inefficient cross-conjugation, probably due in part to steric repulsion between the Si^iPr_3 groups, which distorts the chromophores out of planarity. Strong evidence for the reduced π-electron delocalization was provided by an electrochemical study of **14a**, which underwent a one-electron reduction at a more negative potential than its linear isomer. *Tykwinski* and *Zhao* reported another series of *iso*-PTAs with peripheral methyl moieties and elongated

acetylenic end groups (**16a-c**) (*Figure 1.7*). The oligomer series **16a-c** was obtained by sequential iterations of terminal alkyne deprotection and subsequent Pd-catalyzed $C(sp)-C(sp^2)$ cross-coupling [39]. In general, such *iso*-PTA oligomers displayed a reasonable thermal stability, but the kinetic stability decreased with the increase in chain length. For example, decomposition of **16c** was observed even when stored under nitrogen and at low temperatures. Furthermore, the solubility decreases rapidly with elongation of the backbone. In accord with the previous observations in *iso*-PTA oligomers **14a** and **14b**, the comparison of the UV spectral data of trimer **16b** and pentamer **16c** did not show any significant change in the position of λ_{max} [40]. Instead, a slight but non-negligible red-shift of the longest wavelength maxima and the optical end-absorption with increasing chromophoric length was observed for the expanded dendralene series **17a-c** in the group of *Diederich* [41]. Calculation of the conformational preferences of tetramer **17b** and octamer **17c** presented a general trend for the *iso*-PTA oligomers, namely, the all-s-*trans* conformation is not the most energetically favorable, which is in contrast with the linearly conjugated PTA oligomers. Apparently the conformation of the expanded dendralenes plays an important role in the efficiency of cross-conjugation, which is less effective than the linear π-conjugation exhibited in the PTA oligomers.
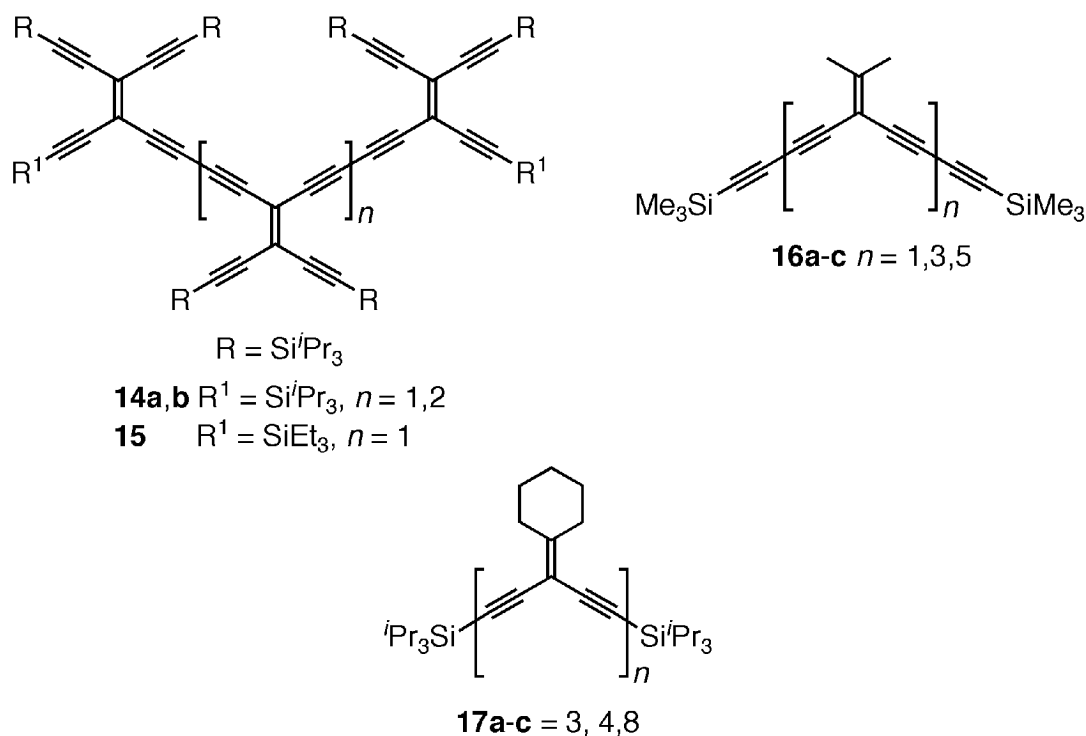

Figure 1.7: Series of *iso*-poly(triacetylene) oligomers.

1.2 Two-Dimensional Scaffolding: Expanded Carbon Cores

1.2.1 Perethynylated Dehydroannulenes

The utility of the TEE module is not limited to the construction of monodimensional systems, but it can also be employed in the preparation of all-carbon molecules with macrocyclic cores. *Diederich* and co-workers accomplished the synthesis of octadehydro[12]annulenes **18a,b** and dodecadehydro[18]annulenes **19a,b** by oxidative *Hay* macrocyclization of appropriate *cis*-bis-deprotected TEEs (*Figure 1.8*) [42]. The perethynylated dehydroannulenes showed a reasonable stability, which increases when changing from $SiMe_3$ to the bulkier Si^iPr_3 groups. As evidenced by X-ray crystal structure analysis, they possess fully planar π-conjugated carbon cores [43]. The yellow-colored [18]annulenes **19a,b** have 18 electrons in the cyclic framework and, obeying *Hückel*'s (4n + 2)-rule, are aromatic, as is their parent, unsubtituted dodecadehydro[18]annulene, synthesized by *Okamura* and *Sondheimer* in 1967 [44]. In contrast, the purple-colored [12]annulenes **18a,b** are antiaromatic (12 electrons are in conjugation) similar to the parent, unsubstituted octadehydro[12]annulene described in two independent studies [45-47]. The electronic absorption spectra revealed a larger HOMO-LUMO gap for **19b** (2.57 eV) than for **18b** (1.87 eV), providing evidence of their aromatic and antiaromatic character, respectively. Strong support for the aromaticity assignment was not only obtained by ^{1}H-NMR spectroscopy of analogs [43] but also in electrochemical studies.
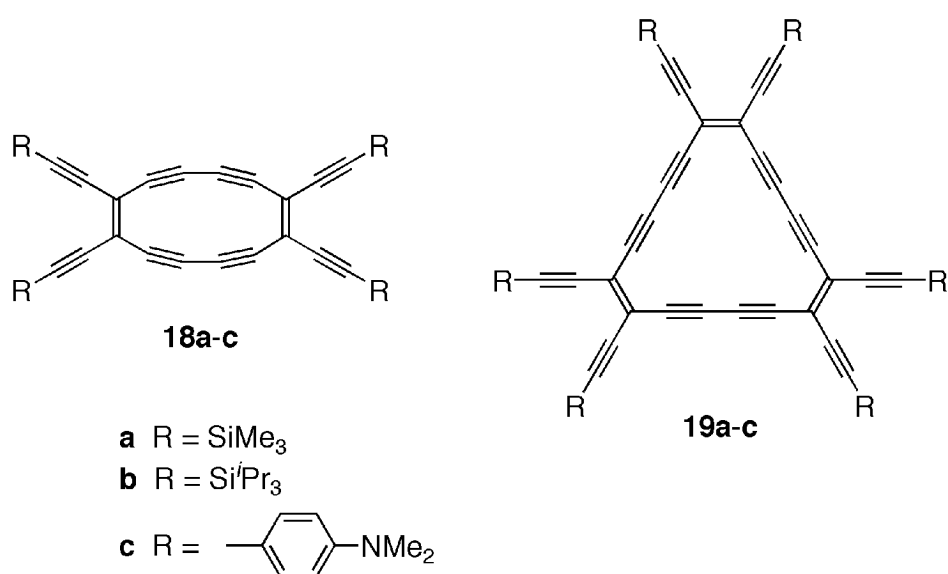

Figure 1.8: Perethynylated antiaromatic (**18a-c**) and aromatic (**19a,b**) dehydroannulenes.

They showed that aromatic **19b** is more difficult to reduce (E_1° = –1.12 V and E_2° = –1.52 V vs. Fc/Fc$^+$), than antiaromatic **18b** (E_1° = –0.99 V and E_2° = –1.46 V), which gains aromaticity when converted to its dianion [43, 48]. Introduction of peripheral N,N-dimethylanilino groups in **18c** and **19c** led to an intense intramolecular charge-transfer between the electron-donating anilino substituents and the electron-accepting core, as revealed in the UV/Vis spectra by broad, bathochromically shifted longest-wavelength absorption bands at λ_{max} = 518 nm. This demonstrates that both [12]annulene **18c** and [18]annulene **19c** are capable of mediating π-electron donor-acceptor conjugation. Interestingly, the intensity of the charge-transfer band of aromatic **19c** is substantially stronger than that of antiaromatic **18c**, which is in contradiction to the expectation of a more efficient charge-transfer in **18c**. Indeed, the uptake of electrons in its core should reduce the antiaromaticity, whereas in the case of **19c** the uptake of electrons results in a loss of aromaticity [49].

Other series of annulenes with the cyclic framework enlarged by buta-1,3-diyne-1,4-diyl fragments have also been synthesized. For instance, a series of dehydroannulenes fused with suitable peripheral leaving groups that can be extruded at the final step, in order to generate cyclic polyynes, have been prepared [10, 50-53]. *Bunz* and co-workers prepared fascinating explosive organometallic dehydro[18]annulenes aiming to convert them into novel carbon structures [54-56]. Furthermore, *Haley et al.* has been involved in the preparation of dehydrobenzo[18]annulenes, which are attractive building blocks for the synthesis of planar carbon networks such as graphdiyne [8].

1.2.2 Perethynylated Expanded Radialenes

Radialenes are a family of cyclic hydrocarbons derived from dendralenes with molecular formula C_nH_n. Upon insertion of ethyne-1,2-diyl or buta-1,3-diyne-1,4-diyl moieties into the cyclic framework between each pair of vicinal exo-methylene units, a homologous series of expanded radialenes with molecular formula $C_{2n}H_n$ and $C_{3n}H_n$ is obtained. Similar to the preparation of perethynylated dehydroannulenes (see Section 1.2.1), versatile TEE modules serve as precursors to perethynylated expanded radialenes.
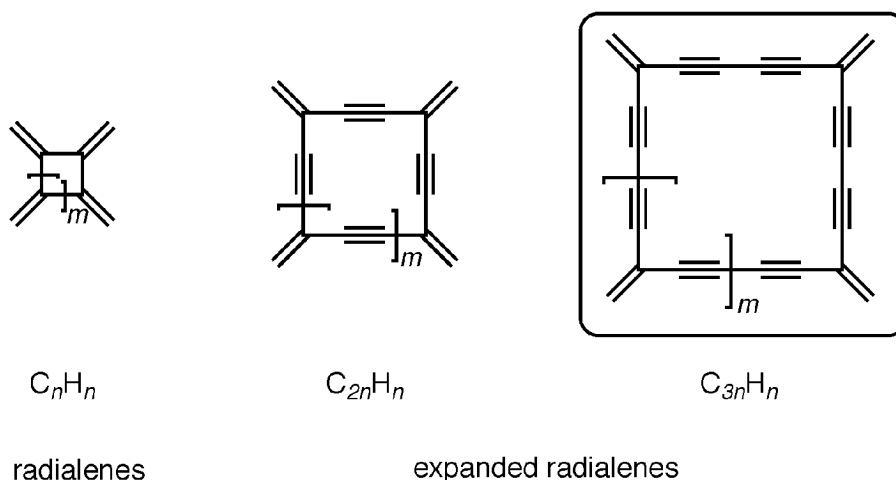
C_nH_n $C_{2n}H_n$ $C_{3n}H_n$

radialenes   expanded radialenes

Figure 1.9: Progression from radialenes to expanded radialenes.

In particular, oxidative alkyne coupling of geminally bis-functionalized TEEs provided, in a one-pot synthesis or after short synthetic sequences, a range of expanded radialenes with diverse peripheral groups, of which macrocycles **20a-c** are the first representatives (*Figure 1.10*). *Boldi* and *Diederich* described them as highly soluble and remarkably stable compounds with melting points above 260 °C [43, 57]. Analysis of their linear optical properties showed that end-absorption in the UV/Vis spectra occurs, independent on size, at nearly the same wavelength (below 500 nm), suggesting a quite inefficient cross-conjugation in the perimeter of the macrocycle. The extent of π-electron delocalization is most likely limited to the longest linearly conjugated π-electron fragment, which is equal to the conjugated dodeca-3,9-diene-1,5,7,11-tetrayne-1,12-diyl π-backbone in **23**. In fact, the end-absorptions of the three expanded radialenes in comparison with the linear TEE dimer **23** are bathochromically shifted by only ~20 nm [58]. Electrochemical analysis shows that the expanded radialenes **20a-c** can reversibly undergo two, three, and four one-electron reduction steps, respectively. All three compounds have a similar first reduction potential (**20a**: −1.08 V, **20b**: −1.35 V, and **20c**: −1.27 V), which is in accord with the limited π-electron delocalization. The slightly lower potential in **20a** was believed to be caused by improved planarity as a result of less steric interactions between the bulky silyl groups [43].

Diederich and co-workers reported that introduction of π-electron donor groups into the periphery of the expanded radialenes, leading to the new macrocycle series **21a-c** and **22a-d**, greatly enhanced their physical properties [59]. A study of the linear optical properties of the arylated expanded radialenes showed an end-absorption remarkably

shifted to higher wavelengths, corresponding to 575 nm in **21a-c** and 750 nm in **22a-d**. The end-absorptions for all members of one series were found to be almost constant in the case of the first series **20a-c**, and identical in **21a-c** and **22a-d**, in such a way as to consider λ_{end} independent of the ring size. More insight into the effects of donor substitution was evidenced by the comparison of the absorption spectra of the expanded radialenes with those of the related TEE dimers, featuring the longest linear conjugation path of the macrocycles. The observed end-absorption in the series **21a-c** is bathochromically shifted by 45 nm when compared with **24**, and in series **22a-d** the bathochromic shift is 100 nm with respect to **25**. Hence, the electronic cross-conjugation in the macrocyclic perimeter is revealed to become increasingly efficient with increasing donor strength. Furthermore, expanded radialenes **22a,b** exhibit large nonlinear optical coefficients [20, 59].

20a-c R = Si^{i}Pr$_3$, n = 2-4

21a-c R = , n = 2,4,6

22a-d R = –N(C$_{12}$H$_{25}$)$_2$, n = 1-4

23 R = Si^{i}Pr$_3$

24 R =

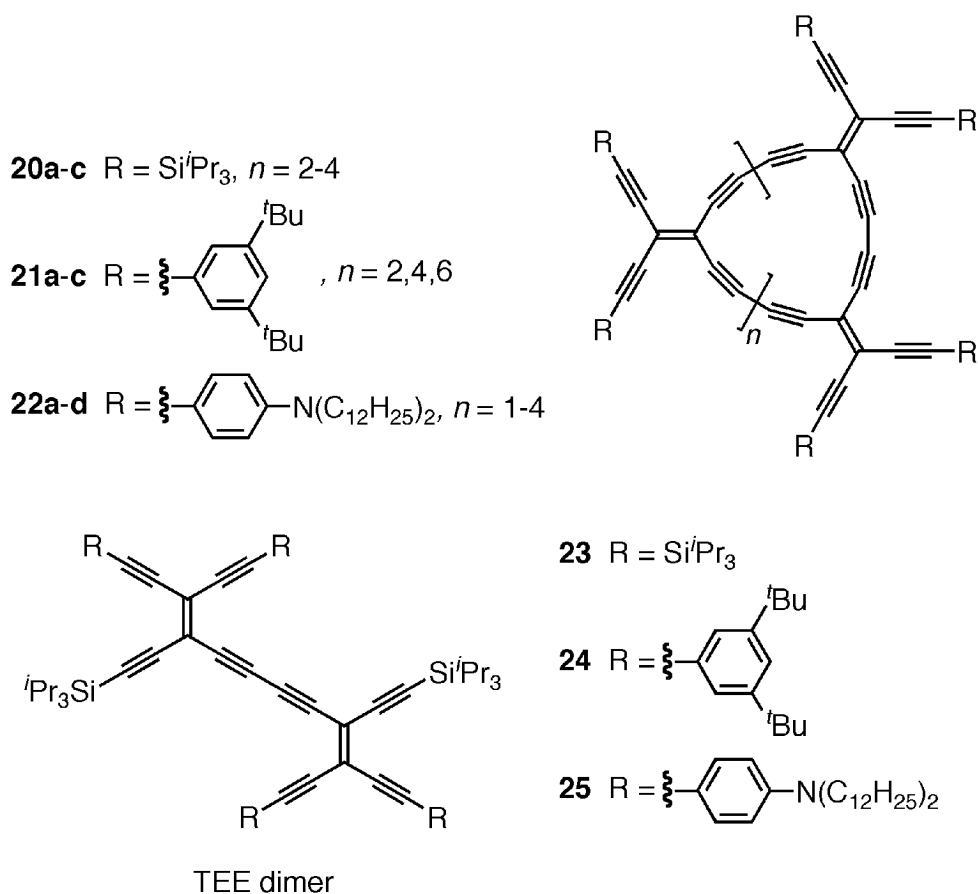**25** R = –N(C$_{12}$H$_{25}$)$_2$

TEE dimer

Figure 1.10: Expanded radialenes **20-22** based on the geminally bis-functionalized TEEs and TEE dimers **23-25**.

Electrochemical measurements revealed that the cyclic conjugated cores of the arylated expanded radialenes **21a-c** and **22a-d** can better accommodate electrons upon reduction than their linear dimeric counterparts, which was tentatively explained with a gain in aromacity with the resulting anionic perimeters.

Cross-conjugation in the expanded radialenes is much more significant than in the acyclic expanded dendralenes, and this is substantiated by their powerful ability to accept electrons in their cores. This can be explained by the greater rigidity of the cyclic π-perimeters, allowing better cross-conjugative and homoconjugation-like orbital overlap [60]. Interestingly, X-ray crystal structure analysis of the expanded radialene **21b** revealed that the cyclic core adopts a nonplanar, "chair-like" conformation and that the six individual TEE units are nearly planar [59].

1.2.3 Peralkynylated Radiaannulenes

Another class of planar and highly conjugated all-carbon macrocyles called "radiaannulenes" has been recently prepared by *Mitzel* and *Diederich* (*Figure 1.11*) [61]. These novel expanded acetylenic chromophores are, from a structural viewpoint, hybrids between perethynylated dehydroannulenes and expanded radialenes. The macrocyclic compounds show a strong reversible electron-accepting ability, dependent on the peripheral groups. The π-acceptor effect of peripheral groups shifts the reduction potential anodically, as shown for **28** (–1.07 V, *vs.* Fc/Fc$^+$), which has two nitrophenyl acceptor and two anilino donor groups. The replacement of the acceptor moieties with donor phenyl groups decreases the reduction power of **26** (–1.19 V) and this trend continues with the tetraanilino-substituted monocycle **27** (–1.36 V). A similar trend also appears in the bicyclic cores **29** and **30**, which display extremely low first reduction potentials at –0.81 V and –0.98 V (in CH_2Cl_2), respectively. These values are even significantly lower than those for a powerful electron acceptor such as buckminsterfullerene (first reduction potential $E^\circ = -1.02$ V, in CH_2Cl_2 [62]). In addition, the electronic absorption spectra of radiaannulene **27** and bicyclic radiaannulene **30** reveal a strong intramolecular charge-transfer absorption.
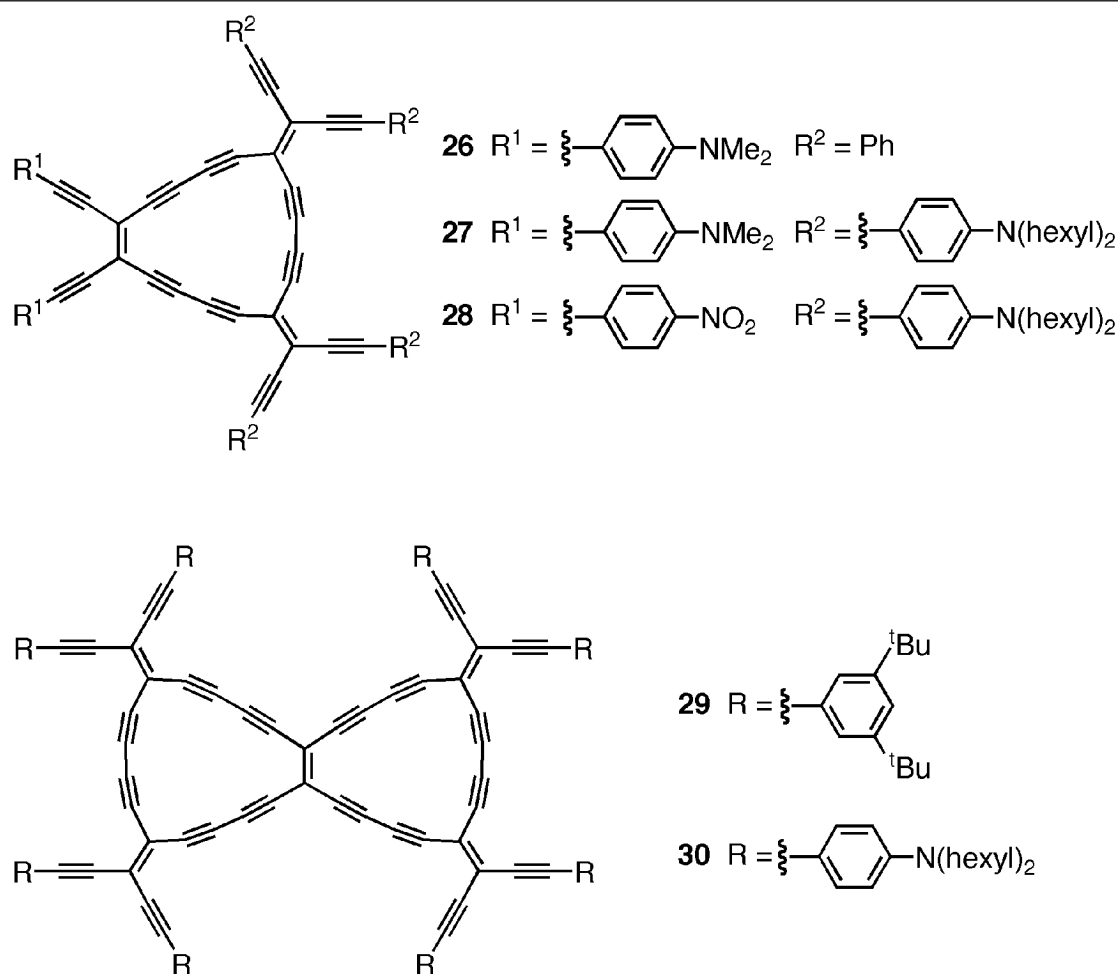
Figure 1.11: "Radiaannulenes": monocycles **26-28** and bicycles **29** and **30**.

1.2.4 Expanded Pericyclynes

In 1990, *Scott et al.* prepared the first macrocyclic oligodiacetylenes **31a-d**, with the aim of investigating the effect of homoconjugation in such neutral molecules (*Figure 1.12*) [63]. Homoconjugation [64], which is a term used to describe a system in which a π-conjugated system is interrupted once or several times by insertion of a single saturated carbon atom, was expected to provide special electronic properties in this class of molecules, arising from the unusual orbital interactions. Such oligodiacetylene ring series, also called expanded (or exploded) [*n*]pericyclynes, consist of a cyclic arrangement of conjugated buta-1,3-diyne-1,4-diyl units and saturated $C(sp^3)$ fragments joined together in alternation, where *n* indicates the number of the vertices (sp^3-carbons) in the perimeter. In a first attempt, the expanded [*n*]pericyclynes **31a-c** were prepared in a one-step "shotgun" synthesis by acetylenic oxidative cyclooligomerization of the monomer 3,3-dimethylpenta-1,4-diyne. Despite its simplicity, this direct technique has found only

limited application because of its low product selectivity and the difficulties associated with the separation of the product mixtures; in general a low yield is obtained [65]. A second, more sophisticated approach, consisting of the stepwise construction of the acyclic oligomers followed by final macrocyclization, provided separately all of the permethylated cyclic oligo(diacetylene)s in the series **31a-d** in better yields. The observed UV absorption spectra of these pericyclynes were virtually all superimposable, with a longest-wavelength absorption maximum at 259 nm, except for that of the expanded [3]pericyclyne **31a**, for which the longest-wavelength absorption was observed at 277 nm. *Scott et al.* explained this bathochromic shift as a manifestation of enhanced homoconjugation in **31a**, caused by a bond-angle compression at the saturated carbon atoms resulting in stronger through-space interactions of the in-plane orbitals, and not resulting from geometric distortions of the oligodiyne chromophore [63, 66].

In order to enhance the through-bond interactions of the out-of-plane p-orbitals, *de Meijere et al.* synthesized the exploded perspirocyclopropanated pericyclynes **32a-g**, also called expanded [*n*]rotanes [67-69]. An increase of the homoconjugative effects in this new series of pericyclynes was expected, since the highest occupied molecular orbitals (HOMOs) of a cyclopropane ring are much closer in energy to the π-MO of the diyne fragments than are the σ-MOs of 2-propylidene moieties [67]. All these expanded rotanes are extremely high-energy molecules, and explode when struck or ground with a spatula.

31a-d n = 1-4   **32a-g** n = 3-8, 10
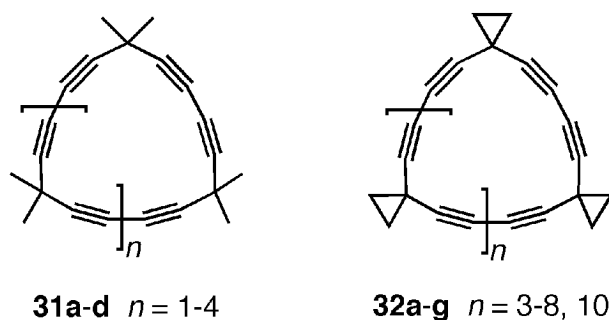
Figure 1.12: Expanded [*n*]pericyclyne (**31a-d**) and expanded [*n*]rotanes (**32a-g**).

Different from permethylated pericyclynes **31a-d**, the electronic absorption spectra of the [5]-(**32a**), [6]-(**32b**), [8]-(**32d**), [9]-(**32e**), and [12]-(**32g**) rotanes revealed a distinct bathochromic shift upon changing from the cyclic pentamer to the dodecamer, not in the long-wavelength region but at shorter wavelengths, between 200 and 220 nm. Furthermore, the absorption bands had enormous amplitudes (ε = 250000-450000). *De*

Meijere et al. concluded that such effects must be related to the expected increase in homoconjugative interaction between ethynyl units and spirocyclopropanes [68].

1.3 Three-Dimensional Acetylenic Scaffolding: Precursors of C_{60}

Although a series of very interesting acetylenic tetrahedral modules [70] has been developed in these last years, the production of three-dimensional acetylenic macrostructures remains quite complicated, mainly due to low stability of certain intermediates in the synthesis.

One goal in the preparation of acetylenic cage compounds has been the total synthesis of buckminsterfullerene C_{60}. Although fullerenes are readily prepared in macroscopic amounts [3], there is still considerable interest in a rational, stepwise synthesis of these geodesic all-carbon compounds, providing isolable quantities. Such approaches may allow the preparation of derivatives of fullerenes and their endohedral complexes that are not obtained from the uncontrolled vaporization of graphite, and also may allow the investigation of the complex fullerene formation processes [51, 71, 72]. A variety of synthetic routes toward the fascinating football-shaped C_{60} have been explored [10, 71, 73-81]. One of them, as already mentioned above, is based on the synthesis of three-dimensional acetylenic scaffolds as precursors.

Rubin et al. proposed a new route for the synthesis of C_{60} [82] inspired by a postulated mechanism of fullerene formation, which includes intermolecular cycloaddition of cyclic polyynes (coalescence) followed by skeletal isomerization (annealing) [51, 83]. The 60-carbon polyacetylenic cyclophanes **33** ($C_{60}H_6$) and **34** (C_{60}) were envisaged to be possible precursors to C_{60}-fullerene. Under *flash vacuum pyrolytic* conditions they were expected to rearrange into buckminsterfullerene, in case of **33** with the loss of hydrogen atoms, in a thermodynamically favorable process, in which highly energetic sp-hybridized carbon centers change into energetically lower sp^2-hybridized ones (*Figure 1.13*) [84]. The spherical acetylenic macrocycle **35** ($C_{60}H_{18}$) was prepared as a more stable precursor, with the intention of generating cyclophyne **33** in the gas phase, which would subsequently undergo rearrangement to C_{60}-fullerene. Disappointingly, **35** was very reluctant to lose hydrogen in laser desorption mass spectroscopic (LD-MS) experiments (negative ion mode) and did not collapse under dehydrogenation to fullerene C_{60}. Only partial dehydrogenation occurred, resulting in the ion $C_{60}H_{14}{}^-$ corresponding to the most abundant peak in the spectrum. The authors speculate that such a system was too flexible

to produce controlled pathways for bond formation [82]. As an extension of this strategy, *Rubin et al.* [85] developed the acetylenic macrocycle **36**, in which the olefinic double bonds of **35** are part of fused cyclobut-3-ene-1,2-dione rings. In a previous work targeting the formation of cyclo[n]carbons the effective and efficient gas phase cleavage of cyclobut-3-ene-1,2-dione moieties producing acetylenic bonds with concomitant loss of carbon monoxide, had been reported [52]. Indeed, LD-MS experiments of **36** in the negative ion mode detected two prominent ions corresponding to $C_{60}H_6^-$ and C_{60}^-. The anion of the carbon cluster C_{60} was unambiguosly identified as a fullerene, since its fragmentation pattern showed the successive loss of C_2 units, which is typical for fullerenes [85].

The same year *Tobe et al.* prepared a stable precursor (**37a**) to cage polyyne $C_{60}H_6$ (**33**), which contains six [4.3.2]propellatriene units, in order to laser-induce the extrusion of the aromatic indane fragments by [2+2] cycloreversion to form $C_{60}H_6$ (*Figure 1.13*). Analysis of **37a** by laser desorption mass spectra in the positive ion mode indeed revealed an intense signal for the C_{60}^+ cation with a C_2-fragmentation pattern down to C_{50}^+. In the negative ion mode, the spectrum is dominated by $C_{60}H_6^-$, whereas C_{60}^- anion appears with much lower intensity [86, 87]. In the positive ion mode LD mass spectrum, the less stable chloro derivative **37b** exhibits a strong peak for C_{60}^+ and the signal-to-noise ratio is remarkably improved compared to that obtained from **37a**. While the negative ion mode experiment shows a small peak due to C_{60}^-, the fragments from $C_{60}Cl_6(Ind)_4^-$ down to $C_{60}Cl_6^-$ are clearly seen due to the successive loss of the indane moieties. Furthermore, intermediate ions such as $C_{60}Cl_5^-$ and $C_{60}Cl_4^-$ are also detected, which contrasts the negative ion mode spectrum of **37a**, but not unexpectedly, since the the bond dissociation energy of a C–H bond (3.9 eV) is higher than that of a C–Cl bond (3.1 eV) [87].

These results constitute an important step toward understanding the formation of C_{60} and in the near future a total synthesis of this fullerene from acetylenic precursors is plausible. Already a remarkably step further in the rational synthesis of C_{60} has recently been made by *Scott et al.* who reported the chemical synthesis of isolable quantities of C_{60} [71]. The strategy was based on the *flash vacuum pyrolysis* of a polycyclic aromatic hydrocarbon (PAH) precursor bearing chlorine substituents ($C_{60}H_{27}Cl_3$) obtained in a multigram scale after eleven synthetic steps. Remarkably, no traces C_{70} and of other fullerenes have been detected by mass spectrometry or high-performance liquid cromatography analysis. However, the overall yield of the twelve-step synthesis remains very low (0.1–1.0%), and from a practical point of view this synthesis will not supplant

graphite vaporization or even the controlled, incomplete combustion of benzene as cheap sources of C_{60}.
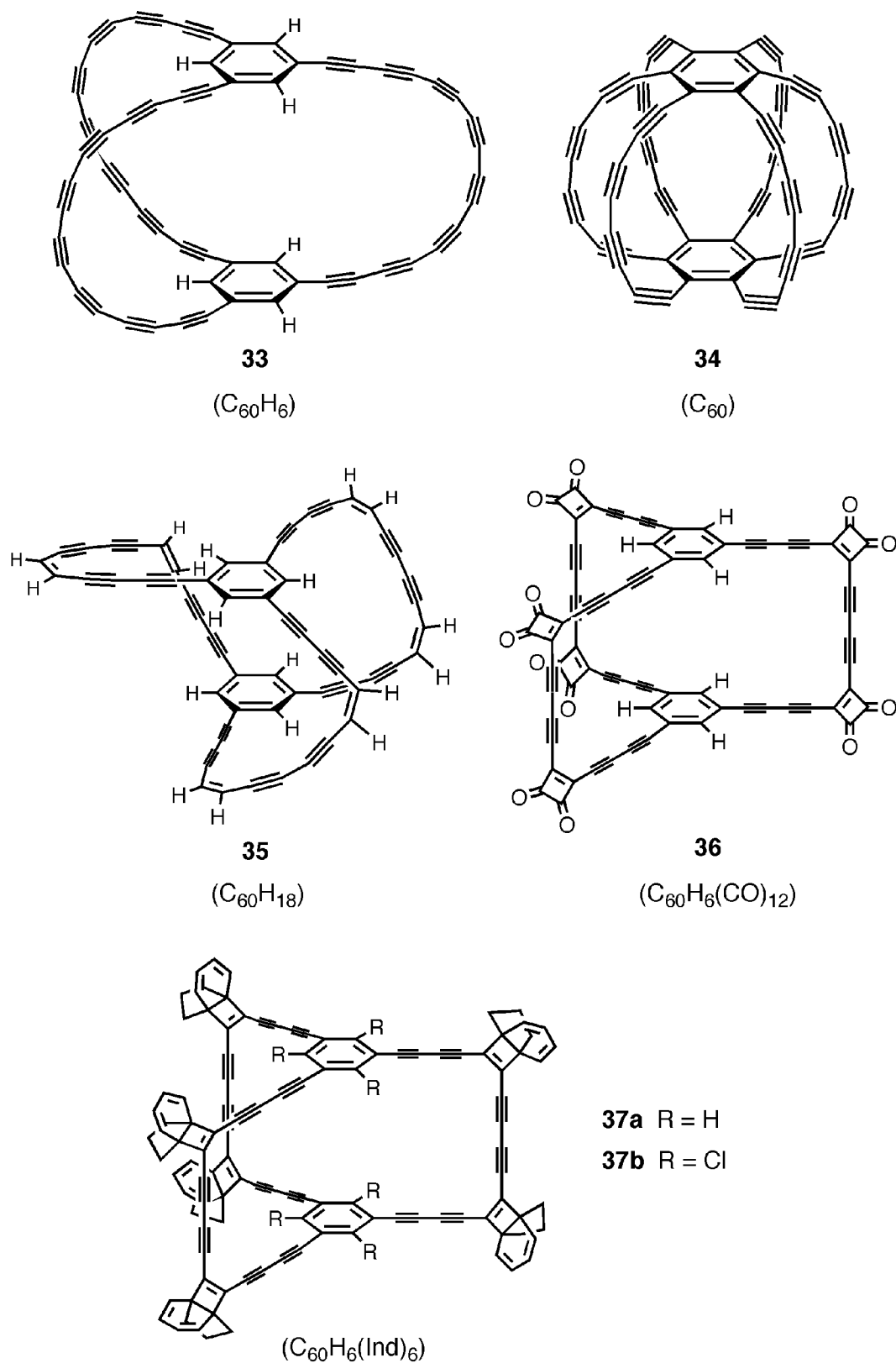

33

$(C_{60}H_6)$

34

(C_{60})

35

$(C_{60}H_{18})$

36

$(C_{60}H_6(CO)_{12})$

37a R = H
37b R = Cl

$(C_{60}H_6(Ind)_6)$

Figure 1.13: Proposed polyyne cages as precursors of fullerene C_{60}. Ind = indane.

1.4 Platonic Structures

A *polyhedron* is a solid bounded by plane polygons, called faces. A polyhedron made of identical regular polygons is called *regular*. Only five such solids exist: tetrahedron, cube, octahedron, icosahedron, and dodecahedron (*Figure 1.14*, *Table 1.1*). To make a regular solid, it is necessary to have at least three triangles meet at each vertex.
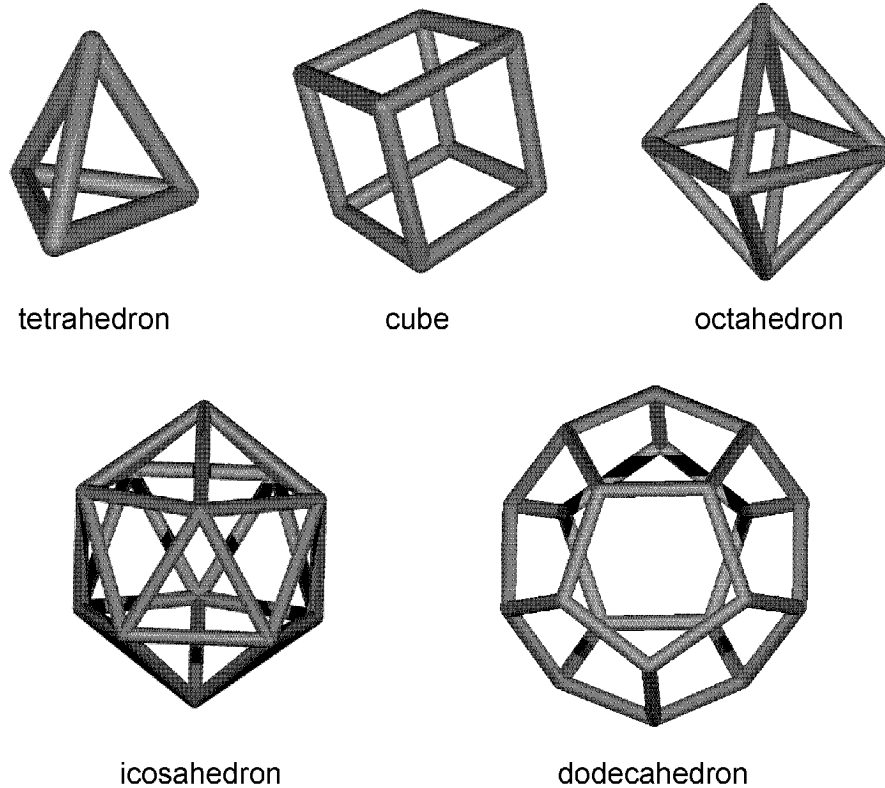

| tetrahedron | cube | octahedron |

| icosahedron | dodecahedron |

Figure 1.14: The five platonic bodies.

Table 1.1: Platonic solids

Solid	Vertices	Edges	Face type	Faces	Symmetry
tetrahedron	4	6	triangle	4	T_d
cube	8	12	square	6	O_h
octahedron	6	12	triangle	8	O_h
icosahedron	12	30	triangle	20	I_h
dodecahedron	20	30	pentagon	20	I_h

When arranging three equilateral triangles in this way, their bases form another equilateral triangle. Thus, a completely symmetrical solid figure with four faces, the *tetrahedron*, is

obtained. On the other hand, if four triangles meet at a vertex, it results in a square-bottomed pyramid. By putting two of these together, base to base, a symmetrical arrangement of eight triangular faces, called *octahedron*, is produced. Next, five equilateral triangles can be connected at a point; adding triangles so that five meet at each vertex gives a complete solid with twenty triangular faces, the *icosahedron*. If six equilateral triangles are put together at a point, a planar arrangement results: no finite solid can be produced. Following again the same procedure with the next polygon shape, the square, it is found that at least three squares are necessary to meet at each vertex. Adding three more provides a perfect solid with six faces, the *cube*. As before, if four square faces join at a point, only a planar surface is obtained. The last regular solid, the *dodecahedron*, is similarly obtained using pentagonal faces. Any other higher regular polygons lead to infinite solids, because the sum of the angles around each vertex is greater than or equal to 360° [88].

The Greek philosopher *Plato* (c. 427 – 347 B.C.), in his *Timaeus*, associated four such regular solids with the four elements. He assigned the cube to earth, because it was the most immobile of the four bodies and most retentive of shape. The second less mobile was the icosahedron and it was assigned to water, the intermediate octahedron to air, and the most mobile, tetrahedron, to fire. The last remaining solid, the dodecahedron, was assigned to an immaterial element, not part of the physical world, but indispensable to construct the "ether" and "to embroider the constellations on the whole heaven", used by God to organize the universe into a beautiful order. From this history, the five solids have become known as the *platonic bodies*.

Beauty and symmetry are strongly connected in the long history of man. Therefore, it is not surprising that people have been attracted by the perfection and harmony of the platonic solids. They have been represented through pieces of art, in architecture, in engineering, furniture, etc. Also in chemistry, where symmetry plays a central role, it is possible to re-create these structures as molecular objects by replacing their vertices by atoms and their edges by bonds. Many examples of inorganic platonic molecules [89-91] can be found, whereas examples from organic chemistry are quite limited. The tetravalence of carbon has been employed to form platonic hydrocarbons such as C_4H_4 (tetrahedrane, see Chapter 3), C_6H_6 (cubane, see Chapter 2), and $C_{20}H_{20}$ (dodecahedrane) [92-94].

2. Expansion of Platonic Structures: Cubane

As already mentioned in the first chapter, the *Diederich* group has been involved in the geometrically defined expansion of molecules by the insertion of buta-1,3-diyne-1,4-diyl fragments between all $C(sp^3)$–$C(sp^3)$ single bonds. The application of this concept [23] to form three-dimensional structures promises to provide a new class of carbon-rich scaffolds, which may be quite attractive with regard to their advanced materials properties.

2.1 From Cubane to the Expanded Cubane

In 1964, *Eaton* and *Cole, Jr.* achieved the first synthesis of cubane **43** [95-97], a molecule that had previously been considered highly unstable and not amenable to synthesis [98]. In fact, cubane has an immensely strained structure; the geometry at each carbon atom is far from tetrahedral (bond angles correspond to 90°) [99]. The original synthesis, based on a twelve-step process, was performed by *Chapman et al.* [100, 101], who shortened the synthesis of the precursor **42**. *Eaton et al.* [102] improved the final step furnishing the octahydro cubane (**43**) (*Scheme 2.1*).
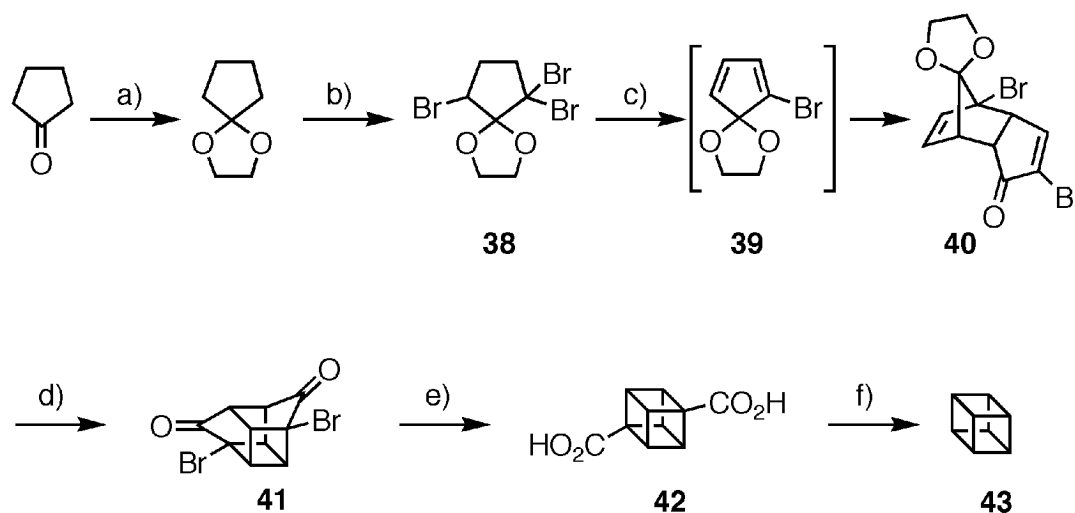

Scheme 2.1: Synthesis of cubane. Conditions and reagents: a) Ethylene glycol, H_2O, HCl; b) Br_2, 1,4-dioxane; c) 1. NaOMe/MeOH, 1,4-dioxane, 2. H^+/H_2O; d) 1. *hv*, benzene; 2. H_2SO_4 (conc.); e) 1. NaOH/H_2O/MeOH, reflux, 2. H^+/H_2O; f) 1. $SOCl_2$, reflux, 2. *N*-hydroxypyridine-2-thione sodium salt, DMAP (cat.), THF, 3. *t*BuSH, *hv*. DMAP = *N,N*-dimethylaminopyridine.

The synthesis starts with the bromination of acetal-protected cyclopentanone to give the brominated ethylene acetal **38**, followed by conversion to the ethylene acetal of 2-bromocyclopentadienone (**39**) by double HBr elimination. Spontaneous *Diels-Alder* dimerization of **39** and mono-deprotection of the ketone functionality gives bromocyclopentenone **40**. Subsequent steps consist of ultraviolet irradiation of **40** in a non-polar solvent, providing intramolecular [2+2] cycloaddition, followed by the cleavage of the acetal, leading to diketone **41**. *Favorsky* [103] rearrangement of the latter provides dicarboxycubane **42**, which is decarboxylated through the *Barton* protocol [104, 105], finally providing cubane **43**. This "platonic hydrocarbon" possesses remarkable kinetic stability, despite its considerable degree of strain (ca. 14 kcal/mol per carbon-carbon bond) and its very high heat of formation ($\Delta H_f^\circ = 144$ kcal mol^{-1}; $\Delta H_f^\circ{}_{C-H} = 18$ kcal mol^{-1}) [106, 107]. Many derivatives have been synthesized and in the following employed as tools in the elucidation of biological mechanisms [108], in the preparation of propellants and explosives [109-111], in the development of nanoarchitectures [112], and as building blocks for potentially new drugs [97, 113].

The proposal to replace the C–C bonds of cubane by rigid acetylenic fragments leads to an expansion of its frame without changing the overall symmetry of the new "exploded" acetylenic cage, even though it may undergo a dramatic change in properties. Hence, the aim of this work consisted in the synthesis of the expanded platonic molecule **44** obtained by formal insertion of buta-1,3-diyne-1,4-diyl moieties into all twelve C–C bonds of octamethoxycubane.
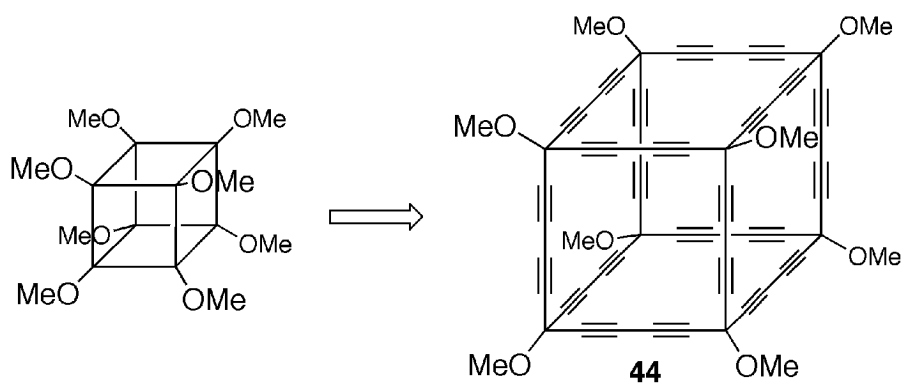
Scheme 2.2: From octamethoxycubane to an expanded cubane by formal insertion of twelve buta-1,3-diyne-1,4-diyl moieties into the C–C bonds.

2.2 Conformational Analysis

Enlargement of cubane by buta-1,3-diyne-1,4-diyl fragments results in a C_{56} core (disregarding the methoxy groups), thereby providing a molecule much larger than its homolog. Submission of the structure of **44** to PM3 calculations using *Spartan* software [114] gives the molecular model displayed in *Figure 2.1*. The expanded cubane **44** has O_h symmetry with a calculated heat of formation of 1023 kcal mol^{-1} ($\Delta H_f{}^{\circ}{}_{C-atom}$ = 18.3 kcal mol^{-1}). Thus, the heat of formation per carbon atom of C_{56} expanded cubane **44** is higher than that of cubane. However, most of it results from the intrinsically high energetic level of the twelve buta-1,3-diyne-1,4-diyl fragments and the strain energy of **44** (22 kcal mol^{-1}) is actually much lower than that calculated for cubane C_8H_8 (*Table 2.1*).

Table 2.1: Heats of formation and strain energies of cubane C_8H_8 and expanded cubane **44**.

	$\Delta H_f{}^{\circ}$ (kcal mol^{-1})		Strain energy (kcal mol^{-1})	
	exp.[a]	PM3[b]	exp.[a]	SYBIL[b]
cubane C_8H_8	144	114	166	193
44	–	1023	–	22

[a]) Experimental values according to literature [106].

[b]) Calculations were performed using *Spartan* software [114]; heats of formation ($\Delta H_f{}^{\circ}$) were calculated using the semiempirical PM3 method [115] and strain energies with the SYBYL [116] force field.

As is apparent from the energy-minimized structure, the angle strain is concentrated primarily in the diyne units causing them to bow substantially out of plane (e.g., C(1)–C(2)–C(3): 172.7°). The angles of the C(sp^3)-atoms at the corners (e.g., C(1')–C(1)–C(2): 107.5°) do not twist much from the normal value of 109.5°. The bond lengths for all of the triple bonds are about 1.20 Å. The single bond lengths between the C(sp^3) and C(sp) atoms are about 1.47 Å and those of the C(sp)–C(sp) single bonds about 1.37 Å. These bond lengths coincide very well with those in hexa-2,4-diyne (C(sp^3)–C(sp): 1.43 Å, C≡C: 1.20 Å, C(sp)–C(sp): 1.37 Å, calculated with PM3 within the *Spartan* package [114]). The calculated distance between the C(sp^3) carbon atoms is determined as 6.6 Å and its volume of the internal cavity has been estimated at a 54 Å^3 [117].
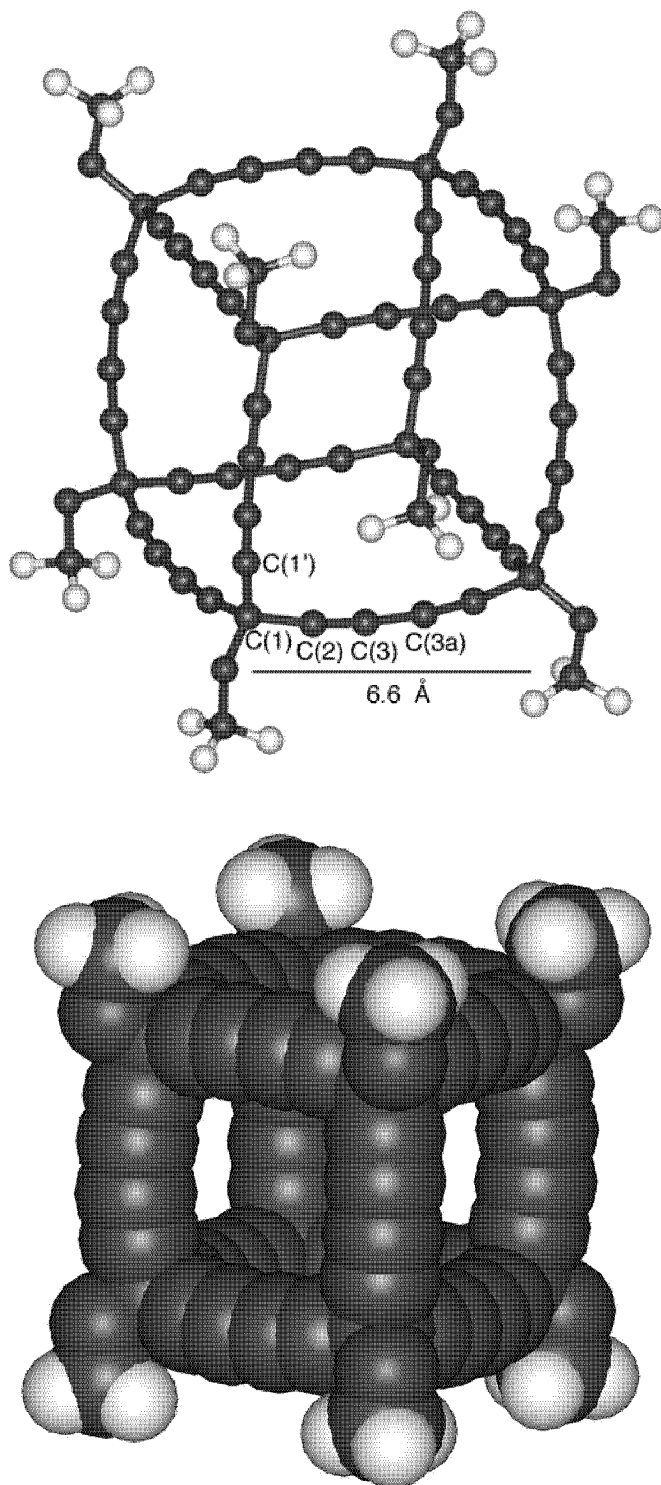
Figure 2.1: Molecular model of expanded cubane **44** generated by PM3 calculations implemented within *Spartan* [114]. Selected bond lenghts [Å] and angles [°]: C(1)–C(2) 1.472, C(2)–C(3) 1.195, C(3)-C(3a) 1.369, C(1')–C(1)–C(2) 107.5, C(1)–C(2)–C(3) 172.7, C(2)–C(3)–C(3a) 173.5.

2.3 Expanded Cubane: Synthetic Approach

Taking advantage of the O_h symmetry, the synthesis of the expanded cubane **44** is remarkably straightforward. The synthesis was planned to proceed through the formation of corners, edges, and faces as key building blocks and intermediates (*Scheme 2.3*). The advantage of this sequential strategy is that one corner module can provide the successive module (edge) simply by alkyne *homo*-coupling, the edge can then be coupled to provide the face, and ultimately, coupling of the face will result in the target molecule.
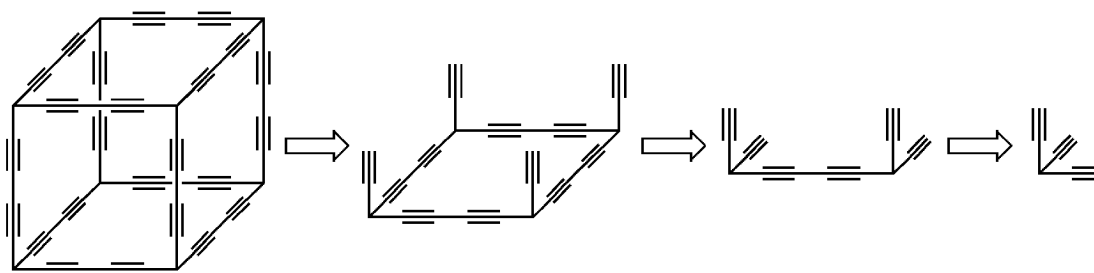
Scheme 2.3: Proposed retrosynthesis. The expanded cubane can be split into its components, face, edge, and corner.

The logical corner module is a trialkynylmethane – it should be readily synthesized in few steps by nucleophilic addition of metal acetylides to a carbonyl group (*Scheme 2.5*) [118]. To advance in an orderly way from the corner to the edge and face modules, and to avoid indesiderable polymerization, the three acetylene residues in the trialkylnylmethane needed to be introduced by oxidative coupling in a controlled, sequential way. Hence, the three acetylene residues needed to be differentially protected in order to be deprotected sequentially, and in a controlled way. These requirements are discussed below.

2.3.1 Coupling of Acetylenes

Glaser was the first to discover that acetylenes could be coupled with each other by observing that copper(I) phenylacetylide stirred in a saturated solution of ammonia in ethanol smoothly underwent dimerization to diphenyldiacetylene [119]. In the following years, the acetylene coupling reaction was investigated with the intention of extending its scope, trying to overcome the need to isolate the potentially explosive copper(I) acetylide in the dry state before oxidation. *Zal'kind* and *Aizikovich* [120] as well as *Reppe* [121] achieved a remarkable improvement of the oxidative acetylenic coupling protocols by

generating the copper acetylide in *situ* without isolation. Later *Eglinton* and *Galbraith* [122] developed a smooth variant using copper(II) salts in methanol/pyridine solution. This method proved of great value within a few years of its discovery, and led to the preparation of a variety of new unsaturated macrocycles [123], including the pioneering annulene syntheses of *Sondheimer* and co-workers [5, 124-126].

In 1962 *Hay* reported another important modification of the *Glaser* coupling, performing the oxidative coupling of terminal alkynes with O_2 in the presence of catalytic amounts of copper(I) chloride and *N,N,N',N'*-tetramethylethylenediamine (TMEDA), a bidentate ligand, which improves the solubility of the catalyst (*Scheme 2.4*) [127]. This protocol has the notable advantage that it can be carried out in a variety of organic solvents such as acetone, dichloromethane, or 1,2-dimethoxyethane [5].

$$2 \ R\!\!-\!\!\equiv\!\!-H \ + \ 1/2 \ O_2 \ \xrightarrow[\text{solvent}]{\text{CuCl, TMEDA}} \ R\!\!-\!\!\equiv\!\!-\!\!\equiv\!\!-R \ + \ H_2O$$
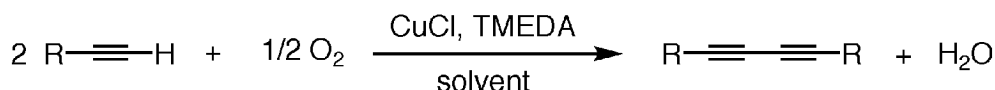
Scheme 2.4: *Hay* coupling conditions [127]. TMEDA = *N,N,N',N'*-tetramethylenediamine.

Hay coupling represents the most important method for the oxidative coupling to provide linear oligo- and polyacetylenes [5, 22, 23, 26, 128]. Furthermore, good results have also been obtained in macrocyclizations to give dehydroannulenes [43], expanded radialenes [59], and acetylenic cage precursors to C_{60} [85] (see Section 1.3).

2.3.2 Protecting Groups for Terminal Alkynes

Terminal acetylenes ($-C\equiv CH$) frequently require protection in organometallic syntheses, due to their rather low pK_a value (25). Many protecting groups have been introduced for this purpose, and the most popular ones are the trialkylsilyl groups [129]. Their effectiveness results from the bulkiness of the alkyl groups that shield the terminal C(sp)–Si bond. As a rule, the bulkier the alkyl substituents on the silicon center, the greater the stability towards acid and base hydrolysis, organolithium or Grignard reagents, oxidation, and reduction. Consequently, they also become more resistant during column chromatography on the rather acidic SiO_2-support. This particularity can be applied to the *principle of modulated lability* [130], consisting in this specific case of the introduction of different trialkylsilyl groups with different kinetic stability towards nucleophilic deprotection agents, in order to obtain an efficient and selective sequential cleavage. Such

protecting groups are required for the corner module in the synthesis of the expanded cubane **44** (*Scheme 2.5*).

Diederich and co-workers have developed a selective deprotection strategy for terminal alkynes, using trimethylsilyl, triethylsilyl, and triisopropylsilyl protecting groups [43, 57]. The advantage of using trialkylsilyl protecting groups is that the C(sp)–Si bonds are stable within the pH range encountered during oxidative coupling; these bonds can be broken subsequently merely by raising the pH. The lability of the trialkylsilyl protecting groups follows the sequence: -SiMe$_3$ > -SiEt$_3$ > -Si^{i}Pr$_3$. Thus, Me$_3$Si- is first cleaved with few drops of aqueous 1N NaOH solution, then SiEt$_3$ with K$_2$CO$_3$ in wet MeOH, and, lastly, Si^{i}Pr$_3$ with basic fluoride agent.
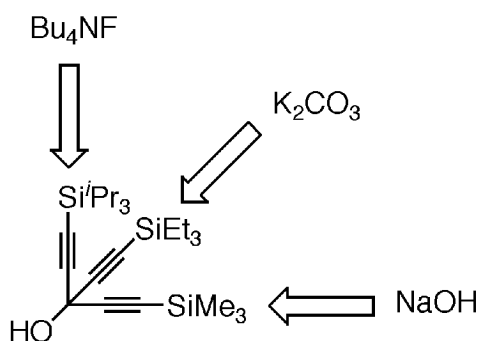
Scheme 2.5: Selective cleavage of differentially trialkylsilyl-protected alkynes.

Cleavage of trimethylsilyl and triethylsilyl groups occurs through hydroxide (OH$^-$) or methoxyde (MeO$^-$) attack on the silicon atom. The C–Si bond (69 kcal mol^{-1}) is cleaved and replaced by the more stable Si–O bond (112 kcal mol^{-1}). The triisopropylsilyl group is too bulky and a smaller nucleophilic agent such as the fluoride anion (F$^-$) is required (Si–F bond strength: 142 kcal mol^{-1}) (*Scheme 2.6*) [131].
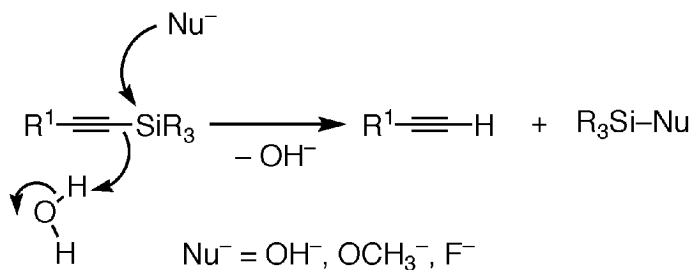

Scheme 2.6: Mechanism of desilylation with nucleophiles.

2.4 Synthesis

2.4.1 Corner, Edge, and Face Modules

The first step toward expanded cubane **44** is the synthesis of the corner module, the trialkylsilyl-protected trialkynylmethanol **49**, which could be prepared in five steps (*Scheme 2.7*). Starting with the oxidation of the readily available trimethylsilylpropargyl alcohol (**45**) with PCC, aldehyde **46** was obtained in good yield [132]. The product was not completely dried (solvent residue: CH_2Cl_2), because of its volatilily, and the crude yield was determined by ^{1}H-NMR integration. Nucleophilic addition of lithium trimethylsilylacetylide at 0 °C to aldehyde **46** afforded racemic dialkynylmethanol (±)-**47** in very high yield. After oxidation, using the same conditions as for **46**, the resulting volatile ketone **48** was readily converted, through addition of lithium triethylsilylacetylide, into the racemic corner module (±)-**49** in satisfactory yield. The tertiary alcohol which has three differentially protected alkyne moieties, was obtained as a stable oil that can be left at r.t. for months without any noticeable decomposition. The subsequent selective deprotection of the trimethylsilylalkyne unit was achieved by stirring (±)-**49** for about 1 h in MeOH/THF (1:1) containing a few drops of 1 N NaOH. The progress of deprotection was checked every 10 min by thin layer chromatography (SiO_2, hexane/CH_2Cl_2 1:1), and it was preferable to stop the reaction before complete conversion to limit cleavage of the triethylsilyl residue. Due to the difficulty of keeping all parameters of the reaction constant (e.g., number of added drops of 1 N NaOH, quality of the solvents), the deprotected alcohol (±)-**50** was obtained, after purification by column chromatography on silica gel, as a colorless oil in a yield ranging from 60 to 85%. Oxidative *homo*-coupling of the alkyne unit of (±)-**50** under *Hay* conditions provided the diastereoisomeric diols *meso*-**51** and *d/l*-**51**. The reaction was carried out in CH_2Cl_2 in the presence of 0.4 equivalents of catalyst (CuCl, TMEDA). During the reaction, decomposition was noticed and the color of the mixture changed from green to dark brown. Therefore, the coupling had to be stopped after 10 min by addition of water. Decreasing the reaction time, even though the reaction was not completed, diminished the amount of decomposed material and provided a satisfactory yield of 70%. Despite purification by column chromatography, it was not possible to eliminate all impurities from compound **51**, which is a colorless oil that crystallized at 4 °C over days. It was hoped that the stereoisomeric diol mixture could be separated at this stage, thus affording pure *meso* form, the only one

that can be coupled to form the face of expanded cubane **44**. Unfortunately, this was not possible, even by HPLC. The hydroxy functionalities are too far away from each other to allow intramolecular hydrogen bonding, leading to different R_f values as reported by *Diederich* and co-workers for a homologous diol (no buta-1,3-diyne-1,4-diyl spacer), with *vicinal* OH groups [133, 134].
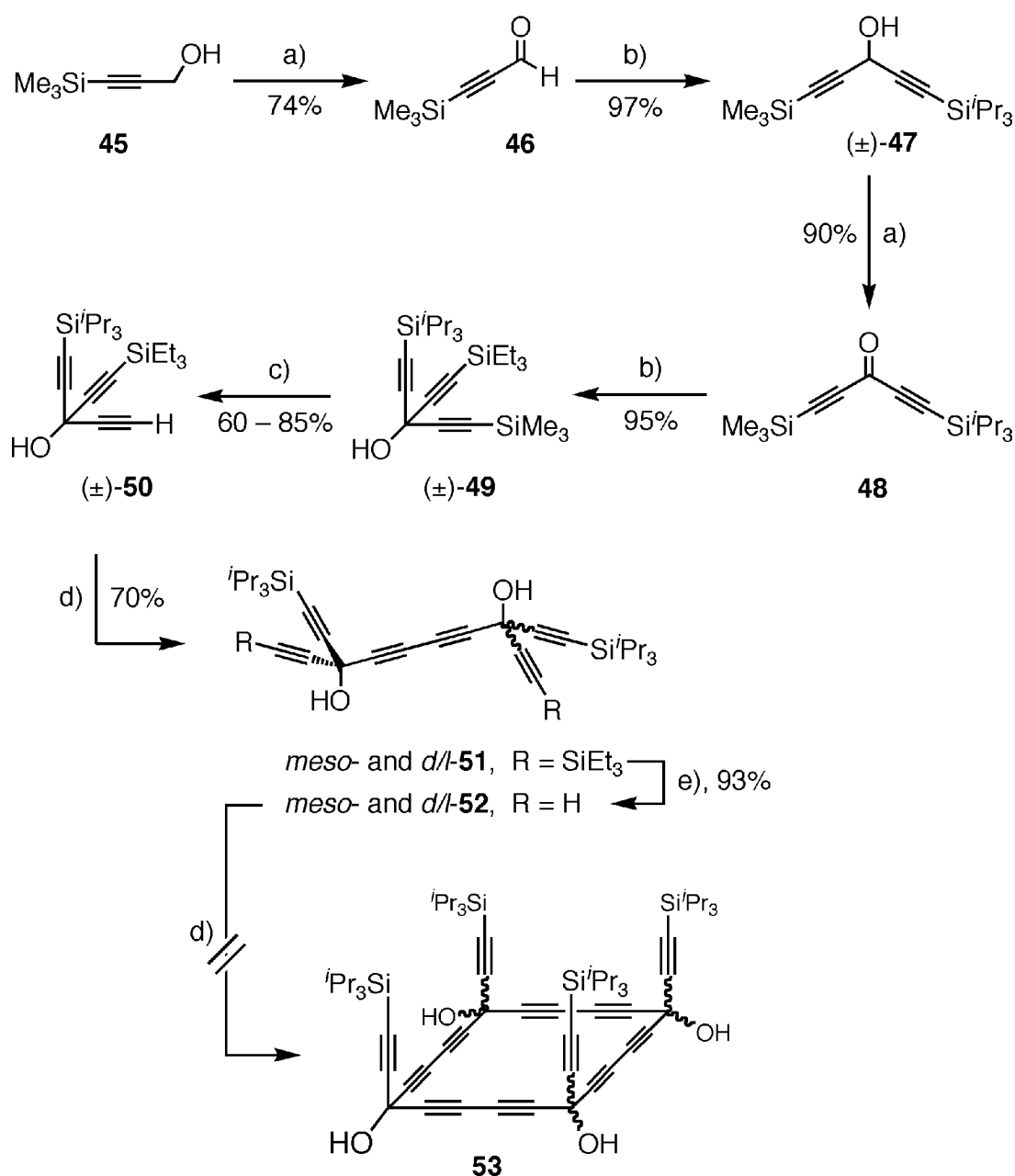
*Scheme 2.7*: Synthesis of diol **52** as a mixture of *meso* and *d/l* diastereoisomers. Reagents and conditions: a) PCC, CH_2Cl_2, molecular sieves, *Celite*; b) $^iPr_3SiC\equiv CH$ or $Et_3SiC\equiv CH$, *n*-BuLi, THF, 0 °C; c) 1 N NaOH, MeOH/THF 1:1; d) CuCl, TMEDA, air, CH_2Cl_2, r.t.; e) K_2CO_3, MeOH/THF 1:1. PCC = pyridinium chlorochromate, TMEDA = N,N,N',N'-tetramethylethylenediamine.

To remove the triethylsilyl protecting groups, diol **51** was stirred in a MeOH/THF (1:1) solution in the presence of K_2CO_3, affording **52** in satisfactory yield as a mixture of stereoisomers (*meso*, *d*, and *l*). Again, separation was not possible, despite of the higher polarity of **52**, compared with **51**. Besides, diol **52** seemed to be unstable; during subsequent oxidative *Hay* coupling in CH_2Cl_2 to provide **53**, the solution turned dark brown and TLC analysis indicated complete decomposition.

According to these first results, modification of the hydroxy functionality was necessary to enhance the stability during the oxidative coupling and to separate the *meso*-dimer from the other diastereoisomers. An ester functionality seemed to be ideal because of its polarity and its ready availability upon reaction with highly reactive acid chloride derivatives. Alcohol (±)-**50** was converted into ester **54** in good yield by addition of the chiral (−)-camphanic acid chloride. It was hoped that conversion of (±)-**50** into a diastereoisomeric mixture **54** could, after coupling, facilitate the separation of the corresponding edge. Unfortunately, dimerization under *Hay* conditions failed because of complete decomposition (*Scheme 2.8*). It seemed that the electron-withdrawing ester functionality decreased the overall stability rather than enhancing it. Another attempt was carried out using ether-bridged **55** that was expected to facilitate the *homo*-coupling of the terminal acetylene by establishing intramolecularity of the reaction. Furthermore it was hoped that the rigid macrocyclic coupling product *meso*-**55** could possibly be separated from *d*/*l*-**55** diastereoisomers and isolated (after ester cleavage) in pure form. Commercial 3,6-dioxaoctanedioic acid was chosen as a tether having the proper chain length and polarity. It was converted into the corresponding acid chloride according to a literature protocol [135, 136] and reacted subsequently with two equivalents of diol (±)-**50**, affording **55**. Product **55** was purified by preparative thin layer chromatography (silica gel), since cleavage of the ester functionalities was observed when employing normal column chromatography. The subsequent intramolecular oxidative coupling was not successful, leading to decomposed material only. Probably, after dimerization, the product did not survive in the presence of oxygen and amine base; the latter could possibly attack the 1,3-diyne under cleavage of the ester, thereby generating an unstable allene, which would readily decompose [137]. To improve to stability of the corner toward oxidative acetylenic coupling, the hydroxy moiety of (±)-**50** was subsequently protected with an electron-donating group such as a trimethylsilyl residue, providing (±)-**56** in quantitative yield. Successive *Hay* coupling gave diyne **57** as a mixture of *meso* and

d/l diastereoisomers in satisfactory yield as a stable oil that could be stored at r.t. for weeks.
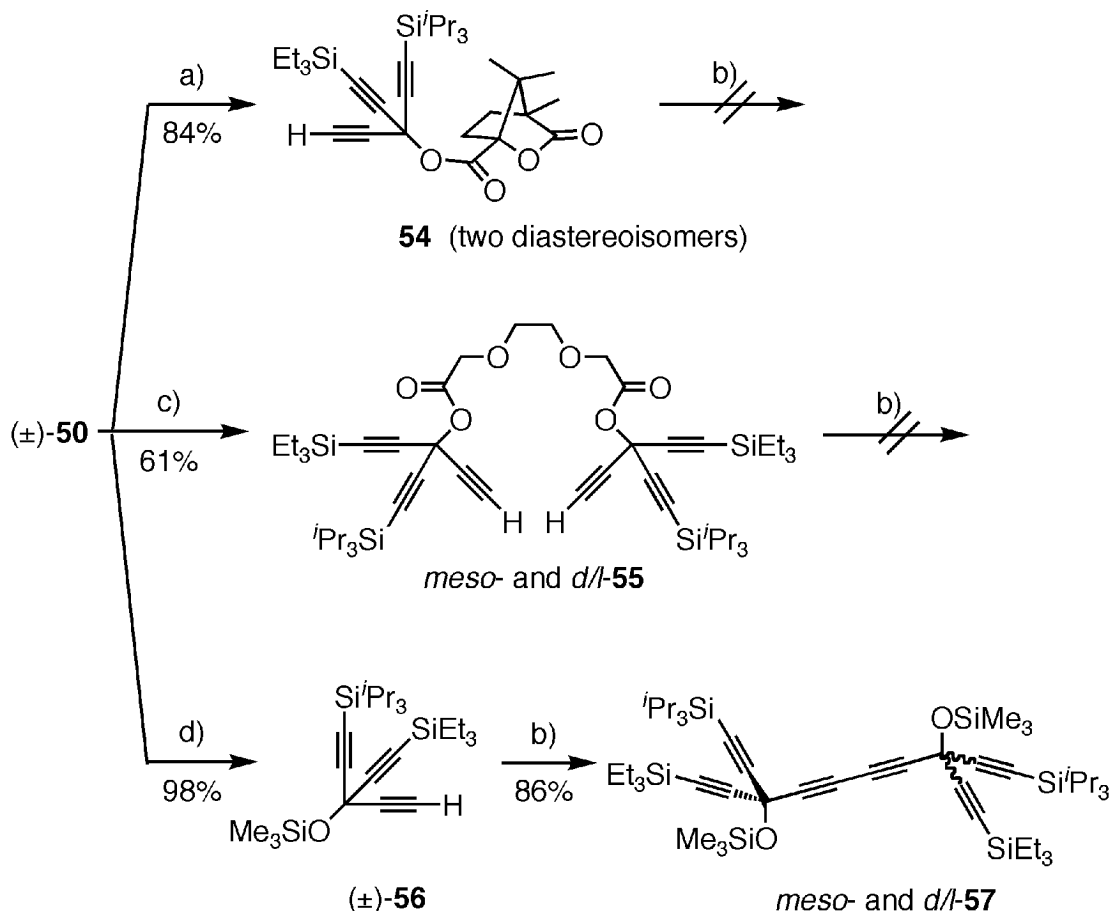
Scheme 2.8: Protection of the hydroxy functionality of (±)-**50** and attempted coupling under edge formation. Reagents and conditions: a) 1. Et₃N, DMAP (cat.), 2. (–)-camphanic acid chloride, CH₂Cl₂, 0 °C; b) CuCl, TMEDA, air, CH₂Cl₂, r.t.; c) 1. Et₃N, DMAP (cat.), 2. (ClOCH₂OCH₂)₂, CH₂Cl₂, 0 °C → r.t.; d) ClSiMe₃, Et₃N, DMAP (cat.), CH₂Cl₂, 0 °C. DMAP = *N*,*N*-dimethylaminopyridine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

In agreement with the necessity of protecting the trialkynylmethanol module (±)-**50** with an electron-rich group, it was decided to methylate the alcohol. It was hoped that the introduction of the polar methoxy group would later assist in the separation of the diastereoisomeric faces that we expected to form upon coupling of two edges (*Scheme 2.9*). Thus, (±)-**50** was deprotonated with 1 equivalent of *n*-BuLi at –78 °C, followed by addition of 8 equivalents of iodomethane; then the temperature was slowly raised [138].
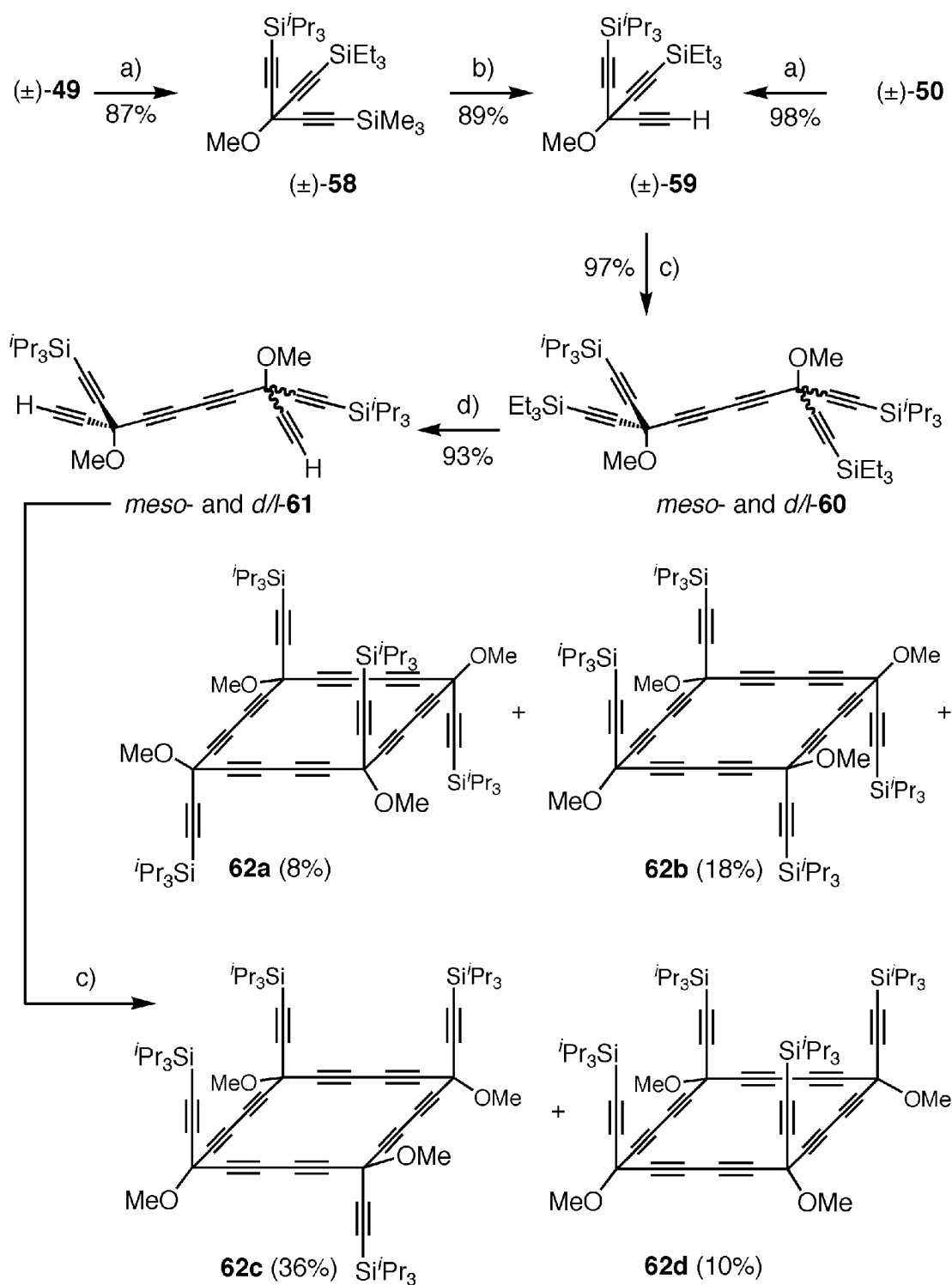
Scheme 2.9: Synthesis of corner, edge, and face modules of the expanded cubane **44**. Reagents and conditions: a) 1. *n*-BuLi, THF, – 78 °C, 2. MeI, – 78 °C → r.t.; b) 1 N NaOH, MeOH/THF 1:1; c) CuCl, TMEDA, air, CH$_2$Cl$_2$, r.t.; d) K$_2$CO$_3$, MeOH/THF 1:1. TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine.

The reaction with exactly 1 equivalent of *n*-BuLi at low temperature guaranteed the deprotonation of the hydroxy group without affecting the less acidic C(sp)–H of the alkyne unit (ΔpK$_a$ ≈ 7). In fact, the corresponding methyl ether (±)-**59** was obtained in

very high yield (97%) as a stable oil. O-Methylation using trimethylsilyldiazomethane and 42% aqueous fluoroboric acid in CH_2Cl_2 was unsuccessful [139]. Alternatively, the trisprotected alcohol (±)-**49** was methylated using the same conditions as for (±)-**59**, leading to (±)-**58** in high yield. The advantage is that the selective trimethylsilyl cleavage with the addition of few drops of 1 N NaOH afforded (±)-**59** in reproducibly higher yields as compared to the deprotection of (±)-**50**. Traces of bisdeprotected compound were readily separated by column chromatography. As expected, oxidative Hay coupling of (±)-**59**, carried out in CH_2Cl_2, occurred cleanly and led to the formation of edge **60** in quantitative yield as an unseparable mixture of stereoisomers (*meso*, *d*, and *l* forms). Successive cleavage of the triethylsilyl protecting groups with K_2CO_3 in MeOH/THF (1:1) gave a mixture of *meso*- and *d/l*-**61** that was subjected to oxidative coupling in CH_2Cl_2 under high dilution conditions. The macrocyclic product **62** was obtained in a remarkable 72% yield as a powder consisting of four diastereoisomers. Separation of the mixture by column chromatography (SiO_2, hexane/CH_2Cl_2 3:1 → 1:3) provided, in the order of elution, **62a** (8%), **62b** (18%), **62c** (36%), and the desired diastereoisomer **62d** (10%). The first three diastereoisomers were further purified by triturating **62a** and **62b** with acetone, and **62c** with hexane, providing a white powder for each compound. The last and most polar square (**62d**), which has a brownish color, could not be completely purified. According to elemental analysis, minor impurities could not be completely eliminated. The diverse retention times of the squares as a result of the rigidity of the macrocycle, enforcing the convergent/divergent orientation of the polar methoxy groups, are nicely seen in the HPL chromatogram (LiChrosorb Si-60, hexane/CH_2Cl_2 9:1) (*Figure 2.2*). Three well separated peaks, corresponding to **62a**, **62b**, and **62c**, respectively, were obtained. The third peak is very broad because of the long retention time. The last and more polar diastereoisomer (**62d**) could not be eluted under these conditions. The diastereoisomeric assignment, largely made possible by the different orientation of the methoxy groups, could in part be derived from differences in polarity and symmetry. As confirmed by PM3 calculation [114], **62a** (μ/4.05 D) and **62b** (μ/3.91 D) have very similar dipole moments, while **62c** (μ/4.26 D) and **62d** (μ/6.64 D) have larger ones. The final assignment, of the two least polar cyclic frameworks in particular, is discussed in the next Section (2.4.2).
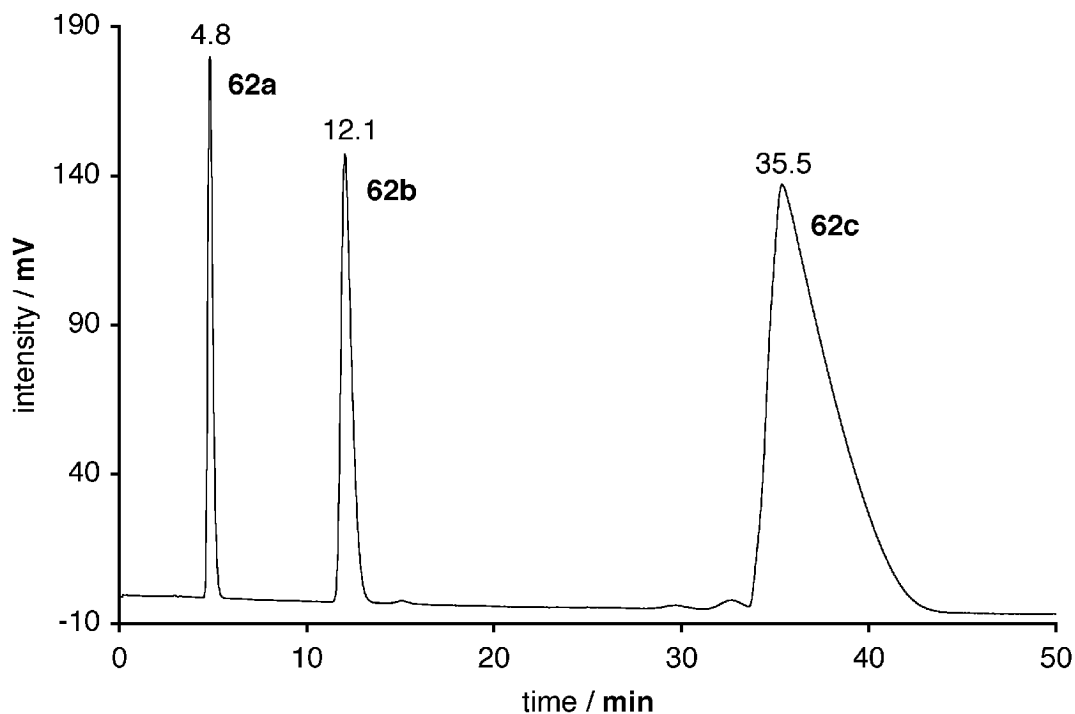
Figure 2.2: The HPL chromatogram shows the good separation of the three first eluting diastereoisomers of "face" **62**. (Column LiChrosorb Si-60, 7 μm, 4mm x 25 cm, elution mixture: hexane/CH_2Cl_2 9:1, flow rate 1 ml min^{-1}, detection at λ = 270 nm).

2.4.2 Structural Assignment of the Diastereoisomers of 62

The structural assignments for the four macrocycles were unambiguosly made based on ^{13}C-NMR spectrometric analysis, X-ray analysis, and chemical reactivity studies. The C_{2h}-symmetrical structure of **62b** was proven by X-ray analysis and ^{13}C-NMR (10 out of 10 resonances observed). Diastereoisomer **62c** possesses the lowest symmetry (C_s), which is reflected by a much larger number of resonances in the ^{13}C-NMR spectrum (15 out of 26 observed). Both D_{2d}-symmetrical **62a** and C_{4v}-symmetrical **62d** show the expected eight resonances in their ^{13}C-NMR spectra; differentiation between the two diastereoisomers is based, besides the different polarity, on the fact that only **62d** continued to react to give expanded cubane **44**.

Crystals of **62b** were obtained by vapor diffusion of hexane into a CH_2Cl_2 solution at 298 K and submitted to X-ray analysis[a]. The X-ray crystal structure of **62b** revealed that the symmetry in the crystal (C_i) is reduced from the ideal C_{2h} symmetry, as a result of crystal packing effects (*Figure 2.3*). The cyclic framework is planar with a mean out-of-plane deviation of 0.041 Å and a maximum deviation of 0.09 Å (C(5)). The distances

34

between neighboring $C(sp^3)$-atoms are 6.64 Å (C(5)-C(10)) and 6.69 Å (C(5)-C(10a)). Strain in the 20-membered ring is mainly expressed by weak bends in the four buta-1,3-diyne-1,4-diyl moieties. The $C\equiv C-C(sp^3)$ angles are as low as 172.4°, and the maximal reduction of the $C\equiv C-C(sp)$ angles from the ideal 180° is approximately 5°. In contrast, the angles at the corner $C(sp^3)$-atoms ((C(9)-C(10)-C(1a) = 106.8°; C(4)-C(5)-C(6) = 107.3°) are close to the ideal tetrahedral angle of 109.5°.
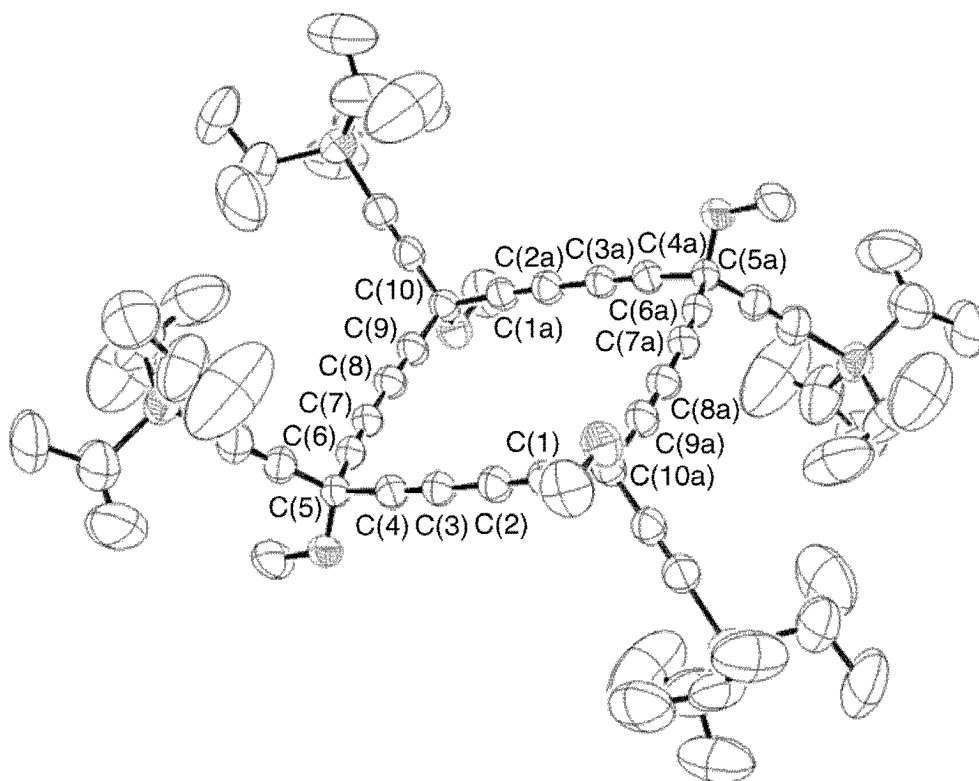
Figure 2.3: ORTEP plot of **62b**; arbitrary numbering, H atoms are omitted for clarity. Atomic displacement parameters at 293 K are drawn at the 50% probability level. Selected bond lenghts [Å] and bond angles [°]: C(1)-C(2) 1.190(5), C(2)-C(3) 1.373(6), C(3)-C(4) 1.188(5), C(4)-C(5) 1.476(5), C(5)-C(6) 1.485(5), C(6)-C(7) 1.193(5), C(7)-C(8) 1.378(6), C(8)-C(9) 1.186(5), C(9)-C(10) 1.481(5), C(10)-C(1a) 1.481(5), C(10a)-C(1)-C(2) 175.5(4), C(1)-C(2)-C(3) 178.3(4), C(2)-C(3)-C(4) 179.0(4), C(3)-C(4)-C(5) 175.9(4), C(4)-C(5)-C(6) 107.3(3), C(5)-C(6)-C(7) 172.7(3), C(6)-C(7)-C(8) 175.2(4), C(7)-C(8)-C(9) 174.7(4), C(8)-C(9)-C(10) 172.4(4), C(9)-C(10)-C(1a) 106.8(3).

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[a] Structure published under CCDC-number 192482. For detailed information see Appendix.

2.4.3 Expanded Cubane 44

For the completion of the synthesis of **44**, **62d** was deprotected with 4 equivalents of Bu_4NF in wet THF at -15 °C to give powdery **63** in 87% yield after column chromatography (SiO_2, hexane/EtOAc 2:1). Deprotection at r.t. failed because of complete decomposition. Although **63** is explosive and detonates upon scratching, it was fully characterized with the ^{1}H-NMR spectra ($CDCl_3$) depicting two signals corresponding to methoxy ($\delta = 3.49$) and to C≡C–H groups ($\delta = 2.74$). The ^{13}C-NMR revealed the expected six signals; three for the C(sp) atoms of the alkyne units at $\delta = 77.42$, 75.97 and 74.50, one for the C(sp)–H carbon atoms ($\delta = 69.03$), one for the quaternary C(sp^3) atoms ($\delta = 61.09$), and one for methoxy groups ($\delta = 53.61$). Two main peaks, detected by mass spectrometric analysis (HR-MALDI positive ion mode), are assigned to the $[M + Na]^+$ and $[M - OCH_3]^+$ ions at 487.0945 and 433.0863, respectively. Oxidative cyclization of **63** under Hay conditions in CH_2Cl_2 afforded expanded cubane **44** in low yield. The reaction was carried out under dilution conditions of 1 mM; lower dilution gave disappointing results affording only traces of **44**.
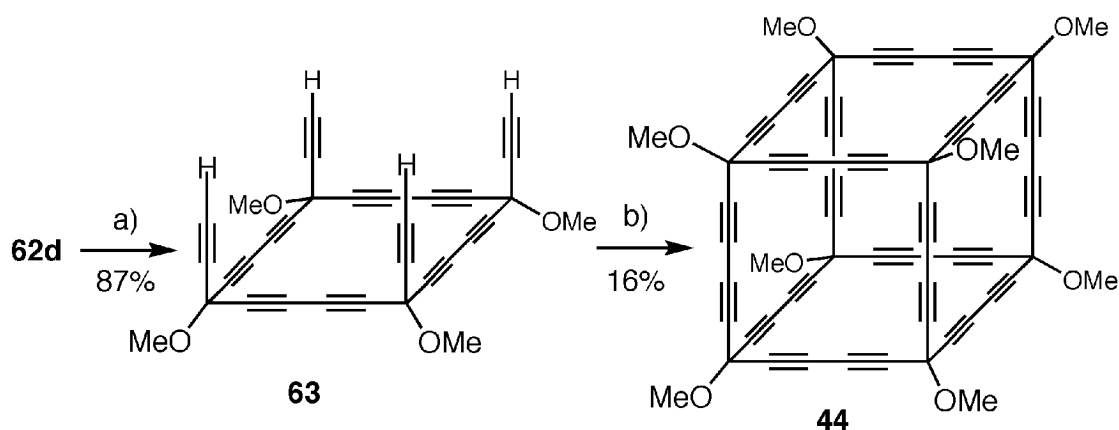
Scheme 2.10: Synthesis of the expanded cubane **44**. Reagents and conditions: a) Bu_4NF, wet THF, -15 °C; b) CuCl, TMEDA, air, CH_2Cl_2, r.t.. TMEDA = N,N,N',N'-tetramethylethylenediamine.

The reaction was followed by thin layer chromatography (hexane/EtOAc 2:1), but not without difficulties, because the product was hardly detectable and could only be visualized with permanganate solution (no heating!). Carrying out the reaction in acetone led to complete decomposition. Purification and characterization of **44** were severely hampered by the instability of the target compound which, similar to **63**, explodes upon scraping, yielding a cloud of black soot [68]. The composition of the black soot was not

analyzed, but in the explosion products of high-energy acetylenic expanded compounds such as pericyclynes and rotanes, amorphous carbon with small graphitic areas was detected [69, 140]. Nevertheless, the substantial amounts of side products could mostly be removed by tedious column chromatography leaving a brownish powder. Further purification by HPLC (hexane/EtOAc) and GPC (CH_2Cl_2) failed.

However, the expanded cubane **44** was obtained with sufficient purity for complete spectral characterization. The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) of **44** demonstrate its O_h-symmetry. The proton resonances of the MeO groups appear as a singlet at $\delta = 3.44$, whereas the ^{13}C-NMR spectrum depicts the expected four resonances at $\delta = 54.38$ (MeO), 61.98 (C(sp^3)), 70.82 (C(sp)), and 79.39 (C(sp)), respectively (*Figure 2.5*).
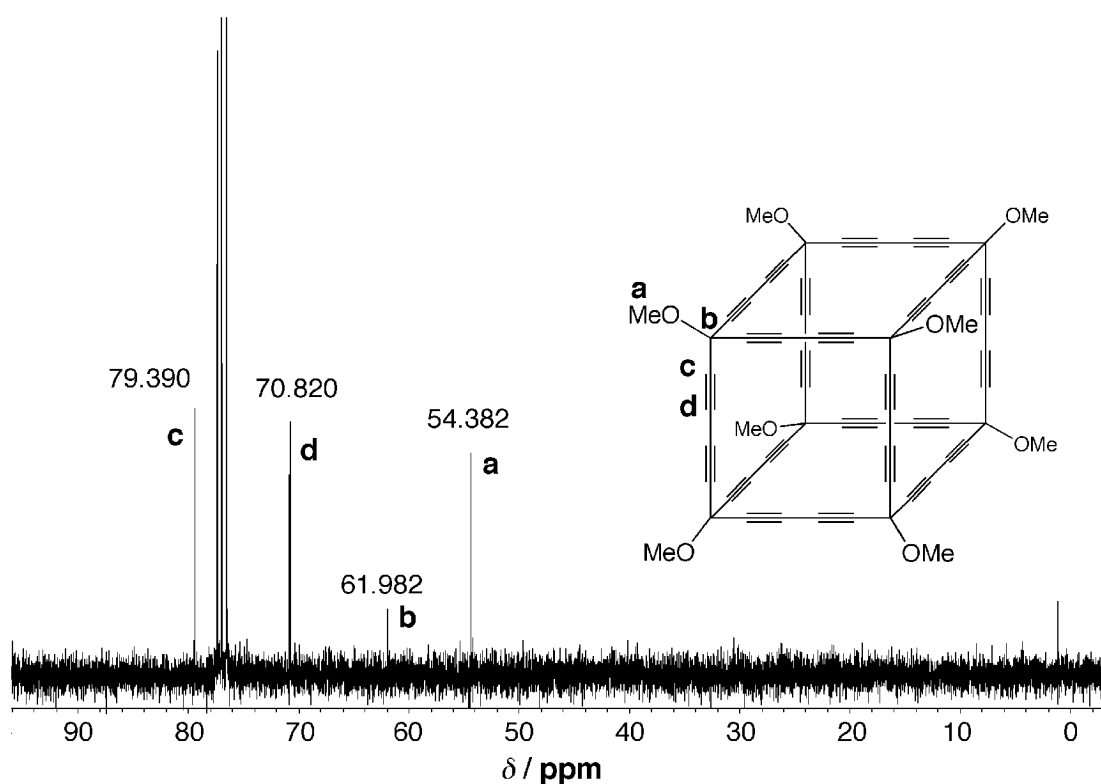
Figure 2.5: ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum of expanded cubane **44** at 298 K.

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In the IR spectrum of **44** the C(sp)–H stretching band at 3302 cm⁻¹, typical of **63**, is completely absent (*Figure 2.6*).
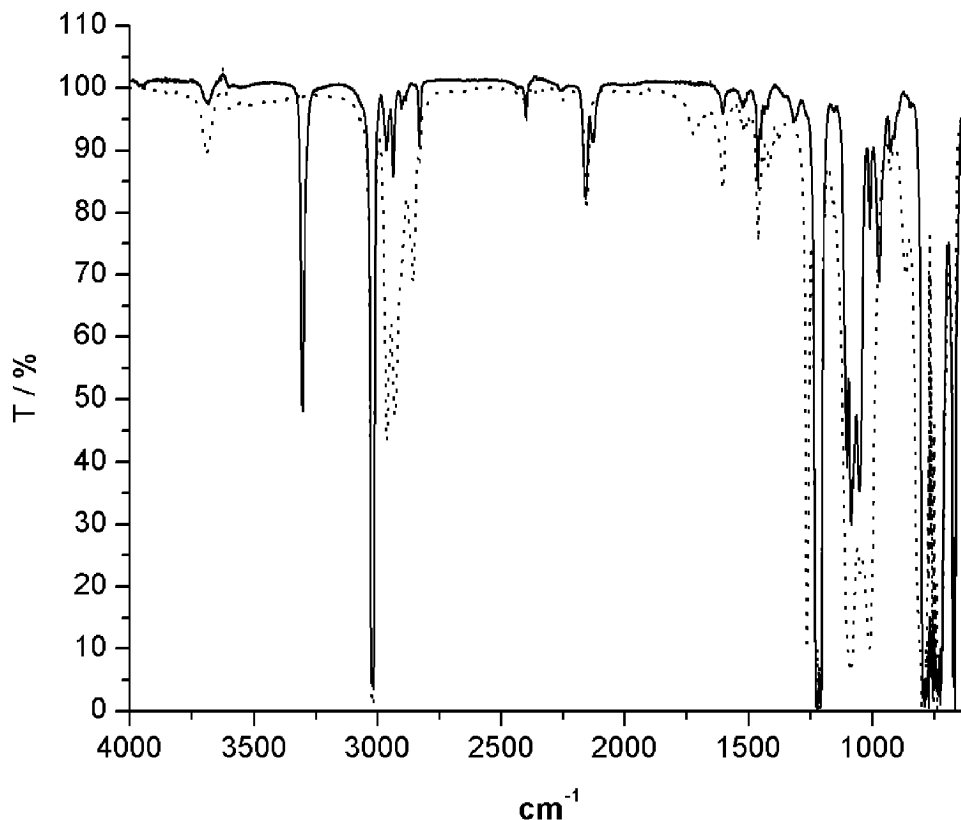
Figure 2.6: IR spectrum of **44** (····) and **63** (—), measured in CHCl₃.

2.5 Mass Spectrometric Analysis of 44: Gas-Phase Transformations into Fullerenes

In matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) experiments in the negative ion mode, expanded cubane **44** readily undergoes a loss of a methoxy group. The peak for the [*M* – OMe]⁻ ion at *m/z* = 889 actually is the only major one in the entire spectrum (*Figure 2.7*). None of the numerous spectra recorded from crude or purified product gave any evidence for oxidative trimerization or higher cyclo-oligomerizations of **63**, leading to larger carbon cages.

Figure 2.7: MALDI-TOF mass spectrum of **44** in the negative ion mode; N_2 laser (337 nm, 7 ns duration), matrix: DCTB (2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile).

Very interesting results were obtained by high-resolution Fourier-transform ion-cyclotron-resonance (HR-FT-ICR) MALDI mass spectrometry. In the negative ion mode, the stepwise loss of up to 6 MeO fragments is observed (*Figure 2.8a*). At lower mass ($m/z =$ 672) the C_{56}^- ion, resulting from loss of all 8 MeO groups, is weakly visible. However, it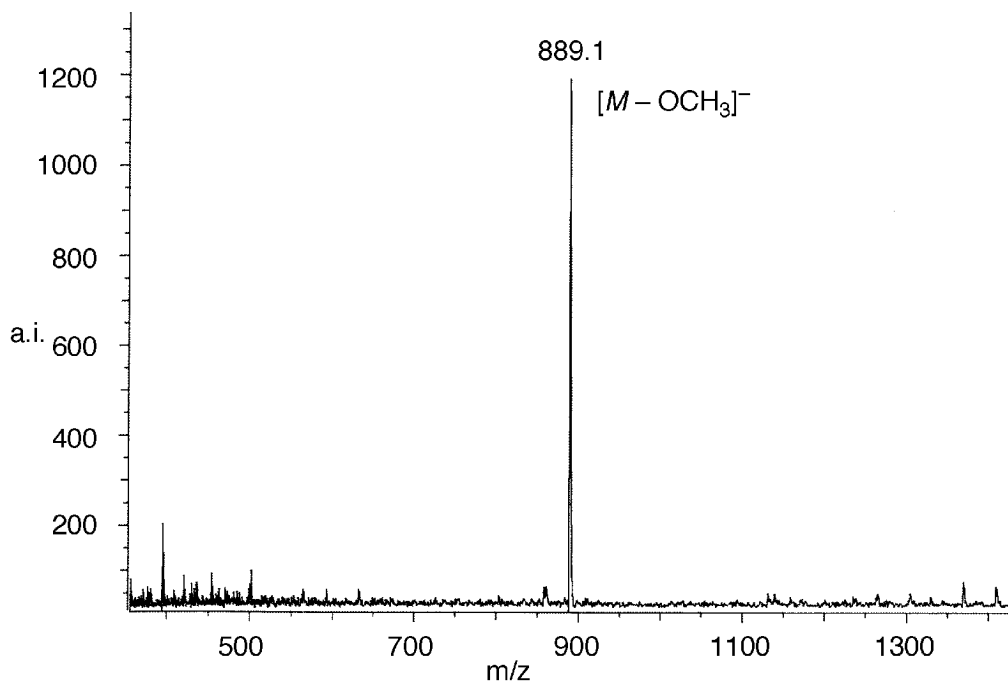 is rather improbable that this ion has the structure of the expanded cubane. Rather, it is preferable assigning this weak peak to a fullerene ion resulting from rapid isomerization of the initially formed anionic C_{56} cluster. This hypothesis is supported by the subsequent facile C_2-fragmentations, that are highly characteristic for fullerenes [93, 141-143]. Thus, C_2-fragmentations of C_{56}^- generate intense peaks which we assign to the fullerene ions C_{54}^- ($m/z =$ 648), C_{52}^- ($m/z =$ 624), and C_{50}^- ($m/z =$ 600). In the positive ion mode, the loss of all methoxy groups and subsequent rearrangement to fullerene ions seem even more favorable (*Figure 2.8b*). Neither the fragment ions $[M - n \text{ OCH}_3]^+$ ($n =$ 1-7) nor the C_{56}^+ ion can be detected. Rather the spectrum is dominated by the fullerene ions C_{54}^+, C_{52}^+, and C_{50}^+, resulting from C_2-fragmentations. Furthermore, these ions undergo remarkable

ion-molecule coalescence reactions [144-146] giving formation of higher fullerene ions from C_{100}^{+} (m/z = 1201) to C_{106}^{+} (m/z = 1272) which, upon C_2-fragmentation, generate the fullerene ions C_{94}^{+}, C_{96}^{+}, and C_{98}^{+}.
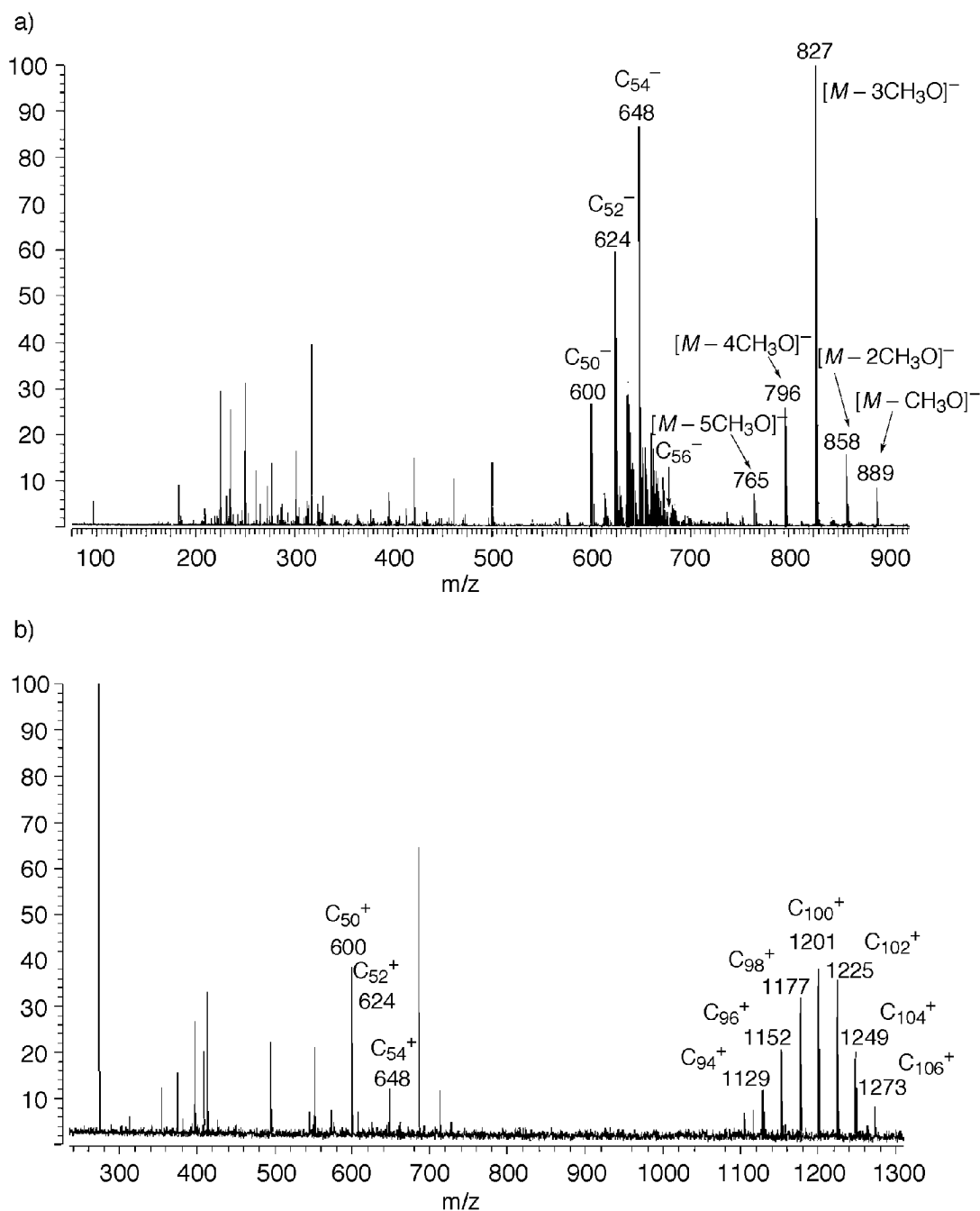

Figure 2.8: HR-FT-ICR-MALDI mass spectra of **44** a) in the negative (matrix: DCTB) and b) in the positive ion mode (matrix DHB (2,5-dihydroxybenzoic acid)). A N_2 laser (337 nm) was employed. All observed m/z values were accurate to within 2 ppm of the postulated elemental compositions.

2.6 Conclusion

In summary, a new acetylenic expanded three-dimensional structure, expanded cubane **44**, was prepared. The vertices of this "platonic" molecule are connected by buta-1,3-diyne-1,4-diyl fragments providing a core of 56 carbon atoms and each corner is substituted with a methoxy group. The strain energy (ΔH_f° = 22 kcal mol^{-1}) of the molecule was estimated to be much lower than that of cubane, C_8H_8, (ΔH_f°(exp.) = 166 kcal mol^{-1}). Its synthesis proceeded by the generation of corners, edges, and faces as key building blocks and intermediates. Corner module ($\pm$)-**58** was obtained in 53% yield after a seven-step synthesis. The three alkyne units of the corner were protected with different trialkylsilyl groups because of their differential kinetic lability under basic conditions. This way, the three acetylene residues could be selectively deprotected, and the edge and face modules were sequentially assembled by the powerful oxidative acetylenic *Hay* coupling in a controlled fashion, avoiding undesirable polymerization. In fact, the coupling of the mono-deprotected corner module ($\pm$)-**59** gave the edge module *meso*-**60** together with two other diastereoisomers (*d*- and *l*-**60**) in an almost quantitative yield (97%). Unfortunately, the diastereoisomer *meso*-**60** could not be isolated in pure form and the subsequent deprotection, followed by coupling of the resulting stereoisomeric mixture under high dilution conditions, led to the face module **62d** together with three other macrocyclic diastereoisomers (**62a**, **62b**, and **62c**). Although this diastereoisomeric mixture was obtained in a remarkable 72% yield, **62d** proved to be a minor diastereoisomer. The four diastereoisomers could be separated by column chromatography, owing to different retention factors and the desired diastereoisomer **62d** was obtained in a yield of 10%. X-ray analysis of diastereoisomer **62b** revealed that the cyclic framework is planar. The internal angles at the corners (ca. 107°) were close to the ideal tetrahedral angle of 109.5°. Strain in the macrocyclic core was mainly expressed by weak bends in the four buta-1,3-diyne-1,4-diyl fragments, resulting in a deviation of approximately 5° from the ideal 180°.

Deprotection of face module **62d** led to the intermediate **63** and successive acetylenic oxidative macrocyclization under high dilution conditions provided the target molecule in low yield as a brownish powder that explodes upon scraping. This instability severely hampered its purification. However, expanded cubane **44** was obtained in sufficient purity for complete spectroscopic characterization (^{1}H-, ^{13}C-NMR, and IR spectroscopy). Further evidence for the successful synthesis of **44** was obtained by MALDI-TOF

experiments in the negative ion mode, where the peak corresponding to $[M - \text{OMe}]^-$ was detected. This high-energy compound (estimated heat of formation of 1023 kcal mol^{-1}) rearranges into fullerenes under conditions of FT-ICR mass spectrometry. In the negative ion mode, in particular, peaks corresponding to fullerene ions C_{50}^-, C_{52}^-, and C_{50}^- were observed. In the positive ion mode, these ions undergo fullerene coalescence reactions providing higher fullerene species.

Further extension of the C_{56}-core of expanded cubane **44** by another two ethynediyl fragments would provide a core of 60 carbon atoms. According to the above-mentioned results, conditions similar to those applied to **44**, should lead to a loss of the methoxy moieties and a thermodynamically driven rearrangement to the more stable fullerene C_{60} (heat of formation c. 610 kcal mol^{-1} [147, 148]).

3. Synthetic Approach Toward an Expanded [3]Prismane and Expanded Tetrahedrane

After the succesful synthesis of the expanded cubane **44**, it was envisaged to synthesize new expanded structures such as expanded [3]prismane and expanded tetrahedrane. *Figure 3.1* shows the shape of a right trigonal prism, which is a polyhedron made of two identical and parallel triangular bases joined by rectangular faces. The regular tetrahedron is a platonic solid (see Section 1.4) and can be described as a regular pyramid with a triangular base. The translation of such aesthetically pleasing geometric forms into the corresponding highly strained organic molecular structures has been a formidable challenge in the last decades.

tetrahedron   trigonal prism
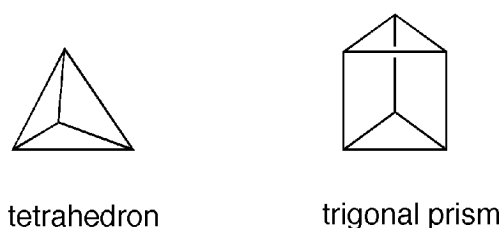
Figure 3.1: Tetrahedron and [3]prism.

3.1 [3]Prismane and Tetrahedrane

Tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane, [3]prismane (**70**, C_6H_6) was first mentioned conceptually by *Ladenburg* in 1869 as the structure for benzene [149]. More than a century passed and after several attempts [150], the first synthesis leading to pure samples of prismane **70** was achieved by *Katz* and *Acton* in 1973 (*Scheme 3.1*) [151]. The procedure started by reacting benzvalene **64** in ether/dioxane with the powerful dienophile 4-phenyltriazolinedione (**65**) giving the 1:1 adduct **68**. Benzvalene **64** could be prepared in preparative amounts by treating lithium cyclopentadienide with dichloromethane and methyllithium [152]. The mechanism by which **68** was formed was investigated by deuterium labelling experiments revealing the probable formation of the zwitterion **66**. Stabilization of the positive charge by σ-bridging led to the delocalized cation **67** which could reclose to the observed hydrazo compound **68**. Subsequent hydrolysis under basic conditions followed by oxidation provided azo compound **69** which was photolyzed with

ultraviolet light, releasing nitrogen and yielding a complex product mixture. Prismane **70** could be isolated in a very modest amount (1.8%) as an explosive colorless liquid. It was found to be stable at r.t. and to decompose in toluene at 90 °C with a half-life of 11 h.
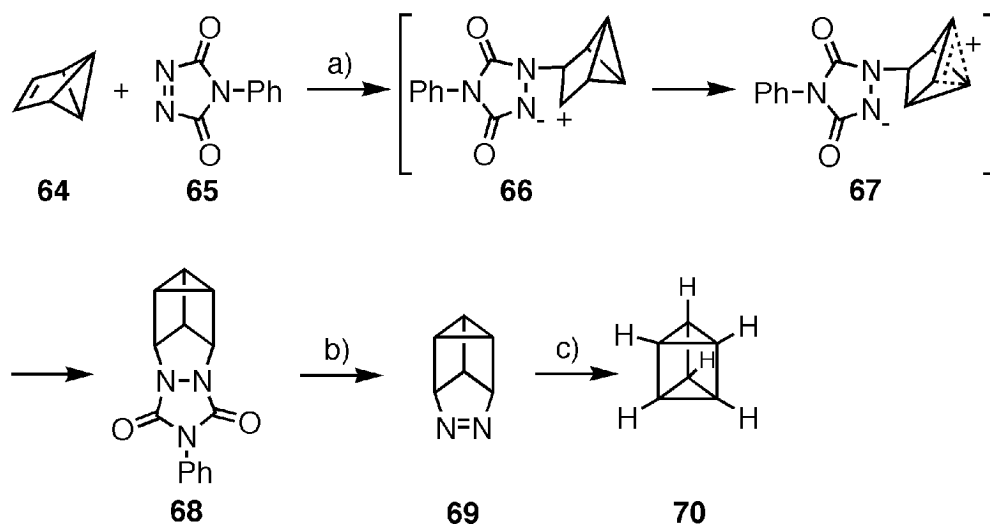
Scheme 3.1: The first synthesis of [3]prismane (**70**). Reagents and conditions: a) Et₂O/1,4-dioxane; b) KOH, MeOH/H₂O (85:15), acidic CuCl₂, aq. NaOH; c) hv, Pyrex.

Later it was shown that *Dewar* benzene (**71**) [153, 154] under certain conditions, can be transformed by ultraviolet irradiation into prismane **70** in an isolated yield of 15%, although benzene was the major product of the synthesis (*Scheme 3.2*) [155].
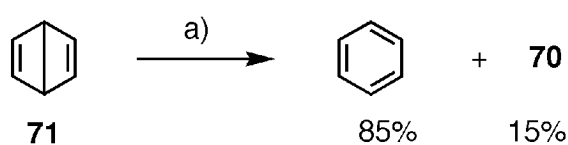
Scheme 3.2: Synthesis of [3]prismane **70** from *Dewar* benzene (**71**). Reagents and conditions: a) 254 nm, initial concentration of **71** less than 10^{-2} M.

Derivatization of *Dewar* benzene provided new precursors which, after photochemical treatment, yielded interesting substituted [3]prismanes [156-159] and some of them could even be characterized by X-ray crystal structure determination [160-164]. The generally low yield of available [3]prismane and its derivatives hampers a complete study of the physical properties, which remain largely unexplored. *Ab initio* calculations of **70** have

estimated a heat of formation and strain energy of 136 kcal mol^{-1} (ΔHf°_{C-H} = 22.7 kcal mol^{-1}) and 148 kcal mol^{-1}, respectively [165].

Besides the fascinating [3]prismane, there is a platonic hydrocarbon named tetrahedrane (**72**), which is considered to have the most highly strained structure among formally saturated hydrocarbons (*Figure 3.2*). Many computational methods have been used to estimate the strain energy and the heat of formation, giving a range from 96 to 150 kcal mol^{-1}, and from 127 to 137 kcal mol^{-1} (ΔHf°_{C-H} = 31.8 to 34.3 kcal mol^{-1}), respectively [166-172]. Thus, it is not surprising that **72** has not yet been prepared. Despite of this, *Maier et al.* were able to synthesize a substituted form of **72**, the tetra-*tert*-butyltetrahedrane (**73**) [173].

72   **73**
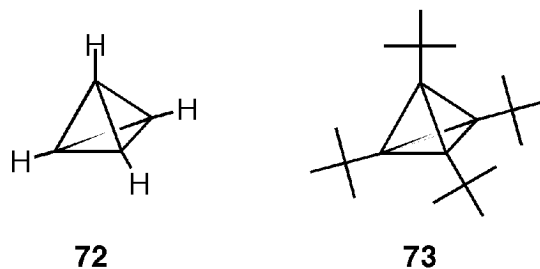
Figure 3.2: Tetrahedrane **72** is a challenging molecule, which remains elusive. Tetra-*tert*-butyltetrahedrane (**73**) was the first derivative that could be prepared.

The voluminous *tert*-butyl groups provide kinetic stability to the tetrahedrane core through steric hindrance preventing the attack of 'outside' reagents and they exert another decisive function for the stability of the structure called 'corset effect'. The intramolecular repulsion between the four *tert*-butyl groups of the tetra-*tert*-butyltetrahedrane is at a minimum when their mutual distance is at a maximum, a condition supplied by the T_d symmetry of the tetrahedron. That is, the favored spherical arrangement of the *tert*-butyl groups forces the tetrahedral geometry on the molecule, and any other conceivable arrangement causes the substituents to be in closer contact providing destabilization and increasing the strain of the hydrocarbon [174, 175]. The synthesis of **73** is shown in *Scheme 3.3*. Tetra-*tert*-butylcyclopentadienone (**74**), readily prepared by a five-step synthesis [176], is isolated in an argon matrix and then excited with 254 nm light resulting in exclusive criss-cross addition to give tricyclopentanone **75** as observed by IR spectroscopy. Prolonged irradiation induces carbon monoxide elimination as well as formation of intermediate ketene **76**. The ketene is photolabile and liberates carbon monoxide, albeit very slowly, leading to di-*tert*-butylacetylene (**77**), resulting the only

end-product of the irradiation at r.t.. Different results are obtained when the irradiation is carried out in an organic matrix at 77 K, where, apart from acetylene 77, hydrocarbon 73 could also be isolated by chromatography as air stable colorless crystals. Upon heating to 135 °C, 73 is quantitatively isomerized into the corresponding cyclobutadiene 78. This process is photochemically reversible. Preparatively, 73 is obtained best with 40% yield relative to transformed 74, when a matrix of this ketone in 2,2-dimethylbutane/n-pentane (8:3) is irradiated at –196 °C [176]. The high-energy hydrocarbon 73 is estimated to have an enthalpy of formation in the gas phase of 6.2 kcal mol^{-1} and a strain energy of 129.2 kcal mol^{-1}, which corresponds to 21.5 kcal mol^{-1} for each skeletal C–C bond of the tetrahedron [174].
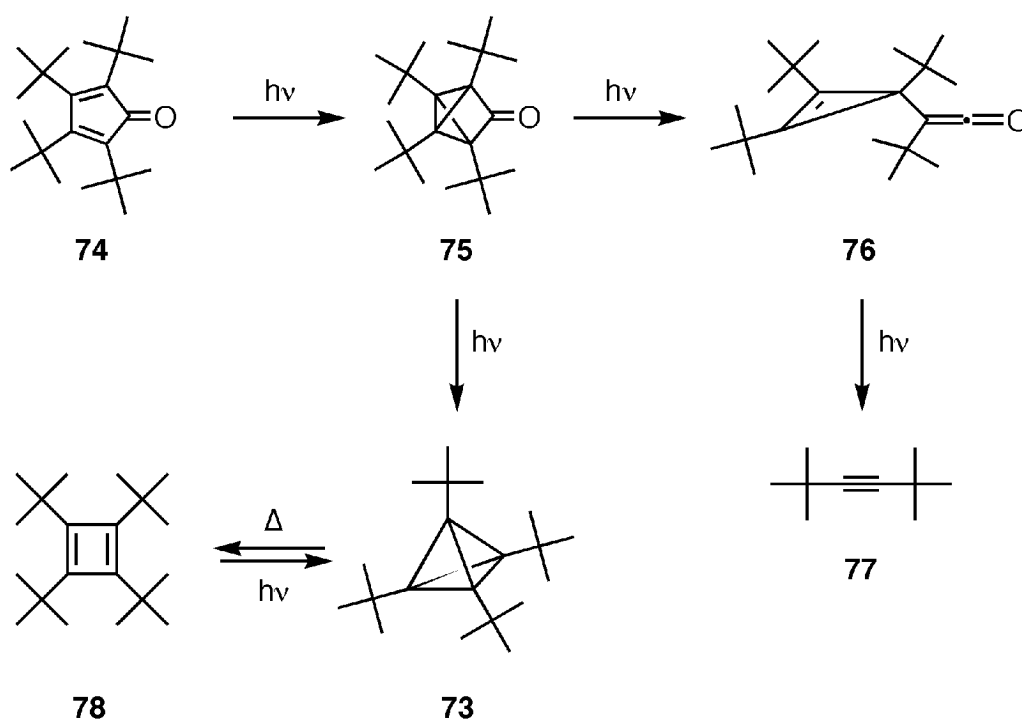
Scheme 3.3: Synthesis of tetra-*tert*-butyltetrahedrane (73) by *Maier et al.* [173].

A derivative of 73 with a ^{13}C-labelled *tert*-butyl group could be prepared in the same way [177], and the chemical shift as well as the ^{13}C-^{13}C coupling constant indicate that the bond connecting the tetrahedral corner with the *tert*-butyl group has a high degree of s-character [178]. The structure of 73 was definitely elucitated by low temperature X-ray analysis, showing that the crystals that were grown at –60 °C were stabilized by entrapped gases (N$_2$, Ar) [179, 180]. After the achievement of the first tetrahedrane synthesis, eight other derivatives have been isolated, in which one *tert*-butyl group of 73 is replaced by the

following substituents: SiMe$_3$ [181, 182], SiMe$_2$Ph [183, 184], SiMe$_2$OCHMe$_2$ [183, 184], SiHMe$_2$ [183, 184], GeMe$_3$ [185], CHMe$_2$ [186], and adamantyl [186]. Another tetrahedrane with only peripheral trimethylsilyl substituents has recently been obtained, the tetrakis(trimethylsilyl)tetrahedrane [187, 188]. Other possible derivatives with different substituents are still under investigation [189, 190], but the synthesis of tetrahedrane **72** seems to be quite far from accomplished.

3.2 Expanded Tetrahedrane and [3]Prismane

3.2.1 Retrosynthetic Aspects

Similar to the expanded cubane **44**, the extension of the edges of a formal tetramethoxytetrahedrane and hexamethoxy[3]prismane with buta-1,3-diyne-1,4-diyl fragments leads to the new homologs, **79** and **80**. Both structures possess a carbon-rich core, containing 28 carbon atoms in **79** and 42 carbon atoms in **80**, without altering the T_d- and D_{3h}-symmetry, respectively. These target compounds have an identical triangular base, which is planned to be a building block on the retrosynthetic route (*Scheme 3.4*). The expanded tetrahedrane **80** can be provided by the oxidative *homo*-coupling of the three unprotected alkyne units of the triangular macrocycle. Contrarily, the assemblage of the expanded pyramid **79** requires an additional component, the corner module, which corresponds to the 'peak' of the pyramid. Thus, the synthesis of **79** is more sophisticated in the final step compared to **80**, and an alkyne *hetero*-coupling is required. Initially focusing on the triangular base, the corresponding synthesis proceeds *via* the alkyne coupling of the corner module, already used in the expanded cubane synthesis, to afford the trimeric skeleton, followed by intramolecular alkyne coupling. Similar to the synthesis of the face (**62d**) of expanded cubane **44**, the base construction is hampered by formation of diastereoisomers originating from the racemic corner module (±)-**58**, although ring closure of the acyclic trimer leads to the base module and only one additional diastereoisomer (in contrast to 4 diastereoisomers formed in the expanded cubane synthesis).
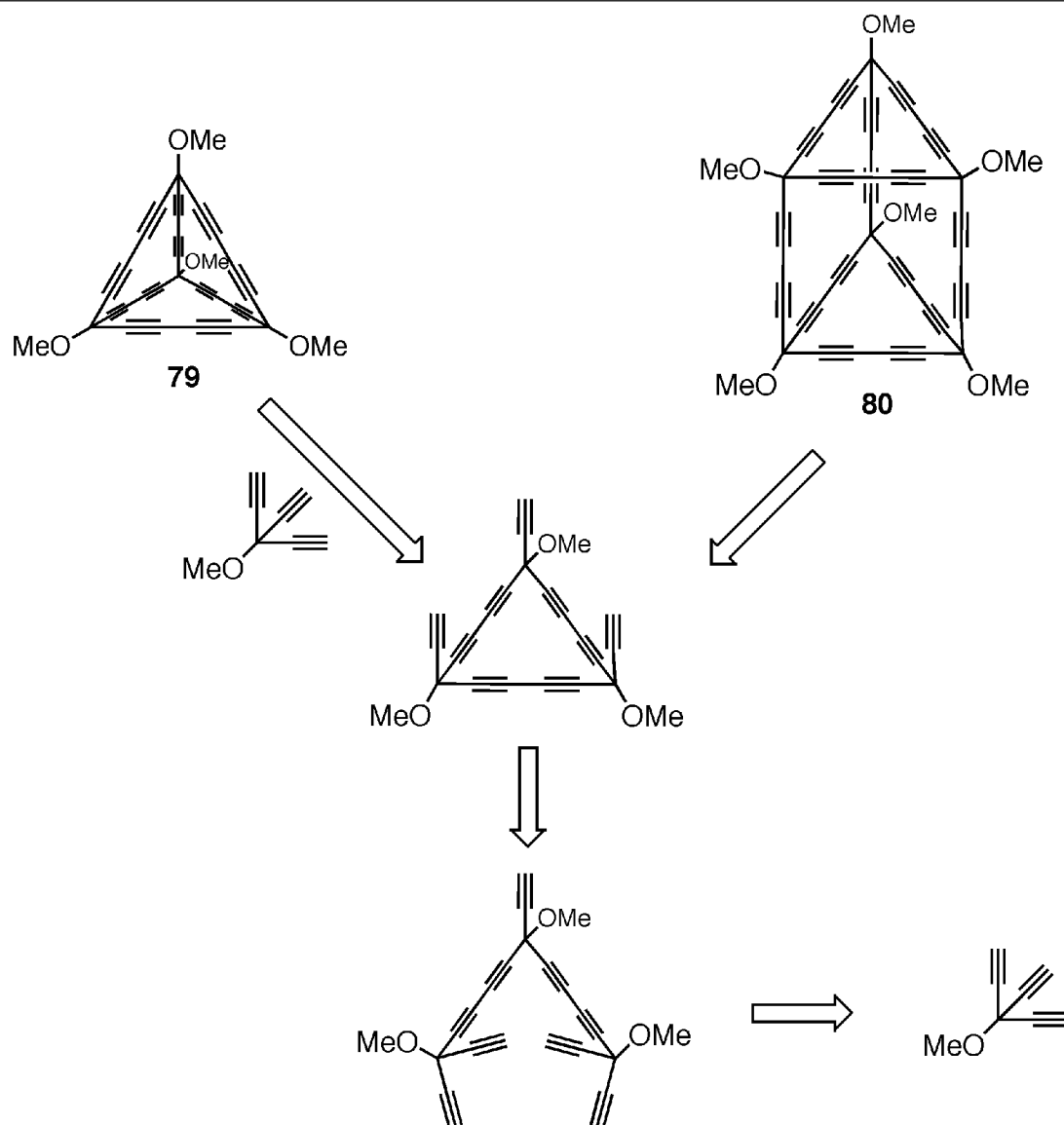
Scheme 3.4: Retrosynthetic route of expanded tetrahedrane **79** and expanded prismane **80**.

3.2.2 Conformational Analysis of the Base Module

The shorter perimeter of the cyclic framework causes an increase in the structural strain. It was decided to submit its structure to PM3 calculations carried out with *Spartan* [114], in order to estimate the degree of angle deformation. As shown in *Figure 3.3*, the silyl-protected cyclic framework is planar with C_{3v}-symmetry. The triisopropyl groups do not influence the structure, being far from each other. In fact, calculation on the deprotected form gives very similar angles and bond lengths. As is noticeable, the angle strain is concentrated primarily in the acetylenic units, resulting in a bending of the perimeter. The maximum deviation occurs in the C(2)–C(3)–C(3a) angle, which

corresponds to a value of 167.7°, not an unusual value in strained acetylenic macrocycles (see [43, 49]). The $C(sp^3)$ atoms at the vertices deviate not much (106.5°) from the normal tetrahedral angle, giving values very close to the X-ray structure of compound **62b**. In the dissertation work of *M. J. Cooney* under the supervision of Prof. *L. T. Scott* is reported the X-ray crystal structure of a permethylated expanded [3]pericyclyne (**31a**, see Section 1.2.4), a compound that decomposes at r.t. in air but is very stable at −30 °C; it could be purified by column chromatography on silica gel [191]. The reported angles at the corners $(C(sp)-C(sp^3)-C(sp))$ and for the diyne units $(C\equiv C-C\equiv C)$ came out to be 103° and 169°, respectively, which is very close to the calculated values for the modeled base module. Also, the length of the single bond between the triple bonds of the pericyclyne (1.38 Å) is similar to that of the calculated base structure (C(3)–C(3a): 1.37 Å), whereas the triple bonds of the X-ray crystal structure are 0.05 Å shorter than those of the modeled structure (C(2)–C(3): 1.20 Å). The calculated distance between the $C(sp^3)$ vertices (6.45 Å) is slightly shorter compared to that in the tetrameric cyclic **62b**.

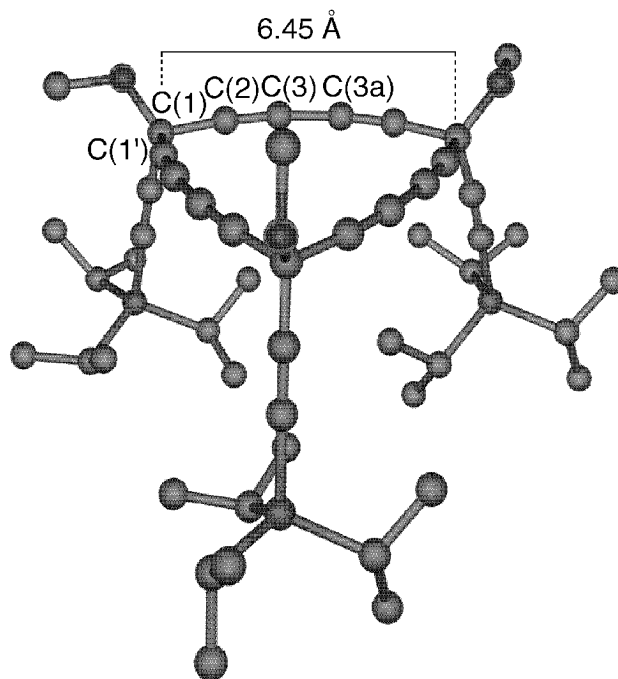*Figure 3.3*: Molecular modeling of the base module. H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C(1)–C(2) 1.484, C(2)–C(3) 1.201, C(3)–C(3a) 1.371, C(1')–C(1)–C(2) 106.5, C(1)–C(2)–C(3) 168.8, C(2)–C(3)–C(3a) 167.7.

3.2.3 Synthetic Route

Unfortunately the synthesis of **85**, which is the base component of expanded tetrahedrane **79** and expanded [3]prismane **80** was unsuccessful. In this Section, the experimental attempts undertaken are described (*Scheme 3.5*).

The first target of the synthesis was linear trimer **83**, the direct precursor of **85**. The first effort to provide **83** used the *Cadiot-Chodkiewicz* coupling *via* intermediate copper derivatives [192, 193], as successfully applied to the synthesis of similar compounds in the synthesis of 'exploded' pericyclynes [63, 69]. The double removal of the trimethylsilyl and triethylsilyl protecting groups in (±)-**58**, using 4 equivalents of K_2CO_3 in MeOH/THF, provides trialkynylmethoxymethane **81** as an oil in very good yield. Adduct (±)-**82**, which was the second building block necessary to create **83**, was easily obtained by an efficient one-step conversion of the trimethylsilylacetylene (±)-**58** into a bromoacetylene [194, 195]. Desilylation occurred with catalytic amounts of $AgNO_3$ in acetone, affording the silver acetylide intermediate, which was readily halogenated with an excess of NBS to give (±)-**82** in satisfactory yield after column chromatography. Lithiation of the free acetylene units in **81** with 2 equivalents of *n*-BuLi at 0 °C in oxygen-free THF and successive transmetallation with CuCl led to the bis(copperacetylide) intermediate (potentially **explosive**!), which was transferred into anhydrous pyridine and then reacted with 2 equivalents of bromoacetylene (±)-**82**. Acyclic trimer **83** could be obtained as a mixture of stereoisomers in poor yield (13%). Alternatively, compound **81** was oxidatively coupled in CH_2Cl_2 under Hay conditions with a large amount of mono-deprotected acetylene (±)-**59** (6 equivalents) to provide **83** in 48% yield. Although the yield was improved considerably, these reaction conditions have the disadvantage of consuming a considerable amount of (±)-**59** by dimerization to the byproduct **60**. Facile cleavage of the triethylsilyl protecting groups with K_2CO_3 in MeOH/THF (1:1) afforded **84** which was subjected to oxidative Hay coupling under high dilution conditions in CH_2Cl_2. The reaction failed and complete decomposition of the starting material occurred. According to literature [63, 67, 69], a reasonable approach toward the formation of such macrocyclic buta-1,3-diyne-1,4-diyl moieties is the oxidative coupling of the terminal alkyne units of the corresponding acetylenic oligomers applying the CuCl/Cu(OAc)$_2$/pyridine system (modified Eglinton conditions) [196]. Therefore, desilylated trimer **84** was added in CH_2Cl_2 under high dilution conditions to a mixture of Cu(OAc)$_2$ in large excess and CuCl in oxygen-free pyridine at r.t., providing a complex product mixture.
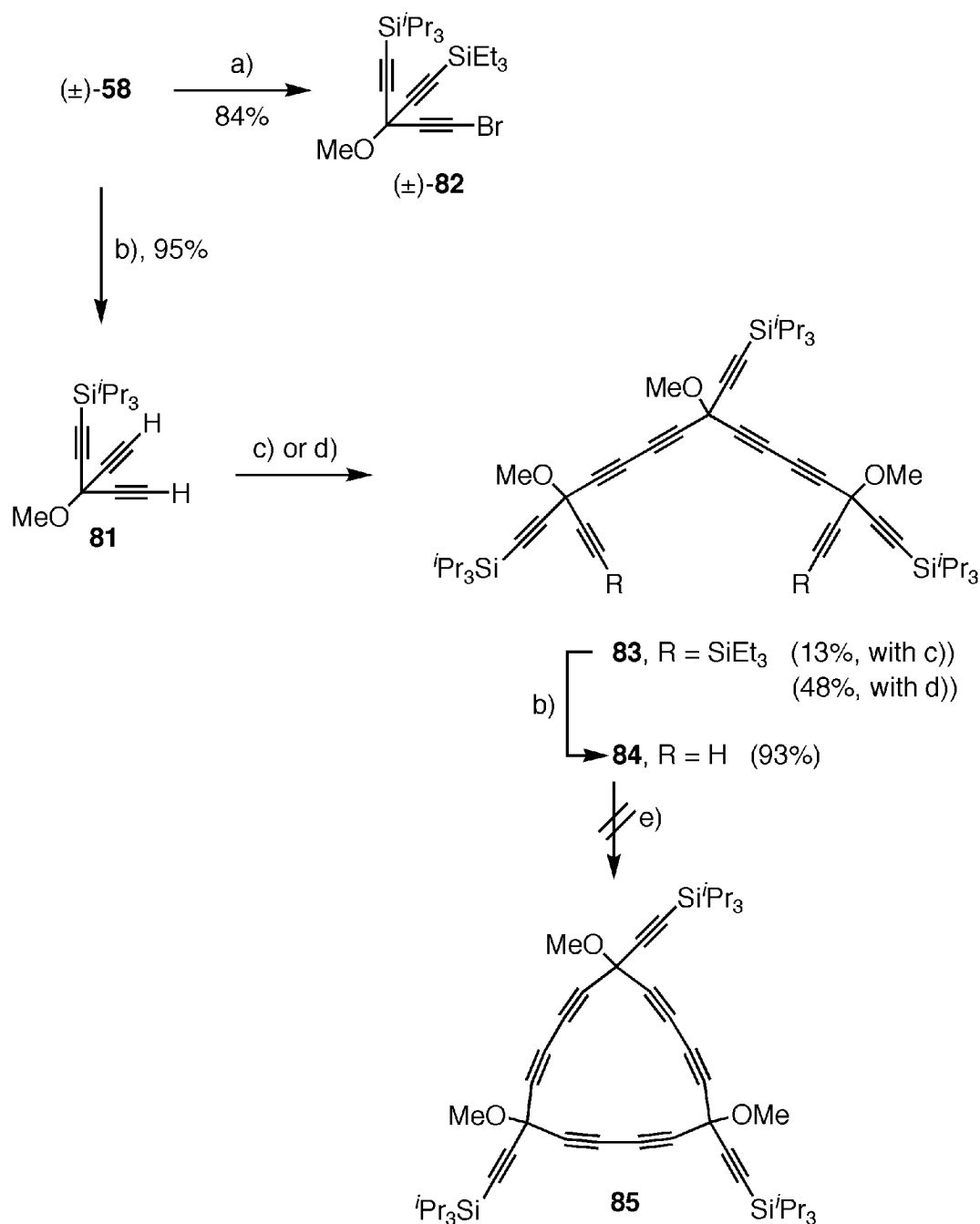
Scheme 3.5: Synthetic approach toward base module **85**. Reagents and conditions: a) AgNO₃ (cat.), NBS, acetone; b) K₂CO₃, MeOH/THF 1:1; c) 1. *n*-BuLi (2 equiv.), THF, 0 °C, 2. CuCl (2 equiv.), –20 °C, 3. pyridine, **82** (2 equiv.), 0 °C or d) (±)-**59** (6 equiv.), CuCl, TMEDA, air, CH₂Cl₂; e) Cu(OAc)₂ (40 equiv.), CuCl (20 equiv.), pyridine, high dilution, inert atmosphere (N₂), 60 °C for 3 h, then r.t. for 12 h. NBS = *N*-bromosuccinimide, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

Mass spectrometric analyses of the mixture showed neither molecular peak nor fragments related to product **85** or to higher oligomeric macrocycles. In a second attempt the reaction was carried out at 60 °C in order to shorten the reaction time [63] but

disappointingly this did not afford any better results. Probably the oxidative cyclization is hampered by the methoxy groups which destabilize the cyclic framework.

3.3 Conclusion

In conclusion, the synthesis of structures such as the expanded tetrahedrane **79** and prismane **80** were attempted. Both structures have the same triangular base which was intended to be used as a crucial building block in their preparation. The synthetic efforts targeting the base module **85** were unsuccesful. The two-step-preparation of trimer **83** was achieved in satisfactory yield starting from the corner module (±)-**58**. Subsequent cleavage of the triethylsilyl groups led to the deprotected compound **84** which provided the desired product **85** neither under *Hay* conditions (CuCl/TMEDA/air) nor under modified *Eglinton* conditions (CuCl/Cu(OAc)$_2$/pyridine/N$_2$) . Oxidative macrocyclization is probably hampered by the methoxy groups destabilizing the cyclic framework which decomposed immediately. Further experiments will be required to accomplish the synthesis of **85**, the key building block in the synthesis of expanded tetrahedrane and [3]prismane.

4. Stereoselective Approach Toward the Synthesis of Expanded Cubane

The preparation of expanded cubane **44**, as described in Chapter 2, was hindered by the great loss of material encountered during the synthesis due to the inevitable formation of many stereoisomers. In order to overcome the ensuing waste of material it was envisioned to improve the synthetic route by developing a stereoselective preparation of the building blocks.

4.1 An Alternative Synthetic Strategy

To improve the previous synthesis of the expanded cubane **44** (Section 2.4), a stereospecific synthesis of the edge module *meso*-**60** was proposed. Such an approach presents a remarkable advantage for the construction and isolation of the suitable face module (**62d**). It would still be generated by acetylenic *homo*-coupling, but in this case the macrocyclization of the appropriate stereoisomer (*meso*-**61**) would lead to only two diastereoisomers (**62b** and **62d**), instead of four diastereoisomers as outlined in *Scheme 2.9*. The edge module *meso*-**60** is obtained by combining the two enantiomeric corner building blocks (*R*)-**59** and (*S*)-**59** with one another (coupling of heterochiral moieties) [197]. The selective *hetero*-coupling of these enantiomers can be achieved using the *Cadiot-Chodkiewicz* protocol [5, 192, 193]. This powerful alkyne *hetero*-coupling is often used in the synthesis of unsymmetrical diynes and consists of the condensation of terminal alkynes with 1-bromoacetylenes in the presence of a copper(I) salt and a suitable amine (*Scheme 4.1*).

$$R\text{---}\!\!\equiv\!\!\text{---}H \xrightarrow{\text{a)}} R\text{---}\!\!\equiv\!\!\text{---}\!\!\equiv\!\!\text{---}R^1$$
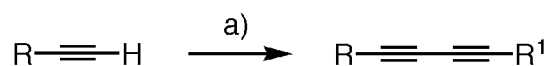
Scheme 4.1: Cadiot-Chodkiewicz hetero-coupling. Conditions: a) 1. CuCl, NH$_2$OH·HCl, EtNH$_2$, MeOH, N$_2$, 2. BrC≡CR^1, MeOH.

This method requires the prior isolation of each enantiomer of the corner module (**59**) and subsequent conversion of one enantiomer into the corresponding bromoalkyne adduct.

4.2 Attempted Resolution of Racemate (±)-49

Most reported separations of enantiomers have been effected by conversion of a racemate into a separable mixture of diastereoisomers as illustrated in *Scheme 4.2*. In this procedure, the substrate to be resolved is treated with one enantiomer of a chiral compound (the resolving agent). The obtained mixture of diastereoisomers is usually separated by crystallization when they have different solubility, or otherwise by chromatography. The pure enantiomers are obtained from the separated diastereoisomers after cleavage of the resolving agent [198].
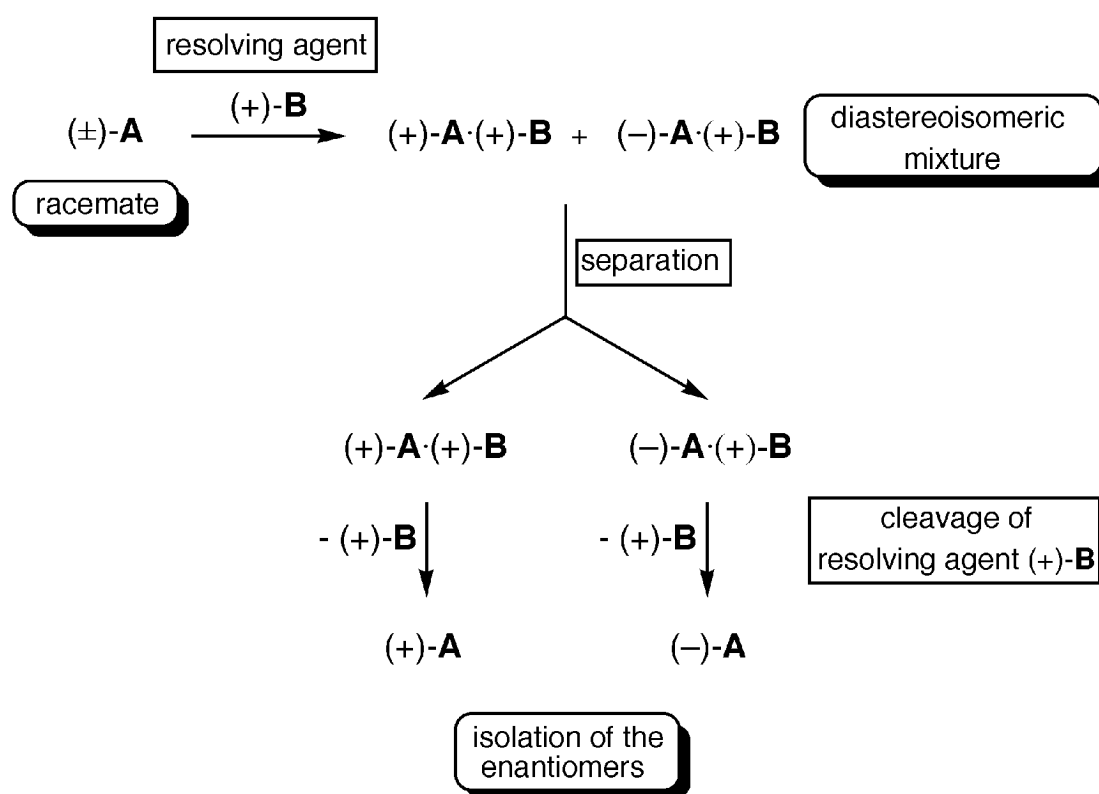
Scheme 4.2: The resolution of racemate (±)-A is based on the conversion with an enantiomerically pure chiral resolving agent (+)-B to afford a mixture of diastereoisomers, that can be separated by cristallization or chromatography. Removal of the resolving agent from the pure diastereoisomers leads to the isolated enantiomers (+)-A and (−)-A.

In the case of (±)-**49**, it was decided to use (*R*)-mandelic acid as chiral auxiliary [199], since it was reported by *Parve et al.* to be a versatile chiral resolving agent for alcohols [200]. In this procedure, racemic alcohols are first esterified with THP-protected mandelic acid and the resulting diastereoisomeric esters are separated by gravity column

chromatography or semi-preparative HPLC after cleavage of the acetal protecting group. The procedure was later confirmed to be very efficient in the resolution of a secondary diethynylmethanol [201].

Hence, commercially available (R)-mandelic acid was reacted with DHP providing compound (R)-**86** in 55% yield (*Scheme 4.3*) [202]. The subsequent step consisted in the esterification of (R)-**86** with trialkynylmethanol (±)-**49** but unfortunately and despite various attempts (*Table 4.1*), the conversion into ester **87** failed.
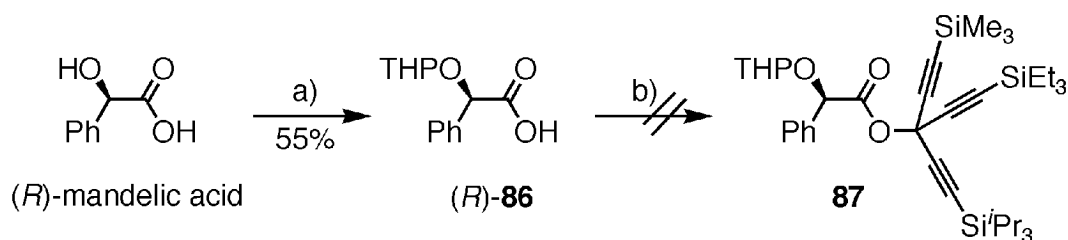
Scheme 4.3: Attempts to prepare ester **87**. Reagents and conditions: a) DHP, TsOH, CHCl₃; b) see *Table 4.1*. DHP = 3,4-dihydro-2H-pyran, TsOH = p-toluenesulfonic acid.

Table 4.1: Attempted transformation of THP-protected mandelic acid (R)-**86** into ester **87**.

Entry	Reaction conditions	Results
1	DCC (1 equivalent), (±)-**49** (0.8 equivalent), CH₂Cl₂ (THF, DMF), 0 °C → r.t., 24 h	No reaction[a]
2	CDI (1.1 equivalent), DMAP (cat.), CH₂Cl₂, then after 1 h addition of a solution of (±)-**49** (0.8 equivalent) and Et₃N in CH₂Cl₂, r.t. for 48 h, reflux for 5 h	Complex product mixture and presence of starting material
3	(±)-**49** (0.5 equivalent), DMAP (0.1 equivalent), DPTC (1 equivalent), THF, reflux, 4.5 h	Starting material destroyed
4	1) 2-PySCOCl (1 equivalent), Et₃N (1.1 equivalent), CH₂Cl₂, 0 °C, 30 min; 2) CuBr₂ (1 equivalent), (±)-**49** (0.8 equivalent), CH₃CN, r.t., 24 h	No reaction
5	(COCl)₂ (1.1 equivalent), DMF (cat.), CH₂Cl₂, 0 °C for 40 min, r.t. for 1.5 h, then addition of DMAP (cat.) and a solution of (±)-**49** and Et₃N in CH₂Cl₂, 0 °C → r.t., 3 h	No reaction

[a] Heating in DMF at 80 °C led to a partial cleavage of the trimethylsilyl group.

Esterification using *N,N'*-dicyclohexylcarbodiimide (DCC) [203] as coupling agent in three different solvents (CH$_2$Cl$_2$, THF, and DMF) was completely ineffective, and cleavage of the trimethylsilyl group of alcohol (±)-**49** was detected during heating in DMF at 80 °C (entry 1). Activation of the carboxylic acid with carbonyldiimidazole (CDI) [204] and catalytic DMAP, followed by addition of alcohol (±)-**49** and Et$_3$N did not provide a better result, and refluxing the reaction led to a complex mixture of products that were not isolated (entry 2). The combination of *O,O'*-di(2-pyridyl)thiocarbonate (DPTC) with DMAP was reported by *Mukaiyama* and co-workers to be very efficient for esterifications even with bulky tertiary alcohols such as adamantan-1-ol and 2-methyl-1-phenylpropan-2-ol [205]. Unfortunately, this method was unsuccessful. Heating the reaction to reflux in THF for more than 4 h led to a complex mixture, likely indicating decomposition (entry 3). In another attempt a procedure described by *S. Kim* and *J. Lee* for the preparation of sterically hindered esters by the reaction of *S*-2-pyridyl thioates with alcohols in the presence of cupric bromide was applied [206]. 2-Thiopyridyl chloroformate, which was prepared according to literature [207], was reacted with carboxylic acid (*R*)-**86** in the presence of Et$_3$N and led to the corresponding (*S*)-2-pyridyl thioate, which was purified by column chromatography. Then, alcohol (±)-**49** was added to a suspension the of (*S*)-2-pyridyl thioate derivative with CuBr$_2$ in anhydrous acetonitrile. In this case the reaction failed, and starting material was recovered (entry 4). In the last attempt, THP-protected (*R*)-mandelic acid (*R*)-(**86**) was converted into the acid chloride with oxalyl chloride and then reacted with a mixture of alcohol (±)-**49** and Et$_3$N in CH$_2$Cl$_2$ (entry 5). Unfortunately the reaction did not proceed, probably due to the premature cleavage of the THP protecting group by the hydrochloric acid generated during acid chloride formation.

After these disappointing results, it was decided to prepare the carboxylic acid chloride following a procedure described by *Wissner* and *Grudzinskas* [208]. This method relies on the treatment of *tert*-butyldimethylsilyl esters with oxalyl chloride in the presence of a catalytic amount of DMF to produce the corresponding carboxylic acid chlorides. The reaction proceeds under neutral conditions, since *tert*-butyldimethylsilyl chloride is formed, instead of hydrochloric acid, as the side product. Thus, (*R*)-mandelic acid was treated with a large excess of *tert*-butyldimethylsilyl chloride and imidazole in DMF affording silyl ester (*R*)-**88** in satisfactory yield (*Scheme 4.4*) [209]. Subsequent treatment of the ester with oxalyl chloride and few drops of DMF in CH$_2$Cl$_2$ generated the carboxylic acid chloride. In the next step, the obtained mixture was treated with a solution

of alcohol (±)-**49** and Et$_3$N in CH$_2$Cl$_2$, providing ester **89**. As the yield was quite low, it was decided to optimize the reaction only after testing the deprotection of the silyl ether. It was expected that the free hydroxy group would allow a chromatographic separation of the diastereoisomers. Cleavage of the *tert*-butyldimethylsilyl group, supposed to afford the corresponding α-hydroxyester **90**, was investigated under several conditions (*Table 4.2*).
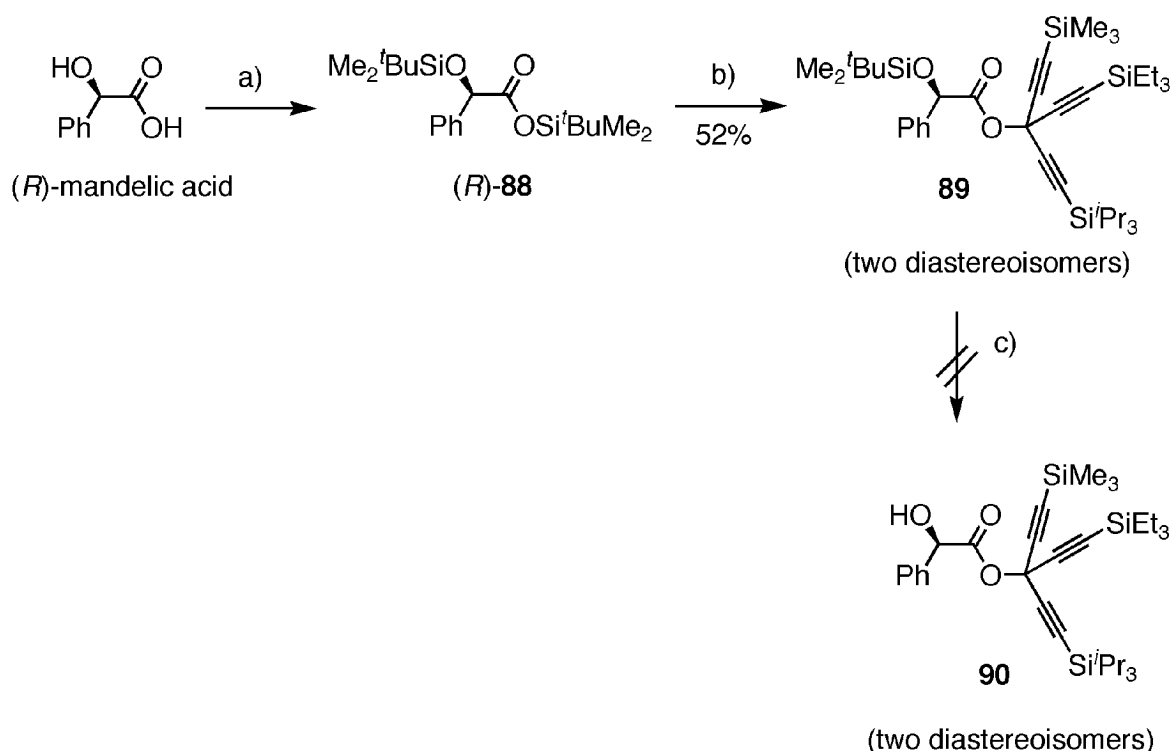
Scheme 4.4: Synthesis of ester **89**. Reactions and conditions: a) Me$_2$^{t}BuSiCl, imidazole, DMF; b) 1. (COCl)$_2$, DMF (cat.), CH$_2$Cl$_2$, 0 °C, 2. DMAP (cat.), (±)-**49**, Et$_3$N, CH$_2$Cl$_2$, 0 °C; c) see *Table 4.2*. DMAP = *N,N*-dimethylaminopyridine.

Table 4.2: Attempted deprotection of ester **89**.

Entry	Reaction conditions	Results
1	1% HCl / 95% aq. EtOH, THF, r.t., 5 h	No cleavage
2	PPTS (cat.), EtOH, r.t. for 2 h, 70 °C for 5 h	Presence of starting material with decomposed material
3	BF$_3$·OEt$_2$ (1 equivalent), CH$_2$Cl$_2$, −78 °C → −50 °C, 2 h	Decomposition
4	TMSOTf (1 equivalent), CH$_2$Cl$_2$, −40 °C, 1h	Decomposition

At first, ester **89** was dissolved in a 1% solution of HCl in 95% aq. EtOH and THF, which improved the solubility, but no deprotection occurred and only starting material was detected (entry 1) [210, 211]. The *tert*-butyldimethylsilyl protecting group also resisted cleavage with catalytic PPTS in EtOH at r.t. [212]. Warming the reaction mixture to 70 °C led to a partial decomposition of starting material (entry 2). Treatment with a strong Lewis acid (BF$_3$·OEt$_2$) at –78 °C gave no reaction (entry 3) [213]. When the temperature was raised to –50 °C, the mixture turned black, revealing complete decomposition. This probably occurs because fluoride anions attack the other silyl groups of ester **89**. The last attempt envisaged an exchange reaction of the *tert*-butyldimethylsilyl ether with trimethylsilyl triflate, providing a trimethylsilyl ether more prone to hydrolysis [214]. Unfortunately, even at low temperature this procedure led to complete decomposition of the ester **89**.

The disappointing results obtained in the attempts to resolve racemate (±)-**49** necessitated the adoption of an alternative approach.

4.3 Stereoselective Synthetic Route Toward the Corner Modules

In the first synthesis of expanded cubane **44**, the construction of the corner module was based on the non-stereoselective insertion of the ethynyl units through nucleophilic addition of lithium acetylides to a carbonyl group providing **49** as a racemate (see *Scheme 2.7* in Section 2.4.1). It was then decided to attempt a stereoselective procedure to afford the pure enantiomers.

4.3.1 Retrosynthetic Plan

As illustrated in *Scheme 4.5a*, it was conceived to stereoselectively generate the stereogenic center of adduct (*R*)-**91** at an early stage of the synthesis, and to introduce the last required ethynyl unit by formation of the activated enol form of enantiopure ketone (*R*)-**92** and subsequent elimination of the leaving group. Ketone (*R*)-**92** could be obtained by oxidation of the hydroxy function resulting from cleavage of the protecting group of (3*R*,1'*S*)-**93**, which, in turn, was accessible in a two-step synthesis from α-oxyketone (*S*)-**94**. The stereogenic center in (*S*)-**94** defines diastereotopic faces for the adjacent carbonyl group (1,2-asymmetric induction). Furthermore, the presence of an α-oxygen donor atom was expected to assist the diastereoselective addition of a metal trimethylsilylacetylide by

leading to chelation of the metal ion, together with the carbonyl oxygen. According to *Cram*'s cyclic model, the nucleophile was expected to attack from the sterically less hindered side, thus leading to the predominant formation of the *anti*-**96** diastereoisomer (*Scheme 4.5b*) [215, 216]. Chiral α-oxyketone (*S*)-**94** could easily be prepared in two steps from ethyl (*S*)-lactate ((−)-(*S*)-**95**). The other enantiomer, (*S*)-**91**, was envisaged to be accessible from ethyl (*R*)-lactate.

a)

b)
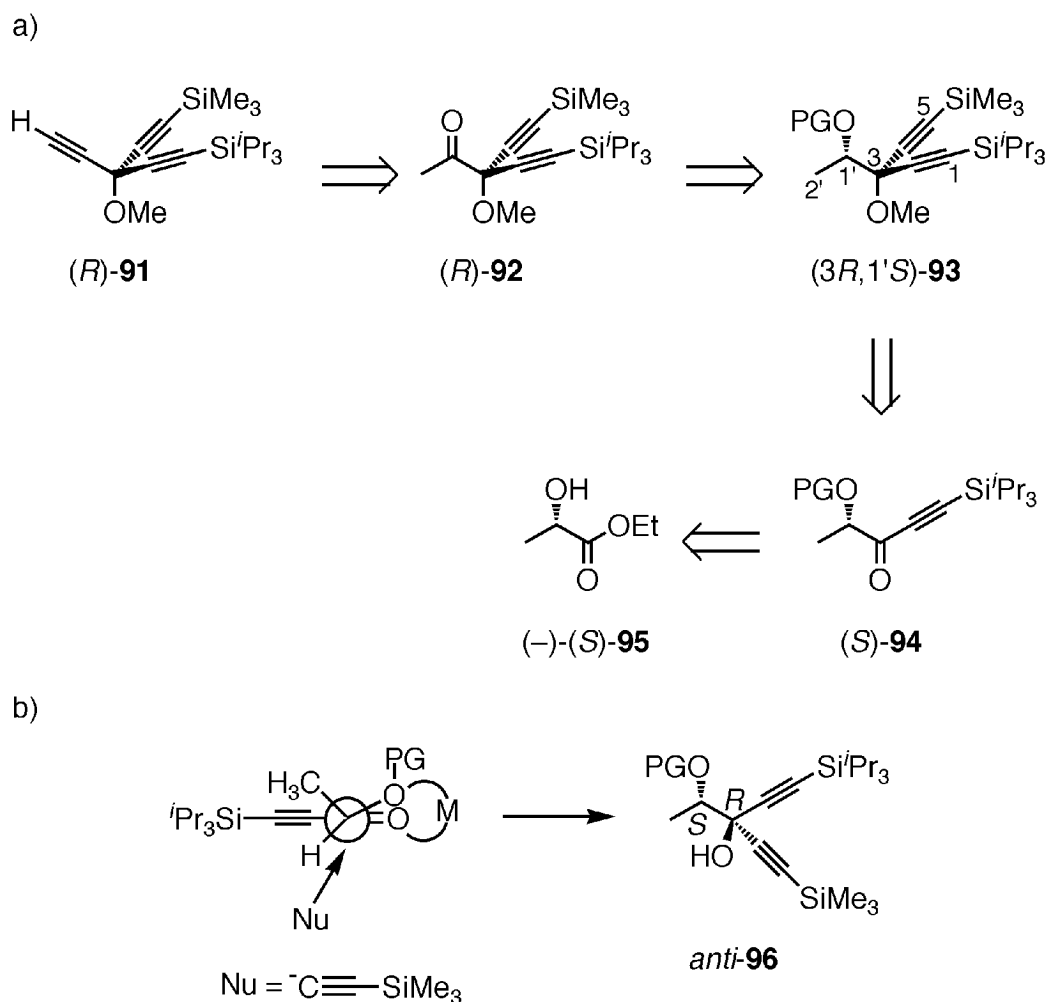
Scheme 4.5: a) Retrosynthetic analysis of corner module (*R*)-**91**. b) According to *Cram*'s cyclic model addition of a metal trimethylsilylacetylide should provide *anti*-**96** as major product. PG = protecting group, M = metal.

4.3.2 Synthesis of the Optically Active Corner Module

The first attempt began with the preparation of alkynyl ketone (−)-(*S*)-**100** by the route shown in *Scheme 4.6*. Protection of ethyl (*S*)-lactate ((−)-(*S*)-**95**) with a triethylsilyl group, following the general procedure decribed by *Cainelli et al.*, afforded ester (−)-(*S*)-

97 in satisfactory yield [217]. This protecting group was chosen owing to its facile cleavage under mild acidic conditions [129] and its ability to confer a high degree of chelation control [218, 219]. In order to obtain ketone (–)-(S)-**100**, silyl-protected ethyl lactate (–)-(S)-**97** was first converted into the corresponding Weinreb amide (–)-(S)-**99** following the protocol reported by *Paterson et al.* [220].
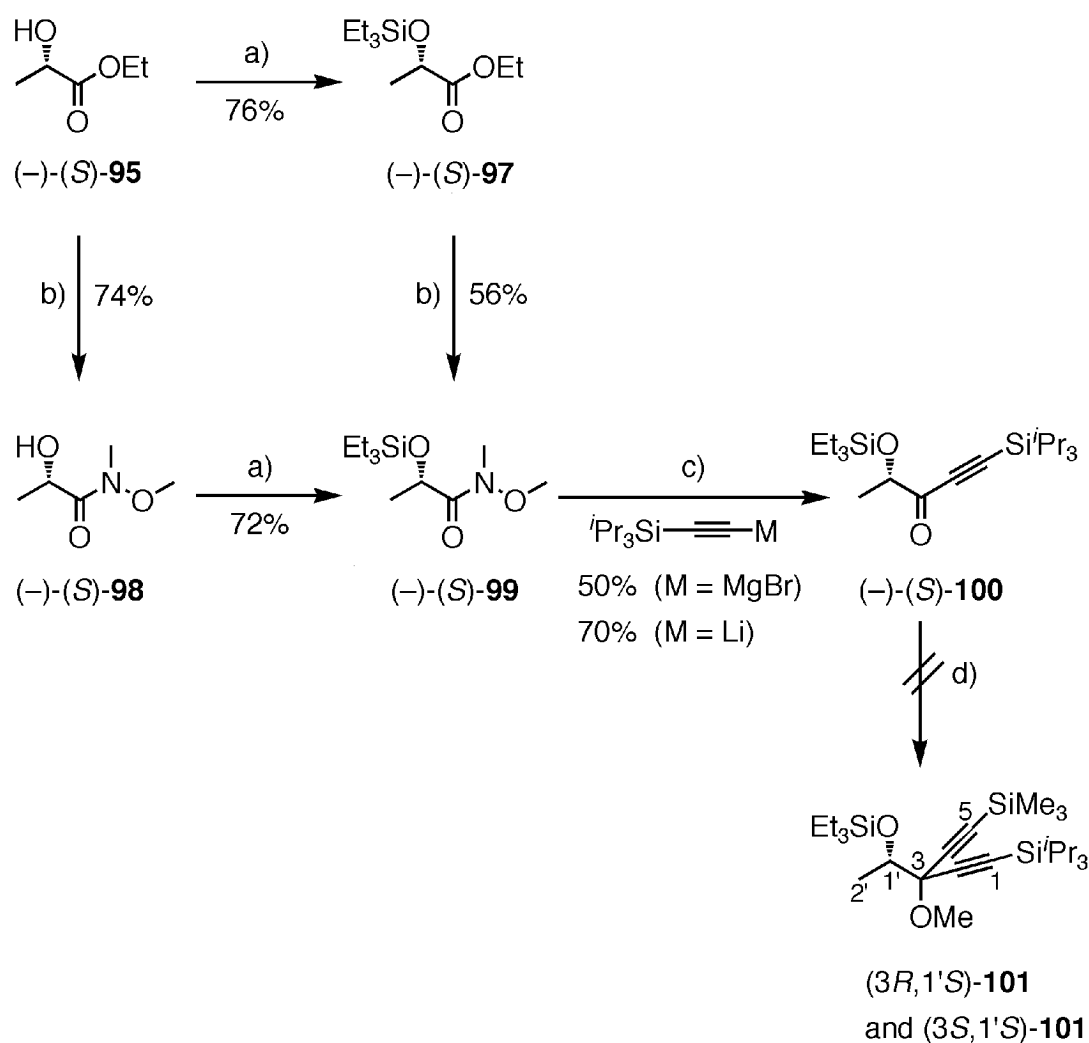
Scheme 4.6: Synthesis of alkynyl ketone (–)-(S)-**100**. Reagents and conditions: a) Et₃SiCl, DMF, imidazole, 0 °C → r.t.; b) ^{i}PrMgCl, Me(MeO)NH·HCl, THF, –20 °C; c) ^{i}Pr₃SiC≡CLi or ^{i}Pr₃SiC≡CMgBr, Et₂O, 0 °C; d) Me₃SiC≡CLi, Et₂O, 0 °C.

Generally, the direct addition of organolithium or *Grignard* reagents to an ester generates the tertiary alcohol resulting from addition of two molecules of the nucleophile to the substrate. This is due to the increased electrophilicity of the ketone product relative to the ester starting material. This common problem is almost completely suppressed by using

the *Weinreb* amide intermediate, owing to the formation of a chelated intermediate which only collapses to the ketone product on aqueous workup [221-223]. The yield of *Weinreb* amide (–)-(*S*)-**99** could be improved when ethyl (*S*)-lactate was first converted into the corresponding α-hydroxyamide (–)-(*S*)-**98**, applying the same procedure adopted for (–)-(*S*)-**97** → (–)-(*S*)-**99**, and then protected. Synthesis of ynone (–)-(*S*)-**100** was achieved by nucleophilic addition of lithium triisopropylsilylacetylide to Weinreb amide (–)-(*S*)-**97** in satisfactory yield (70%). Replacement of the lithium ion with magnesium bromide gave a lower yield (50%). The subsequent addition of a lithium trimethylsilylacetylide to ketone (–)-(*S*)-**100** did not provide the desired tertiary alcohol **101**, but only starting material was recovered. This was quite surprising, but it is explained by the steric hindrance of the trialkylsilyl groups that hampered the approach of the nucleophile to the carbonyl center. It was envisaged to replace the triethylsilyl with the less bulky trimethylsilyl group, but unfortunately the Si–O bond of the latter was readily cleaved during column chromatography (silica gel) and no ethyl (*S*)-*O*-trimethylsilyl lactate could be isolated.

These results led us to exchange the triethylsilyl group for the less sterically demanding *p*-methoxybenzyl (PMB) group. This versatile protecting group was considered to be ideal for use in chelation-controlled nucleophilic addition, since benzyl derivatives are frequently employed for this type of reaction [224]. Furthermore, it can later be removed by oxidation without affecting the alkyne units. Subjecting ethyl (*S*)-lactate to sodium hydride and *p*-methoxybenzyl chloride according to a literature procedure afforded **102** as an enantiomeric mixture in a moderate 59% yield (*Scheme 4.7*) [225]. Indeed, the use of strongly basic conditions has been reported to cause epimerization [226]. In order to determine the degree of racemization, the mixture of esters (*S*)-**102** and (*R*)-**102** was reduced with LiAlH$_4$ to the alcohol ((*S*)-**103** and (*R*)-**103**), which in turn was converted to the corresponding *Mosher* esters (2'*S*,2*R*)-**104** and (2'*R*,2*R*)-**104** with (*R*)-MTPA chloride [227]. Examination of the ^{1}H- and ^{19}F-NMR spectra of this derivative revealed considerable racemization of the ester, and an e.e. of ca. 38% was estimated. Alternatively, a non-basic procedure using *p*-methoxybenzyl 2,2,2-trichloroacetimidate, readily prepared in a one-step reaction [228], and catalytic TfOH was employed [229]. The enantiomeric purity was assayed by conversion of (–)-(*S*)-**102** into (–)-(2'*S*,2*R*)-**104**: it revealed that no racemization had occurred.
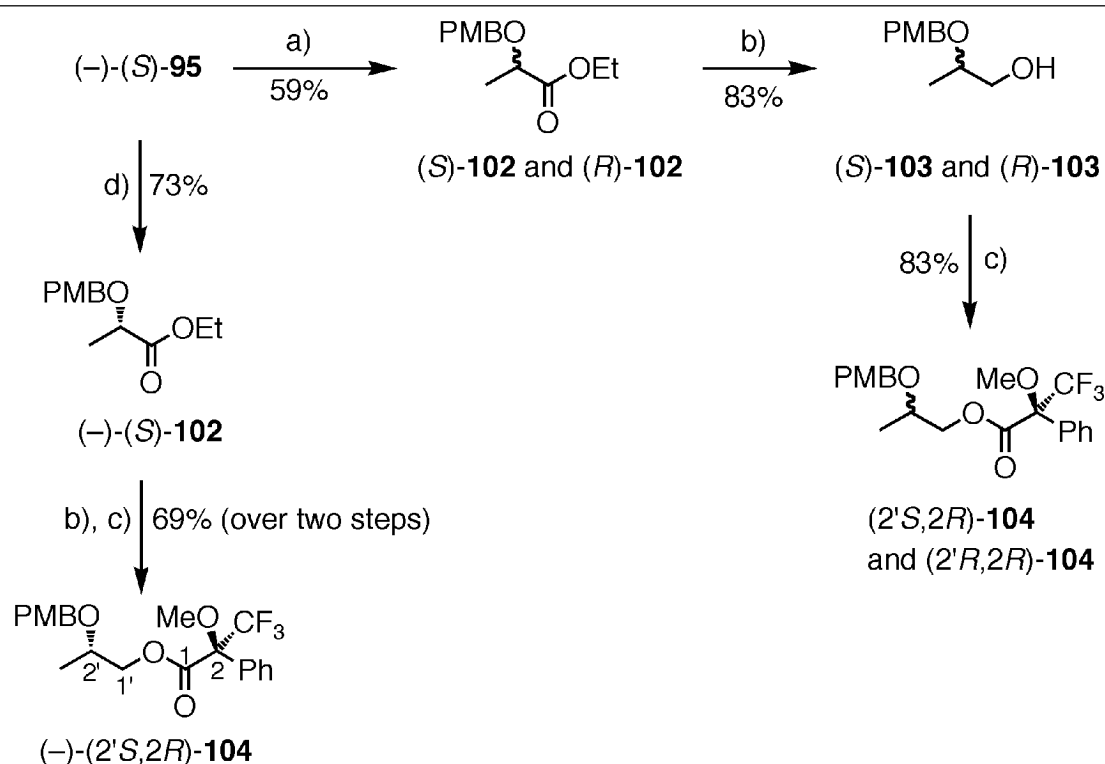
Scheme 4.7: The degree of racemization after the protection of ethyl (*S*)-lactate ((–)-(*S*)-**95**) was estimated by *Mosher*'s method [227]. Reagents and conditions: a) NaH, PMBCl, DMF, 0 °C → r.t.; b) LiAlH₄, Et₂O, 0 °C; c) (*R*)-MTPACl, Et₃N, DMPA (cat.), CH₂Cl₂; d) PMBOC(NH)CCl₃, TfOH (cat.), cyclohexane/CH₂Cl₂ (1:1), 0 °C → r.t.. PMBCl = *p*-methoxybenzyl chloride, (*R*)-MTPACl = α-methoxy-α-trifluoromethylphenylacetyl chloride, DMPA = *N,N*-dimethylaminopyridine, PMBOC(NH)CCl₃ = *p*-methoxybenzyl 2,2,2-trichloroacetimidate, TfOH = trifluoromethanesulfonic acid. The locants next to the stereodescriptors (*R*) and (*S*) refer to the numbering shown for **104**.

The corresponding *Weinreb* amide (–)-(*S*)-**105** was prepared in good yield following the same procedure used for (–)-(*S*)-**99** (*Scheme 4.8*). Subsequently, ketone (–)-(*S*)-**106** was readily formed in high yield by reaction with lithium triisopropylsilylacetylide; the use of the corresponding organomagnesium acetylide led to a reduced yield. The subsequent chelation-controlled addition of trimethylsilylacetylide was investigated with a variety of metals, and the results are tabulated in *Table 4.3*. In all cases, the major diastereoisomer (3*R*,1'*S*)-**107** was presumed to arise from chelation control and was not separated from the minor diastereoisomer (3*S*,1'*S*)-**107**. The diastereomeric ratio (d.r.) was determined by integrating the OH resonance (δ = 3.15 and 3.19 in CDCl₃) in the ¹H-NMR spectrum. A more precise assignment of the d.r. by HPLC analysis is under investigation in another current doctoral work. The lithium acetylide reacted with good diastereoselectivity, but gave a moderate yield (entry 1). The Grignard (entry 2) and organozinc (entry 3) reagents were prepared by transmetallation of the lithium acetylide with MgBr₂·OEt₂ and ZnBr₂,

respectively [230]. Addition did not occur at $-78\ ^\circ C$ and, therefore, the temperature was raised slowly to r.t.. The product was obtained in poor yields along with many side products which were not isolated. Furthermore, the starting material was not completely consumed during the reaction.
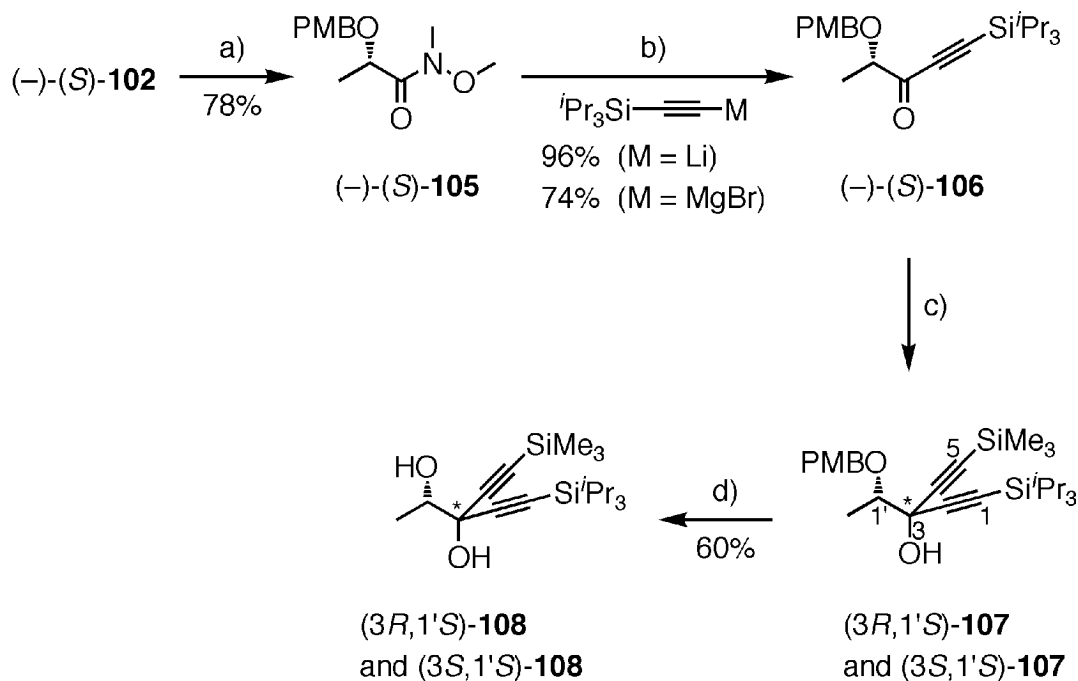
Scheme 4.8: Diastereoselective synthesis of dialkynyl alcohol **107** and of the related deprotected diol **108**. Reagents and conditions: a) ^iPrMgCl, $Me(MeO)NH \cdot HCl$, THF, $-20\ ^\circ C$; b) $^iPr_3SiC \equiv CLi$ or $^iPr_3SiC \equiv CMgBr$, THF, $-78\ ^\circ C$; c) $Me_3SiC \equiv CM$, Et_2O (conditions and yields are reported in *Table 4.3*); d) CAN, CH_3CN/H_2O 9:1. M = metal, CAN = cerium(IV) ammonium nitrate. The locants next to the stereodescriptors (*R*) and (*S*) refer to the numbering shown for **107**.

Table 4.3: Diastereoselective addition of acetylide nucleophiles ($Me_3SiC \equiv CM$) to ketone $(-)$-(S)-**106** providing alcohols ($3R$,$1'S$)-**107** and ($3S$,$1'S$)-**107**. M = metal.

Entry	M	Conditions	Yield	d.r. (d.e.) [($3R$,$1'S$)/($3S$,$1'S$)]
1	Li	$-78\ ^\circ C$, 1.5 h	60%	89:11 (78%)
2	MgBr	$-78\ ^\circ C$ → r.t., 24 h	17%	77:23 (54%)
3	ZnBr	$-78^\circ C$ → r.t., 15 h	32%	79:21 (58%)
4	$CeCl_2$	$-78\ ^\circ C$, 30 min	82%	55:45 (10%)
5	$CeCl_2/TiCl_4$	$-78\ ^\circ C$, 30 min	65%	51:49 (2%)

The estimated d.e. was slightly higher for the zinc acetylide than for the Grignard reagent, but both were lower than under conditions of entry 1. Extremely high reactivity was observed for the organocerium reagent, which is in accord with its noted high nucleophilicity [231, 232]. In this case, mixture of tertiary alcohol $(3R,1'S)$-**107** and $(3S,1'S)$-**107** was obtained in high yield and the reaction was complete after a few minutes at −78 °C (entry 4). Such high reactivity may also account for the low d.e. (10%), resulting from incomplete chelate formation. Finally, the pre-chelation of the ketone (−)-(S)-**106** with $TiCl_4$ followed by the addition of the cerium(III) trimethylsilylacetylide led to no improvement and, moreover, the diastereoselectivity was lost (entry 5) [233]. Considering that the resulting d.e., combined with the low yield of entry 1, was not satisfactory, it was thought that the diastereoisomeric mixture obtained in entry 4 could be separated, once the PMB group was removed. Hence, deprotection of the mixture of alcohols $(3R,1'S)$-**107** and $(3S,1'S)$-**107** by treatment with CAN in aqueous acetonitrile afforded diols $(3R,1'S)$-**108** and $(3S,1'S)$-**108** in an unoptimized 60% yield after purification by column chromatography (SiO_2, hexane/CH_2Cl_2 1:2) [234, 235]. Oxidative cleavage with DDQ led to complete decomposition of the tertiary alcohol [236]. As expected, the two diol diastereoisomers showed different R_f values on TLC (0.28 and 0.22; hexane/Et_2O 4:1). Nevertheless, in order to avoid such tedious separation, it was envisaged to improve the diastereoselectivity and the yield, replacing the triisopropylsilyl protecting group by a smaller one. The triethylsilyl group was preferred to trimethylsilyl because the lability of the latter is enhanced when the acetylene is conjugated to a carbonyl group as it is the case for the ketone formed from the Weinreb amide [230]. Therefore, the chelation-controlled addition of lithium triethylsilylacetylide to the *Weinreb* amide (−)-(S)-**105**, following the procedure used for (−)-(S)-**106** (entry 1), gave ketone (−)-(S)-**109** in very good yield (*Scheme 4.9*). The successive diastereoselective addition of lithium trimethylsilylacetylide in Et_2O at −78 °C finally provided alcohol **110** as a mixture of diastereoisomers in satisfactory yield (83%). A remarkably d.e. of 86% was determined by integrating the OH resonance (δ = 3.16 and 3.18 in CDCl$_3$) (*Figure 4.1*). A more precise assignment of the d.r. by HPLC analysis is under investigation in another current doctoral work. Thus, according to *Cram*'s cyclic model, alcohol (+)-$(3R,1'S)$-**110** was the major diastereoisomer of the mixture (d.r. 93:7). The minor diastereoisomer $(3S,1'S)$-**110** was present in trace amount.
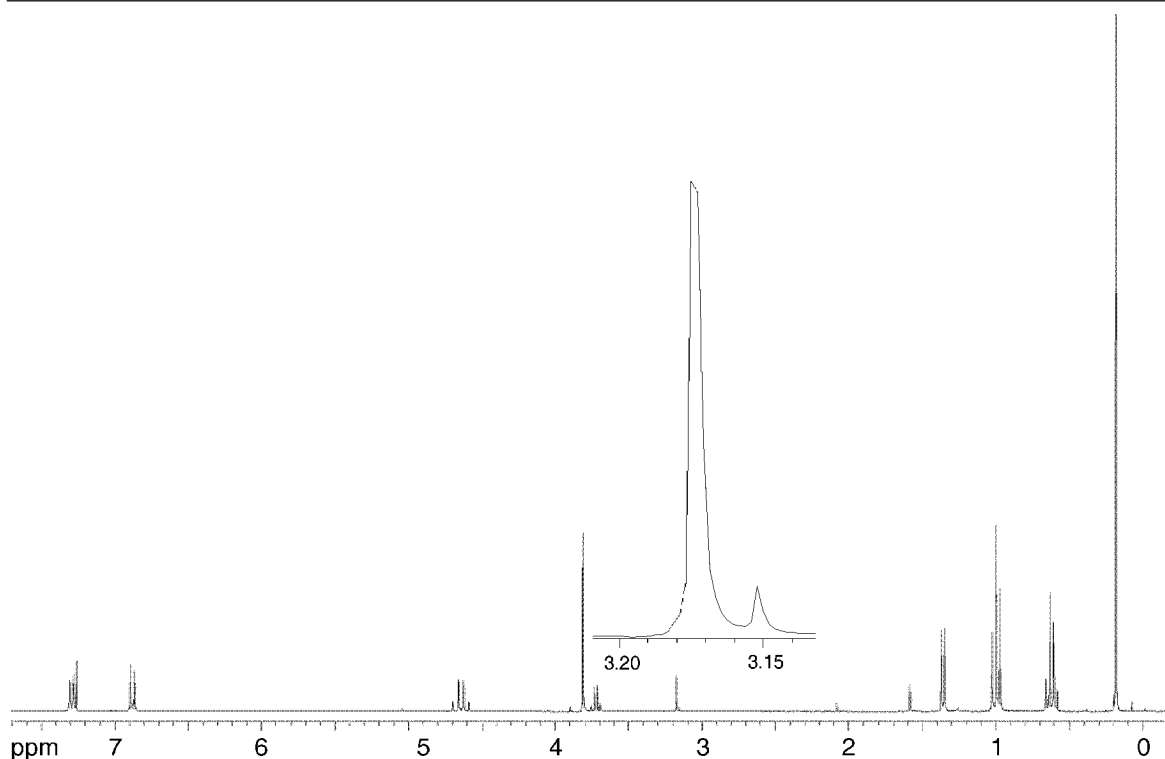
Figure 4.1: ¹H-NMR spectrum (300 MHz, CDCl₃) of diastereoisomeric mixture of (+)-(3*R*,1'*S*)-**110** (major) and (3*S*,1'*S*)-**110** (minor). A d.e. of 86% was determined by integrating the OH resonance.

Alkylation of the hydroxy functionality in adduct (+)-(3*R*,1'*S*)-**110** by deprotonation at –78 °C with *n*-BuLi, followed by addition of an excess of iodomethane, led to the stable methyl ether (–)-(3*R*,1'*S*)-**111**. Subsequently, the PMB protecting group was removed by oxidation using 2.2 equivalents of CAN in a MeCN/H₂O (9:1) mixture, thus providing alcohol (–)-(3*R*,1'*S*)-**112** in good yield after purification by column chromatography (hexane/CH₂Cl₂ 1:2). Alcohol (–)-(3*R*,1'*S*)-**112** was readily oxidized to the corresponding ketone (–)-(3*R*,1'*S*)-**113** with the mild *Dess-Martin* periodinane (DMP) reagent [237, 238]. The final step of this sequence required the dehydration of methylketone (–)-(3*R*,1'*S*)-**113** to trialkynylmethanol (+)-(*R*)-**114**. In collaboration with Ph.D. student *V. Convertino*, it was planned to generate the ethynyl fragment in two steps, consisting of: 1) preparation of an activated enolate and 2) elimination of the leaving group from the latter by a strong and non-nucleophilic base. Unfortunately, enolization of the methylketone with 1 equivalent of lithium diisopropylamide (LDA) in dry THF at –78 °C, followed by trapping with a triflating agent such as *N*-(5-chloro-2-pyridyl)triflimide (*Comins'* reagent) [239] led only to decomposition of the starting material without affording the desired vinyl triflate. Due to the instability of the enol triflate, it was envisaged to use the one-pot procedure developed by *Negishi et al.* [240-242]. Treatment of methylketone (–)-(3*R*,1'*S*)-**113** with

LDA in THF at −78 °C gave the enolate that was trapped with diethyl chlorophosphate; subsequent elimination of the phosphate with LDA gave the trialkynylmethyl methyl ether (+)-(*R*)-**114** as a stable oil in 16%, isolated yield after purification by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 8:1). This low yield was obtained in a first attempt and the reaction can certainly be improved.
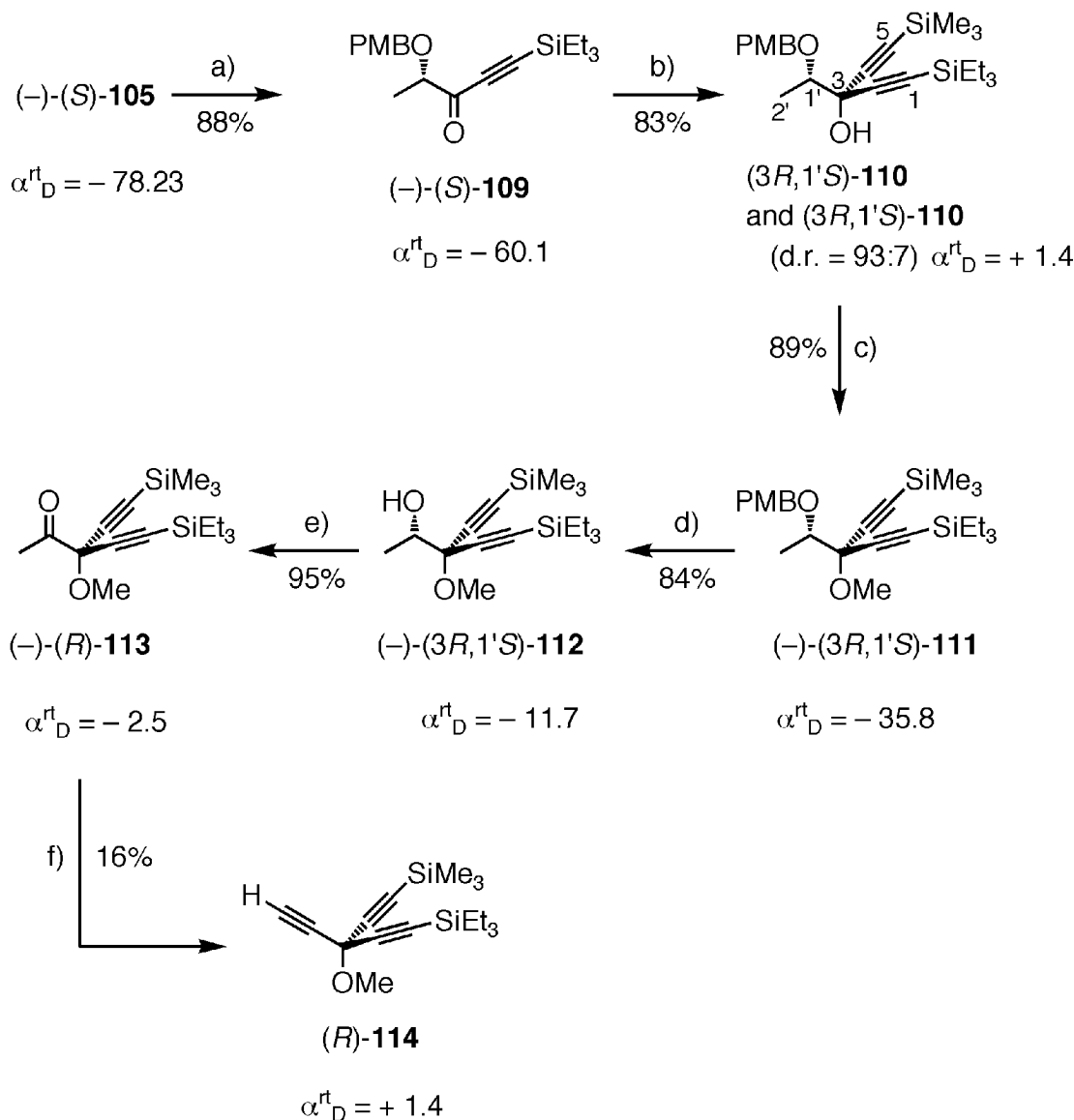
Scheme 4.9: Synthesis of the corner module (+)-(*R*)-**114**. Reagents and conditions: a) Et$_3$SiC≡CLi, THF, −78 °C; b) Me$_3$SiC≡CLi, Et$_2$O, −78 °C; c) 1. *n*-BuLi, THF, −78 °C, 2. MeI, −78 °C → r.t.; d) CAN, MeCN/H$_2$O 9:1; e) DMP, CH$_2$Cl$_2$; f) 1. LDA (1 equiv.), THF, −78 °C, 2. ClPO(OEt)$_2$, −78 °C → r.t., 3. LDA (2.25 equiv.), −78 °C → r.t.. CAN = cerium(IV) ammonium nitrate, DMP = *Dess-Martin* periodinane, LDA = lithium diisopropylamide. The locants next to the stereodescriptors (*R*) and (*S*) refer to the numbering shown for **110**.

4.4 Conclusion

In summary, a new strategy for the improvement of the synthetic route toward the expanded cubane **44** was attempted in order to obtain sufficient quantities for a complete characterization. The loss of material encountered in the above-described synthesis (see Chapter 2) was mainly due to the inevitable formation of many stereoisomers. To overcome this problem, a stereoselective preparation of the building blocks was targeted. As a first step, it was planned to prepare isomerically pure corner modules which would then provide the desired *meso* edge module by oxidative *hetero*-coupling (coupling of heterochiral moieties). A first attempt to resolve the corner module (±)-**49** using a chiral auxiliary failed. Preparation of one optically pure corner module ((+)-(*R*)-**114**) was achieved by a stereoselective procedure extending over eight synthetic steps. The yield attained in each step was generally high, except for the last one ((–)-(*R*)-**113** → (+)-(*R*)-**114**) which is under current investigation. The stereogenic center of the corner module ((–)-(*S*)-**109** → (3*R*,1'*S*)-**110**) was formed with high diastereoselectivity (d.e. 86%). Nevertheless, this key step may be further improved by using a different protecting group such as methoxymethyl (MOM) or methoxyethoxymethyl (MEM). The latter, in particular, with its two additional oxygen atoms can provide a stronger metal chelation involving a podand effect [233]. An unambiguous assignment of the configuration of the corner module (+)-(*R*)-**114** is currently undertaken. Conversion of ketone (–)-(*R*)-**113** to the corresponding tosylhydrazone under *Shapiro* conditions [243, 244] is expected to provide a crystalline derivative for X-ray analysis. The other enantiomer of the corner module ((*S*)-**114**) can be readily prepared in the same way, simply starting from ethyl (*R*)-lactate. As soon as both enantiomers are available in pure form, the edge module can be readily synthesized according to the *Cadiot-Chodkiewicz* protocol.

5. Experimental Part

5.1 General Methods and Instrumentation

Chemicals were purchased from *Acros, Aldrich, Fluka,* and *ABCR* and were used as received. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions except the oxidative couplings were carried under a slight positive pressure of argon.

Thin layer chromatography (TLC) was conducted on glass sheets precoated with 0.2 mm *Merck* silica gel, with 254 nm fluorescent indicator. Compounds were visualized by treatment with an anisaldehyde solution [EtOH (250 mL), conc. H_2SO_4 (9.2 mL), anisaldehyde (6.8 mL) and AcOH (2.8 mL)] or a $KMnO_4$ solution [$KMnO_4$ (1.5 g), K_2CO_3 (10 g), 5% NaOH (2.5 mL) and H_2O (150 mL)], and subsequent heating.

Column chromatography was carried out with *Fluka* silica gel 60 (particle size 40-63 μm, 230-400 mesh) and distilled technical solvents.

Analytical *high performance liquid chromatography* (HPLC) was carried out on a *Merck-Hitachi LaChrom* system, composed of a L-7100 pump, L-7200 autosampler, L-7400 UV detector, and D-7000 interface. A *LiChrosob* Si-60, 7 μm, 4 mm x 25 cm column was used with hexane/CH_2Cl_2 9:1 as eluent.

Analytical GPC was carried out with *Merck-Hitachi LaChrom* equipment (L-7100 pump, L-7360 column oven, L-7400 UV detector) operated at 40 °C with THF as solvent, and a flow rate of 1.0 mL min^{-1}.

Melting points (M.p.) were measured in open capillaries with a *Büchi Melting Point B540* apparatus and are uncorrected.

Optical rotation: Perkin-Elmer 241 polarimeter using a 1 dm cell at 25 °C, $\lambda = 589$ nm (Na D-line). Concentrations are given in grams of solute per 100 mL of solvent.

UV/Vis spectra were recorded on a *Varian CARY-5* spectrophotometer. The spectra were measured in $CHCl_3$ in a 1 cm quartz cuvette. The absorption wavelengths are reported in nm with the extinction coefficients in M^{-1} cm^{-1} in brackets. Shoulders are indicated as "sh".

Infrared spectra (IR) were recorded on a *Perkin-Elmer FT1600* spectrometer or a *Perkin-Elmer Spectrum BX II*. The spectra were measured as solutions in $CHCl_3$. Selected absorption bands are reported in wavenumbers (cm^{-1}) and their relative intensities are described as *s* (strong), *m* (medium), *w* (weak), or br. (broad).

Nuclear magnetic resonance spectra (NMR). 200 MHz ^{1}H-NMR and 50 MHz ^{13}C-NMR spectra were obtained on a *Varian Gemini 200* spectrometer. 300 MHz ^{1}H-NMR and 75 MHz ^{13}C-NMR spectra were measured on a *Varian Gemini 300* spectrometer. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectra were measured on an *AMX-400* spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane ($SiMe_4$) using the solvent's residual signal as an internal reference ($CDCl_3$: δ_H = 7.27 ppm, δ_C = 77.0 ppm). Coupling constants (J) are given in Hz. The resonance multiplicity is described as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet). All spectra were recorded at room temperature.

Mass spectra were performed by the MS service at *Laboratorium für Organische Chemie* of ETH Zürich. EI-MS (*m/z* (%)): *VG Tribid* instrument, 70 eV. ESI-MS (m/z (%)): *Finnigan TSQ 7000* instrument, positive mode. HR-MALDI-FT-MS (*m/z* (%)): *Ion Spec Ultima 4.7* ion cyclotron resonance mass spectrometer, positive or negative ion mode, matrix: DHB (2,5-dihydroxybenzoic acid) or DCTB (2-[(2E)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile). MALDI-TOF-MS measured with reflectron detection on a *Brucker REFLEX* spectrometer or with linear detection on an *Ionspec Fourier Transform Mass Spectrometer ULTIMA FT-ICR* (337 nm N_2-Lasersystem), positive or negative ion mode , matrix: DCTB.

Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich.

Nomenclature follows the proposals of the *AutoNom* application of the *Beilstein Commander 2000* program.

5.2 Experimental Procedures

3-(Trimethylsilyl)propynal (46) [245]
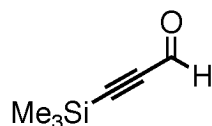
To a mixture of 3-trimethylsilyl-prop-2-yn-1-ol (8.65 g, 67.4 mmol), *Celite* (29.4 g), and molecular sieves (4 Å, 25 g) in CH_2Cl_2 (253 mL), PCC (26.3 g, 122 mmol) was added. After stirring for 2.5 h at r.t., the mixture was passed through a plug (SiO_2, CH_2Cl_2) and the filtrate was evaporated *in vacuo*, affording **46** (6.3 g, 74%) as a slight yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 0.26 (*s*, 9 H, $Si(CH_3)_3$); 9.17 (*s*, 1 H, COH). ^{13}C-NMR (50 MHz, $CDCl_3$): 176.60; 102.90; 102.20; –0.90.

1-(Triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((±)-47) [132]
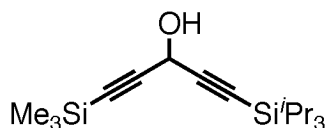
A solution of (triisopropylsilyl)acetylene (13.44 mL, 59.9 mmol) in THF (240 mL) was cooled to 0 °C and 1.6 M *n*-BuLi in hexane (37.4 mL, 59.9 mmol) added dropwise over 20 min. Compound **46** (6.3 g, 49.9 mmol) was then added dropwise over 1 h, and the solution was stirred for 4 h and then quenched with sat. aq. NH_4Cl solution. The organic phase was washed twice with water and sat. aq. NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 3:1) afforded (±)-**47** (14.9 g, 97%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 0.20 (*s*, 9 H, $Si(CH_3)_3$); 1.10 (*s*, 21 H, Si^iPr_3); 2.21 (*d, J* = 7.8, 1 H, OH); 5.10 (*d, J* = 7.8, 1 H, CH). ^{13}C-NMR (75 MHz, $CDCl_3$): 104.0; 102.20; 89.30; 86.20; 52.90; 18.50; 11.10; –0.40.

1-(Triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-one (48) [132]
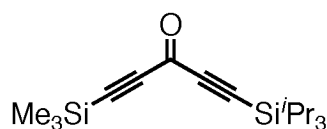
To a mixture of (±)-**47** (14.9 g, 48.3 mmol), *Celite* (15.2 g), and molecular sieves (4 Å, 22.3 g) in CH_2Cl_2 (800 mL), PCC (16.7 g, 77.5 mmol) was added. After stirrring for 18 h at r.t., the mixture was passed through a plug (SiO_2, CH_2Cl_2) and the filtrate was evaporated *in vacuo*, affording **48** (13.4 g, 90%) as a yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): 0.28 (s, 9 H, Si(CH_3)$_3$); 1.13 (s, 21 H, Si^{i}Pr$_3$). ^{13}C-NMR (75 MHz, $CDCl_3$): 160.0; 105.0; 102.80; 99.20; 98.0; 18.40; 11.0; –1.0.

3-(Triethylsilyl)ethynyl-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((±)-49)
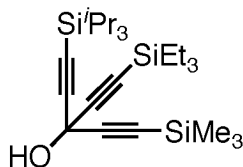
A solution of (triethylsilyl)acetylene (0.25 mL, 1.39 mmol) in THF (9 mL) was cooled to 0 °C, and 1.6 M *n*-BuLi in hexane (0.87mL, 1.39 mmol) was added dropwise over 3 min. After 15 min, compound **48** (346 mg, 1.13 mmol) in THF (4 mL) was added dropwise over 10 min, and the solution was stirred for 3 h at 0 °C and then quenched with sat. aq. NH_4Cl solution. The organic phase was washed twice with water and sat. aq. NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 3:1) afforded (±)-**49** (478 mg, 95 %) as an orange oil.

R_f (hexane/CH_2Cl_2 2:1) 0.35. IR (CHCl$_3$): 3555m, 3300w (br.), 2944s, 2855s, 2166w, 1722w, 1594w, 1456s, 1417m, 1383m, 1322m, 1244s, 1089s, 1006s, 861s. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.19 (s, 9 H, Si(CH_3)$_3$); 0.62 (q, J = 8.1, 6 H, Si(CH_2CH$_3$)$_3$); 1.00 (t, J = 8.1, 9 H, Si($CH_2$$CH_3$)$_3$); 1.09 ($s$, 31 H, Si^{i}Pr$_3$); 2.76 ($s$, 1 H, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 104.18; 101.87; 87.74; 84.97; 77.02; 54.73; 29.72; 18.52; 11.20; 7.32; 4.13; –0.52. EI-MS: 446 (<10, M^+), 403 (7, $[M - C_3H_7]^+$), 306 (17), 305 (53), 277 (14), 264 (13), 263 (51), 249 (14), 236 (14), 235 (42), 221 (21), 208 (10), 207 (48), 193 (22), 179 (40), 165 (20), 157 (15), 155 (13), 150 (17), 141 (11), 139 (20), 136 (12), 134 (11), 132

(11), 123 (12), 121 (10), 115 (20), 111 (67), 110 (33), 107 (10), 103 (11), 97 (23), 96 (41), 89 (13), 87 (22), 83 (100), 82 (14), 75 (18), 72 (44), 69 (15), 59 (24). Anal. calc. for $C_{25}H_{46}OSi_3$ (446.89): C 67.19, H 10.37; found: C 67.11, H 10.41.

3-Ethynyl-1-triethylsilyl-5-(triisopropylsilyl)penta-1,4-diyn-3-ol ((±)-50)

To a solution of (±)-**49** (249 mg, 0.56 mmol) in MeOH/THF 1:1 (134 mL), 1 M aq. NaOH (12 drops) was added. According to TLC control, the reaction was completed after stirring for 1 h. It was then quenched with sat. aq. NH_4Cl solution, extracted with Et_2O, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 2:1) afforded (±)-**50** (178 mg, 85%) as a colorless oil.

R_f (hexane/CH_2Cl_2 2:1) 0.17. IR (CHCl$_3$): 3571*m*, 3307*s*, 2958*s*, 2867*s*, 2728*w*, 2130*w*, 1600*w*, 1463*s*, 1415*m*, 1384*m*, 1369*m*, 1322*m*, 1237*m*, 1217*m*, 1095*s*, 1067*s*, 1011*m*, 920*w*, 883*s*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.62 (*q*, *J* = 7.9, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 1.01 (*t*, *J* = 7.9, 9 H, Si(CH$_2$*CH$_3$*)$_3$); 1.10 (*s*, 21 H, Si^{i}Pr$_3$); 2.65 (*s*, 1 H, C≡CH); 2.76 (*s*, 1 H, OH). ^{13}C-NMR (75 MHz, CDCl$_3$): 103.87; 103.00; 86.07; 85.39; 81.46; 70.98; 54.39; 18.53; 11.17; 7.32; 4.08. EI-MS: 374 (<10, M^+), 331 (14, $[M - C_3H_7]^+$), 307 (10), 306 (27), 305 (100), 277 (23), 263 (17), 264 (13), 249 (22), 235 (22), 221 (25), 207 (21), 193 (20), 191 (31), 179 (16), 165 (16), 164 (10), 163 (56), 151 (15), 145 (11), 143 (11), 139 (22), 137 (16), 135 (47), 133 (11), 131 (11), 123 (21), 121 (18), 119 (11), 117 (11), 115 (13), 111 (74), 110 (38), 109 (21), 107 (24), 105 (12), 103 (16), 97 (20), 96 (24), 95 (21), 87 (21), 83 (65), 81 (15), 79 (13), 75 (22), 73 (13), 69 (22), 59 (23), 55 (16), 53 (17). Anal. calc. for $C_{22}H_{38}OSi_2$ (374.71): C 70.52, H 10.22; found: C 70.74, H 10.21.

(*R*,*R*)- and **(*S*,*S*)-3,8-Bis[(triethylsilyl)ethynyl]-1,10-bis(triisopropylsilyl)-deca-1,4,6,9-tetrayn-3,8-diol (*d/l*-51)**

(*R*,*S*)-3,8-Bis[(triethylsilyl)ethynyl]-1,10-bis(triisopropylsilyl)-deca-1,4,6,9-tetrayn-3,8-diol (*meso*-51)

To a solution of (±)-**50** (219 mg, 0.59 mmol) in CH_2Cl_2 (57 mL) open to air, *Hay* catalyst [2 mL, prepared by stirring CuCl (23.2 mg, 0.236 mmol) and TMEDA (70.6 µL, 0.472 mmol) in CH_2Cl_2 (2 mL) for 5 min] was added. After stirring for 10 min, the solution turned from green to dark brown and it was then washed twice with water (30 mL, pH = 3-4) to extract copper(I)-salts into the aqueous phase. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (SiO_2, CH_2Cl_2/hexane 1:1) afforded a mixture of diastereoisomers *d/l*-**51** and *meso*-**51** (153 mg, 70%) as a pale brown foam. The brown color was interpreted as originating from decomposed compound.

R_f (hexane/CH_2Cl_2 1:1) 0.18. IR ($CHCl_3$): 3567*m*, 3273*w* (br.), 3020*s*, 2958*s*, 2867*s*, 2162*w*, 1463*s*, 1415*w*, 1383*w*, 1331*w*, 1238*w*, 1066*s*, 1018*s*, 920*w*, 883*m*, 794*m*, 759*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.64 (*q*, *J* = 7.8, 12 H, Si(*CH$_2$*CH$_3$)$_3$); 1.01 (*t*, *J* = 7.8, 18 H, Si(CH$_2$*CH$_3$)$_3$); 1.10 (*s*, 42 H, Si^{i}Pr$_3$); 2.90 (*s*, 2 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 102.59; 101.68; 86.88; 86.24; 66.31; 54.71, 18.50, 11.12, 7.32, 4.02. EI-MS: 747 (<10, M^+), 305 (23), 111 (18), 110 (20), 88 (11), 86 (64), 84 (100), 83 (12), 49 (19). Anal. calc. for $C_{44}H_{74}O_2Si_4$ (747.41): C 70.71, H 9.98; found: C 70.81, H 9.94.

(R,R)- and **(S,S)-3,8-Diethynyl-1,10-[bis(triisopropylsilyl)]deca-1,4,6,9-tetrayn-3,8-diol (d/l-52)**

(R,S)-3,8-Diethynyl-1,10-[bis(triisopropylsilyl)]deca-1,4,6,9-tetrayn-3,8-diol (meso-52)

To a solution of a mixture of diastereoisomers *meso*-**51** and *d/l*-**51** (207 mg, 0.277 mmol) in MeOH/THF 1:1 (60 mL), K_2CO_3 (191 mg, 1.38 mmol) was added and the reaction was stirred overnight. Two portions of K_2CO_3 (95 mg, 0.69 mmol) were added, 1 h apart. After 3 h of stirring, the mixture was washed with sat. aq. NH_4Cl solution, extracted with Et_2O, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/EtOAc 5:1) afforded a mixture of diastereoisomers *d/l*-**52** and *meso*-**52** (103 mg, 72%) as an orange oil.

R_f (hexane/EtOAc 4:1) 0.26. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.09 (*s*, 42 H, Si^iPr_3); 2.69 (*s*, 2 H, C≡CH); 3.06 (*s*, 2 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 102.04; 87.14; 80.20; 77.45; 72.12; 66.48; 54.43; 18.51; 11.12. EI-MS: 518 (<10, M^+), 215 (11), 192 (19), 191 (100), 163 (54), 161 (29), 149 (14), 139 (16), 137 (21), 136 (11), 135 (75), 121 (24), 111 (13), 109 (32), 107 (26), 93 (22), 86 (53), 85 (11), 84 (77), 83 (22), 77 (13), 69 (11), 53 (10), 51 (22), 49 (65), 47 (19), 35 (11).

(3R)-3-Ethynyl-1-triethylsilyl-5-(triisopropylsilyl)hexa-1,4-diyn-3-yl (4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-carboxylate and **(3S)-3-Ethynyl-1-triethylsilyl-5-(triisopropylsilyl)hexa-1,4-diyn-3-yl (4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-carboxylate (54)**

To a solution of (±)-**50** (362 mg, 0.97 mmol) in CH_2Cl_2 (7 mL), DMAP (35.6 mg, 0.29 mmol) was added and the mixture was cooled to 0 °C. Et_3N (266 µL, 1.91 mmol) was

added, then (–)-camphanic acid chloride (287 mg, 1.32 mmol) in CH_2Cl_2 (2.7 mL), and the mixture was stirred at 0 °C for 45 min. CH_2Cl_2 (100 mL) was added, and the mixture was washed with water (100 mL). The organic phase was separated and washed with 1 N $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 2:1 to 4:1) afforded **54** (451 mg, 84%) as a mixture of diastereoisomers.

Yellow oil. R_f (hexane/CH_2Cl_2 1:1) 0.24. IR ($CHCl_3$): 3307m, 3024w, 2959s, 2867s, 2120w, 1779s, 1747m, 1464m, 1415w, 1400w, 1381w, 1338w, 1315w, 1262m, 1226w, 1140s, 1053s, 1018m, 998m, 932m, 883m, 836w. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.63 (q, J = 8.0, 6 H, Si(CH_2CH$_3$)$_3$); 0.99 (t, J = 8.0, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.08 ($s$, 3 H, H-C(8)); 1.08 ($s$, 21 H, Si^{i}Pr$_3$); 1.09 ($s$, 3 H, H-C(10)); 1.11 ($s$, 3 H, H-C(9)); 1.66 – 1.72 (m, 1 H, H-C(4)); 1.89 – 1.96 (m, 1 H, H-C(4)); 2.03-2.10 (m, 1 H, H-C(5)); 2.17 – 2.48 (m, 1 H, H-C(5)); 2.74 (s, 1 H, H-C(15)). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.95 (C(2)O); 163.84 (C(11)O); 99.59 (C(6)); 98.80 (C(17)); 90.57 (C(19)); 89.07 (C(18)); 88.38 (C(16)); 77.74 (C(15)); 73.35 (C(13)); 58.31 (C(3)); 54.81 (C(7)); 30.38 (C(14)); 29.01 (C(5)); 18.48 (C(4)); 16.73; 16.59 (C(9)); 11.12 (C(8)); 9.68 (C(10)); 7.31; 4.03. EI-MS: 554 (<10, M^+), 511 (100, [M – C$_3$H$_7$]$^+$), 373 (14), 364 (48), 319 (100), 316 (12), 315 (33), 273 (18), 245 (10), 231 (63), 219 (12), 217 (10), 193 (12), 183 (13), 182 (10), 181 (36), 179 (13), 170 (11), 169 (76), 167 (15), 165 (13), 163 (12), 161 (10), 159 (11), 155 (16), 152 (12), 151 (15), 150 (16), 149 (47), 145 (12), 141 (15), 140 (10), 139 (16), 137 (18), 135 (13), 133 (14), 130 (43), 127 (16), 126 (15), 125 (27), 124 (12), 123 (22), 121 (11), 119 (73), 117 (18), 115 (13), 114 (10), 112 (18), 111 (34), 110 (14), 109 (35), 105 (20), 100 (12), 99 (16), 98 (13), 97 (47), 96 (16), 95 (29), 92 (13), 91 (25), 86 (59), 85 (39), 84 (96), 83 (37), 82 (16), 81 (21), 71 (38), 70 (14), 69 (62), 67 (12), 57 (28), 55 (19), 49 (22), 43 (11). Anal. calc. for $C_{32}H_{50}OSi_2$ (554.92): C 69.26, H 9.08; found: C 69.39, H 9.08.

(R,R)- and **(S,S)-Bis{[3-ethynyl-1-triethylsilyl-5-(triisopropylsilyl)penta-1,4-diyn-3-yl]} 3,6-dioxaoctan-1,8-dioate (d/l-55)**

(R,S)-Bis{[3-ethynyl-1-triethylsilyl-5-(triisopropylsilyl)penta-1,4-diyn-3-yl]} 3,6-dioxa-octan-1,8-dioate (meso-55)
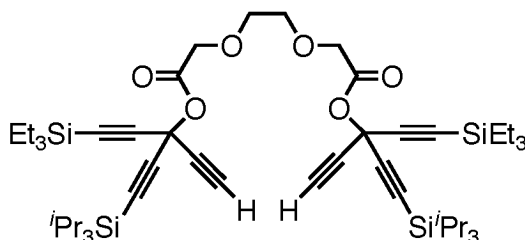
To a solution of (±)-**50** (68 mg, 0.181 mmol) and DMAP (4.4 mg, 0.036 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C, Et_3N (28 µL, 0.199 mmol) was added dropwise and the mixture was stirred for 5 min. Then a solution of 3,6-dioxaoctanedioic acid chloride (19.46 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added dropwise at r.t. over 15 min. The mixture was stirred for 2 h, then Et_3N (3 µL, 0.021 mmol) was added and stirring was continued for 19 h. A solution of 3,6-dioxaoctanedioic acid chloride (7.8 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added, followed 10 min later by another portion (10 mg, 0.05 mmol, dissolved in CH_2Cl_2 (1.5 mL)). The mixture was evaporated *in vacuo* and purified by preparative TLC (SiO_2, hexane/CH_2Cl_2 2:1), affording a mixture of diastereoisomers *d/l*-**55** and *meso*-**55** (42 mg, 61%) as a pale yellow oil.

R_f (hexane/CH_2Cl_2 2:1) 0.40. IR (CHCl₃): 3302*m*, 2953*s*, 2872*s*, 2359*w*, 2133*w*, 1774*s*, 1605*w*, 1463*m*, 1390*w*, 1118*s*, 1015*m*, 949*m*, 877*m*. ¹H-NMR (300 MHz, CDCl₃): 0.64 (*q*, *J* = 7.9, 12 H, Si(C*H₂*CH₃)₃); 1.01 (*t*, *J* = 7.9, 18 H, Si(CH₂C*H₃*)₃); 1.10 (*s*, 42 H, Si*i*Pr₃), 2.74 (*s*, 2 H, C≡CH); 3.80 (*s*, 4 H, OCH₂CH₂O); 4.21 (*s*, 4 H, OCOCH₂). ¹³C-NMR (75 MHz, CDCl₃): 166.78; 99.87; 99.10; 88.55; 87.95; 78.03; 73.00; 70.90; 68.46; 57.59; 18.50; 11.12; 7.34; 4.02. EI-MS: 890 (<10, [*M* − 1]⁺), 847 (<10, [*M* − C₃H₇]⁺), 375 (13), 374 (31), 373 (93), 359 (16), 358 (36), 357 (100), 356 (11), 316 (17), 315 (48), 314 (10), 291 (13), 287 (15), 277 (28), 273 (15), 258 (14), 249 (16), 245 (19), 231 (13), 217 (21), 203 (16), 201 (11), 189 (22), 187 (15), 185 (14), 175 (17), 173 (13), 165 (10), 161 (17), 159 (16), 157 (23), 149 (11), 147 (14), 145 (18), 143 (13), 137 (11), 135 (11), 133 (13), 131 (14), 129 (13), 125 (15), 117 (13), 115 (55), 113 (10), 111 (17), 103 (14), 101 (19), 97 (12), 88 (15), 87 (57), 86 (55), 85 (11), 84 (82), 83 (14), 73 (20), 56 (16), 51 (13), 49 (38). Anal. calc. for $C_{50}H_{82}O_6Si_4$ (891.54): C 67.36, H 9.27; found: C 67.51, H 9.30.

3-Ethynyl-1-triethylsilyl-5-(triisopropylsilyl)-3-(trimethylsilyloxy)penta-1,4-diyne ((±)-56)
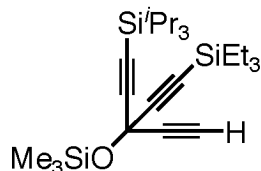
To a solution of (±)-**50** (145 mg, 0.39 mmol) and DMAP (9.1 mg, 0.07 mmol) in CH_2Cl_2 (35 mL) cooled to 0 °C, Et_3N (78 μL, 0.59 mmol) was added. After stirring for 15 min, the mixture was removed from the ice bath and trimethylsilyl chloride (70 μL, 0.55 mmol) was added dropwise. After stirring for 2.5 h, trimethylsilyl chloride (10 μL, 0.08 mmol) was added again and the mixture was stirred for 30 min. The mixture was evaporated *in vacuo* and column chromatography (SiO_2, hexane/CH_2Cl_2 5:1) afforded (±)-**56** (170 mg, 98%) as a colorless oil.

R_f (hexane/CH_2Cl_2 5:1) 0.28. IR (CHCl$_3$): 3307s, 2958s, 2887s, 2722w, 2144w, 2119w, 1600w, 1463s, 1416m, 1383m, 1252s, 1221m, 1098s, 1051s, 1018s, 987m, 864s, 848s, 827s. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.32 (s, 9 H, OSi(CH$_3$)$_3$); 0.64 (q, J = 7.7, 6 H, Si(CH_2CH$_3$)$_3$); 1.01 (t, J = 7.7, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.11 ($s$, 21 H, Si^{i}Pr$_3$), 2.61 ($s$, 1 H, C≡CH). ^{13}C-NMR (75 MHz, CDCl$_3$): 104.92; 104.10; 85.52; 84.78; 82.76; 69.98; 55.09; 18.52; 11.24; 10.87; 7.32; 4.07; 1.62. EI-MS: 446 (<10, M^+), 403 (100, [M − C$_3$H$_7$]$^+$), 221 (12), 147 (18), 145 (22), 133 (23), 131 (15), 119 (15), 101 (10), 87 (47), 73 (73), 59 (31). Anal. calc. for C$_{25}$H$_{46}$OSi$_3$ (446.89): C 67.17, H 10.67; found: C 67.21, H 10.39.

(*R*,*R*)- and (*S*,*S*)-3,8-Bis[(triethylsilyl)ethynyl]-1,10-bis(triisopropylsilyl)-3,8-{bis[(trimethylsilyl)oxy]}deca-1,4,6,9-tetrayne (*d/l*-57)

(*R*,*S*)-3,8-Bis[(triethylsilyl)ethynyl]-1,10-bis(triisopropylsilyl)-3,8-{bis[(trimethylsilyl)oxy]}deca-1,4,6,9-tetrayne (*meso*-57)

To a solution of (±)-**56** (124 mg, 0.277 mmol) in CH_2Cl_2 (26 mL) open to air, *Hay* catalyst [2 mL, prepared by stirring CuCl (11 mg, 0.11 mmol) and TMEDA (33.4 µL, 0.22 mmol) in CH_2Cl_2 (2 mL) for 5 min] was added. After stirring for 6 h, more *Hay* catalyst (2 mL) was added, the mixture was stirred for 28 h and then concentrated *in vacuo*. Column chromatography (SiO_2, CH_2Cl_2/hexane 9:1) afforded a mixture of diastereoisomers *d/l*-**57** and *meso*-**57** (106 mg, 86%) as a colorless oil.

R_f (hexane/CH_2Cl_2 6:1) 0.55. IR (CHCl₃): 2957*s*, 2867*s*, 2722*w*, 2164*w*, 1463*m*, 1415*w*, 1384*w*, 1253*s*, 1082*s* (br.), 1018*m*, 884*s*, 847*s*. ¹H-NMR (300 MHz, CDCl₃): 0.31 (*s*, 18 H, OSi(CH₃)₃); 0.64 (*q*, *J* = 7.9, 12 H, Si(*CH₂*CH₃)₃); 1.01 (*t*, *J* = 7.9, 18 H, Si(CH₂*CH₃*)₃); 1.10 (*s*, 42 H, Si*ⁱ*Pr₃). ¹³C-NMR (75 MHz, CDCl₃): 104.09; 103.17; 86.30; 85.62; 78.57; 66.03; 55.56; 18.52; 11.22; 7.32; 4.04; 1.54. EI-MS: 890 (<10, *M⁺*), 421 (11), 203 (17), 175 (15), 161 (13), 157 (23), 147 (48), 133 (38), 129 (15), 119 (19), 115 (77), 111 (12), 101 (24), 87 (100), 75 (11), 73 (66), 59 (29). Anal. calc. for $C_{50}H_{90}O_2Si_6$ (891.77): C 67.34, H 10.17; found: C 67.38, H 9.98.

3-Methoxy-3-(triethylsilyl)ethynyl-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyne ((±)-58)

n-BuLi (9.36 mL of a 1.6 M solution in hexane, 15.0 mmol) was added dropwise over 40 min to a solution of (±)-**49** (6.38 g, 14.3 mmol) in THF (38 mL) at –78 °C. The mixture

was stirred for 10 min, followed by addition of iodomethane (7.1 mL, 56.8 mmol). The temperature was raised to –10 °C and then gradually to r.t. overnight. After completion of the reaction according to TLC control, the reaction mixture was poured into sat. aq. NH$_4$Cl solution and extracted with Et$_2$O (2 x). The combined organic layers were washed with sat. aq. NaCl solution, dried (MgSO$_4$), and concentrated *in vacuo*. Column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 4:1) afforded (±)-**58** (5.78 g, 87%) as a colorless oil.

R_f (hexane/CH$_2$Cl$_2$ 2:1) 0.63. IR (CHCl$_3$): 3003*s*, 2956*s*, 2864*s*, 2825*s*, 2760*w*, 2728*w*, 2717*w*, 2173*m*, 2011*w*, 1950*w*, 1870*w*, 1602*w*, 1462*s*, 1433*m*, 1415*s*, 1383*s*, 1367*m*, 1320*w*, 1290*w*, 1127*s*, 1094*s*, 1055*s*, 1018*s*, 997*s*, 960*s*, 882*s*, 853*s*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.19 (*s*, 9 H, Si(CH$_3$)$_3$), 0.62 (*q*, *J* = 7.9, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 1.00 (*t*, *J* = 7.9, 9 H, Si(CH$_2$*CH$_3$*)$_3$); 1.09 (*s*, 21 H, Si^{i}Pr$_3$); 3.49 (*s*, 3 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 101.78; 100.99; 99.90; 88.57; 86.71; 86.15; 61.19; 52.40; 18.60; 11.28; 7.45; 4.26; – 0.36. EI-MS: 460 (<10, [*M*]$^+$), 445 (<10, [*M* – CH$_3$]$^+$), 431 (<10, [*M* – C$_2$H$_5$]$^+$), 417 (<10, [*M* – C$_3$H$_7$]$^+$), 418 (11), 417 (27), 272 (13), 189 (12), 175 (14), 173 (11), 171 (11), 166 (31), 165 (12), 161 (11), 159 (32), 157 (22), 155 (17), 153 (11), 152 (10), 151 (15), 145 (19), 143 (11), 141 (30), 139 (13), 137 (27), 131 (12), 129 (16), 127 (22), 125 (23), 123 (23), 122 (15), 121 (10), 117 (28), 116 (12), 115 (57), 112 (14), 111 (29), 109 (15), 108 (22), 107 (13), 103 (23), 101 (18), 99 (10), 97 (28), 89 (54), 87 (64), 82 (25), 75 (20), 73 (100), 59 (70). Anal. calc. for C$_{26}$H$_{48}$OSi$_3$ (460.92): C 67.75, H 10.50; found: C 67.76, H 10.48.

3-Ethynyl-3-methoxy-1-triethylsilyl-5-(triisopropylsilyl)penta-1,4-diyne ((±)-59)

Method A

A solution of *n*-BuLi (2.08 mL, 1.6 M in hexane, 3.34 mmol) was added dropwise over 10 min to a solution of (±)-**50** (1.25 g, 3.34 mmol) in THF (9 mL) cooled to –78 °C. The mixture was stirred for 10 min, and then iodomethane (1.67 mL, 26.7 mmol) was added. The temperature was raised to –25 °C, then slowly raised to 0 °C, and then slowly allowed to reach r.t.. The mixture was stirred for 16 h at r.t., poured into sat. aq. NH$_4$Cl, extracted

with Et_2O (2 x), washed with sat. aq. NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 4:1) afforded (±)-**59** (1.28 g, 98%) as a colorless oil.

Method B

To a solution of (±)-**58** (1.68 g, 3.64 mmol) in MeOH/THF 1:1 (400 mL), 1 M aq. NaOH solution (12 drops) was added, followed by a further addition of 6 drops 30 min later. According to TLC control, the reaction was completed after stirring for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with Et_2O, dried ($MgSO_4$), and the solvents were evaporated in *vacuo*. The residue was passed through a plug (SiO_2, CH_2Cl_2), and the filtrate was evaporated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 3:1) provided (±)-**59** (1.26 g, 89%) as a colorless oil. Compound **81** (80 mg, 8%) was isolated as a side product.

R_f (hexane/CH_2Cl_2 1:1) 0.65. IR (CHCl$_3$): 3307s, 3015m, 2958s, 2890s, 2866s, 2729w, 2172w, 2126w, 2115w, 1602w, 1462s, 1415m, 1383m, 1367m, 1238m, 1208m, 1203m, 1126s, 1091s, 1074s, 1053s, 1018s, 998m, 954s, 919m, 882s, 679s, 676s, 663s, 648s, 569m. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.65 (q, J = 8.1, 6 H, Si(CH_2CH$_3$)$_3$); 1.02 (t, J = 8.1, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.11 ($s$, 21 H, Si^{i}Pr$_3$); 2.63 ($s$, 1 H, C≡CH); 3.53 ($s$, 3 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 101.33; 100.64; 86.91; 86.35; 79.41; 71.64; 60.75; 52.47; 18.58; 11.25; 7.45; 4.21. EI-MS: 388 (<10, M^+), 373 (<10, [M − CH$_3$]$^+$), 357 (<10, [M − OCH$_3$]$^+$), 345 (100, [M − C$_3$H$_7$]$^+$), 130 (13), 123 (10), 117 (11), 116 (17), 102 (11), 95 (11), 89 (14), 87 (12), 59 (18). Anal. calc. for C$_{23}$H$_{40}$OSi$_2$ (388.73): C 71.06, H 10.37; found: C 71.04, H 10.54.

(*S*,*S*)- and (*R*,*R*)-3,8-Dimethoxy-3,8-bis[(triethylsilyl)ethynyl]-
1,10-[bis(triisopropylsilyl)]deca-1,4,6,9-tetrayne (*d/l*-60)

(*R*,*S*)-3,8-Dimethoxy-3,8-bis[(triethylsilyl)ethynyl]-
1,10-[bis(triisopropylsilyl)]deca-1,4,6,9-tetrayne (*meso*-60)
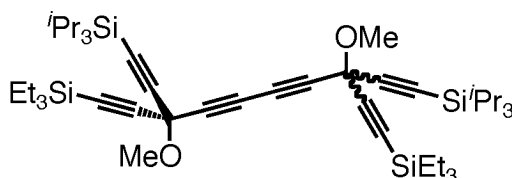
To a solution of (±)-**59** (1.26 g, 3.26 mmol) in CH_2Cl_2 (300 mL) open to air, *Hay* catalyst [5 mL, prepared by stirring CuCl (323 mg, 3.26 mmol) and TMEDA (871 µL, 6.52 mmol) in CH_2Cl_2 (5 mL) for 5 min] was added. After stirring for 17.5 h, more *Hay* catalyst (5 mL) was added and the mixture was stirred for an additional for 5 h. The mixture was washed with water, and the organic layer was concentrated *in vacuo*. Column chromatography (SiO$_2$, CH_2Cl_2/hexane 2:1) afforded a mixture of diastereoisomers *d/l*-**60** and *meso*-**60** (1.23 g, 97%) as a yellow oil, which crystallized upon standing.

R_f (hexane/CH_2Cl_2 2:1) 0.67. M.p. 44 °C. IR (CHCl$_3$): 2956*s*, 2887*s*, 2722*w*, 2163*w*, 1462*m*, 1415*w*, 1384*w*, 1361*w*, 1124*s*, 1091*s*, 1056*m*, 1000*m*, 972*w*, 953*m*, 683*m*, 704*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.63 (*q*, *J* = 8.0, 12 H, Si(*CH$_2$*CH$_3$)$_3$); 1.00 (*t*, *J* = 8.0, 18 H, Si(CH$_2$*CH$_3$)$_3$); 1.09 (*s*, 42 H, Si^{i}Pr$_3$); 3.50 (*s*, 6 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 100.50; 99.78; 87.87; 87.38; 75.67; 67.23; 61.24; 52.68; 18.50; 11.13; 7.34; 4.07. EI-MS: 775 (63, *M*H$^+$), 774 (100, *M*$^+$), 364 (10), 363 (29), 157 (26), 145 (31), 141 (10), 117 (46), 115 (69), 111 (11), 103 (15), 101 (19), 89 (43), 87 (88), 75 (21), 73 (39), 59 (48), 42 (12), 41 (14). Anal. calc. for C$_{46}$H$_{78}$O$_2$Si$_4$ (775.46): C 71.25, H 10.14; found: C 71.52, H 10.26.

(*S*, *S*)- and (*R*,*R*)-3,8-Diethynyl-3,8-dimethoxy-1,10-[bis(triisopropylsilyl)]-deca-1,4,6,9-tetrayne (*d/l*-61)

(*R*,*S*)-3,8-Diethynyl-3,8-dimethoxy-1,10-[bis(triisopropylsilyl)]-deca-1,4,6,9-tetrayne (*meso*-61)
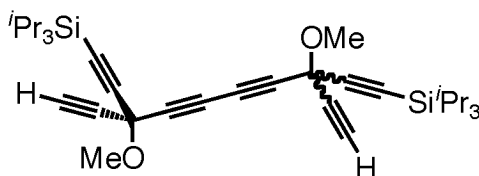
To a solution of a mixture of diastereoisomers *d/l*-60 and *meso*-60 (1.2 g, 1.57 mmol) in MeOH/THF 1:1 (300 mL), K_2CO_3 (868 mg, 6.28 mmol) was added. After stirring for 2.5 h, the mixture was washed with sat. aq. NH_4Cl solution, extracted with Et_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was passed through a plug (SiO_2, CH_2Cl_2), and the filtrate was evaporated *in vacuo*. Column chromatography (SiO_2, hexane/ CH_2Cl_2 3:1) afforded a mixture of diastereoisomers *d/l*-61 and *meso*-61 (802 mg, 93%) as an orange oil.

R_f (hexane/CH_2Cl_2 2:1) 0.39. IR (CHCl₃): 3300*m*, 2944*s*, 2889*m*, 2867*s*, 2722*w*, 2156*w*, 2122*w*, 1461*m*, 1383*w*, 1361*w*, 1294*w*, 1189*w*, 1122*s*, 1069*s*, 1067*s*, 1016*w*, 994*w*, 944*w*, 917*w*, 878*m*. ¹H-NMR (300 MHz, CDCl₃): 1.09 (*s*, 42 H, Si^{i}Pr₃); 2.68 (*s*, 2 H, C≡CH); 3.50 (*s*, 6 H, OCH₃). ¹³C-NMR (75 MHz, CDCl₃): 99.59; 88.17; 78.27; 75.45; 72.74; 67.30; 60.81; 52.29; 18.52; 11.11. EI-MS: 545 (<10, M^+), 272 (12), 270 (11), 258 (12), 256 (13), 249 (15), 246 (15), 244 (19), 242 (22), 241 (12), 233 (10), 231 (10), 229 (14), 219 (11), 217 (12), 215 (13), 205 (10), 189 (14), 181 (17), 179 (10), 169 (11), 165 (18), 159 (11), 157 (19), 153 (16), 151 (20), 147 (11), 146 (11), 145 (69), 144 (12), 143 (16), 141 (37), 139 (16), 136 (10), 133 (23), 131 (12), 129 (22), 127 (18), 125 (21), 123 (14), 119 (11), 117 (75), 115 (46), 113 (14), 111 (30), 109 (13), 107 (11), 105 (31), 103 (23), 101 (21), 99 (54), 97 (10), 93 (11), 91 (13), 89 (100), 88 (12), 87 (36), 86 (61), 85 (18), 84 (95), 83 (30), 77 (11), 75 (75), 73 (46), 69 (18), 59 (81), 51 (30), 49 (88), 47 (14), 43 (17), 41 (13). Anal. calc. for $C_{34}H_{50}O_2Si_2$ (546.94): C 74.67, H 9.21; found: C 74.88, H 9.30.

(5r,10r,15r,20r)-5,10,15,20-Tetramethoxy-5,10,15,20-tetrakis[(triisopropylsilyl)-ethynyl]-cycloeicosa-1,3,6,8,11,13,16,18-octayne (62a)

(5R,10R,15S,20S)-5,10,15,20-Tetramethoxy-5,10,15,20-tetrakis[(triisopropylsilyl)-ethynyl]-cycloeicosa-1,3,6,8,11,13,16,18-octayne (62b)

(5S,10r,15R,20s)-5,10,15,20-Tetramethoxy-5,10,15,20-tetrakis[(triisopropylsilyl)-ethynyl]-cycloeicosa-1,3,6,8,11,13,16,18-octayne (62c)

(5s,10s,15s,20s)-5,10,15,20-Tetramethoxy-5,10,15,20-tetrakis[(triisopropylsilyl)-ethynyl]-cycloeicosa-1,3,6,8,11,13,16,18-octayne (62d)
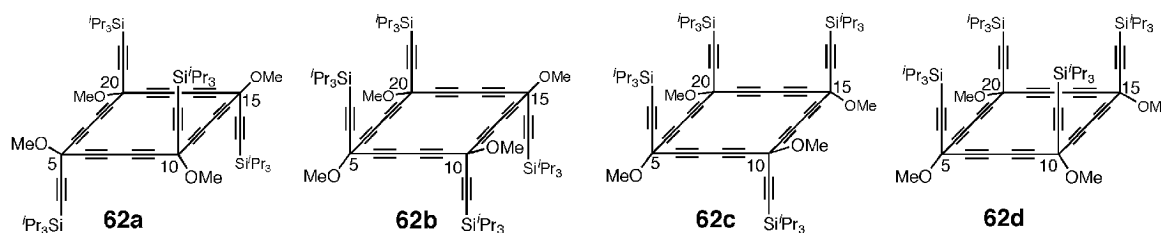
To a solution of a mixture of diastereoisomers *d/l*-**61** and *meso*-**61** (1.97 g, 3.61 mmol) in CH₂Cl₂ (3.4 L) open to air, *Hay* catalyst [300 mL, prepared by stirring CuCl (10.15 g, 101 mmol) and TMEDA (30.74 mL, 202 mmol) in CH₂Cl₂ (300 mL) for 50 min] was added. After stirring for 18 h, the mixture was washed with water and the organic phase separated, dried (MgSO₄), and evaporated *in vacuo*. Column chromatography (SiO₂, hexane/ CH₂Cl₂ 3:1 to 1:3) afforded four products: **62a**, **62b**, **62c**, **62d**. The first three compounds were further purified; **62a** and **62b** were triturated with acetone, **62c** with hexane, then filtered and dried under high vacuum. An overall yield of 72% was obtained.

62a: 168.1 mg (8%)

R_f (hexane/CH₂Cl₂ 4:1) 0.6. M.p. 135 °C (dec.). Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 17.18 min. IR (CHCl₃): 3020s, 2960s, 2945s, 2866s, 2760w, 2727w, 2717w, 2249w, 2156m, 1598w, 1462s, 1384m, 1367m, 1245w, 1199m, 1108s, 1091s, 1069s, 1019m, 996m, 953m, 883s, 678s, 662m, 612w, 570w, 541w. ¹H-NMR (300 MHz, CDCl₃): 1.09 (s, 84 H, Si^{i}Pr₃); 3.49 (s, 12 H, OCH₃). ¹³C-NMR (75 MHz, CDCl₃): 97.83; 89.50; 77.63; 68.63; 61.52; 53.27; 18.52; 11.06. HR-MALDI (DHB): 1127.5903 (2, $[M + K]^+$, C₆₈H₉₆O₄Si₄K; calc.: 1127.6023), 1111.6220 (5, $[M + Na]^+$, C₆₈H₉₆O₄Si₄Na; calc.: 1111.6283), 1081.6094 (5), 1057.6199 (100, $[M - OCH_3]^+$, C₆₇H₉₃O₃Si₄; calc.: 1057.6202), 1027.6059 (37), 1021.5962 (12), 991.5813 (58). Anal. calc. for C₆₈H₉₆O₄Si₄ (1089.85): C 74.94, H 8.88; found: C 74.91, H 8.85.

62b: 344.6 mg (18%)

R_f (hexane/CH$_2$Cl$_2$ 4:1) 0.45. M.p. 182 °C (dec.). Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 17.18 min. IR (CHCl$_3$): 3023s, 3014m, 2959s, 2944s, 2892s, 2866s, 2827m, 2760w, 2728w, 2718w, 2250w, 2156m, 1601w, 1461s, 1384m, 1368m, 1216s, 1205s, 1199m, 1108s, 1090s, 1066s, 1018m, 996m, 987m, 919m, 883s, 609w, 569w, 542w. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.08 (s, 84 H, Si^{i}Pr$_3$); 3.48 (s, 12 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 98.10; 89.50; 77.61; 77.54; 68.67; 68.63; 61.49; 53.32; 18.49; 11.06. HR-MALDI (DHB): 1111.6160 (6, [M + Na]$^+$, C$_{68}$H$_{96}$O$_4$Si$_4$Na; calc.: 1111.6283), 1081.6119 (7), 1057.6188 (100, [M − OCH$_3$]$^+$, C$_{67}$H$_{93}$O$_3$Si$_4$; calc.: 1057.6202), 1027.6051 (43), 1021.5959 (12), 991.5813 (67). Anal. calc. for C$_{68}$H$_{96}$O$_4$Si$_4$ (1089.85): C 74.94, H 8.88; found: C 74.84, H 8.87.

62c: 712.6 mg (36%)

R_f (hexane/CH$_2$Cl$_2$ 4:1) 0.33. M.p. 163 °C (dec.). Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 17.18 min. IR (CHCl$_3$): 3023m, 2941s, 2895s, 2860s, 2825m, 2761w, 2726w, 2244w, 2156m, 1598w, 1459s, 1383m, 1363w, 1241w, 1107s, 1090s, 1064s, 1014m, 991s, 916m, 881s, 658s, 608w, 567w, 544w. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.08 (s, 84 H, Si^{i}Pr$_3$); 3.47 (s, 12 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 98.37; 98.13; 97.82; 89.50; 77.65; 77.60; 68.70; 68.63; 61.50; 53.36; 53.33; 53.28; 18.50; 11.08; 10.70. HR-MALDI (DHB): 1127.6039 (3, [M + K]$^+$, C$_{68}$H$_{96}$O$_4$Si$_4$K; calc.: 1127.6023), 1111.6296 (12, [M + Na]$^+$, C$_{68}$H$_{96}$O$_4$Si$_4$Na; calc.: 1111.6283), 1081.6267 (9), 1057.6318 (100, [M − OCH$_3$]$^+$, C$_{67}$H$_{93}$O$_3$Si$_4$; calc.: 1057.6202), 1027.6182 (39), 1021.6054 (11), 991.5933 (34). Anal. calc. for C$_{68}$H$_{96}$O$_4$Si$_4$ (1089.85): C 74.94, H 8.88; found: C 74.97, H 8.67.

62d: 190.4 mg (10%)

R_f (hexane/CH$_2$Cl$_2$ 2:1) 0.14. M.p. 145 °C (dec.). Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 17.18 min. IR (CHCl$_3$): 3021m, 2960s, 2944s, 2892s, 2866s, 2828m, 2759w, 2729w, 2249w, 2157m, 1598w, 1462s, 1384m, 1367w, 1198w, 1107s, 1090s, 1066s, 1018m, 995s, 988s, 919m, 883s, 661s, 608w, 568w, 542w. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.11 (s, 84 H, Si^{i}Pr$_3$), 3.49 (s, 12 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 98.29; 89.44; 77.53; 68.65; 61.49; 53.39; 18.57; 11.18. HR-MALDI (DHB): 1127.5994 (7, [M + K]$^+$, C$_{68}$H$_{96}$O$_4$Si$_4$K; calc.: 1127.6023), 1111.6295 (25, [M + Na]$^+$, C$_{68}$H$_{96}$O$_4$Si$_4$Na; calc.: 1111.6283), 1081.6132 (18), 1057.6275 (100, [M − OCH$_3$]$^+$, C$_{67}$H$_{93}$O$_3$Si$_4$; calc.: 1057.6202), 1027.6135 (39), 1021.6031 (22), 991.5900 (61).

(5s,10s,15s,20s)-5,10,15,20-Tetraethynyl-5,10,15,20-tetramethoxy-cycloeicosa-1,3,6,8,11,13,16,18-octayne (63)
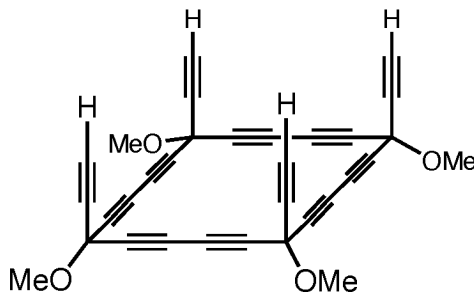
A solution of 1 M Bu$_4$NF in THF (0.198 mmol, 198 μL) was added during 1 h to a cooled solution (–15 °C) of **62d** (54 mg, 0.0495 mmol) in THF (30 mL). The mixture was stirred for 2.5 h, then ice water was added and the mixture was extracted with Et$_2$O. The combined organic layers were washed with sat. aq. NaCl solution, dried (MgSO$_4$), and the solvents evaporated *in vacuo*. Column chromatography (SiO$_2$, hexane/EtOAc 2:1) afforded **63** (20 mg, 87%) as a brown explosive powder, which decomposed over days.

R_f (hexane/EtOAc 2:1) 0.40. Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 18.43 min. IR (CHCl$_3$): 3303s, 3022s, 3015s, 2963w, 2935w, 2901w, 2887w, 2829w, 2399w, 2158w, 2126w, 1601w, 1460w, 1448w, 1311w, 1227s, 1218s, 1211s, 1205s, 1103s, 1085s, 1052s, 1010m, 973m, 927w, 793 – 717s (br.), 673s, 670s, 665s, 547w, 539w, 532w. ^{1}H-NMR (300 MHz, CDCl$_3$): 2.74 (s, 4 H, C≡CH); 3.49 (s, 12 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 77.42; 75.97; 74.50; 69.03; 61.09; 53.61. HR-MALDI (DHB): 487.0945 (19, [M + Na]$^+$, C$_{32}$H$_{16}$O$_4$Na; calc.: 487.0946), 433.0863 (100, [M – OCH$_3$]$^+$, C$_{31}$H$_{13}$O$_3$; calc.: 433.0865).

1,6,11,16,21,26,31,36-Octamethoxypentacyclo[24.14.4.4^{6,21}.4^{11,36}.4^{16,31}]hexapentaconta-2,4,7,9,12,14,17,19,22,24,27,29,32,34,37,39,41,43,45,47,49,51, 53,55-tetracosayne (44)
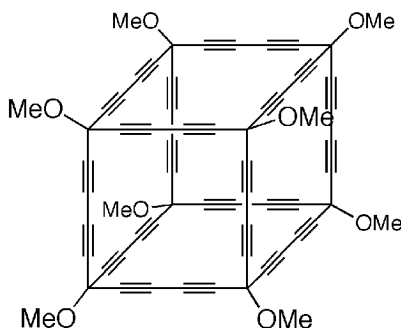
To a solution of **63** (17 mg, 0.0366 mmol) in CH$_2$Cl$_2$ (35 mL) open to air, *Hay* catalyst [5 mL, prepared by stirring CuCl (145 mg, 1.464 mmol) and TMEDA (440 µL, 2.928 mmol) in CH$_2$Cl$_2$ (5 mL) for 5 min] was added. The mixture was stirred for 3 h, then washed with water, then the organic layer was dried over MgSO$_4$ and concentrated in *vacuo*. Column chromatography (SiO$_2$, CH$_2$Cl$_2$/hexane 2:1) afforded **44** (3 mg, 16%) as a dark brown impure powder. Compound **44** explodes if it is scratched.

R_f (hexane/EtOAc 2:1) 0.50. Analytical GPC (THF, 40 °C, λ = 270 nm); t_R = 18.31 min. IR (CHCl$_3$): 3022s, 3015s, 2961m, 2929m, 2855w, 2829w, 2399w, 2252w, 2153w, 1715w, 1601w, 1458w, 1437w, 1413w 1377w, 1262s, 1226s, 1223s, 1088s, 1050s, 1012s, 928w, 864w, 800s, 540w. ^{1}H-NMR (300 MHz, CDCl$_3$): 3.44 (s, 24 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 79.39; 70.82; 61.98; 54.38. MALDI-TOF (DCTB): 889 ([M – OCH$_3$]$^-$). HR–MALDI (DCTB): 889.1276 (9, [M – OCH$_3$]$^-$, C$_{63}$H$_{21}$O$_7$; calc.: 889.1287), 858.1132 (16, [M – 2OCH$_3$]$^-$, C$_{62}$H$_{18}$O$_6$; calc.: 858.1103), 827.0888 (100, [M – 3OCH$_3$]$^-$, C$_{61}$H$_{15}$O$_5$; calc.: 827.0919), 796.0755 (26, [M – 4OCH$_3$]$^-$, C$_{60}$H$_{12}$O$_4$; calc.: 796.0736), 765.0564 (7, [M – 5OCH$_3$]$^-$, C$_{59}$H$_9$O$_3$; calc.: 765.0552).

3-Ethynyl-3-methoxy-5-(triisopropylsilyl)penta-1,4-diyne (81)
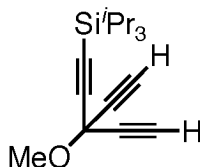
To a solution of (±)-**58** (490 mg, 1.06 mmol) in MeOH/THF 1:1 (150 mL), K$_2$CO$_3$ (587 mg, 4.24 mmol) was added. After stirring for 3 h, the mixture was washed with sat. aq.

NH$_4$Cl, extracted with Et$_2$O, dried (MgSO$_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 2:1) providing **81** (276 mg, 95%) as a colorless oil.

R_f (hexane/CH$_2$Cl$_2$ 2:1) 0.36. IR (CHCl$_3$): 3305s, 2959s, 2945s, 2866s, 2862s, 2829m, 2759w, 2727w, 2127m, 1995w, 1896w, 1460s, 1381m, 1367m, 1295m, 1247w, 1124s, 1088s, 1071s, 1055s, 1018m, 997s, 952s, 883s. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.09 (s, 21 H, Si^{i}Pr$_3$); 2.64 (s, 2 H, C≡CH); 3.52 (s, 3 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 100.51; 87.04; 79.05; 72.05; 60.34; 52.64; 18.60; 11.24. EI-MS: 274 (<10, M^+), 243 (<10, [M − OCH$_3$]$^+$), 231 (<10, [M − C$_3$H$_7$]$^+$), 173 (10), 163 (11), 161 (13), 160 (10), 159 (15), 157 (11), 152 (13), 151 (98), 145 (14), 135 (10), 133 (11), 131 (13), 130 (15), 127 (35), 117 (11), 115 (12), 109 (20), 99 (100), 93 (11), 89 (15), 83 (14), 77 (11), 75 (14), 69 (14), 59 (26). Anal. calc. for C$_{17}$H$_{26}$OSi (274.48): C 74.39, H 9.55; found: C 74.33, H 9.57.

1-Bromoethynyl-3-methoxy-3-triethylsilyl-5-(triisopropylsilyl)penta-1,4-diyne ((±)-82)
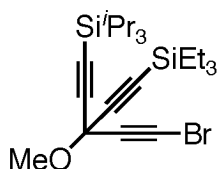
To a solution of (±)-**58** (452 mg, 0.98 mmol) in acetone (4.2 mL), NBS (209 mg, 1.2 mmol) and then AgNO$_3$ (17 mg, 0.1 mmol) were added. The reaction mixture was stirred for 2 h, then cooled to 0 °C, and cold H$_2$O (2 mL) was added. The mixture was extracted with Et$_2$O (2 x), the combined organic phases dried (MgSO$_4$), and concentrated *in vacuo*. Purification of the crude product by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 4:1) afforded (±)-**82** (408 mg, 84%) as a colorless oil.

R_f (hexane/CH$_2$Cl$_2$ 4:1) 0.46. IR (CHCl$_3$): 3002m, 2960s, 2891s, 2866s, 2826s, 2759w, 2728w, 2621w, 2214s, 2173m, 2009w, 1868w, 1601w, 1463s, 1433m, 1415m, 1383m, 1367m, 1289w, 1264w, 1132s, 1098s, 1055s, 1018s, 997s, 962s, 918m, 908s, 883s, 814s. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.63 (q, J = 7.6, 6 H, Si(CH_2CH$_3$)$_3$); 1.00 (t, J = 7.6, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.09 ($s$, 21 H, Si^{i}Pr$_3$); 3.49 ($s$, 3 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 101.19; 100.36; 87.14; 86.61; 75.86; 61.70; 52.61; 46.02; 18.64; 11.27; 7.50; 4.25. EI-MS: 363 (<10, [M − C$_2$Br]$^+$), 207 (12), 154 (20), 152 (19), 141 (13), 131 (18), 129 (32),

128 (34), 127 (11), 119 (23), 89 (16). Anal. calc. for $C_{24}H_{43}OSi_2Br$ (483.68): C 59.60, H 8.96, Br 16.52; found: C 59.54, H 8.68, Br 16.79.

(3R,8R,13R)-, (3R,8S,13R)-, (3S,8R,13S)-, (3S,8S,13S)-, (3R,8R,13S)-, and (3R,8S,13S)-3,13-Bis[(triethylsilyl)ethynyl]-1,15-bis(triisopropylsilyl)-8-[(triisopropylsilyl)-ethynyl]-3,8,13-(trimethoxy)pentadeca-1,4,6,9,11,14-hexayne (83)

Method A

n-BuLi (0.22 mL of a 1.6 M solution in hexane, 0.35 mmol) was added dropwise over 20 min to an oxygen-free solution of **81** (48 mg, 0.18 mmol) in THF (0.6 mL) at 0 °C, then the mixture was stirred at 0 °C for additional 15 min (the mixture turned red color). The reaction mixture was cooled to –20 °C, and CuCl (34.6 mg, 0.35 mmol) was added. While stirring for 1 h, the solution first turned violet, and then green. The solvent was then carefully removed *in vacuo* and replaced by anhydrous pyridine (1 mL), and a solution of (±)-**82** (165 mg, 0.35 mmol) in THF (0.5 mL) at 0 °C over a period of 30 min was added. The mixture was stirred at r.t. for 20 h, then poured into an ice-cold 15% HCl solution (10 mL), and extracted with CH_2Cl_2 (40 mL). The organic layer was washed with a 5% aq. $NaHCO_3$ solution, H_2O (50 mL, 2 x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (SiO_2, hexane/CH_2Cl_2 2:1), affording **83** (24 mg, 13%) as a mixture of stereoisomers.

Method B

To a solution of (±)-**59** (1.69 g, 4.35 mmol) and **81** (199 mg, 0.73 mmol) in CH_2Cl_2 (840 mL) open air, *Hay*-catalyst [60 mL, prepared by stirring CuCl (600 mg, 6.06 mmol) and TMEDA (1.8 mL, 13.47 mmol) in CH_2Cl_2 (60 mL) for 30 min] was added. After stirring for 15 h, the solvent was concentrated *in vacuo* to 1/3 of the volume, and the mixture was

filtered over a plug (SiO$_2$) and washed with CH$_2$Cl$_2$. The remaining solvent was evaporated in *vacuo*. Column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 3:1) afforded **83** (363 mg, 48%) as a mixture of stereoisomers.

Yellow oil. R_f (hexane/CH$_2$Cl$_2$ 1:1) 0.33. IR (CHCl$_3$): 3004w, 2958s, 2945s, 2891s, 2866s, 2827w, 2760w, 2727w, 2717w, 2161w, 1462s, 1414w, 1384w, 1367w, 1262w, 1239w, 1122s, 1109s, 1090s, 1070s, 1060s, 1018s, 998s, 970m, 917w, 881s. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.63 (q, J = 7.8, 12 H, 2 x Si(CH_2CH$_3$)$_3$); 1.00 (t, J = 7.8, 18 H, 2 x Si(CH$_2$$CH_3$)$_3$); 1.09 ($s$, 63 H, 3 x Si^{i}Pr$_3$); 3.49 ($s$, 9 H, 3 x OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 100.29; 99.56; 98.79; 88.96; 87.92; 87.44; 76.30; 74.26; 68.14; 66.78; 61.29; 61.20; 53.02; 52.70; 18.57; 11.22; 7.43; 4.17. MALDI-TOF (DCTB): 1070.4 ([M + Na]$^+$); 1015.4 ([M – OCH$_3$]$^+$). Anal. calc. for C$_{63}$H$_{102}$O$_3$Si$_5$ (1047.92): C 72.21, H 9.81; found: C 72.08, H 9.93.

(3R,8R,13R)-, (3R,8S,13R)-, (3S,8R,13S)-, (3S,8S,13S)-, (3R,8R,13S)-, and (3R,8S,13S)-3,13-Diethynyl-1,15-bis(triisopropylsilyl)-8-[(triisopropylsilyl)ethynyl]-3,8,13-(trimethoxy)pentadeca-1,4,6,9,11,14-hexayne (84)
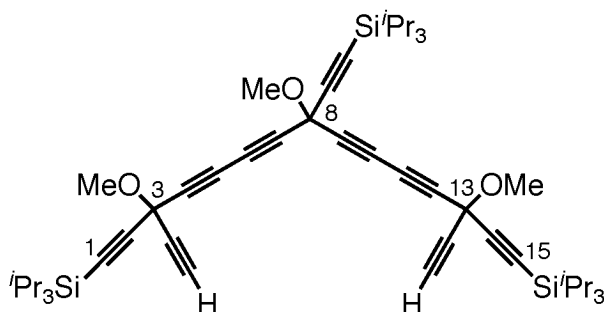
To a solution of the stereoisomeric mixture **83** (344 mg, 0.33 mmol) in MeOH/THF 1:1 (115 mL), K$_2$CO$_3$ (170 mg, 1.31 mmol) was added. After stirring for 2.5 h, the mixture was washed with sat. aq. NH$_4$Cl solution, extracted with Et$_2$O, dried (MgSO$_4$), and evaporated *in vacuo*. The residue was purified by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 2:1) to provide **84** (250 mg, 93%) as mixture of stereoisomers.

Orange oil. R_f (hexane/CH$_2$Cl$_2$ 2:1) 0.30. IR (CHCl$_3$): 3299m, 2960s, 2945s, 2866s, 2823s, 2756w, 2722w, 2358w, 2156w, 2123w, 1640m, 1381w, 1365w, 1258m, 1118s, 1107s, 1088s, 1068s, 995m, 951m, 920w, 878m. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.09 (s, 63 H, 3x Si^{i}Pr$_3$); 2.68 (s, 2 H, 2 x C≡CH); 3.49 (s, 3 H, C(8)-OCH$_3$); 3.51 (s, 6 H,

C(3)–OCH$_3$ and C(13)–OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 99.43; 98.52; 89.15; 88.20; 78.17; 75.81; 74.53; 72.75; 67.89; 67.17; 61.25; 60.81; 53.10; 52.92; 18.61; 11.21. MALDI-TOF (DCTB): 787.9 ([M – OCH$_3$]$^-$).

(2R)-Phenyl(tetrahydro-2H-pyran-2-yloxy)acetic acid ((R)-86) [202]
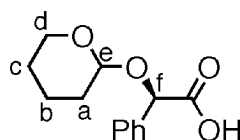
3,4-Dihydro-2H-pyran (2.55 mL, 28 mmol) was added dropwise to a stirred supension of (R)-mandelic acid (3.04 g, 20 mmol) and TsOH (76 mg, 0.4 mmol) in CHCl$_3$ (40 mL) at 0 °C. After 5 min, the ice bath was removed and the mixture allowed to warm to r.t.. After 16 h, all of the compounds had completely dissolved and a violet color began to appear. After 1.5 h more, the reaction mixture was extracted with 0.2 N KOH (50 mL, 2 x). The combined aqueous layers were acidified with 6 N HCl to pH 3–4 and extracted with CH$_2$Cl$_2$ (3 x). The pH of the aqueous layer was controlled between extractions, with more HCl added if necessary. The combined CH$_2$Cl$_2$ extracts were washed with water, dried (MgSO$_4$), and concentrated *in vacuo* to give (R)-**86** (2.61 g, 55%) as a sticky colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): 1.40 – 2.00 (*m*, 6 H, H-C(a, b, c)); 3.41 – 3.60 (*m*, 1 H, H–C(d)); 3.62 – 3.74 (*m*, 1 H, H–C(d)); 3.89 – 4.02 (*m*, 1 H, H-C(e)); 5.25 and 5.33 (*s*, 1 H, H-C(f)); 7.30 – 7.50 (*m*, 5 H, C$_6$H$_5$); 10.85 (br. *s*, 1 H, CO$_2$H). ^{13}C-NMR (75 MHz, CDCl$_3$): 176.18; 174.48; 136.00; 135.41; 128.83; 128.62; 128.48; 127.48; 127.15; 97.36; 96.93; 76.56; 75.53; 62.87; 62.11; 30.31; 30.21; 25.30; 25.25; 19.35; 18.75.

tert-Butyldimethylsilyl (2*R*)-2-(*tert*-butyldimethylsilyloxy)phenyl acetate ((*R*)-88) [209]
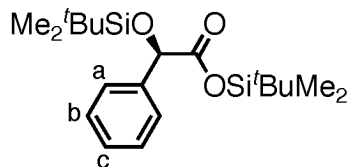
Tert-butyldimethylsilyl chloride (4.5 g, 29.6 mmol) was added to a solution of (*R*)-mandelic acid (1.5 g, 9.9 mmol) and imidazole (2.8 g, 41.4 mmol) in DMF (20 mL). The reaction mixture was stirred at r.t. for 42 h, extracted with Et$_2$O, and the organic phase was washed with sat. aq. NaCl solution. The organic layer was dried (MgSO$_4$) and concentrated *in vacuo*. Bulb-to-bulb distillation (b.p. $_{0.5}$ 110 – 120 °C, air bath) yielded (*R*)-88 as a colorless oil (3.24 g, 86%).

^{1}H-NMR (300 MHz, CDCl$_3$): 0.02 (*s*, 3 H, OSi(CH_3)$_2^t$Bu); 0.13 (*s*, 3 H, OSi(CH_3)$_2^t$Bu); 0.15 (*s*, 3 H, COOSi(CH_3)$_2^t$Bu); 0.20 (*s*, 3 H, COOSi(CH_3)$_2^t$Bu); 0.83 (*s*, 9 H, OSiMe$_2^tBu$); 0.93 (*s*, 9 H, COOSiMe$_2^tBu$); 5.15 (*s*, 1 H, CH); 7.23 – 7.36 (*m*, 3 H, C$_6$H$_5$ (a, c)); 7.43 – 7.49 (m, 2 H, C$_6$H$_5$ (a)). ^{13}C-NMR (75 MHz, CDCl$_3$): 171.96; 139.57; 128.07; 127.81; 126.41; 75.30; 25.86; 25.47; 18.45; 17.75; –4.78; –4.93; –5.02.

(3*R*)-3-(Triethylsilyl)ethynyl-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-yl (2*R*)-2-[(*tert*-butyldimethylsilyl)oxy]phenyl acetate and (3*S*)-3-(Triethylsilyl)-ethynyl-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-yl (2*R*)-2-[(*tert*-butyl-dimethylsilyl)oxy]phenyl acetate (89)
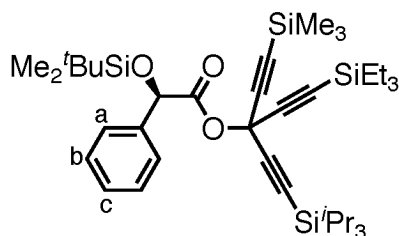
To a solution of (*R*)-88 (212 mg, 0.056 mmol) in CH$_2$Cl$_2$ (1 mL) with a drop of DMF, (COCl)$_2$ (0.69 mmol, 58 μL) was added dropwise at 0 °C. After the reaction mixture was stirred for 6 h, DMAP (14 mg, 0.11 mmol) was added, followed by a solution of (±)-49 (158 mg, 0.36 mmol) and Et$_3$N (99 μL, 1.12 mmol) in CH$_2$Cl$_2$ at 0 °C. After stirring for

30 min, the reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (10 mL, 2 x). The collected organic phases were washed with a 1 M $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane/CH_2Cl_2 2:1) to give **89** (127 mg, 52%) as a mixture of diastereoisomers.

Colorless oil. R_f (hexane/CH_2Cl_2 2:1) 0.33. IR ($CHCl_3$): 3090w, 3066w, 3035w, 3008w, 2958s, 2890s, 2866s, 2735w, 2716w, 2176w, 1950w, 1770s, 1746m, 1602w, 1494m, 1471s, 1462s, 1413m, 1389m, 1383m, 1361m, 1313w, 1131s, 1072m, 1018m, 1006m, 952s, 862s, 845s. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.08 (s, 3 H, $Si^tBu(CH_3)_2$); 0.14 (s, 9 H, $Si(CH_3)_3$); 0.16 (s, 3 H, $Si^tBu(CH_3)_2$); 0.57 (q, J = 7.6, 6 H, $Si(CH_2CH_3)_3$); 0.91 – 0.98 (m, 18 H, $Si(CH_2CH_3)_3$ and Si^tBuMe_2); 1.04 (s, 21 H, Si^iPr_3); 5.23 (s, 1 H, $C_6H_5CHO^tBuMe_2$); 7.23 – 7.35 (m, 3 H, C_6H_5 (b, c)); 7.46 – 7.52 (m, 2 H, C_6H_5 (a)). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.80; 138.36; 128.02; 127.76; 126.30; 100.34; 99.53, 99.48 (diastereoisomers); 98.29; 89.67; 87.74, 87.67 (diastereoisomers); 87.08; 74.25; 58.27; 25.84; 18.56; 11.21; 7.41; 4.16; –0.49; –4.64; –5.07. HR-MALDI (DHB): 717.3989 (100, $[M + Na]^+$, $C_{39}H_{66}O_3Si_4Na$; calc.: 717.3987).

Ethyl (2*S*)-2-(triethylsilyloxy)propanoate ((–)-(*S*)-97) [217]

$$Et_3SiO$$
$$\text{OEt}$$
$$\text{O}$$
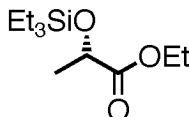
To a solution of ethyl (*S*)-lactate (1 mL, 8.75 mmol) and DMAP (32 mg, 0.27 mmol) in CH_2Cl_2 cooled to 0 °C, Et_3N (1.7 ml, 12.3 mmol) was added and subsequently triethylsilyl chloride (1.9 mL, 11.34 mmol). A white precipitate formed immediately. The mixture was stirred for 1 h at 0 °C and for 5 h at r.t.. Then the reaction solution was washed with sat. aq. NaCl solution and the organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (SiO_2, hexane/CH_2Cl_2 1:1) provided (–)-(*S*)-**97** as a colorless oil (1.55 g, 76 %).

R_f (hexane/CH_2Cl_2 1:1) 0.38. $[\alpha]_D^{25}$ = – 28.3 (c = 1.03, $CHCl_3$). IR ($CHCl_3$): 2986s, 2959s, 2940s, 2914s, 2805w, 2736w, 1743s, 1457m, 1446m, 1414w, 1373m, 1348w, 1301m, 1277m, 1140s, 1107m, 1060m, 1017m, 1005m, 979m, 966m, 890m, 860m. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.60 (q, J = 7.9, 6 H, $Si(CH_2CH_3)_3$); 0.94 (t, J = 7.9, 9 H, $Si(CH_2CH_3)_3$);

1.26 (t, J = 7.2, 3 H, OCH$_2$CH$_3$); 1.38 (d, J = 6.9, 3 H, CH$_3$); 4.10 – 4.21 (m, 2 H, OCH$_2$CH$_3$); 4.29 (q, J = 6.9, 1 H, CH). ^{13}C-NMR (75 MHz, CDCl$_3$): 173.88; 68.10; 60.76; 21.56; 14.28; 6.77; 4.68.

(2*S*)-2-Hydroxy-*N*-methyl-*N*-methoxypropanamide ((–)-(*S*)-98) [220]
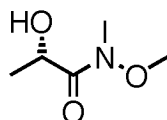
To a cooled (–20 °C) mixture of ethyl (*S*)-lactate (2.0 g, 16.9 mmol) and (MeO)MeNH·HCl (4.1 g, 42 mmol) in THF (50 mL), a 2 M solution of ^{i}PrMgCl in Et$_2$O (42 mL, 84 mmol) was added over 30 min. The reaction mixture was stirred at –20 °C for 30 min and at 0 °C for a further 30 min. Then the reaction was quenched by dropwise addition of sat. aq. NH$_4$Cl solution (5 mL). The solution was poured into Et$_2$O/NH$_4$Cl solution (200 mL, 1:4), and the phases were separated. The aqueous phase was extracted with Et$_2$O (50 mL, 3 x) and then with CH$_2$Cl$_2$ (50 mL, 2 x). The combined organic fractions were dried (MgSO$_4$) and then concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO$_2$, EtOAc/hexane 50:50 to 70:30 gradient) provided *Weinreb* amide (–)-(*S*)-98 (1.68g, 74%) as a colorless oil.

R_f (hexane/EtOAc 1:1) 0.24. $[\alpha]_D^{25}$= – 48.2 (c = 1.12, CHCl$_3$). IR (CHCl$_3$): 3458m (br.), 3010s, 2982m, 2939m, 2903w, 2872w, 2818w, 1655s, 1482m, 1461m, 1448m, 1397w, 1372s, 1362s, 1178m, 1132m, 1085s, 1032s, 995s, 885w, 612w. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.32 (d, J = 6.9, 3 H, CH(CH$_3$)OH); 3.21 (s, 3 H, NCH$_3$); 3.68 (s, 3 H, OCH$_3$); 4.53 (q, J = 6.9, 1 H, CH(CH$_3$)OH). ^{13}C-NMR (75 MHz, CDCl$_3$): 175.52; 64.99; 61.35; 32.53; 21.12.

(2*S*)-*N*-Methoxy-*N*-methyl-2-[(triethylsilyl)oxy]propanamide ((–)-(*S*)-99)
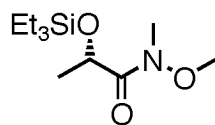
Method A

A 2 M solution of *i*PrMgCl in Et$_2$O (5.64 mL, 11.3 mmol) was added dropwise over 30 min to a vigorously stirred suspension of (MeO)MeNH·HCl (550 mg, 5.64 mmol) and (–)-(*S*)-**97** (545 mg, 2.35 mmol) in THF (7 mL) at –20 °C. After 30 min, the reaction was stirred for a further 1 h at 0 °C, then a sat. aq. NH$_4$Cl solution (2 mL) was added dropwise to the reaction mixture. The reaction solution was poured into an Et$_2$O/NH$_4$Cl mixture (50 mL, 1:4), and the phases were separated. The aqueous phase was extracted with Et$_2$O (30 mL) and with CH$_2$Cl$_2$ (30 mL), and the combined organic fractions were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 2:1) afforded 327 mg (56%) of (–)-(*S*)-**99** as a colorless oil.

Method B

(2*S*)-*N*-methoxy-*N*-methyl-2-(hydroxy)propanamide (–)-(*S*)-**98** (282 mg, 2.1 mmol), imidazole (577 mg, 8.44 mmol), and triethylsilylchloride (0.43 mL, 2.54 mmol) were dissolved in dry DMF (3 mL) at 0 °C, then after 30 min the reaction mixture was allowed to warm up at r.t.. After stirring for 18 h, the reaction was poured in Et$_2$O, then the organic layer was washed with sat. aq. NaCl solution (2 x), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 2:1) afforded 378 mg (72%) of (–)-(*S*)-**99** as a colorless oil.

R_f (hexane/EtOAc 2 : 1) 0.5. $[\alpha]_D^{25} = -17.9$ ($c = 0.97$, CHCl$_3$). IR (CHCl$_3$): 3003*s*, 2958*s*, 2938*s*, 2912*s*, 2878*s*, 2817*w*, 2734*w*, 1666*s*, 1459*s*, 1415*m*, 1389*m*, 1366*w*, 1336*w*, 1294*w*, 1239*m*, 1150*s*, 1101*s*, 1052*m*, 1000*s*, 977*m*, 963*m*, 903*m*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.60 (*q*, *J* = 7.8, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 0.93 (*t*, *J* = 7.8, 9 H, Si(CH$_2$*CH$_3$*)$_3$); 1.33 (*d*, *J* = 6.8, 3 H, CH$_3$); 3.17 (*s*, 3 H, NCH$_3$); 3.67 (*s*, 3 H, NOCH$_3$); 4.66 (*q*, *J* = 6.8, 1 H, CH$_3$*CH*OSiEt$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 174.50; 65.80; 61.17; 32.62; 21.02; 6.76; 4.76. EI-MS: 247 (<10, M^+), 219 (17), 218 (100, $[M - C_2H_5]^+$), 159 (34), 158 (18), 131 (18), 117 (10), 115 (33), 87 (14). Anal. calc. for C$_{11}$H$_{25}$NO$_3$Si (247.41): C 53.40, H 10.18, N 5.66; found: C 53.57, H 10.13, N 5.65.

(4*S*)-4-(Triethylsilyl)oxy-1-(triisopropylsilyl)penta-1-yn-3-one ((–)-(*S*)-100)

$$\text{Et}_3\text{SiO} \quad \text{Si}^i\text{Pr}_3$$
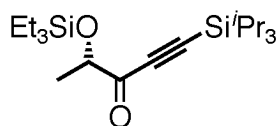
Method A

n-BuLi (0.56 mL of 1.6 M solution in hexane, 0.89 mmol) was added dropwise to a solution of (triisopropylsilyl)acetylene (207 μL, 0.89 mmol) in THF (2 mL) at 0 °C. After 20 min, MgBr₂·OEt₂ (231 mg, 0.89 mmol) was added in one portion. The resulting suspension was stirred vigorously for 75 min. The resulting clear solution was cooled to –78 °C, whereupon the reaction mixture became slightly turbid. *Weinreb* amide (–)-(*S*)-**99** (170 mg, 0.69 mmol) was added dropwise over 10 min as a solution in THF (0.6 mL). The reaction mixture was allowed to warm to 0 °C over 2.5 h and then quenched by dropwise addition of sat. aq. NH₄Cl sol. (ca. 80 μL). The reaction mixture was then partitioned with an Et₂O/NH₄Cl solution (20 mL, 1:1). The phases were separated, and the aqueous layer was extracted with Et₂O (20 mL, 2 x). The combined organic fractions were washed with sat. aq. NaCl solution (50 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO₂, hexane/CH₂Cl₂ 2:1) provided ketone (–)-(*S*)-**100** (127 mg, 50%) as a colorless oil.

Method B

n-BuLi (0.75 mL of 1.6 M solution in hexane, 1.2 mmol) was added dropwise to a solution of (triisopropylsilyl)acetylene (280 μL, 1.25 mmol) in Et₂O (2 mL) at 0 °C. After 20 min a solution of *Weinreb* amide (–)-(*S*)-**99** in Et₂O (1 mL) was added dropwise over 5 min, and the reaction was stirred for a further 2 h. The reaction mixture was then partitioned with an Et₂O/NH₄Cl solution (20 mL, 1:1). The phases were separated, and the aqueous layer was extracted with Et₂O (20 mL, 2 x). The combined organic fractions were washed with sat. aq. NaCl solution (50 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO₂, hexane/CH₂Cl₂ 2:1) provided ketone

(–)-(*S*)-**100** (209 mg, 70%) as a colorless oil.

R_f (hexane/CH₂Cl₂ 2:1) 0.4. $[\alpha]_D^{25} = -24.0$ (*c* = 1.00, CHCl₃). IR (CHCl₃): 2956*s*, 2865*s*, 2808*m*, 2760*w*, 2730*w*, 2719*w*, 2145*m*, 1678*s*, 1462*s*, 1414*m*, 1385*m*, 1368*m*, 1240*m*,

1174m, 1094s, 1038m, 1011s, 977m, 961m, 939s, 883s, 682m. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.60 (q, J = 7.8, 6 H, Si(CH_2CH$_3$)$_3$); 0.94 (t, J = 7.8, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.10 ($s$, 21 H, Si^{i}Pr$_3$); 1.39 ($d$, J = 6.9, 3 H, CH$_3$); 4.25 (q, J = 6.9, 1 H, CH(CH$_3$)OSiEt$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 189.72; 102.53; 99.40; 75.13; 20.92; 18.67; 11.21; 6.90; 4.91. EI-MS: 368 (<10, M^+), 339 (23, [M – C$_2$H$_5$]$^+$), 255 (14), 253 (13), 225 (12), 160 (14), 159 (100), 133 (13), 131 (37), 115 (49), 106 (23), 105 (14), 99 (11), 91 (13), 87 (21). Anal. calc. for C$_{20}$H$_{40}$O$_2$Si$_2$ (368.71): C 65.15, H 10.93; found: C 65.35, H 10.97.

Ethyl (2S)-2-[(4-Methoxybenzyl)oxy]propanoate ((–)-(S)-102) [229]

Trifluoromethanesulfonic acid (0.66 µL, 7.4·10^{-4} mmol) was added to a solution of ethyl (S)-lactate (1.11 mL, 9.8 mmol) and 4-methoxybenzyl trichloroacetimidate (4.15 g, 14.7 mmol) in cyclohexane (16 mL) and CH$_2$Cl$_2$ (16 mL) at 0 °C. A white precipitate formed immediately. After 10 min, the mixture was warmed to r.t. and stirred for 17 h. A second portion of 4-methoxybenzyl trichloroacetimidate (1.4 g, 4.9 mmol) in CH$_2$Cl$_2$ (3 mL) was added, and the mixture was stirred for 3 h more. Hexane (40 mL) was added, and the resulting white precipitate was removed by filtration and washed again with hexane (20 mL). The organic phase was washed with sat aq. NaHCO$_3$ solution (40 mL), sat. aq. NaCl solution (40 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 10:1) afforded 1.71 g (73%) of (–)-(S)-**102** as a colorless oil.

R_f (hexane/EtOAc 10:1) 0.24. $[\alpha]_D^{25}$ = – 78.7 (c = 1.08, CHCl$_3$). IR (CHCl$_3$): 3010s, 2984m, 2960w, 2937m, 2904w, 2837w, 2059w, 1887w, 1739s, 1612s, 1586w, 1513s, 1465m, 1456m, 1443m, 1422w, 1395w, 1374m, 1302m, 1249s, 1142s, 1110s, 1062m, 1034s, 845w, 825m. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.29 (t, J = 7.1, 3 H, CH_3CH$_2$O); 1.41 (d, J = 6.8, 3 H, CH_3CHO); 3.80 (s, 3 H, OCH$_3$); 4.02 (q, J = 6.8, 1 H, CH$_3$$CH$O); 4.21 ($dq$, J = 7.0, J' = 1.6, 2 H, CH$_3$$CH_2$O); 4.38 ($d$, J = 11.2, 1 H, CH$_3OC_6H_4$CHHO); 4.62 (d, J = 11.2, 1 H, CH$_3$OC$_6$H$_4$CHHO); 6.87 (d, J = 8.7, 2 H, C$_6$H$_4$); 7.29 (d, J = 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 173.18; 159.18; 129.53; 113.71; 73.70; 71.61; 60.81; 55.30; 18.82; 14.35. HR-EI-MS: 238.1210 (1, M^+, C$_{13}$H$_{18}$O$_4$; calc.: 238.1205); 137.0598

(20, $[CH_3OC_6H_4CH_2O]^+$, $C_8H_9O_2$; calc.: 137.0603); 121.0640 (100, $[CH_3OC_6H_4CH_2]^+$, C_8H_9O; calc.: 121.0653). Anal. calc. for $C_{13}H_{18}O_4$ (238.28): C 65.53, H 7.61; found: C 65.52, H 7.47.

(2S)-2-(4-Methoxybenzyloxy)propan-1-ol ((–)-(S)-103)
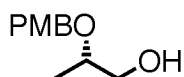
LiAlH$_4$ (27 mg, 0.70 mmol) was added in one portion to a solution of ester (–)-(S)-**102** (209 mg, 0.88 mmol) in Et$_2$O (5 mL) at 0 °C. After stirring for 30 min, the temperature was raised to r.t. and the mixture was stirred for a further 3.5 h. Then, the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of a sat. aq. Na$_2$SO$_4$ solution (1 mL). Solid Na$_2$SO$_4$ (ca. 120 mg) was then added. The cooling bath was removed and the mixture stirred vigorously for 1 h over which time a floculent white precipitate was produced. This was removed by filtration through a pad of *Celite*, and the residue was washed with EtOAc (20 mL) and then with CH$_2$Cl$_2$ (20 mL). The filtrate was dried (MgSO$_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 6:1 to 4:1) provided (–)-(S)-**103** (143 mg, 83%) as a colorless oil.

R_f (hexane/EtOAc 10:1) 0.1. $[\alpha]_D^{25}$= + 40.6 (c = 1.02, CHCl$_3$). IR (CHCl$_3$): 3585w, 3456w (br.), 3010s, 2972m, 2935m, 2912m, 2874m, 2839m, 2060w, 1889w, 1612s, 1586w, 1513s, 1465m, 1456m, 1441m, 1396w, 1375m,1337m, 1302m, 1249s, 1181m, 1173m, 1148m, 1111m, 1080s, 1036s, 983w, 935w, 908w, 865w, 822m. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.16 (d, J = 6.2, 3 H, CH_3CHOCH$_2$C$_6$H$_4$OCH$_3$); 2.18 (br. s, 1 H, OH); 3.44 – 3.50 (m, 1 H, CH$_3$CHOCH$_2$C$_6$H$_4$OCH$_3$); 3.54 – 3.73 (m, 2 H, HOCH_2); 3.80 (s, 3 H, OCH$_3$); 4.35 (d, J = 11.2, 1 H, CH$_3$OC$_6$H$_4$CHHO); 4.58 (d, J = 11.2, 1 H, CH$_3$OC$_6$H$_4$CHHO); 6.88 (d, J = 8.7, 2 H, C$_6$H$_4$); 7.27 (d, J = 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 159.06; 130.39; 129.24; 113.79; 75.20; 70.46; 66.34; 55.30; 15.99. HR-EI-MS: 196.1099 (7, M^+, $C_{11}H_{16}O_3^+$; calc.: 196.1099); 137.0593 (4, $[CH_3OC_6H_4CH_2O]^+$; calc.: 137.0603); 121.0633 (100, $[CH_3OC_6H_4CH_2]^+$; calc.: 121.0653). Anal. calc. for $C_{11}H_{16}O_3$ (196.25): C 67.32, H 8.22; found: C 67.17, H 8.01.

(2*S*)-2-{[(4-Methoxybenzyl)oxy]propyl} (2*R*)-2-methoxy-(2-trifluoromethyl) phenylacetate ((−)-(2'*S*,2*R*)-104)
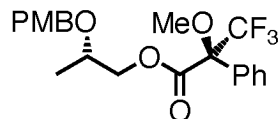
A solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (33 µL, 0.176 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a solution of alcohol (−)-(*S*)-**103** (31 mg, 0.147 mmol), Et_3N (41 µL, 0.294 mmol), and DMAP (few crystals) in CH_2Cl_2 (0.9 mL) at 0 °C. After 1 h, the reaction was diluted with Et_2O (6 mL) and then poured into a sat. aq. $NaHCO_3$ solution (10 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (10 mL, 2 x). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, hexane/EtOAc 10:1) providing 47 mg (83%) of (−)-(2'*S*,2*R*)-**104** as a colorless oil.

R_f (hexane/EtOAc 10:1) 0.25. $[\alpha]_D^{25} = -33.5$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3005*m*, 2983*m*, 2951*m*, 2937*m*, 2911*w*, 2869*w*, 2849*w*, 2838*w*, 2069*w*, 1957*w*, 1889*w*, 1748*s*, 1612*m*, 1585*w*, 1513*s*, 1465*m*, 1451*m*, 1441*w*, 1377*w*, 1343*w*, 1122*m*, 1107*m*, 1081*m*, 1030*s*, 1001*m*, 972*w*, 945*w*, 916*w*, 824*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21 (*d*, *J* = 6.2, 3 H, $CH_3CHOCH_2C_6H_4OCH_3$); 3.55 − 3.57 (*m*, 3 H, C(OCH_3)CF$_3$); 3.76 − 3.87 (*m*, 1 H, CH$_3$C*H*OCH$_2$C$_6$H$_4$OCH$_3$); 3.80 (*s*, 3 H, OCH$_3$); 4.27 − 4.50 (*m*, 4 H, CHC*H$_2$*OCO and O*CH$_2$*C$_6$H$_4$OCH$_3$); 6.85 (*d*, *J* = 8.7 , 2 H, C$_6$H$_4$); 7.20 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 7.34 − 7.44 (*m*, 3 H, C$_6$H$_5$C(CF$_3$)); 7.54 − 7.59 (*m*, 2 H, C$_6$H$_5$C(CF$_3$)). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.32; 159.01; 132.10; 130.14; 129.50; 129.09; 128.31; 127.32; 123.22 (*q*, J_{CF} = 288.1); 113.66; 84.66 (*q*, J_{CF} = 27.8); 72.08; 70.80; 69.05; 55.49; 55.27; 16.89. ^{19}F-NMR (282 MHz, $CDCl_3$): −71.46 (CF$_3$). HR-MALDI (DHB): 435.1386 (100, [M + Na]$^+$, $C_{21}H_{23}F_3O_5Na$; calc.: 435.1395). Anal. calc. for $C_{21}H_{23}F_3O_5$ (412.40): C 61.16, H 5.62; found: C 61.28, H 5.91.

(2*S*)-*N*-Methoxy-2-(4-methoxybenzyloxy)-*N*-methylpropanamide ((–)-(*S*)-105)
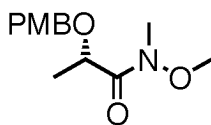
A 2 M solution of ^{i}PrMgCl in Et$_2$O (10.9 mL, 21.8 mmol) was added dropwise over 40 min to a vigorously stirred suspension of (MeO)MeNH·HCl (1.07 g, 10.9 mmol) and (–)-(*S*)-**102** (1.04 g, 4.37 mmol) in THF (13 mL) at –30 °C. The mixture was stirred for 1 h, and during that time, the temperature increased to –5 °C. A sat. aq. NH$_4$Cl solution (4 mL) was then added dropwise to the mixture. The solution was poured into a mixture of Et$_2$O/NH$_4$Cl (40 mL, 1:4) and the phases were separated. The aqueous phase was extracted with Et$_2$O (50 mL) and with CH$_2$Cl$_2$ (40 mL), and the combined organic fractions were dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 2:1 to 1:1) afforded 864 mg (78%) of (–)-(*S*)-**105** as a colorless oil.

R_f (hexane/EtOAc 1:1) 0.36. $[\alpha]_D^{25} = -78.3$ (c = 1.00, CHCl$_3$). IR (CHCl$_3$): 3478m (br.), 3003s, 2961s, 2938s, 2909s, 2869s, 2837s, 2641w, 2596w, 2549w, 2462w, 2061w, 2006w, 1888w, 1663s, 1612s, 1585s, 1512s, 1464s, 1442s, 1420s, 1391s, 1368s, 1321s, 1302s, 1172s, 1154s, 1105s, 1058s, 1035s, 994s, 937w, 913w, 894m, 860m, 845s, 825s. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.36 (d, J = 6.5, 3 H, CH$_3$); 3.20 (s, 3 H, NCH$_3$); 3.58 (s, 3 H, NOCH$_3$); 3.79 (s, 3 H, OCH$_3$); 4.38 (q, J = 6.5, 1 H, C*H*(CH$_3$)OCH$_2$C$_6$H$_4$OCH$_3$); 4.34 (d, J = 11.2, 1 H, CH$_3$OC$_6$H$_4$CH*H*O); 4.59 (d, J = 11.2, 1 H, CH$_3$OC$_6$H$_4$C*H*HO); 6.85 (d, J = 8.7, 2 H, C$_6$H$_4$); 7.28 (d, J = 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 173.54; 159.07, 129.75; 129.48; 113.62, 71.08, 70.79, 61.30, 55.25, 32.41, 18.07. ESI-MS: 529.1 ([2M + Na]$^+$), 292.1 ([M + K]$^+$), 276.2 ([M + Na]$^+$), 254.1 ([M + H]$^+$). Anal. calc. for C$_{13}$H$_{19}$NO$_4$ (253.30): C 61.64, H 7.56, N 5.53; found: C 61.86, H 7.40, N 5.31.

(4*S*)-4-[4-(Methoxybenzyl)oxy]-1-(triisopropylsilyl)penta-1-yn-3-one ((–)-(*S*)-106)
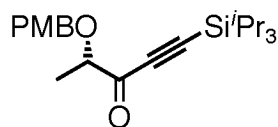
Method A

n-BuLi (0.45 mL of 1.6 M solution in hexane, 0.72 mmol) was added dropwise to a solution of (triisopropylsilyl)acetylene (162 µL, 0.72 mmol) in THF (1.1 mL) at 0 °C. After stirring for 15 min, the mixture was cooled to –78 °C and a solution of *Weinreb* amide (–)-(*S*)-**105** (122 mg, 0.48 mmol) in THF (12 mL) was added dropwise over 75 min. After stirring for 30 min at –78 °C, the mixture was placed in an ice bath and a sat. aq. NH₄Cl solution (0.6 mL) was added. After that, the mixture was partitioned with an Et₂O/NH₄Cl solution (20 mL, 1:1). The phases were separated, and the aqueous layer was extracted with Et₂O (20 mL, 2 x). The combined organic fractions were washed with sat. aq. NaCl solution (30 mL), dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO₂, hexane/CH₂Cl₂ 1:1) provided ketone (–)-(*S*)-**106** (153 mg, 96%) as a colorless oil.

Method B

n-BuLi (2.3 mL of 1.6 M solution in hexane, 3.7 mmol) was added dropwise over 30 min to a solution of (triisopropylsilyl)acetylene (0.83 mL, 3.7 mmol) in THF (5.5 mL) at 0 °C. After 15 min, MgBr₂·OEt₂ (957 mg, 3.7 mmol) was added in one portion. The resulting suspension was stirred vigorously for 1 h and then cooled to –78 °C. Then, *Weinreb* amide (–)-(*S*)-**105** (625 mg, 2.47 mmol) was added as a solution in THF (2.3 mL) over 10 min. The mixture was stirred at –78 °C and then allowed to warm to r.t. overnight (15 h). The mixture was cooled to 0 °C, and 300 µL of a sat. aq. NH₄Cl solution were added. After 5 min, the mixture was partitioned between Et₂O/NH₄Cl mixture (40 mL 1:1). The phases were separated, and the organic layer was extracted with Et₂O (3 x). The combined organic fractions were washed with sat. aq. NaCl solution, dried (MgSO₄), and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, hexane/EtOAc 10:1) affording (–)-(*S*)-**106** (687 mg, 74%) as a colorless oil.

R_f (hexane/CH₂Cl₂ 1:1) 0.28. $[\alpha]_D^{25} = -58.26$ (*c* = 1.09, CHCl₃). IR (CHCl₃): 3008*s*, 2944*s*, 2894*s*, 2867*s*, 2839*s*, 2761*w*, 2728*w*, 2719*w*, 2620*w*, 2596*w*, 2549*w*, 2145*s*,

2061w, 2007w, 1886w, 1676s, 1612s, 1586m, 1513s, 1464s, 1442s, 1422w, 1389m, 1384m, 1369s, 1319m, 1303s, 1180s, 1174s, 1083s, 1035s, 1019s, 997s, 976s, 935w, 919m, 906m, 882s, 846m. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.11 (s, 21 H, Si^{i}Pr$_3$); 1.43 (d, $J =$ 6.9, 3 H, CH$_3$); 3.80 (s, 3 H, OCH$_3$); 4.03 (q, $J =$ 6.9, 1 H, CH(CH$_3$)OCH$_2$C$_6$H$_4$OCH$_3$); 4.39 (d, $J =$ 11.2, 1 H, CH$_3$OC$_6$H$_4$CHHO); 4.66 (d, $J =$ 11.2, 1 H, CH$_3$OC$_6$H$_4$CHHO); 6.87 (d, $J =$ 8.7, 2 H, C$_6$H$_4$); 7.29 (d, $J =$ 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 189.10; 159.18; 129.49; 129.43; 113.70; 102.26; 99.3; 80.53; 71.69; 55.29; 18.57; 17.93; 11.09. HR-MALDI (DHB): 398.2191 (21, [MH + Na]$^+$, C$_{22}$H$_{34}$O$_3$SiNa; calc.: 398.2253); 397.2173 (100, [M + Na]$^+$, C$_{22}$H$_{33}$O$_3$SiNa; calc.: 397.2175). Anal. calc. for C$_{22}$H$_{34}$O$_3$Si (374.59): C 70.54, H 9.15; found: C 70.52, H 8.99.

(3R)-3-{(1S)-1-[(4-Methoxybenzyl)oxy]ethyl}-1-(triisopropylsilyl)-5-(trimethylsilyl)-penta-1,4-diyn-3-ol ((3R,1'S)-107)

(3S)-3-{(1S)-1-[(4-Methoxybenzyl)oxy]ethyl}-1-(triisopropylsilyl)-5-(trimethylsilyl)-penta-1,4-diyn-3-ol ((3S,1'S)-107)

(3R,1'S)-**107**   (3S,1'S)-**107**
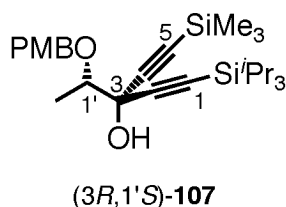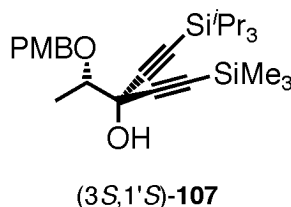
a   b

Method A (entry 1)

n-BuLi (0.28 mL of 1.6 M solution in hexane, 0.45 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (64 µL, 0.45 mmol) in Et$_2$O (0.4 mL) at 0 °C, and the mixture was stirred for 15 min. Then, the mixture was cooled to –78 °C and a solution of ketone (–)-(S)-**106** (112 mg, 0.30 mmol) in Et$_2$O (0.8 mL) was added dropwise and stirred for 1.5 h. After that, the mixture was placed in an ice bath and quenched by the dropwise addition of sat. aq. NH$_4$Cl solution (0.5 mL) and then extracted with Et$_2$O (2 x), dried (MgSO$_4$), and evaporated *in vacuo*. Purification of the residue by column chromatography (SiO$_2$, hexane/EtOAc 96:4) provided the desired alcohol **107** (85 mg, 60%) as a mixture of diastereoisomers (d.r. = 89:11, de = 78%).

The diastereomeric ratio of the mixture was determined by integrating the *OH* resonance.

Colorless oil. R_f (hexane/CH_2Cl_2 1:2) 0.38. IR ($CHCl_3$): 3534*m*, 3006*m*, 2960*s*, 2944*s*, 2892*s*, 2866*s*, 2840*m*, 2759*w*, 2726*w*, 2716*w*, 2614*w*, 2549*w*, 2174*w*, 2058*w*, 2007*w*, 1947*w*, 1885*w*, 1673*w*, 1612*s*, 1586*m*, 1514*s*, 1463*s*, 1442*m*, 1421*m*, 1409*m*, 1382*m*, 1375*m*, 1367*m*, 1352*m*, 1328*m*, 1302*s*, 1173*s*, 1077*s*, 1034*s*, 1019*s*, 996*s*, 972*s*, 919*m*, 882*s*, 862*s*, 845*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.17 (*s*, 9 H, $Si(CH_3)_3$); 1.08 (*s*, 21 H, Si^iPr_3); 1.38 (*d*, *J* = 6.2, 3 H, *CH₃*CHOCH$_2$C$_6$H$_4$OCH$_3$); 3.15 (*s*, 0.1 H, OH); 3.19 (*s*, 0.9 H, OH); 3.72 (*q*, *J* = 6.2, 1 H, CH$_3$*CH*OCH$_2$C$_6$H$_4$OCH$_3$); 3.81 (*s*, 3 H, OCH$_3$); 4.59 (*d*, *J* = 11.2, 1 H, C*H*HC$_6$H$_4$OCH$_3$); 4.67 (*d*, *J* = 11.2, 1 H, CH*H*C$_6$H$_4$OCH$_3$); 6.87 (*d*, *J* = 8.4, 2 H, C$_6$H$_4$); 7.29 (*d*, *J* = 8.4, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, $CDCl_3$, resonances of major diastereoisomer **a** only): 159.06; 130.11; 129.19; 113.66; 104.57; 103.80; 88.74; 86.40; 80.41; 71.52; 67.41; 55.30; 18.65; 15.35; 11.31; –0.21. HR-MALDI (DHB): 511.2461 (4, $[M + K]^+$, $C_{27}H_{44}NO_3Si_2K$; calc.: 511.2466); 495.2734 (100, $[M + Na]^+$, $C_{27}H_{44}NO_3Si_2Na$; calc.: 495.2727). Anal. calc. for $C_{27}H_{44}O_3Si_2$ (472.81): C 68.59, H 9.38; found: C 68.39, H 9.31.

Method B (entry 3)

n-BuLi (408 µL of 1.6 M solution in hexane, 0.65 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (92.1 µL, 0.65 mmol) in Et$_2$O (1 mL) at 0 °C, and the mixture was stirred for 30 min. A suspension of ZnBr$_2$ (154 mg, 0.69 mmol) in Et$_2$O (2 mL) was added at 0 °C, and the mixture was stirred for 20 min, then cooled to –78 °C. After that, a solution of ketone (–)-(*S*)-**106** (122 mg, 0.33 mmol) in Et$_2$O (0.8 mL) was added dropwise over 10 min to the mixture, which was allowed to warm to r.t. over 15 h. Aqueous workup as described above provided the crude alcohol. Purification by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 3:2) afforded **107** (50 mg. 32%) as a mixture of diastereoisomers (d.r. = 79:21, d.e. = 58%).

^{1}H-NMR (300 MHz, $CDCl_3$; **a**:**b** 79:21): 0.17 (*s*, 1.9 H, $Si(CH_3)_3$); 0.18 (*s*, 7.1 H, $Si(CH_3)_3$); 1.08 (*s*, 21 H, Si^iPr_3); 1.37 (*d*, *J* = 6.2, 0.6 H, *CH₃*CHOCH$_2$C$_6$H$_4$OCH$_3$); 1.38 (*d*, *J* = 6.2, 2.4 H, *CH₃*CHOCH$_2$C$_6$H$_4$OCH$_3$); 3.19 (*s*, 0.2 H, OH); 3.22 (*s*, 0.8 H, OH); 3.73 (*q*, *J* = 6.2, 1 H, CH$_3$*CH*OCH$_2$C$_6$H$_4$OCH$_3$); 3.81 (*s*, 3 H, OCH$_3$); 4.59 (*d*, *J* = 11.2, 1 H, C*H*HC$_6$H$_4$OCH$_3$); 4.67 (*d*, *J* = 11.2, 1 H, CH*H*C$_6$H$_4$OCH$_3$); 6.87 (*d*, *J* = 8.4, 2 H, C$_6$H$_4$); 7.29 (*d*, *J* = 8.4, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, $CDCl_3$; **a**:**b** 79:21): 159.05; 130.10 (a), 130.02 (b); 129.25 (b), 129.19 (a); 113.85 (b), 113.66 (a); 105.94 (b), 104.59

(a); 103.82 (a), 102.79 (b); 89.57(b), 88.74 (**a**); 86.38 (b), 85.75 (a); 80.41 (2x, a and b); 72.05 (b), 71.86 (a); 67.42 (2x, a and b); 55.29; 18.66; 15.44 (b), 15.35 (a); 11.30; –0.18 (b), –0.22 (a).

Method C (entry 4)

Approximately 1 g of $CeCl_3 \cdot H_2O$ was ground to a fine powder using a mortar and pestle and then dried overnight at 140 °C *in vacuo* (0.1 Torr) in Kugelrohr oven.

$CeCl_3$ (124 mg, 0.50 mmol) in THF (1.6 mL) was stirred at r.t. for 14 h under argon atmosphere and afterwards cooled to –78 °C. A solution of the lithium acetylide derived from *n*-BuLi (313 µL of a 1.6 M solution in hexane, 0.50 mmol) and (trimethylsilyl)acetylene (71 µL, 0.50 mmol) in THF (1 mL) was then added *via* cannula whereupon the white slurry became yellowish. After 30 min, a solution of ketone (–)-(*S*)-**106** (125 mg, 0.33 mmol) in THF (1.5 mL) was added. After 6 h, the temperature was raised to –20 °C and the mixture was quenched by dropwise addition of sat. aq. NH_4Cl solution (0.3 mL). Aqueous workup as described above provided **107** (130 mg, 82%) as a mixture of diastereoisomers (d.r. = 55:45, d.e. = 10%).

^{1}H-NMR (300 MHz, $CDCl_3$; **a:b** 55:45): 0.17 (*s*, 4.0 H, $Si(CH_3)_3$); 0.18 (*s*, 5.0 H, $Si(CH_3)_3$); 1.08 (*s*, 21 H, Si^iPr_3); 1.36 (*d*, *J* = 6.2, 1.3 H, $CH_3CHOCH_2C_6H_4OCH_3$); 1.38 (*d*, *J* = 6.2, 1.7 H, $CH_3CHOCH_2C_6H_4OCH_3$); 3.18 (*s*, 0.4 H, OH); 3.21 (*s*, 0.6 H, OH); 3.72 (*q*, *J* = 6.2, 0.4 H, $CH_3CHOCH_2C_6H_4OCH_3$); 3.73 (*q*, *J* = 6.2, 0.6 H, $CH_3CHOCH_2C_6H_4OCH_3$); 3.81 (*s*, 3 H, OCH_3); 4.57 – 4.70 (*m*, 2 H, $CH_2C_6H_4OCH_3$); 6.87 (*d*, *J* = 8.4, 2 H, C_6H_4); 7.29 (*d*, *J* = 8.4, 2 H, C_6H_4). ^{13}C-NMR (75 MHz, $CDCl_3$; **a:b** 55:45): 159.06; 130.09 (2x, a and b); 129.27 (b), 129.20 (a); 113.66 (2x, a and b); 105.89 (b), 104.54 (a); 103.78 (a), 102.72 (b); 89.61 (b), 88.75 (a); 86.41 (b), 85.76 (a); 80.38, 80.34; 72.04 (b), 71.85 (a); 67.40, 67.37; 55.30; 18.67; 15.44 (b), 15.35 (a); 11.30; –0.17 (b), –0.21 (a).

(3R)-3-[(1S)-1-(Hydroxyethyl]-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((3R,1'S)-108)

(3S)-3-[(1S)-1-(Hydroxyethyl]-1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((3S,1'S)-108)

(3R,1'S)-**108**   (3S,1'S)-**108**
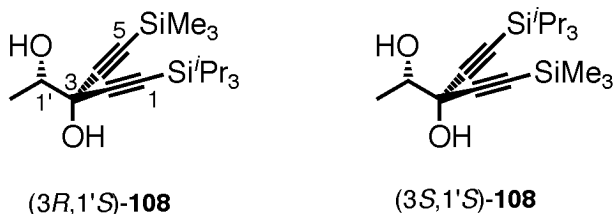
A solution of the diastereoisomeric mixture **107** (94 mg, 0.199 mmol, d.r. = 55:45) and CAN (218 mg, 0.40 mmol) in MeCN/H$_2$O 9:1 (1 mL) was stirred for 2 h, and then more CAN (55 mg, 0.10 mmol) was added to the reaction mixture. After 1.5 h, the mixture was washed with sat. aq. NaHCO$_3$ and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x). The combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 1:2) afforded a mixture of diastereoisomers (3R,1'S)-**108** and (3S,1'S)-**108** 43 mg (60%) as a colorless oil.

R_f (hexane/EtOAc 30:1) 0.21. IR (CHCl$_3$): 3582m, 3344w (br.), 2959s, 2945s, 2892m, 2866s, 2726w, 2169w, 1702w, 1601w, 1463m, 1384m, 1367m, 1362m, 1342m, 1308w, 1263m, 1251s, 1142m, 1094m, 1060s, 1014m, 997m, 970m, 919w, 896m, 883m, 859s, 845s. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.17 (s, 5.9 H, Si(CH$_3$)$_3$); 0.18 (s, 4.1 H, Si(CH$_3$)$_3$); 1.07 (s, 9.5 H, Si^{i}Pr$_3$); 1.08 (s, 11.5 H, Si^{i}Pr$_3$); 1.39 (d, J = 6.5, 3 H, CH$_3$); 2.31 (br. s, 1 H, OH); 3.03 (br. s, 1 H, OH); 3.87 (q, J = 6.5, 1 H, CH). ^{13}C-NMR (75 MHz, CDCl$_3$): 104.98, 101.79; 103.84, 102.92; 90.44, 86.83; 89.89, 87.24; 74.02; 68.39; 18.64; 17.63, 17.60; −0.19, −0.25. EI-MS: 319 (<10, [M − CH$_3$OH]$^+$), 308 (<10, [M − C$_3$H$_7$ − H]$^+$), 291 (12), 269 (11), 218 (14), 168 (11), 130 (21), 119 (26), 103 (18), 75 (24), 73 (28), 69 (100). Anal. calc. for C$_{19}$H$_{36}$O$_2$Si$_2$ (352.66): C 64.71, H 10.29; found: C 64.81, H 10.37.

(4*S*)-4-[(4-Methoxybenzyl)oxy]-1-(triethylsilyl)penta-1-yn-3-one ((–)-(*S*)-109)
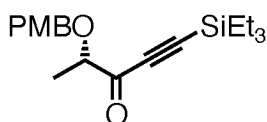
n-BuLi (7.12 mL of 1.6 M solution in hexane, 11.4 mmol) was added dropwise to a solution of (triethylsilyl)acetylene (2.04 mL, 11.4 mmol) in THF (18 mL) at 0 °C. After stirring for 30 min, the mixture was cooled to –78 °C and a solution of *Weinreb* amide (–)-(*S*)-**105** (1.92 mg, 7.6 mmol) in THF (12 mL) was added dropwise over 10 min. After stirring for 30 min, the mixture was allowed to warm to 0 °C and stirred for a further 30 min. Then, the mixture was quenched with a sat. aq. NH$_4$Cl solution (4 mL). The mixture was extracted with Et$_2$O (2 x), and the combined organic fractions were washed with sat. aq. NaCl solution, dried (MgSO$_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO$_2$, hexane/EtOAc 98:2) gave ketone (–)-(*S*)-**109** (2.21 g, 88%) as a colorless oil.

R_f (hexane/EtOAc 98:2) 0.17. $[\alpha]_D^{25}$= – 60.1 (*c* = 1.00, CHCl$_3$). IR (CHCl$_3$): 3008*m*, 2958*s*, 2936*m*, 2913*m*, 2876*m*, 2838*w*, 2736*w*, 2146*w*, 2058*w*, 1886*w*, 1675*s*, 1612*m*, 1586*w*, 1513*s*, 1465*m*, 1457*m*, 1442*w*, 1415*w*, 1393*w*, 1370*w*, 1318*w*, 1303*m*, 1180*m*, 1173*m*, 1083*s*, 1035*m*, 1018*m*, 1006*m*, 977*m*, 847*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.69 (*q*, *J* = 7.9, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 1.02 (*t*, *J* = 7.6, 9 H, Si(CH$_2$*CH$_3$*)$_3$); 1.42 (*d*, *J* = 6.9, 3 H, CH$_3$); 3.80 (*s*, 3 H, OCH$_3$); 4.03 (*q*, *J* = 6.9, 1 H, *CH*(CH$_3$)OCH$_2$C$_6$H$_4$OCH$_3$); 4.39 (*d*, *J* = 11.2, 1 H, CH$_3$OC$_6$H$_4$CH*H*O); 4.65 (*d*, *J* = 11.2, 1 H, CH$_3$OC$_6$H$_4$C*H*HO); 6.87 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 7.29 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 189.20; 159.20; 129.48 (one peak overlaps); 113.70; 101.41; 99.96; 80.45; 71.73; 55.30; 17.89; 7.43; 3.92. HR-MALDI (DHB): 355.1703 (49, [*M* + Na]$^+$, C$_{19}$H$_{28}$O$_3$SiNa; calc.: 355.1705). Anal. calc. for C$_{19}$H$_{28}$O$_3$Si (332.51): C 68.63, H 8.49; found: C 68.66, H 8.43.

(3*R*)-3-{(1*S*)-1-[(4-Methoxybenzyl)oxy]ethyl}-1-triethylsilyl-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((3*R*,1'*S*)-110)

(3*S*)-3-{(1*S*)-1-[(4-Methoxybenzyl)oxy]ethyl}-1-triethylsilyl-5-(trimethylsilyl)penta-1,4-diyn-3-ol ((3*S*,1'*S*)-110)

(3*R*,1'*S*)-**110**   (3*S*,1'*S*)-**110**
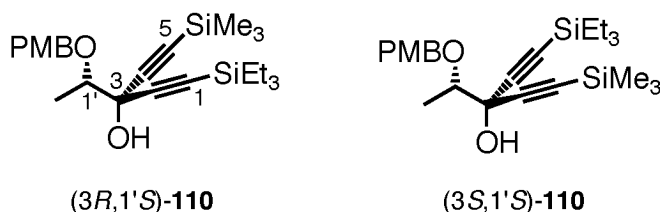
n-BuLi (8.25 mL of 1.6 M solution in hexane, 13.2 mmol) was added dropwise over 40 min to a solution of (trimethylsilyl)acetylene (1.85 mL, 13.2 mmol) in Et_2O (0.4 mL) at 0 °C and the mixture was stirred for 15 min. The mixture was cooled to −78 °C, and a solution of ketone (−)-(*S*)-**109** (2.20 g, 6.6 mmol) in Et_2O (12 mL) was added dropwise. After stirring for 1.5 h, the mixture was placed in an ice bath, quenched by the dropwise addition of sat. aq. NH_4Cl solution (0.5 mL), extracted with Et_2O (2 x), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, hexane/EtOAc 96:4) provided the desired alcohol (+)-(3*R*,1'*S*)-**110** with a small amount of diastereoisomer (3*S*,1'*S*)-**110** (2.26 g. 83%), (d.r. = 93:7, d.e. = 86%).

The diastereomeric ratio of the mixture was determined by integrating the *OH* resonance.

Colorless oil. R_f (hexane/EtOAc 4:1) 0.52. $[\alpha]_D^{25}$= + 1.4 (*c* = 0.96, $CHCl_3$). IR ($CHCl_3$): 3534*m*, 3007*s*, 2957*s*, 2936*s*, 2912*s*, 2875*s*, 2837*m*, 2734*w*, 2687*w*, 2641*w*, 2598*w*, 2547*w*, 2173*w*, 2057*w*, 2005*w*, 1949*w*, 1885*w*, 1612*s*, 1586*m*, 1513*s*, 1464*s*, 1457*s*, 1442*s*, 1414*s*, 1375*s*, 1352*s*, 1328*s*, 1302*s*, 1180*s*, 1173*s*, 1164*s*, 1123*s*, 1110*s*, 1079*s*, 1034*s*, 1018*s*, 972*s*, 860*s*, 842*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.18 (*s*, 9 H, Si(CH_3)_3); 0.62 (*q*, *J* = 7.5, 6 H, Si(C*H_2*CH_3)_3); 1.00 (*t*, *J* = 7.5, 6 H, Si(CH_2C*H_3*)_3); 1.36 (*d*, *J* = 6.2, 3 H, C*H_3*CHOCH_2C_6H_4OCH_3); 3.16 (*s*, 0.1 H, OH); 3.18 (*s*, 0.9 H, OH); 3.72 (*q*, *J* = 6.2, 1 H, CH_3C*H*OCH_2C_6H_4OCH_3); 3.81 (*s*, 3 H, OCH_3); 4.61 (*d*, *J* = 11.2, 1 H, C*H*HC_6H_4OCH_3); 4.68 (*d*, *J* = 11.2, 1 H, CH*H*C_6H_4OCH_3); 6.88 (*d*, *J* = 8.7, 2 H, C_6H_4); 7.29 (*d*, *J* = 8.7, 2 H, C_6H_4). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.12; 130.09; 129.29; 113.72; 103.86; 103.81; 88.78; 87.48; 80.30; 72.00; 67.38; 55.33; 15.32; 7.56; 4.40; −0.18. HR-MALDI (DHB): 453.2257 (100, [*M* + Na]$^+$, $C_{24}H_{38}O_3Si_2Na$; calc.: 453.2257). Anal. calc. for $C_{24}H_{38}O_3Si_2$ (430.73): C 66.92, H 8.89; found: C 66.78, H 8.76.

(3*R*)-3-{(1*S*)-1-[(4-Methoxybenzyl)oxy]ethyl}-3-methoxy-1-triethylsilyl-5-(trimethylsilyl)penta-1,4-diyne ((3*R*,1'*S*)-111)
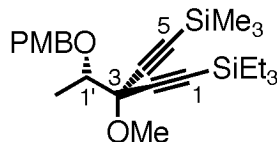
n-BuLi (3.4 mL of a 1.6 M solution in hexane, 5.49 mmol) was added dropwise to a solution of (+)-(3*R*,1'*S*)-**110** (2.06 g, 4.99 mmol) in THF (20 mL) cooled to –78 °C. After 20 min, iodomethane (2.5 mL, 40 mmol) was added. The temperature was slowly raised to –20 °C and then allowed to reach r.t. over 16 h. The mixture was poured into sat. aq. NH$_4$Cl solution (50 mL), extracted with Et$_2$O (2 x), washed with sat. aq. NaCl solution, dried (MgSO$_4$), and evaporated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/EtOAc 30:1) provided (–)-(3*R*,1'*S*)-**111** (1.97 g, 89%) as a pale yellow oil.

R_f (hexane/EtOAc 30:1) 0.21. $[\alpha]_D^{25} = -35.8$ (*c* = 0.96, CHCl$_3$). IR (CHCl$_3$): 3006*m*, 2956*s*, 2936*m*, 2911*m*, 2874*m*, 2837*w*, 2827*w*, 2167*w*, 1611*m*, 1585*w*, 1513*s*, 1464*m*, 1456*w*, 1441*w*, 1415*w*, 1372*w*, 1303*w*, 1250*s*, 1173*m*, 1143*w*, 1081*s*, 1035*m*, 1019*m*, 976*w*, 952*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.19 (*s*, 9 H, Si(CH$_3$)$_3$); 0.63 (*q*, *J* = 7.8, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 1.00 (*t*, *J* = 7.8, 9 H, Si(CH$_2$*CH$_3$)$_3$), 1.29 (*d*, *J* = 6.2, 3 H, *CH$_3$*CHOC$_6$H$_4$OCH$_3$); 3.51 (*s*, 3 H, OCH$_3$); 3,71 (*q*, *J* = 6.2, 1 H, CH$_3$*CH*OC$_6$H$_4$OCH$_3$); 3.80 (*s*, 3 H, *CH$_3$*OC$_6$H$_4$); 4.64 (*d*, *J* = 11.8, 1 H, CH$_3$OC$_6$H$_4$CH*H*O); 4.79 (*d*, *J* = 11.8, 1 H, CH$_3$OC$_6$H$_4$C*H*HO); 6.85 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$); 7.32 (*d*, *J* = 8.7, 2 H, C$_6$H$_4$). ^{13}C-NMR (75 MHz, CDCl$_3$): 159.06; 130.11; 129.19; 113.66; 104.57; 103.80; 88.74; 86.40; 80.41; 71.85; 67.41; 55.27; 18.65; 15.35; 11.31; –0.21. HR-MALDI (DHB): 483.2143 (4, [*M* + K]$^+$, C$_{25}$H$_{40}$O$_3$Si$_2$K; calc.: 483.2153); 467.2403 (100, [*M* + Na]$^+$, C$_{25}$H$_{40}$O$_3$Si$_2$Na; calc.: 467.2414). Anal. calc. for C$_{25}$H$_{40}$O$_3$Si$_2$ (444.76): C 67.5, H 9.06; found: C 67.37, H 9.09.

(3R)-3-[(1S)-1-Hydroxyethyl]-3-methoxy-1-triethylsilyl-5-(trimethylsilyl)penta-1,4-diyne ((–)-(3R,1'S)-112)
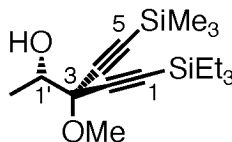
A solution of (–)-(3R,1'S)-**111** (1.97 g, 4.4 mmol) and CAN (5.3 g, 9.7 mmol) in MeCN/ H_2O 9:1 (27 mL) was stirred for 2 h. The mixture was poured into CH_2Cl_2 (20 mL) and washed with sat. aq. $NaHCO_3$. The aqueous phase was further extracted with CH_2Cl_2 (10 mL, 2 x), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, hexane/CH_2Cl_2 1:2) afforded 1.21 g (84%) of (–)-(3R,1'S)-**112** as a yellow oil.

R_f (hexane/CH_2Cl_2 1:2) 0.38. $[\alpha]_D^{25}$= – 11.7 (c = 1.00, $CHCl_3$). IR ($CHCl_3$): 3572w, 2988w, 2957s, 2936m, 2911m, 2875m, 2828w, 2734w, 2170w, 1463m, 1414w, 1398w, 1379w, 1361w, 1339w, 1270m, 1251s, 1151m, 1120w, 1077s, 1017m, 983m, 956m, 897w, 861s, 845s. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.18 (s, 9 H, Si(CH_3)$_3$); 0.63 (q, J = 7.8, 6 H, Si(CH_2CH$_3$)$_3$); 1.00 (t, J = 7.8, 9 H, Si(CH$_2$$CH_3$)$_3$); 1.36 ($d$, J = 6.2, 3 H, CH$_3$); 2.53 (d, J = 3.4, 1 H, OH); 3.51 (s, 3 H, OCH$_3$); 3.81 – 3.91 (m, 1 H, CH$_3$$CH$OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 100.94; 100.76; 91.40; 89.65; 75.48; 73.39; 53.27; 17.40; 7.54; 4.42; –0.18. EI-MS: 324 (<10, M^+), 279 (57, [M – C_2H_3O]$^+$), 266 (46), 252 (34), 248 (13), 237 (38), 220 (19), 207 (13), 191 (11), 151 (15), 148 (35), 147 (17), 134 (20), 133 (10), 127 (11), 121 (14), 120 (13), 119 (14), 117 (42), 115 (66), 107 (12), 97 (22), 89 (54). Anal. calc. for $C_{17}H_{32}O_2Si_2$ (324.61): C 62.90, H 9.94; found: C 63.11, H 9.85.

(3R)-3-Methoxy-3-(triethylsilyl)ethynyl-5-(trimethylsilyl)penta-1,4-yn-2-one ((–)-(R)-113)
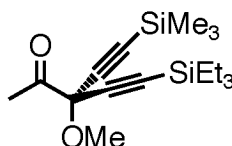
DMP (7.8 mL of a 15 wt% solution in CH_2Cl_2, 3.70 mmol) was added to a solution of (–)-(3R,1'S)-**112** (800 mg, 2.46 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After 10 min, the

mixture was allowed to warm to r.t. and stirred for 22 h. Then, MeOH (1 mL) was added and the solvent was evaporated *in vacuo*. The crude material was purified by column chromatography (SiO_2, hexane/CH_2Cl_2 1:1) leading to 756 mg (95%) of (–)-(*R*)-**113** as a colorless oil.

R_f (hexane/CH_2Cl_2 1:1) 0.47. $[\alpha]_D^{25} = -2.5$ ($c = 0.97$, $CHCl_3$). IR ($CHCl_3$): 2958s, 2935m, 2911m, 2875m, 2829w, 2734w, 2165w, 1740s, 1601w, 1463m, 1458w, 1437w, 1414w, 1379w, 1355w, 1263w, 1252m, 1176m, 1128m, 1092m, 1053m, 1018m, 1003m, 975m, 949m, 916m, 859s, 847s. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.19 (s, 9 H, $Si(CH_3)_3$); 0.63 (q, J = 7.8, 6 H, $Si(CH_2CH_3)_3$); 1.00 (t, J = 7.8, 9 H, $Si(CH_2CH_3)_3$); 2.41 (s, 3 H, CH_3); 3.52 (s, 3 H, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.55; 99.43; 98.22; 93.29; 91.34; 75.90; 53.33; 24.12; 7.48; 4.25; –0.36. HR-EI-MS: 322.1785 (44, M^+, $C_{17}H_{30}O_2Si_2$; calc.: 322.1784); 307.1575 (3, $[M - CH_3]^+$, $C_{18}H_{27}O_2Si_2$; calc.: 307.1550); 279.1628 (100, $[M - C_2H_3O]^+$, $C_{15}H_{27}O_1Si_2$; calc.: 279.1600). Anal. calc. for $C_{17}H_{30}O_2Si_2$ (322.59): C 63.30, H 9.37; found: C 63.46, H 9.20.

(3*R*)-3-Ethynyl-3-methoxy-1-triethylsilyl-5-(trimethylsilyl)penta-1,4-diyne ((+)-(*R*)-114)
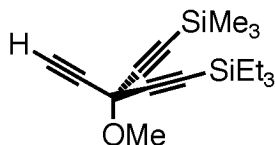
To a stirred solution of ^{i}Pr$_2$NH (58 µL, 0.44 mmol) in THF (0.5 mL) cooled to –78 °C, *n*-BuLi (275 µL of a 1.6 M solution in hexane, 0.44 mmol) was added. The mixture was stirred for 10 min at –78 °C and then for 30 min at r.t.. The mixture was again cooled to –78°C, and a solution of ketone (–)-(*R*)-**113** (130 mg, 0.40 mmol) in THF (0.5 mL) was added dropwise. After stirring for 1 h, diethylchlorophosphate (64 µL, 0.44 mmol) was added and the mixture allowed to warm up to r.t. over 3 h. This solution was added dropwise to a solution of LDA at –78 °C [prepared as described above from ^{i}Pr$_2$NH (119 µl, 0.91 mmol), *n*-BuLi (567 µL of 1.6 M solution in hexane, 0.91 mmol), and THF (1.0 mL)]. The resulting mixture was allowed to warm to r.t. over 3 h, quenched with a sat. aq. solution NH$_4$Cl (1.0 mL) at 0 °C, and extracted with Et$_2$O (20 mL, 2 x). The combined organic fractions were washed with sat. aq. NaCl solution, dried over MgSO$_4$, and

concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, hexane/CH$_2$Cl$_2$ 9:1) afforded 20 mg (16 %) of the desired product (+)-(R)-**114** as a colorless oil.

R_f (hexane/CH$_2$Cl$_2$ 1:1) 0.65. IR (CHCl$_3$): 3302m, 2961s, 2939s, 2917s, 2866m, 2844m, 2735w, 2183w, 2125w, 1733w, 1457m, 1406w, 1370w, 1123s, 1086s, 1050m, 1006m, 948m. ^{1}H-NMR (300 MHz, CDCl$_3$): 0.20 (s, 9 H, Si(CH$_3$)$_3$); 0.64 (q, J = 7.8, 6 H, Si(*CH$_2$*CH$_3$)$_3$); 1.01 (t, J = 7.8, 9 H, Si(CH$_2$*CH$_3$*)$_3$); 2.63 (s, 1 H, CH); 3.49 (s, 3 H, OCH$_3$). ^{13}C-NMR (75 MHz, CDCl$_3$): 100.42; 99.22; 89.21; 87.46; 79.21; 72.03; 60.76; 52.49; 7.45; 4.25; −0.38. HR-EI-MS: 289.1455 (23, [M − CH$_3$]$^+$, C$_{16}$H$_{25}$OSi$_2$; calc.: 289.1444); 279.1629 (12, [M − C≡CH]$^+$, C$_{15}$H$_{27}$OSi$_2$; calc.: 279.1600); 273.1537 (10, [M − OCH$_3$]$^+$, C$_{16}$H$_{25}$Si$_2$; calc.: 273.1495).

6. Appendix

6.1 Crystal Structure Data of 62b

Table 6.1: Crystal data and structure refinement for **62b** (solved by Prof. Dr. Volker Gramlich).

Identification code	**62b**	
Empirical formula	$C_{68}H_{96}O_4Si_4$	
Formula weight	1089.81	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.789(10) Å	α = 90 deg.
	b = 14.865(13) Å	β = 94.23(8) deg.
	c = 23.07(2) Å	γ = 90 deg.

113

Volume	3690(6) Å^3
Z	2
Density (calculated)	0.981 Mg/m^3
Absorption coefficient	1.045 mm^{-1}
F(000)	1184
Crystal size	1 x 1.04 x 1.03 mm
θ range for data collection	3.54 to 50.00 deg.
Index ranges	$-10 \leq h \leq 10, 0 \leq k \leq 14, 0 \leq l \leq 22$
Reflections collected	3795
Independent reflections	3795 [R(int) = 0.0000]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3795 / 0 / 343
Goodness-of-fit on F^2	1.084
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0615, wR2 = 0.1566
R indices (all data)	R1 = 0.0751, wR2 = 0.1692
Largest diff. peak and hole	0.279 and -0.187 e.A^{-3}

Table 6.2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **62b**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U(eq)
Si(29)	2014(1)	4186(1)	1146(1)	80(1)
Si(15)	-2421(1)	9867(1)	1123(1)	85(1)
O(25)	-2277(2)	2960(2)	1733(1)	66(1)
O(11)	-5871(2)	7656(2)	1698(1)	78(1)
C(5)	-2056(3)	3613(2)	1307(1)	54(1)
C(10)	-5044(3)	7523(2)	1254(1)	59(1)
C(6)	-2639(3)	4491(3)	1430(1)	58(1)
C(3)	-3168(3)	3056(2)	302(2)	61(1)
C(7)	-3152(3)	5197(3)	1465(1)	60(1)
C(8)	-3775(3)	6007(3)	1457(1)	62(1)
C(9)	-4338(3)	6691(3)	1404(1)	62(1)
C(13)	-4169(4)	8279(3)	1211(2)	64(1)
C(27)	-719(4)	3759(2)	1244(2)	64(1)
C(14)	-3466(4)	8894(3)	1179(2)	74(1)
C(28)	352(4)	3905(3)	1199(2)	77(1)
C(26)	-1723(4)	3153(3)	2300(2)	92(1)
C(12)	-6645(4)	8435(3)	1603(2)	112(2)
C(36)	2196(5)	5372(4)	1390(3)	125(2)
C(37)	1344(7)	5997(4)	1022(4)	186(3)
C(16)	-3303(5)	10861(3)	1371(2)	107(2)
C(19)	-1022(5)	9632(5)	1632(3)	149(2)
C(30)	2891(4)	3406(5)	1662(3)	135(2)
C(18)	-4506(6)	11017(4)	1004(3)	150(2)
C(34)	1832(10)	3473(9)	20(4)	318(8)

C(17)	-3519(7)	10810(4)	2017(3)	155(3)
C(38)	1951(8)	5492(6)	2035(4)	220(4)
C(33)	2388(5)	4055(5)	388(3)	150(2)
C(22)	-2087(8)	9981(4)	352(3)	155(2)
C(31)	2528(6)	2463(5)	1652(4)	215(4)
C(20)	-409(6)	8735(7)	1507(4)	208(4)
C(24)	-2561(11)	9438(9)	-63(3)	320(8)
C(32)	4292(4)	3580(5)	1718(3)	167(3)
C(23)	-1495(7)	10846(4)	189(3)	174(3)
C(35)	3631(5)	4466(5)	241(2)	144(2)
C(4)	-2662(3)	3275(2)	755(2)	59(1)
C(21)	-138(7)	10457(7)	1676(4)	261(5)
C(2)	-3763(3)	2817(2)	-222(2)	62(1)
C(1)	-4277(3)	2634(2)	-681(2)	61(1)

Table 6.3: Bond lengths [Å] and angles [deg] for **62b**.

Si(29)-C(33)	1.833(6)
Si(29)-C(28)	1.853(5)
Si(29)-C(36)	1.857(6)
Si(29)-C(30)	1.868(6)
Si(15)-C(14)	1.844(5)
Si(15)-C(22)	1.848(7)
Si(15)-C(16)	1.869(5)
Si(15)-C(19)	1.875(6)
O(25)-C(5)	1.415(4)
O(25)-C(26)	1.426(4)
O(11)-C(10)	1.419(4)
O(11)-C(12)	1.435(5)
C(5)-C(4)	1.476(5)
C(5)-C(27)	1.476(5)
C(5)-C(6)	1.485(5)
C(10)-C(13)	1.476(5)
C(10)-C(9)	1.481(5)
C(10)-C(1)#1	1.481(5)
C(6)-C(7)	1.193(5)
C(3)-C(4)	1.188(5)
C(3)-C(2)	1.373(6)
C(7)-C(8)	1.378(6)
C(8)-C(9)	1.186(5)
C(13)-C(14)	1.194(5)
C(27)-C(28)	1.187(5)
C(36)-C(37)	1.521(9)
C(36)-C(38)	1.540(9)
C(16)-C(18)	1.515(8)

C(16)-C(17)	1.528(7)
C(19)-C(20)	1.525(10)
C(19)-C(21)	1.552(9)
C(30)-C(31)	1.455(9)
C(30)-C(32)	1.530(7)
C(34)-C(33)	1.326(9)
C(33)-C(35)	1.534(7)
C(22)-C(24)	1.326(9)
C(22)-C(23)	1.496(8)
C(2)-C(1)	1.190(5)
C(1)-C(10)#1	1.481(5)
C(33)-Si(29)-C(28)	108.7(2)
C(33)-Si(29)-C(36)	111.3(3)
C(28)-Si(29)-C(36)	106.0(2)
C(33)-Si(29)-C(30)	113.9(3)
C(28)-Si(29)-C(30)	105.4(2)
C(36)-Si(29)-C(30)	111.0(3)
C(14)-Si(15)-C(22)	107.7(3)
C(14)-Si(15)-C(16)	105.7(2)
C(22)-Si(15)-C(16)	111.2(3)
C(14)-Si(15)-C(19)	106.1(2)
C(22)-Si(15)-C(19)	114.4(4)
C(16)-Si(15)-C(19)	111.1(3)
C(5)-O(25)-C(26)	114.8(3)
C(10)-O(11)-C(12)	113.1(3)
O(25)-C(5)-C(4)	106.2(3)
O(25)-C(5)-C(27)	112.7(3)
C(4)-C(5)-C(27)	109.9(3)
O(25)-C(5)-C(6)	111.9(3)
C(4)-C(5)-C(6)	107.3(3)
C(27)-C(5)-C(6)	108.7(3)
O(11)-C(10)-C(13)	112.4(3)
O(11)-C(10)-C(9)	106.7(3)
C(13)-C(10)-C(9)	109.3(3)
O(11)-C(10)-C(1)#1	111.7(3)
C(13)-C(10)-C(1)#1	109.6(3)
C(9)-C(10)-C(1)#1	106.8(3)
C(7)-C(6)-C(5)	172.7(3)
C(4)-C(3)-C(2)	179.0(4)
C(6)-C(7)-C(8)	175.2(4)
C(9)-C(8)-C(7)	174.7(4)
C(8)-C(9)-C(10)	172.4(4)
C(14)-C(13)-C(10)	179.5(3)
C(28)-C(27)-C(5)	177.9(4)
C(13)-C(14)-Si(15)	178.2(3)
C(27)-C(28)-Si(29)	177.2(4)
C(37)-C(36)-C(38)	109.2(6)
C(37)-C(36)-Si(29)	111.4(5)
C(38)-C(36)-Si(29)	112.4(5)
C(18)-C(16)-C(17)	111.5(5)

C(18)-C(16)-Si(15)	112.7(4)
C(17)-C(16)-Si(15)	112.2(4)
C(20)-C(19)-C(21)	115.5(7)
C(20)-C(19)-Si(15)	112.7(5)
C(21)-C(19)-Si(15)	110.9(5)
C(31)-C(30)-C(32)	115.3(6)
C(31)-C(30)-Si(29)	117.7(5)
C(32)-C(30)-Si(29)	113.5(4)
C(34)-C(33)-C(35)	118.6(6)
C(34)-C(33)-Si(29)	124.1(6)
C(35)-C(33)-Si(29)	115.3(4)
C(24)-C(22)-C(23)	119.3(7)
C(24)-C(22)-Si(15)	123.2(6)
C(23)-C(22)-Si(15)	116.0(5)
C(3)-C(4)-C(5)	175.9(4)
C(1)-C(2)-C(3)	178.3(4)
C(2)-C(1)-C(10)#1	175.5(4)

Symmetry transformations used to generate equivalent atoms:
#1 -x-1,-y+1,-z.

Table 6.4: Anisotropic displacement parameters (Å^2 x 10^3) for **62b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^2U_{11} + ... + 2hk \cdot ab \cdot U_{12}]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Si(29)	57(1)	99(1)	85(1)	2(1)	4(1)	-9(1)
Si(15)	86(1)	74(1)	93(1)	5(1)	-6(1)	-15(1)
O(25)	79(2)	56(1)	59(2)	5(1)	-15(1)	-10(1)
O(11)	79(2)	88(2)	65(2)	-8(1)	1(1)	10(2)
C(5)	53(2)	52(2)	55(2)	1(2)	-13(2)	-3(2)
C(10)	69(2)	52(2)	54(2)	-4(2)	-11(2)	1(2)
C(6)	55(2)	57(3)	59(2)	0(2)	-12(2)	-5(2)
C(3)	66(2)	54(2)	61(2)	0(2)	-11(2)	-3(2)
C(7)	61(2)	58(3)	59(2)	3(2)	-13(2)	-5(2)
C(8)	70(2)	55(3)	59(2)	-1(2)	-11(2)	-4(2)
C(9)	72(2)	56(2)	56(2)	-3(2)	-15(2)	-2(2)
C(13)	73(3)	53(2)	64(2)	-7(2)	-17(2)	6(2)
C(27)	56(3)	65(2)	71(2)	-3(2)	-8(2)	-2(2)
C(14)	80(3)	60(3)	78(3)	-3(2)	-16(2)	3(2)
C(28)	63(3)	83(3)	84(3)	-4(2)	-5(2)	-1(2)
C(26)	129(4)	85(3)	58(2)	7(2)	-23(2)	-11(3)
C(12)	102(4)	116(4)	120(4)	-18(3)	13(3)	35(3)
C(36)	82(3)	115(4)	181(6)	-28(4)	23(4)	-29(3)
C(37)	147(6)	105(5)	311(10)	13(6)	60(6)	-2(4)
C(16)	142(5)	61(3)	119(4)	-1(3)	15(3)	-22(3)

C(19)	90(4) 186(6) 165(6) 31(5) -25(4) -42(4)
C(30)	72(3) 168(6) 164(5) 49(4) -5(3) 2(3)
C(18)	151(6) 104(4) 195(6) 22(4) 20(5) 33(4)
C(34)	305(13) 485(20) 178(8) -158(11) 109(8) -213(14)
C(17)	243(8) 102(4) 127(5) -15(3) 49(5) -7(4)
C(38)	217(8) 255(10) 193(8) -130(7) 35(7) -51(7)
C(33)	109(4) 231(8) 110(4) -44(5) 19(3) -41(5)
C(22)	208(7) 127(5) 134(5) 4(4) 47(5) -28(5)
C(31)	131(6) 158(7) 353(12) 125(7) -1(6) 11(5)
C(20)	109(5) 280(11) 232(8) 52(8) -3(5) 73(6)
C(24)	400(17) 459(18) 106(6) -58(8) 39(8) -260(15)
C(32)	66(3) 232(8) 197(6) 49(6) -27(4) 7(4)
C(23)	201(7) 142(6) 189(7) 61(5) 84(6) 25(5)
C(35)	108(4) 204(7) 125(4) 16(4) 42(3) 1(4)
C(4)	57(2) 56(2) 61(2) 2(2) -6(2) 1(2)
C(21)	164(7) 340(13) 263(10) 81(9)-90(7) -158(8)
C(2)	68(2) 56(2) 60(3) -4(2) -9(2) 0(2)
C(1)	66(2) 54(2) 62(2) -2(2) -10(2) 3(2)

Table 6.5: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for **62b**.

Atom	x	y	z	U(eq)
H(26A)	-1917(4)	2679(3)	2562(2)	138
H(26B)	-2040(4)	3713(3)	2434(2)	138
H(26C)	-838(4)	3195(3)	2286(2)	138
H(12A)	-7182(4)	8491(3)	1915(2)	168
H(12B)	-7137(4)	8372(3)	1241(2)	168
H(12C)	-6133(4)	8961(3)	1589(2)	168
H(36A)	3056(5)	5553(4)	1343(3)	151
H(37A)	1494(7)	5925(4)	620(4)	279
H(37B)	1508(7)	6609(4)	1137(4)	279
H(37C)	494(7)	5853(4)	1077(4)	279
H(16A)	-2780(5)	11390(3)	1320(2)	128
H(19A)	-1337(5)	9568(5)	2017(3)	178
H(30A)	2636(4)	3606(5)	2040(3)	162
H(18A)	-4340(6)	11046(4)	601(3)	224
H(18B)	-4871(6)	11574(4)	1117(3)	224
H(18C)	-5071(6)	10532(4)	1062(3)	224
H(34A)	1070(10)	3273(9)	167(4)	477
H(34B)	2368(10)	2966(9)	-25(4)	477
H(34C)	1656(10)	3758(9)	-351(4)	477
H(17A)	-2741(7)	10710(4)	2237(3)	233
H(17B)	-4075(7)	10323(4)	2082(3)	233
H(17C)	-3876(7)	11365(4)	2137(3)	233

H(38A)	2486(8)	5099(6)	2269(4)	331
H(38B)	1100(8)	5348(6)	2089(4)	331
H(38C)	2114(8)	6104(6)	2149(4)	331
H(33A)	1888(5)	4570(5)	246(3)	180
H(22A)	-1296(8)	9655(4)	402(3)	185
H(31A)	1638(6)	2419(5)	1616(4)	322
H(31B)	2844(6)	2177(5)	2005(4)	322
H(31C)	2863(6)	2170(5)	1327(4)	322
H(20A)	-1024(6)	8268(7)	1487(4)	311
H(20B)	218(6)	8603(7)	1812(4)	311
H(20C)	-34(6)	8771(7)	1143(4)	311
H(24A)	-2904(11)	8915(9)	109(3)	481
H(24B)	-1919(11)	9259(9)	-306(3)	481
H(24C)	-3204(11)	9748(9)	-294(3)	481
H(32A)	4443(4)	4217(5)	1721(3)	251
H(32B)	4666(4)	3313(5)	1394(3)	251
H(32C)	4648(4)	3321(5)	2073(3)	251
H(23A)	-1199(7)	11162(4)	535(3)	261
H(23B)	-2096(7)	11210(4)	-30(3)	261
H(23C)	-811(7)	10721(4)	-42(3)	261
H(35A)	3923(5)	4872(5)	545(2)	216
H(35B)	3518(5)	4787(5)	-120(2)	216
H(35C)	4230(5)	3995(5)	206(2)	216
H(21A)	-604(7)	10988(7)	1755(4)	391
H(21B)	243(7)	10531(7)	1316(4)	391
H(21C)	495(7)	10363(7)	1985(4)	391

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