Chiral Molecules

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"Hexacarboxytrindanes": Benzene Rings with Homotopic Faces as Scaffolds for the Construction of D_3 Chiral Architectures**

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The advantages offered by high-symmetry chiral molecules are largely recognized in asymmetric synthesis[1] and can be readily applied in several other fields (e.g., material science, liquid crystal technology, and nanoscience). For example, in asymmetric synthesis high symmetry can enhance chiral recognition because of the reduction in the number of the possible diastereomorphic transition states, the equivalence of the functionalities, and the improvement of the ratio between the functional groups and the chiral framework.[2] Other advantages are offered by the opportunities for metal multi-coordination or high metal loading, the simplification of the spectral features, high crystallinity, and so forth. These features can benefit the design of highly efficient catalysts.

Although C_2-symmetrically chiral molecules, exemplified by binaphthol and its derivatives,[3] are quite popular, and chiral structures that possess C_3 symmetry do not attract a lot of attention but are nevertheless numerous,[4] chiral compounds with D_3 or higher symmetry are less common. Within the field of organic chemistry, the following classes of D_3 chiral structures have been reported: perhydrotriphenylenes,[5] trishomocubanes,[6] cyclotriveratrylenes,[7] macrocyclic alkanes, polyethers and polyesters with three groups of strategically positioned substituents,[8] and fullerenes.[9] Other high-symmetry chiral molecules are represented by benzene rings joined (through at least three bonds) with six homotopic centers.[10] The symmetry of these molecules is C_6 or D_6 (from dynamic averaging).

We present herein the first examples of D_3 benzene rings with six directly bound homotopic groups. The homotopicity is attained exactly because of the proximity and the reciprocal steric interaction of the groups. The common structure is that

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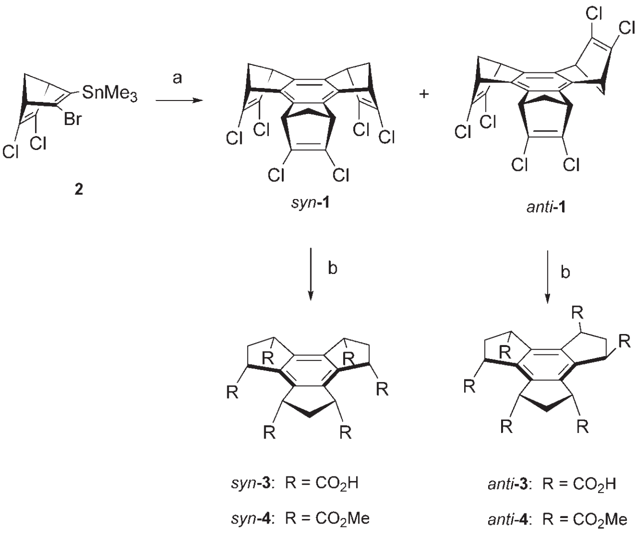
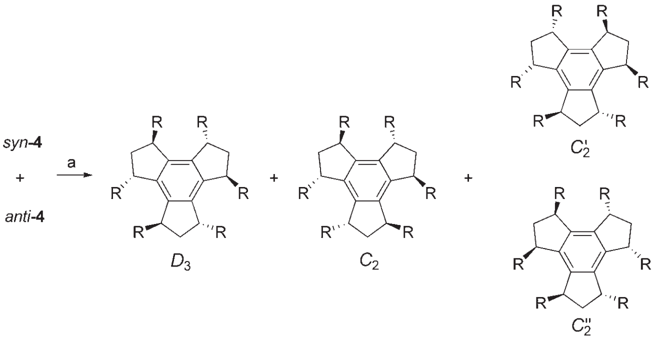
of 2,3,4,5,6,7,8,9-octahydro-1*H*-trindene-1,3,4,6,7,9-hexacarboxylic acid or ester (“hexacarboxytrindane”), which also, at variance from other D_3 molecules, is functionalized and thus amenable to further synthetic elaborations.

The access to these high-symmetry chiral molecules is described in Scheme 1 and Table 1 and originates from the recently synthesized cyclotrimers *syn*-**1** and *anti*-**1**, which are functionalized with three dichlorovinylene moieties on the edge.[11] These substrates could be obtained on multigram scales by cyclotrimerization of bromotrimethylstannylnorbornadiene (**2**) in the presence of copper(I) 2-thiophenecarboxylate (CuTC; Scheme 1). The oxidative cleavage of the three vinyl bonds of a mixture of *syn*-**1** and *anti*-**1** was carried out using $RuCl_3{\cdot}3\,H_2O/NaIO_4$,[12] thus leading to the quantitative and stereospecific formation of two isomeric trindane molecules *syn*-**3** and *anti*-**3**, in which the sets of the carboxylic groups reflect the same C_{3v} and C_s symmetries of the starting materials.



Scheme 1. Reagents and conditions: a) CuTC, NMP, −15 °C, 2 h, (>90 %). b) 1. $RuCl_3{\cdot}3\,H_2O/NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C, 3 h, (**3**: 99 %); 2. O_3/MeOH, RT, 1 h, (**4**: >95 %); 3. **3**, PTSA, MeOH, reflux, 3 days (**4**: 10 %). NMP = *N*-methylpyrrolidone, PTSA = *para*-toluenesulfonic acid.

Table 1: Epimerization, transesterification, and cleavage reactions



R	D_3	C_2	C_2''	D_3:C_2	Yield [%]
CO_2Me	D_3-(*R*,*S*)-**4**	C_2-**4**		1:2.1	70[a]
CO_2*i*Pr	D_3-(*R*,*S*)-**5**	C_2-**5**		1:1.2	60[a]
CO_2(−)ment	D_3-(*S*)-**6**		C_2''-**6** or C_2'-**6**	3:1	45[b]
CO_2H[c]	D_3-(*S*)-**3**			–	90
CO_2Cl[d]	D_3-(*S*)-**7**			–	>90
CO_2Me[e]	D_3-(*S*)-**4**			–	>90

[a] Yield determined spectroscopically. [b] Yield after flash-chromatographic purification. [c] Formed from CO_2(−)ment under conditions (b). [d] Formed from CO_2H under conditions (c). [e] Formed from CO_2Cl under conditions (d). Reagents and conditions: a) **4**: MeOLi, THF; **5**: *i*PrOLi, THF; **6**: (−)mentOLi, THF; b) Me_3SiI, CCl_4; c) $(COCl)_2$/DMF, CH_2Cl_2; d) MeOH. DMF = dimethylformamide, ment = menthyl.

The hexamethyl esters *syn*-**4** and *anti*-**4** can be obtained by two different synthetic approaches: oxidation by $RuCl_3$ to the corresponding acids *syn*-**3** and *anti*-**3**,[12] followed by esterification or direct oxidation of *syn*-**1** and *anti*-**1** by using ozone in methanol.[13] The first approach gives the hexaacids quantitatively, but Fischer esterification affords the esters in poor yield. As the second approach gives *syn*-**4** and *anti*-**4** directly in quantitative yield, we did not investigate any alternative to Fischer esterification.

The two base sensitive positions in *syn*-**4** and *anti*-**4**, that is, the benzylic proton and the carboxylic group, can be exploited in transesterification and epimerization processes.[14] The epimerization process may be governed by the steric hindrance between groups on the same five-membered ring or between facing groups on different rings.

The addition of MeOLi to a solution of either pure *syn*-**4** or *anti*-**4** in THF (Table 1) leads to only two out of the ten possible diastereomers, that is, D_3-(*R*,*S*)-**4** and C_2-**4**,[15] obtained in ratios of 1:2.0 (from *syn*-**4**) and 1:2.1 (from *anti*-**4**) in 70 % overall yield. These results imply that the mixture of cyclotrimers, *syn*-**1** and *anti*-**1**, can be oxidized without previous separation and used in the rearrangement process. The ratios, measured from the integrated signals in the NMR spectra of the crude reaction mixture, are equal within the measurement error. When corrected for the statistical factor of 1:3, the ratio of D_3-(*R*,*S*)-**4**/C_2-**4** becomes 1:0.68, which is a thermodynamic ratio, as no change was observed from prolonged action of the base. Thus, D_3-(*R*,*S*)-**4** is somewhat more stable than C_2-**4**.

The effect of the steric hindrance of different esters was evaluated by changing the alcohol. A mixture of the isopropyl esters D_3-(*R*,*S*)-**5** and C_2-**5** was obtained from a mixture of *syn*-**4** and *anti*-**4** esters using *i*PrOLi as the base in 60 % yield and in a ratio of 1:1.2, thus corresponding to a ratio of 1:0.40 after correction. The main steric hindrance is between ester groups located on the same five-membered ring, but also the steric hindrance between facing groups on different five-membered rings plays a role, which increases with the bulk of the group, thus favoring the D_3 structure.

The homotopicity of the six benzylic groups in the D_3 esters **4** and **5** allows recognition of the D_3-*R* and D_3-*S* enantiomeric forms in which the faces of the benzene ring are also homotopic.

Transesterification with a chiral alcohol allows the diastereomeric isolation of the pure enantiomers. Reaction of the mixture of *syn*-**4** and *anti*-**4** esters with lithium (−)-mentholate gives two isomers of **6** in a ratio of 3:1 and in 45 % yield after flash-chromatographic purification.

The indane protons in D_3-(*S*)-**6** are represented by a unique AA′XX′ system, in the form of two pseudo triplets.

The detection of weak transitions at the triplet sides allowed second-order spin analysis.[15] The verification of three equivalent AA′XX′ spin systems provides a rigorous argument for D_3 symmetry. The diastereomeric purity of D_3-(*S*)-**6** can be determined by careful analysis of the ^{13}C NMR spectrum (Figure 1), in which only the signals of a single compound were detected. The dipolar interactions measured by NOESY or differential NOE spectroscopy allowed, together with HMQC spectroscopy, the unequivocal assignment of ^{1}H and ^{13}C NMR resonances.

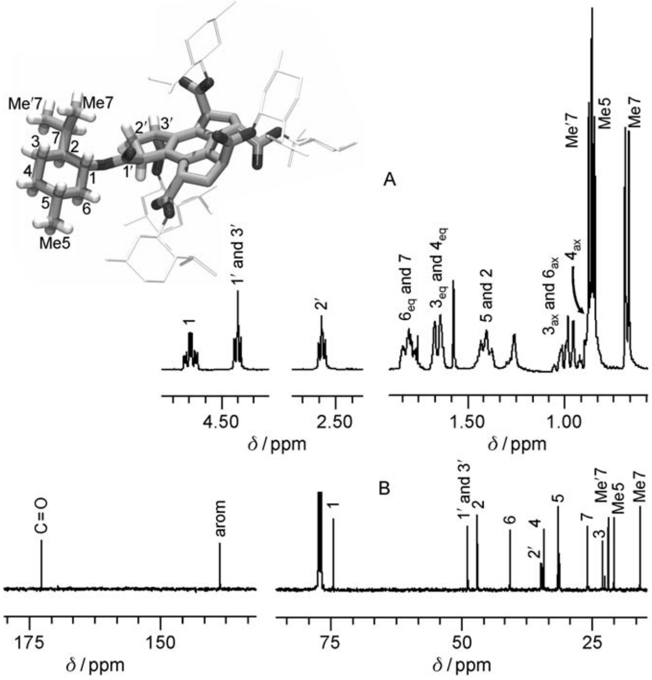


Figure 1. Complete assignment of NMR signals of D_3-(*S*)-**6** (only the relevant parts are shown). A) ^{1}H NMR (400 MHz), B) ^{13}C NMR (100 MHz) spectra.

The *S* configuration of the homotopic benzylic carbons in D_3-(*S*)-**6** was established unambiguously by single-crystal X-ray diffraction analysis[16] on the basis of the known 1*R*,2*S*,5*R* configuration of the menthyl ester units (Figure 2).

We could not find any indication of the formation of the D_3-(*R*)-**6** isomer. The isolated minor isomer displays the four protons of one five-membered ring in the form of two pseudo triplets, which is indicative of *trans* substitution, whereas the eight protons of the other rings present patterns similar to those of *syn*-**4** and *anti*-**4**, which is, therefore, indicative of *cis* substitution. Both the two C_2 structures, C_2'-**6** (more probable) or C_2''-**6**, can accommodate these features, and so we could not make an assignment.

It is appropriate to develop derivatization processes that will preserve the most valuable characteristics of the described hexaesters, particularly the up/down alternating substituents in D_3-**4**, D_3-**5**, and D_3-**6** and the enantiomeric purity of D_3-(*S*)-**6.** This possibility was verified by cleavage and esterification reactions.

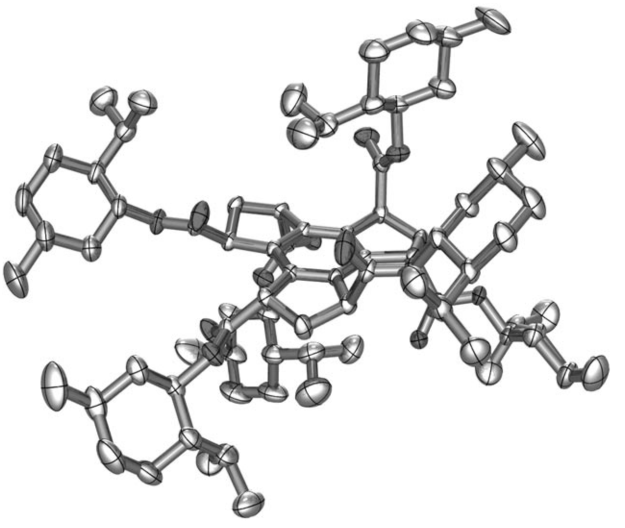


Figure 2. Structure of hexamenthyl ester D_3-(*S*)-**6** obtained by X-ray diffraction studies. Hydrogen atoms have been omitted for clarity. Ellipsoids drawn at 20% probability.

The removal of the chiral auxiliary in D_3-(*S*)-**6** gives the enantiopure hexaacid D_3-(*S*)-**3** ($[\alpha]_D^{20} = +18.16$, $c = 0.49$, dimethyl sulfoxide (DMSO)) in quantitative yield (Table 1). The cleavage reaction was carried out under neutral conditions using Me_3SiI in CCl_4.[17] The hexaacid D_3-(*S*)-**3** can be converted into the acid chloride D_3-(*S*)-**7** by using $(COCl)_2$/DMF,[17] and then esterified with MeOH giving D_3-(*S*)-**4** ($[\alpha]_D^{20} = +3.9$, $c = 0.23$, CH_2Cl_2). Compounds D_3-(*S*)-**3** and D_3-(*S*)-**4** are enantiopure, that is, the reactions occur with no rearrangement at the benzylic carbon atoms, as verified in the ^{1}H NMR spectra of the crude reaction mixture, in which no signal from the C_2 isomers could be detected.

Our approach suggests the following requirement for the generation of chiral D_3 molecules built around a benzene ring: a reversible epimerization process that will ensure the most stable configuration of the six substituents. However, in an open situation this process will lead to the alternation of *R* and *S* topicities in a molecule with C_3 symmetry (Figure 3 A). However, when the substituents with equal priority are forced toward each other by ring closures, a D_3 chiral molecule with six homotopic groups is produced (Figure 3 B).

The trindane framework with homotopic faces is the first example of an enantiopure D_3 molecule with six reactive units

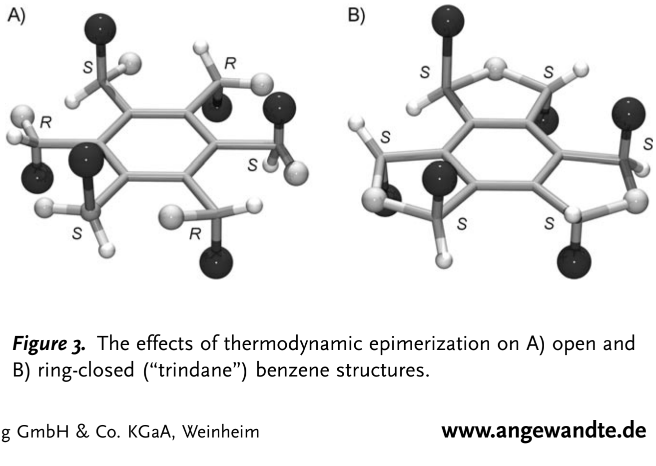


Figure 3. The effects of thermodynamic epimerization on A) open and B) ring-closed ("trindane") benzene structures.

joined directly in a rigid structure. This feature makes D_3-(*S*)-**7** an attractive core for the construction of new macromolecules, such as dendrimers,[18] liquid crystals,[19] supramolecular polymers,[10d,20] and molecular receptors,[21] in which asymmetric induction is not driven by the periphery of the molecule but by the center.

Experimental Section

D_3-(*S*)-**6**: A solution of *n*BuLi in hexanes (2.5 M, 24 mL, 59 mmol) was added dropwise to a solution of (−)-menthol (9.27 g, 59 mmol) in dry THF (80 mL) at room temperature under argon. A solution of *syn*-**4** and *anti*-**4** (3.24 g, 5.9 mmol) was added after 10 min at −78 °C. The dark solution was quenched after 2 days with saturated NaCl solution (100 mL), extracted with Et_2O (3 × 100 mL), the organic layers dried over $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography (CH_2Cl_2/hexane 1:1) to give the white solid D_3-(*S*)-**6** (2.5 g, 33 %; m.p. 78.8 °C) as the first product and C_2'-**6** or C_2''-**6** (0.89 g, 11 %; m.p. 101.7 °C) as the second product. D_3-(*S*)-**6** was recrystallized from CH_3CN/CH_2Cl_2 by slow solvent evaporation. 1H NMR ($CDCl_3$, 400 MHz): $\delta = 4.66$ (6H, H1, td, $J = 10.8, 4.2$ Hz), 4.42 (6H, H1′ and H3′, pseudo t), 2.57 (6H, H2′, pseudo t), 1.82 (6H, $H6_{eq}$, m), 1.79 (6H, H7, m). 1.65 (12H, $H3_{eq}$ and $H4_{eq}$, m), 1.42 (6H, H5, m), 1.40 (6H, H2, m), 1.00 (6H, $H3_{ax}$, m), 0.89 (6H, $H4_{ax}$, m), 0.87 (18H, Me7, d, $J = 6.4$ Hz), 0.85 (18H, Me5, d, $J = 6.8$ Hz), 0.68 ppm (18H, Me7, d, $J = 6.9$ Hz); 13C NMR ($CDCl_3$, 100 MHz): $\delta = 172.79$ (6C, carboxyl), 138.66 (6C, aromatic), 74.41 (6C, C1), 48.81 (6C, C1′ and C3′), 47.06 (6C, C2), 40.73 (6C, C6), 34.71 (3C, C2′), 34.27 (6C, C4), 31.42 (6C, C5), 25.93 (6C, C7), 23.13 (6C, C3), 22.01 (6C, Me′7), 20.94 (6C, Me5), 15.88 ppm (6C, Me7).

X-ray diffraction: The data were collected on a Philips PW1100 four-circle diffractometer. Single crystals suitable for X-ray diffraction analysis were grown by slow evaporation from a solution of CH_3CN/CH_2Cl_2.[16]

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[15] The protons of the indane rings in D_3-(*R*,*S*)-**4** give rise to one AA′XX′ spin system, whereas the protons of C_2-**4** to give rise to one AA′XX′ and two ABXY systems, which are a good approximation of AA′XX′ systems. Each AA′XX′ system is in the form of two deceptively simple pseudo triplets. A rigorous second-order analysis was performed on the AA′XX′ spectrum of D_3-(*S*)-**6**: A (H2′) = 1027.8 ± 0.1 Hz (at 400 MHz), X (H1′ and H3′) = 1766.7 ± 0.1 Hz, $J(AA') = -12.5 \pm 0.1$ Hz, $J(XX') = 0$ Hz, $J(AX) = J(A'X') = 7.6 \pm 0.2$ Hz, $J(AX') = J(A'X) = 6.3 \pm 0.2$ Hz. LAOCOON program: A. A. Bothner-by, S. Castellano, *J. Chem. Phys.* **1964**, *41*, 3863.

[16] Crystal-structure determination of D_3-(*S*)-**6** ($C_{81}H_{126}O_{12}$): crystal dimensions $0.45 \times 0.40 \times 0.40$ mm^3; orthorhombic, space group $C222_1$; $a = 19.469(3)$, $b = 21.761(3)$, $c = 38.254(5)$ Å; $V = 16207(4)$ Å^3; $\rho_{calcd} = 1.059$ Mg m^{-3}; $2\theta_{max} = 120 =$; $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å), θ–2θ scan mode, $T = 293$ K; 6504 independent reflections collected; h,k,l limits: $0 \le h \le 21$, $0 \le k \le 24$, $0 \le l \le 42$. Intensities were corrected for Lorentz and polarization effects, not for absorption ($\mu = 0.544$ mm^{-1}) The structure was solved ab initio by using the SIR 2004 program and anisotropically refined by full-matrix block least-squares on F^2 by application of the SHELXL 97 program. Data/restraints/parameters: 6504/0/839. Hydrogen atoms were calculated at idealized positions and refined as riding. $R1 = 0.056$ (on $F \ge 4\sigma(F)$); $wR2 = 0.159$ (on F^2, all data). Max./min. residual electron density peaks: $+0.201/-0.212$ e Å^{-3}. CCDC-272639 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. SIR 2004 program: M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **2005**, *38*, 381; SHELXL 97 program: G. M. Sheldrick et al., *SHELXL 97, Program for Crystal Structure Refinement*, University of Göttingen, Göttingen, **1997**.

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