First asymmetric synthesis of a differentially silyl-protected tris(alkynyl)methyl methyl ether†

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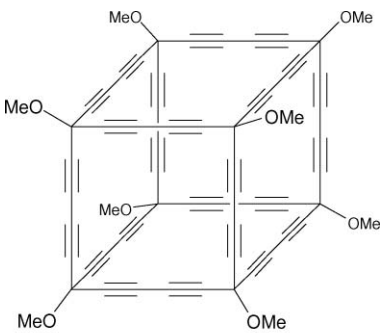
For an improved synthesis of the recently described expanded octamethoxycubane with a central C_{56} core, formally obtained by inserting buta-1,3-diynediyl moieties into all C(sp^3)–C(sp^3) bonds of octamethoxycubane, the preparation of the optically pure methyl ether of a differentially silyl-protected trispropargylic alcohol was required. The key step of the preparation involved a diastereoselective addition of a lithium acetylide to an optically active alkynyl ketone under *Cram* chelation control.

Since the early 1990s, we have pursued the geometrically defined expansion of molecules by insertion of buta-1,3-diynediyl fragments into all C–C single bonds of polyacetylenes, arenes, annulenes, radialenes or dendralenes, thereby generating new one- and two-dimensional carbon-rich chromophores with enhanced optoelectronic properties.[1] The application of this concept to three-dimensional structures recently led to the synthesis of the first expanded cubane **1**.[2,3] However, passing *via* the sequential construction of corners, edges and faces, an overall yield of **1** of only 0.2% was obtained. The main drawback of this first synthesis, which employed a racemic corner building block as starting material, was the formation of undesired as well as inseparable stereoisomers at the stage of the various intermediates. By starting from optically pure corner modules, the formation and low-yielding transformations of mixtures of stereoisomers can be largely avoided and the overall yield of **1** improved. This should provide sufficient material for desirable investigations such as the experimental determination of the heat of formation of the highly strained carbon cage.[2,3] Here, we report the stereoselective synthesis of the differentially silyl-protected tris(alkynyl)methyl methyl ether (*R*)-**2**, the first optically active trispropargylic alcohol derivative.[4]



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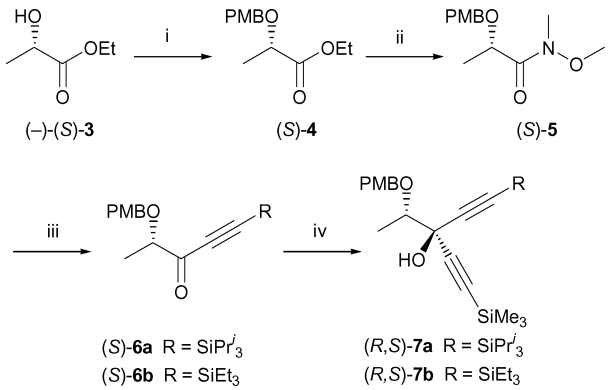
We envisaged the asymmetric synthesis to begin with enantiomerically pure ethyl lactate (−)-(*S*)-**3** (Scheme 1). Our strategy hinged on the presence of an α-oxygen donor atom that was expected to assist, by chelation, the diastereoselective addition of a metal acetylide to an alkynyl ketone. According to *Cram's* cyclic model, the nucleophile would be expected to attack from the sterically less hindered side, thus leading to the predominant formation of the *anti*-diastereoisomer (1,2-asymmetric induction).[5]



Scheme 1 Synthesis of the optically active bispropargylic alcohols (*R*,*S*)-**7a**/**b**. *Reagents and conditions*: (i) PMB-OC(NH)CCl_3, TfOH (cat.), cyclohexane–CH_2Cl_2 1 : 1, 0 → 20 °C; 86%; (ii) Pr^{i}MgCl, Me(MeO)NH·HCl, THF, −20 °C; 78%; (iii) RC≡CLi, THF, −78 °C; 96% [(*S*)-**6a**], 89% [(*S*)-**6b**]; (iv) $Me_3SiC{\equiv}CLi$, Et_2O, −78 °C; 83% (**7b**); for conditions and yields in the conversion (*S*)-**6a** → (*S*)-**7a**, see Table 1. PMB = *p*-methoxybenzyl, Tf = CF_3SO_2, THF = tetrahydrofuran.

We chose the *p*-methoxybenzyl (PMB) residue as a protecting group for the hydroxy function in (−)-(*S*)-**3**, since benzyl ethers are frequently employed in chelation-controlled nucleophilic additions[6] and since this group can be oxidatively removed without affecting the alkyne moieties. In order to avoid epimerization, the introduction of the PMB group under formation of (*S*)-**4** was achieved by employing a non-basic procedure[7] using catalytic TfOH and *p*-methoxybenzyl 2,2,2-trichloroacetimidate.[8] The *Weinreb* amide (*S*)-**5** was prepared following a protocol reported by Paterson *et al.*[9] and subsequently transformed into ketone (*S*)-**6a** by reaction with lithium (triisopropylsilyl)acetylide.

The subsequent chelation-controlled addition of (trimethylsilyl)acetylide was investigated under a variety of conditions summarized in Table 1. The lithium acetylide reacted with good diastereoselectivity (diastereoisomeric excess, de = 82%) but gave a moderate yield (64%) only (entry 1). The *Grignard* reagent (entry 2) was prepared by transmetallation of the lithium acetylide with $MgBr_2{\cdot}OEt_2$. Addition did not occur at −78 °C and therefore the temperature was raised slowly to 20 °C. The products were

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Table 1 Diastereoselective addition of acetylide nucleophiles ($Me_3SiC{\equiv}CM$) to ketone (*S*)-**6a** providing alcohols (*R*,*S*)-**7a** and (*S*,*S*)-**7a**

Entry	M	Conditions	Total yield (%)	dr (*R*,*S*)-**7a** : (*S*,*S*)-**7a** (de) ^{1}H NMR[a]	dr (de) GC[b]
1	Li	−78 °C, 1.5 h	64	91 : 9 (82%)	91 : 9 (82%)
2	MgBr	−78 → 20 °C, 24 h	76	83 : 17 (66%)	86 : 14 (72%)
3	$CeCl_2/TiCl_4$	−78 °C, 30 min	65	51 : 49 (2%)	50 : 50 (0%)

[a] Determined by integrating the HO resonances (δ = 3.15 and 3.19 in $CDCl_3$) in the ^{1}H NMR spectrum. [b] Determined by GC analysis (Column: WCOT Fused Silica, CP-Sil 8CB, 30 m × 0.32 mm; Detector: FID; Isotherm: 210 °C; Carrier gas: Helium).

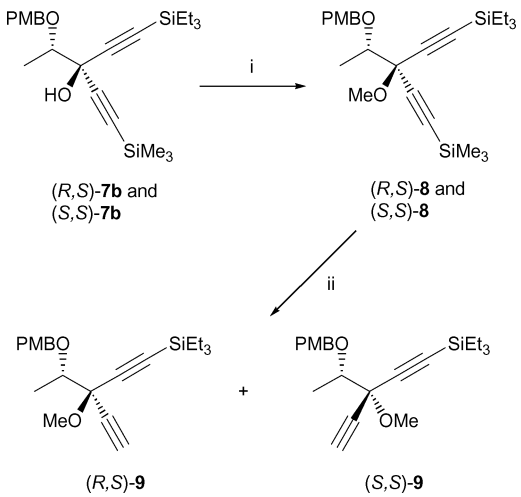
obtained in good yield (76%) but the diastereoselectivity was lower than in the previous case. The pre-chelation of ketone (*S*)-**6a** with $TiCl_4$, followed by the addition of Ce(III) (trimethylsilyl)acetylide, did not improve the yield and, moreover, the diastereoselectivity was lost (entry 3).[10] Extremely high reactivity was observed and this may account for the lack of diastereoselection. In all cases, the major diastereoisomer (*R*,*S*)-**7a**, presumed to arise from chelation control, was not separable from the minor diastereoisomer (*S*,*S*)-**7a**. The diastereoisomeric ratio (dr) was determined by integrating the HO resonances [δ = 3.19 (*R*,*S*) and 3.15 (*S*,*S*)] in the ^{1}H NMR spectrum in $CDCl_3$. Separation of the diastereoisomers by analytical gas chromatography (GC) supported the ^{1}H NMR results.

Within the context of the synthesis of the expanded cubane **1**, the yield (64%) together with the optical purity (de 82%) of (*R*,*S*)-**7a** obtained in entry 1 were not very satisfactory. Therefore, we changed from the larger triisopropylsilyl to the smaller triethylsilyl protecting group. Chelation-controlled addition of lithium (triethylsilyl)acetylide to *Weinreb* amide (*S*)-**5**, as described above, gave ketone (*S*)-**6b** in high yield (Scheme 1). The following addition of lithium (trimethylsilyl)acetylide in Et_2O at −78 °C finally provided the diastereoisomeric mixture (*R*,*S*)-**7b**/(*S*,*S*)-**7b** in a total yield of 83%. Gratifyingly, the diastereoselectivity had improved to dr 95 : 5 (de 90%), as determined by integrating the HO resonances [δ = 5.13 (*R*,*S*) and 5.16 (*S*,*S*)] in the ^{1}H NMR spectrum in $(CD_3)_2CO$, with (*R*,*S*)-**7b** being the major product as predicted by *Cram's* cyclic model.

Methylation of (*R*,*S*)-**7b** and (*S*,*S*)-**7b** by deprotonation at −78 °C with *n*-BuLi, followed by addition of an excess of iodomethane, led to the stable methyl ethers (*R*,*S*)-**8** and (*S*,*S*)-**8** (Scheme 2). All attempts to separate the diastereoisomeric mixture of (*R*,*S*)-**7b**/(*S*,*S*)-**7b** or (*R*,*S*)-**8**/(*S*,*S*)-**8** by either column chromatography, GC or HPLC were unsuccessful.

The subsequent selective deprotection of the trimethylsilylalkyne unit by stirring (*R*,*S*)-**8** and (*S*,*S*)-**8** for about 1 h in MeOH–THF (1 : 1) containing a few drops of 1 M NaOH afforded (*R*,*S*)-**9** and (*S*,*S*)-**9** in very good yield (89%). Gratifyingly, separation by preparative HPLC ('Hibar® 250–25') of the diastereoisomeric mixture was possible at this stage. Both diastereoisomers were obtained in pure form and the major isomer (*R*,*S*)-**9** was used for the completion of the synthesis.

Indeed, treating the semi-protected bispropargyl methyl ether (*R*,*S*)-**9** with NaHMDS and trimethylchlorosilane in THF at −78 °C furnished the differentially protected bispropargyl methyl ether (*R*,*S*)-**8** as a single diastereoisomer (Scheme 3). Subsequently, the PMB protecting group was removed by oxidation using 2.2 equivalents of CAN in $MeCN/H_2O$ 9:1, providing alcohol (*R*,*S*)-**10** in 90% yield after purification by column chromatography (SiO_2; hexane/CH_2Cl_2 1:2). Alcohol (*R*,*S*)-**10** was readily oxidized

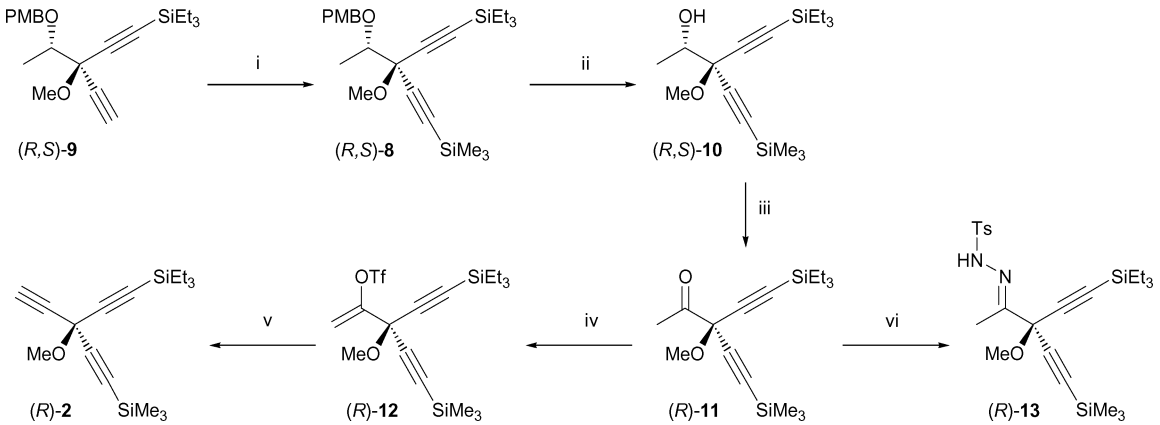


Scheme 2 Synthesis of the optically active mono-protected bispropargyl methyl ether (*R*,*S*)-**9**. *Reagents and conditions*: (i) *n*-BuLi, THF, −78 °C, then MeI, −78 → 20 °C; 91%; (ii) 1 M NaOH, MeOH–THF 1 : 1, 20 °C, 89%.

to the corresponding ketone (*R*)-**11** using the mild *Dess-Martin* periodinane (DMP) reagent.[11] Finally, the generation of the targeted tris(alkynyl)methyl methyl ether (*R*)-**2** was accomplished in two steps, comprising (i) the preparation of an enol triflate and (ii) elimination of the leaving group from the latter by a strong, non-nucleophilic base. Trapping of the enolate of (*R*)-**11** with a triflating agent such as *N*-(5-chloro-2-pyridyl)triflimide (*Comins* reagent)[12] afforded enol triflate (*R*)-**12**. Subsequent elimination with LDA provided (*R*)-**2** in 37% yield (from (*R*)-**11**).

An unambiguous assignment of the configuration of the induced stereogenic center in **7b** was achieved by means of converting ketone (*R*)-**11** into the corresponding tosylhydrazone (*R*)-**13**. Upon evaporation of a hexane solution, crystals suitable for X-ray analysis were obtained.‡ The crystal structure (Fig. 1) confirms the absolute configuration of the major diastereoisomer of **7b** to be (*R*,*S*), in accordance with the *Cram* chelate model. The unit cell contains six symmetrically independent molecules. The silyl groups are heavily disordered. Three dimers are formed by pairs of N(8)–H···O(5) H-bonds (N···O distance 2.87 to 2.98 Å), with a *gauche* orientation of the phenyl ring and the N–N bond [dihedral angle N(7)–N(8)–S(1)–C(26) = 57 to 67°]. All dimers show a *pseudo*-centre of symmetry when ignoring the different silyl substituents. Each dimer combines two molecules with the C(10)–N(7) bond eclipsed to C(9)–C(17) (dihedral angle = 4 to 10°) or to C(9)–C(12) (dihedral angle = −5 to −2°), respectively.

In summary, we accomplished the first synthesis of an optically pure tripropargylic alcohol derivative, (*R*)-**2**, by a stereoselective,



Scheme 3 Synthesis of the optically active tris(alkynyl)methyl methyl ether (*R*)-**2**. *Reagents and conditions*: (i) NaHMDS, THF, −78 °C, then Me_3SiCl, −78 °C; 86%; (ii) CAN, MeCN–H_2O 9 : 1, 20 °C; 90%; (iii) DMP, CH_2Cl_2, 20 °C; 96%; (iv) NaHMDS, THF, −78 °C, then *Comins* reagent, −78 → −40 °C; 45%; (v) LDA, THF, −78 → −40 °C; 82%; (vi) *p*-$TsNHNH_2$, EtOH, 20 °C; 95%. Ts = toluenesulfonyl, CAN = cerium ammonium nitrate, DMP = *Dess–Martin* periodinane, NaHMDS = sodium hexamethyldisilazane, LDA = lithium diisopropylamide.

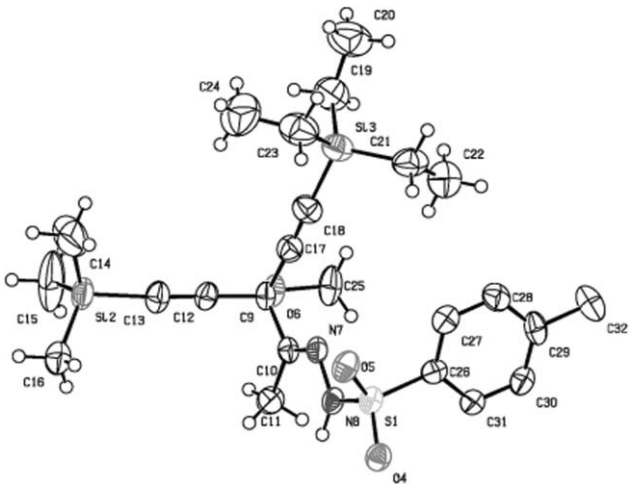


Fig. 1 ORTEP plot of (*R*)-**13**, showing one of the six independent molecules contained in the unit cell. Arbitrary numbering. Atomic displacement parameters obtained at 172 K are drawn at the 50% probability level.

11-step synthesis involving preparative HPLC separation. The other enantiomer, (*S*)-**2** is readily prepared in the same way, starting from (+)-lactate. We are now applying the optically active corner modules to an improved synthesis of expanded cubane **1**, providing sufficient material for a detailed investigation of the physical properties of this interesting cage compound.

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Notes and references

‡ X-Ray data for (*R*)-**13**: crystal data at 172 K for ($C_{24}H_{38}N_2O_3SSi_2$) (M_r = 490.81): triclinic, space group *P*1, Z = 6, D_c = 1.095 g cm^{-3}, a = 11.2537(2), b = 13.9426(2), c = 28.9064(5) Å, α = 83.0511(6), β = 88.3274(5), γ = 82.8675(9)°, V = 4466.96(13) Å^3. Bruker-Nonius Kappa-CCD diffractometer, Mo-Kα radiation, λ = 0.7107 Å. Number of reflections measured = 24 791. The structure was solved by direct methods (SIR97)[13] and refined by full-matrix least-squares analysis (SHELXL-97),[14] using an isotropic extinction correction. Final $R(F)$ = 0.0724, w$R(F^2)$ = 0.1961 for 1727 parameters and 22370 reflections with $I > 2\sigma(I)$ and 0.998 < θ < 25.028° (corresponding *R*-values based on all 24 791 reflections are 0.0827 and 0.2102 respectively). CCDC reference number 275886. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601380e

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