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MULTIPLY METALLATED ORGANIC INTERMEDIATES: A TRIS(LITHIOMETHYL)CYCLOHEXANE AND A HEXALITHIOTRIMETHYLCYCLOHEXANETRIOLATE

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Summary

Lithium di-t-butylbiphenyl (LiDBB) readily cleaves alkyl–sulphur bonds to yield long-lived organolithiums. Using this reagent trilithio species (**2b**) was obtained from tris-phenylthioether (**1b**). The organometallic intermediates (**2b**) and (**5b**) were characterised by their reactions with electrophiles (e.g. D_2O, CO_2, Me_3Si-OTf, Me-OTf) to yield di- and hexasubstituted cyclohexanes (**3**) and (**6**). Prolonged treatment of the trilithoxy tris-phenylthioether (**1c**) with excess LiDBB followed by addition of D_2O and aqueous work-up gave a methyl-deuterated trimethylcyclohexanetriol ($D_{2.5}$-**3a**α) demonstrating that at least one penta- and one hexalithio intermediate are involved. The structure of the latter intermediate could not be established unambiguously, but the unsymmetrical 1,1-dilithiated species (**22**) is prefered over the symmetrical hexalithio species (**2c**) on the basis of extensive transmetallation observed at the tetra- or pentalithio stage (as seen in the deuterated phenylthiomethylcyclohexanetriol (**15**)) and the absence of compelling evidence for the symmetrical tri(deuteriomethyl)cyclohexanetriol (**3a**β), as judged from the CH_3, CH_2D, and CHD_2 ratios in the deuterated product ($D_{2.5}$-**3a**α).

The structures and reactivities of polymetallated species derived from unsaturated molecules have attracted much interest in recent years [1], but only few attempts have been made to prepare polymetallated intermediates from small saturated molecules. Most of these involve molecules bearing two or more metal atoms at the same carbon atom [2a–d], whereas organopolymetallics bearing one metal atom on each of several carbons are scarce [2e–i]. Thus a tri-Grignard reagent based on a simple substituted cyclohexane was not reported until 1985 [3].

Lithium di-t-butylbiphenyl (LiDBB), a reagent developed by Freeman and Hutchinson [4] for the rapid reductive cleavage of carbon–halogen bonds to yield organolithiums, seemed to us likely to react in a similar way with carbon–sulphur bonds. Thioethers **1**, which were prepared recently from *cis*-benzene trioxide [5], seemed to offer suitable models for finding out how many lithio substituents could be placed in close proximity in a small molecule with no special electronic features

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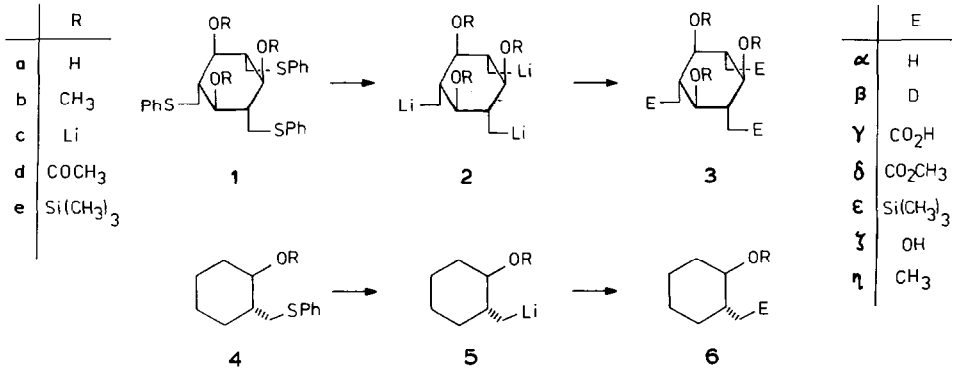


SCHEME 1

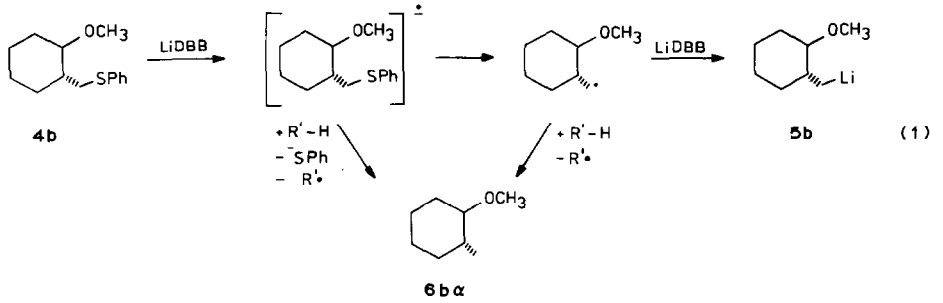
beyond possible stabilisation by neighbouring oxygen atoms [6]. In the present paper it is shown that: (i) LiDBB is a suitable reagent for the preparation of C–Li from C–S bonds in the model compounds **4a,b** (section A); (ii) the trilithio species **2b** is formed rapidly from **1b** at −78°C when this reagent is used (section B); and (iii) a hexalithio species formed slowly from **1c** under the same conditions is probably not the symmetrical species **2c**, but the 1,1-dilithiated species **22** (section C).

A. Formation of organolithiums from thioethers using LiDBB

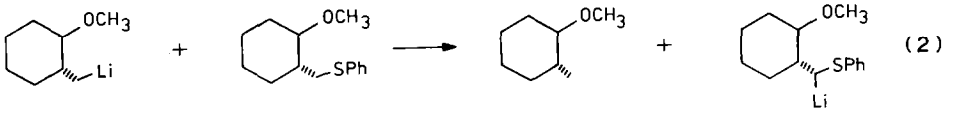
The model compound **4b** was used. The reaction between LiDBB and substrate **4b** is rapid and self-indicating. When a dark blue-green THF solution of LiDBB is added at −78°C under N_2 to a solution of **4b** in THF at the same temperature, the reagent is immediately consumed, as judged by the fading of the colour of the reagent, which persists only when excess is present. When intermediate **5b** was treated with an excess of H_2O, D_2O, CO_2, $ClCO_2CH_3$, Me_3Si-OTf, O_2 or Me-OTf, the products **6bα**–**6bη** were isolated in 81, ≥ 90 (degree of deuteration), 81, 14, 78, 35 and 79% yield, respectively, after appropriate work-up, always along with some **6bα**.

There are several possible ways of forming **6bα**. Apart from trivial ones (traces of moisture in the reagents, too short reaction times in the case of less reactive electrophiles, transmetallation with the product in the case of **6bδ**), at least three more serious possibilities must be considered:

(a) **6bα** may arise from hydrogen transfer to radical intermediates in the C–S bond cleavage process (eq. 1).



(b) **6bα** may be formed by transmetallation between **5b** and unreacted substrate **4b**, (eq. 2).



5b 4b 6bα i

Experimental evidence for this side reaction was obtained: When the reaction mixture from **4b** and LiDBB was quenched with D_2O after a few seconds, the small amount of recovered **4b** was ~ 15% D_1, consistent with formation of species **i** by eq. 2. A control experiment showed that **4b** is not deuterated by LiOD/D_2O.

(c) **6bα** may arise from protonation of the carbanion of **5b** by the solvent [7] or any other species present in the reaction mixture (LiSPh, DBB). This possibility was excluded as a major pathway by allowing the solution of **5b** slowly to warm to −10°C during 90 min before quenching with Me_3Si-OTf, whereby **6bε** was obtained in a yield not significantly lower than after immediate quenching at −78°C (72 vs. 78%). Thus intermediate **5b** is long-lived under the conditions of its formation.

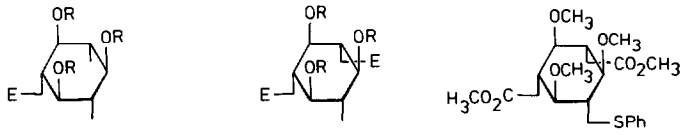
A free hydroxy group in a substrate is, in principle, compatible with the LiDBB method, as shown by the reaction of alcohol **4a**, from which **6aα** or **6aβ** was obtained exclusively after successive treatment with n-BuLi, LiDBB, and H_2O or D_2O (cf. ref. 8). Likewise, **6aε** was obtained in 61% yield after quenching with Me_3Si-OTf, the remaining product being **6aα**. To obtain this yield, however, a reaction time of 30 min at −78°C was required, shorter reaction times leading to recovery of some starting material; e.g. 15% of **4a** after 5 min reaction. Thus on going from **4b** to **4a** the rate of reductive lithiation falls sharply, and so transmetallation between the substrate and lithio derivative **5** may become a major problem.

The silyl ether **4e** behaves differently: **5e** is formed, apparently as readily as **5b**, but it undergoes rapid 1,4 O → C Si migration to give **6aε** after aqueous work-up, as reported previously [9].

B. Formation and reactions of the trilithio intermediate 2b

The tris-phenylthioether **1b** apparently reacted with LiDBB in THF at −78°C as rapidly as did **4b**. Quenching with H_2O after a few seconds gave **3bα** as the exclusive product in almost quantitative yield. Since protonation occurs in all the LiDBB reactions (see above), this result alone does not prove the presence of **2b**. Use of D_2O instead of H_2O gave a product shown (by MS) to be a mixture of D_3-**3bα** (probably structure **3bβ**) and D_2-**3bα** in a ~ 2/1 ratio.

Treatment of the intermediate(s) with CO_2 followed by non-aqueous work-up and esterification (CH_2N_2) resulted in esters **7bδ**, **8bδ** and **3bδ** in a 1/3.5/3 ratio, but the total yield was low (~ 35%).



7 8 9

E and R as specified in Scheme 1 .

However, when Me_3Si-OTf was used as electrophile (−78°C, aqueous work-up after 10 min), **7bε**, **8bε** and **3bε** were isolated in 2, 21, and 59% yields, respectively. Me-OTf, likewise, gave **7bη**, **8bη**, **3bη** along with **3bα**, all in ~ 20% yield.

In all of these experiments no sulphur-containing products were found. However, in an experiment in which an excess of LiDBB was not used, after carboxylation and esterification the sulphur-containing ester **9** was isolated.

The rates of formation and decay of the intermediate responsible for products **3b** were estimated as follows. When the reaction mixture from **1b** and excess LiDBB was quenched with D_2O a few seconds after the blue colour persisted, or after 2 min, 8 min, or 32 min, respectively, both the yield of product D_n-**3bα** (determined by capillary GLC against an internal standard, and by isolation in 89% yield) and the degree of deuteration (capillary-GLC/MS, D_3-**3bα**/D_2-**3bα** ~ 3/1) were found to remain nearly constant. Thus **2b** (like **5b**) is formed rapidly and is long-lived at −78°C in THF.

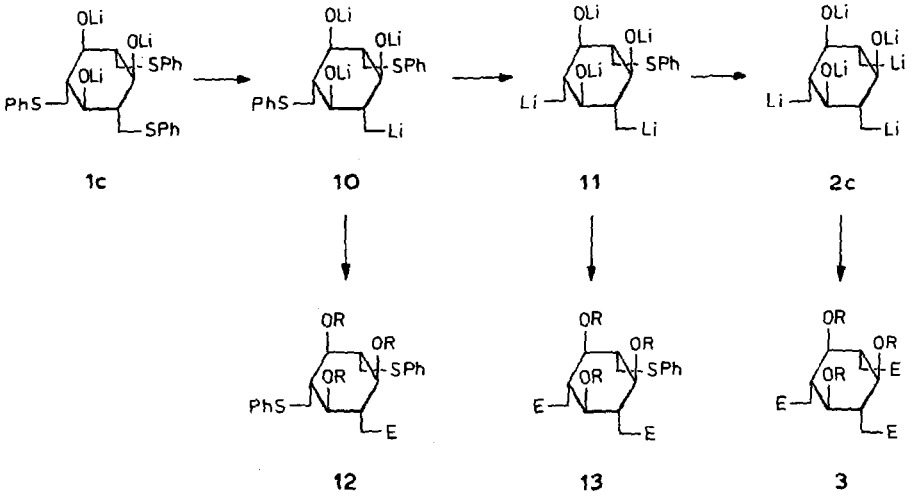
While formation of products **7b** and **8b** may not require the intermediacy of trilithio species **2b**, it is difficult to account for formation of products **3b** without the intervention of **2b**. Alternative stepwise sequences leading to products **3bβ**, **3bδ**, **3bε** and **3bη** necessarily imply that a partially lithiated intermediate reacts first with the electrophile (D_2O, CO_2, Me_3Si-OTf, Me-OTf) and then with two more molecules of LiDBB to cleave the remaining C–S bond. Since LiDBB and these electrophiles react with one another very rapidly, the product forming steps would have to proceed at the very moment of adding the electrophile to the deeply blue-green solution of the intermediate and excess LiDBB and such a possibility is less likely than the presence of **2b**. The formation of sulphur-containing products under identical conditions from **1c** (see below) supports this view.

C. Formation and reactions of a hexalithio intermediate

To decide whether or not the tetra-, penta- and hexa-lithio species **10**, **11** and **2c** can exist, solutions of **1c**, obtained from triol **1a** and n-BuLi, were treated with LiDBB and then with an electrophile (Scheme 2). Isolation of products **12**, **13** and **3** (with E ≠ H) should confirm the intermediacy of **10**, **11**, and **2c**, but isolation of **12α**, **13α** and **3α** (E = H) can be regarded only as an indication of the presence of these intermediates.

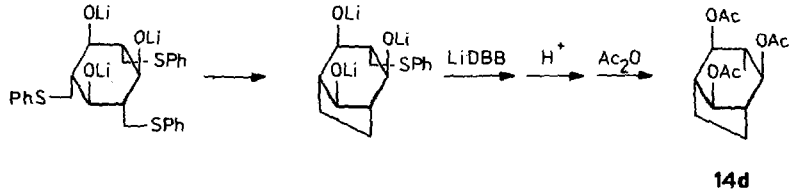
LiDBB was initially consumed by **1c** rapidly at −78°C. However, a bluegreen colour developed even when much less than the expected amount LiDDB had been added. When such a deeply coloured solution was quenched with ethanol after 3 min (30 min, 5 h), after acetylation **12dα**, **13dα** and **3dα** were found in 17 (6.5, trace), 54 (55, 36), and 6 (32, 44) % yield, respectively. (Authentic **3dα**, made for comparison, was readily prepared from **1a** by Na/NH_3 reduction followed by acetylation.) Thus although some higher lithiated species are formed under these conditions, **2c** is formed from trisalkoxide **1c** much more slowly, if at all, than is **2b** from the trisether **1b**. Treatment of **1c** with an excess of LiDBB at −70°C for 20 h, followed by quenching with EtOH, then acetylation gave **3dα** (65% yield) containing only a trace of **13dα**.

In all these experiments 10% of the bicyclic side product **14d** was found; this may



SCHEME 2. E and R as specified in Scheme 1.

be formed either via intramolecular nucleophilic substitution, e.g. in **10** [10], or via a radical intermediate.



When D_2O was used in place of EtOH, the D_n-**3a**α formed (up to 57% yield) contained D_3/D_2 species in a ratio of ~ 1/1 (MS), with 2.5 D in the exocyclic methyl positions exclusively (250 MHz ^{1}H NMR). The D_n-**13a**α formed in the same experiment was almost exclusively D_2 ($D_2/D_1 \geq 9/1$, MS). These isotopic compositions were independent of the reaction time, being the same in D_n-**13a**α and D_n-**3a**α obtained after 10 h or after 30 h., i.e. when the product ratio D_n-**13a**α/D_n-**3a**α had changed from 4/1 to 1/7.

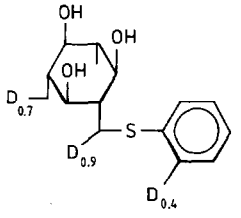
Control experiments confirmed that there is no reaction path leading to incorporation of deuterium in **3d**α or **13d**α after their formation. Thus authentic **3a**α was treated with n-BuLi, LiDBB, D_2O, and Ac_2O under identical conditions to give **3d**α containing $\leq 5\%$ D_1 (MS), and this deuterium content vanished completely after methanolysis back to **3a**α. Thus there is no deuterium incorporation except for that into the acetyl groups, which would be expected.

^{1}H NMR analysis revealed that the structure of the D_2-**13a**α was not **13a**β but that the D content was scrambled as follows: 0.9 D in the methylene positions, 0.7 D in the methyl positions and 0.4 D in the phenyl *ortho* positions, structure **15**.

By analogy the $D_{2.5}$-**3a**α was thought also not to be simply a mixture of species **16** and **3a**β, and this was confirmed by the NMR spectra (both 400 MHz ^{1}H and ^{13}C) which exhibited signals not only from CH_3 and CH_2D, but also from CHD_2

groups [ratio $CH_3/CH_2D/CHD_2 = 45.5/30/24.5\%$ (average of two measurements)] demonstrating the presence of at least one of the 1,1-dideuterated species **17** and **18**. Thus a transmetallation had occurred in at least one organometallic intermediate.

Mathematical treatment (with the assumption that the $D_{2.5}$-**3a**α consists of the species **16**, **17**, **3a**β, and **18** exclusively, i.e. that the monodeuterio isotopomer is absent) leads to a system of three linear equations for the four unkown relative concentrations. Thus although the individual concentrations cannot be determined, it is possible to calculate upper and lower limits viz.: **16** 0–26.5, **17** 36.5–63, **3a**β 0–26.5, **18** 10.5–37%.



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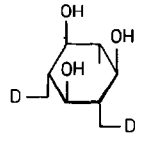

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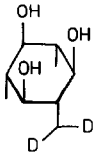

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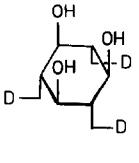
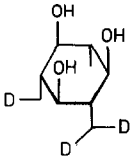


3aβ



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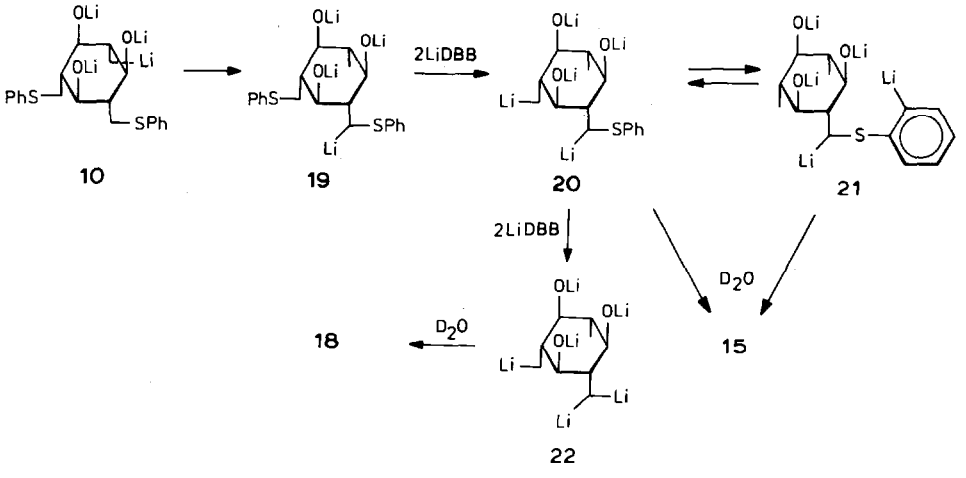
To rationalise these results the following simplified interpretation is proposed (see Scheme 3):



SCHEME 3

From **1c** the tetralithio intermediate **10** is formed as usual. This species, however, instead of accumulating even more negative charge (→ **11**) either undergoes (intramolecular) transmetallation to place the lithium in a more favorable position (→ **19**), or loses LiSPh, thus alleviating its burden of charge and leading eventually to **14d**. Further reaction of **19** with LiDBB leads to the long-lived key pentalithio intermediate equilibrium **20/21**, (cf. ref. 11). From **20** and excess LiDBB in a very slow reaction hexalithio species **22** is formed. D_2O quench of the **20/21/22** mixture yields products **15** and **18**.

Steps **10** → **19** and **20** ⇌ **21** are reasonable, since both the phenyl *ortho* positions and a methylene group next to a sulphur atom are known to be more acidic than a methyl group [12]. Thus formation of **11**, and therefore **2c**, is improbable, and if the system is forced to accomodate six lithiums the 1,1-dilithiated species **22** is formed. These results throw no light on the interesting question of whether or not the symmetrical hexalithio species **2c** (once formed) would isomerise to **22**.

Attempts to trap **2c** or **22** with electrophiles other than EtOH or D_2O have so far failed. Thus Me-OTf did not give **3bη**, even after further treatment of the product mixture with KOH/MeI. TMS-OTf likewise did not give the known [9a] products **3aε** or **8aε** after acidic work-up or **3dε** or **8dε** after acetylation. Instead complex mixtures were formed in all these cases.

Preparative implications

Since the starting phenylthioethers can be prepared by nucleophilic additon of α-lithiothioanisole [13] to carbon electrophiles (epoxides [5], ketones, alkyl iodides [13]), the reactions of the organometallics produced in this study with common electrophiles establish thioanisole as a $^-CH_3$, $^-CH_2D$, $^-CH_2CH_3$, $^-CH_2CO_2H$, $^-CH_2CO_2CH_3$, $^-CH_2SiMe_3$ or $^-CH_2OH$ equivalent, or as a general CH_2^{2-} equivalent that can be attached successively to two different electrophiles. A severe limitation of this method is its incompatibility with many common functional groups which are reduced by LiDBB or which contain acidic protons. Lithium naphthalenide or its dimethylamino derivative, or lithium metal have recently been used for similar transformations, but require longer reaction times and/or higher reaction temperatures [8,10a,14].

Experimental

THF was distilled from sodium/benzophenone. All organometallic reactions were performed under dry nitrogen using syringe techniques. TLC was performed on Merck 60 F-254 precoated silica plates, column chromatography on Macherey-Nagel 60 (0.06–0.2 mm) silica gel; eluents are described as, e.g. "10% EtOAc", denoting 10% EtOAc in petroleum ether (b.p. 60–70°C). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution on a Bruker WM 250 instrument (250 MHz) unless stated otherwise. Chemical shifts are reported in δ units downfield from TMS = 0 ppm, coupling constants are given in Hz. Mass spectra were recorded on a Finnigan MAT 44 S instrument. Preparative GLC was performed on a 2 m by 5 mm 1% OV-17 on Chromosorb G column, with He as carrier gas.

*(DL)-trans-2-Phenylthiomethylcyclohexanol (**4a**)*

8.1 ml n-BuLi solution (1.3 *M*, 10.5 mmol) was added at 0°C to a solution of 1.12 g 1,4-diazabicyclo[2.2.2]octane (10 mmol) and 1.17 ml thioanisole (10 mmol) in 12 ml THF. The mixture was stirred at 0°C for 30 min, then at room temperature for 15 min [13]. After cooling to −20°C, 0.9 ml epoxycyclohexane (8.7 mmol) was added. After slow warming to room temperature aqueous work-up and column chromatography (20% EtOAc) gave 1.06 g pure crystalline **4a** with m.p. 51–52°C (petroleum ether) (55%) and 0.92 g of a slightly impure oily sample.

NMR: 7.4–7.0 (m, Ph), 3.4 (br, OH), 3.37 (dd A) and 2.82 (dd B, α-CH_2), 2.0–1.0 (m, 10H); $J_{2,A}$ 4, $J_{2,B}$ 8, $J_{A,B}$ 13 Hz. IR: 3600–3300, 2925, 2850, 1580, 1479, 1445, 1436, 1061, 1029, 1022, 733, 687. MS (NH_3): 240 ($M + NH_4$), 223 ($M + 1$), 205 ($M + 1 - H_2O$). Analysis: Found: C, 70.34; H, 8.06; S, 14.31. $C_{13}H_{18}OS$ calcd.: C, 70.22; H, 8.16; S, 14.42%.

*(DL)-trans-2-Phenylthiomethylcyclohexyl methyl ether (**4b**)*

4a was treated in DMSO with CH_3I and solid KOH [15] to yield **4b** as a colourless oil, 79%, b.p. 145°C/0.3 mmHg.

NMR: 7.36–7.07 (m, Ph), 3.42 (dd A) and 2.77 (dd B, α-CH_2), 3.30 (s, OMe), 2.85 (td, 1-H), 2.13 (m, 1H), 2.01 (m, 1H), 1.81–1.00 (m, 7H); $J_{2,A}$ 3.5, $J_{2,B}$ 8, $J_{A,B}$ 13.5 Hz. IR: 3050, 2920, 2850, 2815, 1580, 1477, 1446, 1436, 1190, 1177, 1094, 1023, 735, 688. MS (NH_3): 254 ($M + NH_4$), 237 ($M + 1$), 205 ($M + 1 - MeOH$). Analysis: Found: C, 71.28; H, 8.59; S, 13.74. $C_{14}H_{20}OS$ calcd.: C, 71.14; H, 8.53; S, 13.56%.

Preparation of a LiDBB solution

58 mg of a 30% Li dispersion in mineral oil (2.5 mmol) was suspended in 5 ml THF under N_2 and a solution of 800 mg di-t-butylbiphenyl (DBB, 3 mmol) [16] in 5 ml THF was made up. Both flasks were cooled to 0°C and 2 drops of 2 *M* n-BuLi in hexane were added to effect rigorous drying. The DBB solution was then added to the Li suspension, the blue-green colour of LiDBB forming immediately throughout the solution. (Without n-BuLi there is an induction period, and the eventual LiDBB concentration is lower.) After stirring for 5 h at 0°C the LiDBB solution was cooled to −78°C and added to the substrate via a double-tipped canula under N_2.

*General procedure for the preparation of ethers **6bα–6bη***

A solution of ~0.3 mmol **4b** in 1 ml THF was cooled to −78°C and a LiDBB solution (−78°C) was added via a canula until the reagent colour persisted. An excess of the electrophile was added from a syringe (liquids) or bubbled in via a canula (CO_2, O_2). The blue-green colour faded immediately, and after an appropriate time at the temperature indicated the mixture was quenched by adding a pH 7 buffer solution at −78°C. After extractive work-up (usually with dilute aqueous NaOH/ether to remove the thiophenol) the product was separated from the mineral oil and DBB either by flash distillation (10^{-2} mmHg/liq. N_2 trap) or by chromatography (pure petroleum ether elutes the mineral oil and DBB, more polar eluents then elute the products). Since the products are volatile colourless liquids, final purification was achieved by preparative GLC. Yields were determined by adding a known amount of styrene before work-up and observing the integrated NMR signal at 5.22 relative to that of a characteristic signal of the product after flash distillation.

*(DL)-trans-2-Methylcyclohexyl methyl ether (**6bα**) [17].* Yield 81%. NMR: 3.35 (s, OMe), 2.66 (td, 1-H), 2.09 (m, 1H), 1.8–1.0 (m, 8H), 0.99 (d, Me); $J_{1,2}$ 9.7, $J_{1,6}$ 9.7, $J_{1,6'}$ 4.2, $J_{2,Me}$ 6.5 Hz. MS: 128 (*M*), 96 (*M* − MeOH), 85, 81, 71.

*(DL)-trans-2-Monodeuteriomethylcyclohexyl methyl ether (**6bβ**).* The degree of deuteration was found by MS to be ≥ 90%. MS: 129 (*M*), 97 (*M* − MeOH), 86, 81, 71.

*(DL)-trans-2-Methoxycyclohexylacetic acid (**6bγ**).* Yield 81%. NMR: 3.25 (s, OMe), 2.74 (td, 2-H), 2.59 (dd A) and 2.06 (dd B, α-CH_2), 2.05 (m, 1H), 1.75 (m, 3H), 1.55 (m, 1H), 1.27–0.88 (m, 5H); $J_{1,2}$ 10, $J_{2,3}$ 10, $J_{2,3'}$ 4.2, $J_{1,A}$ 5.5, $J_{1,B}$ 7, $J_{A,B}$ 14.5 Hz. MS (CH_4): 173 (*M* + 1), 155, 141, 123.

*(DL)-Methyl trans-2-methoxycyclohexyl acetate (**6bδ**).* Yield 14% along with much **6bα**, R_f 0.15 (10% EtOAc). NMR: 3.63 (s, CO_2Me), 3.28 (s, OMe), 2.74 (dt, 2-H), 2.57 (dd A) and 2.08 (dd B, α-CH_2), 2.15–0.9 (m, 9H); $J_{1,2}$ 9.5, $J_{2,3}$ 9.5, $J_{2,3'}$ 4, $J_{1,A}$ 6, $J_{1,B}$ 7, $J_{A,B}$ 15 Hz. MS (CH_4): 187 (*M* + 1), 155, 123.

*(DL)-trans-2-Trimethylsilylmethylcyclohexyl methyl ether (**6bε**).* Reaction time 10 min at −78°C. (Since triflates are known to catalyse polymerisation of THF, warming up before quenching must be avoided [18].) Yield 79% along with 9% **6bα**. NMR: 3.31 (s, OMe), 2.63 (dt, 1-H), 2.09–0.84 (m, 9H), 1.08 (dd A) and 0.24 (dd B, α-CH_2), −0.03 (s, $SiMe_3$); $J_{1,2}$ 10, $J_{1,6}$ 10, $J_{1,6'}$ 3.5, $J_{2,A}$ 3.5, $J_{2,B}$ 10, $J_{A,B}$ 14.5 Hz. MS: 185 (*M* − Me), 89, 73 ($SiMe_3$).

The experiment was repeated, except that the solution of **5b** was allowed slowly to warm to −10°C during 90 min then recooled to −78°C and quenched with Me_3Si-OTf. This time the yield of **6bε** was 72%, of **6bα** 7%.

*(DL)-trans-2-Methoxycyclohexylmethanol (**6bζ**).* Reaction of **5b** with O_2 at −78° → −20°C was followed by $LiAlH_4$ reduction at −20°C. Final purification by preparative GLC at 110°C gave **6bζ** in 35% yield along with 8% **6bα**. NMR: 3.60 (dd A) and 3.49 (dd B, α-CH_2), 3.35 (s, OMe), 3.04 (td, 2-H), 2.15 (m, 1H), 1.77 (m, 1H), 1.63 (m, 3H), 1.29–0.81 (m, 5H); $J_{1,2}$ 10.5, $J_{2,3}$ 10.5, $J_{2,3'}$ 4, $J_{1,A}$ 9, $J_{1,B}$ 3.5, $J_{A,B}$ 10.5 Hz. MS: 129 (*M* − Me), 126 (*M* − H_2O), 112 (*M* − MeOH), 97, 94, 71.

*(DL)-trans-2-Ethylcyclohexyl methyl ether (**6bη**).* Obtained in 79% yield along with 16% **6bα**; final purification was by preparative GLC at 80°C. NMR: 3.32 (s, OMe), 2.75 (td, 1-H), 2.06 (m, 1H), 1.86–1.00 (m, 10H), 0.85 (t, CH_3); $J_{1,2}$ 9.6, $J_{1,6}$ 9.6, $J_{1,6'}$ 4, J_{CH_2,CH_3} 7.3 Hz. MS: 142 (*M*), 110 (*M* − MeOH), 99, 71.

*(DL)-trans-2-Methylcyclohexanol (**6aα**)*

A solution of 178 mg **4a** (0.80 mmol) in 2 ml THF was treated with 0.75 ml of a 1.33 *M* n-BuLi solution in hexane (1.0 mmol) at −78°C, then with LiDBB as described above. The colour of the reagent faded immediately until sufficient LiDBB was added for the colour to persist. An excess of H_2O was added at −78°C, then aqueous work-up (dilute NaOH/ether) and flash distillation (12 mmHg, dry ice trap) gave a single product containing some solvent; 70% yield by integration relative to a known amount of styrene. Preparative GLC (50°C) gave **6aα** as a pure colourless liquid. NMR: 3.08 (td, 1-H), 1.91–0.9 (m, 10H), 0.97 (d, Me); $J_{1,2}$ 9.5, $J_{1,6}$ 9.5, $J_{1,6'}$ 3.8, $J_{2,Me}$ 7 Hz [17]. MS: 114 (*M*), 96 (*M* − H_2O), 81, 68, 57. Use of D_2O instead of H_2O gave **6aβ**, ≥ 90% D_1 by MS.

*(DL)-trans-2-Trimethylsilylmethylcyclohexanol (**6aε**)*

A solution of 111 mg **4a** (0.50 mmol) in 1 ml THF was treated with 0.28 ml 2.2

M n-BuLi solution in hexane (0.6 mmol) at −30°C for 7 min, then with an excess LiDBB at −78°C for 30 min. 0.54 ml TMS-OTf was added (3 mmol), and after stirring for 1 h at −78°C a pH 7 buffer solution was added. The usual work-up (dilute H_2SO_4, then dilute NaOH/ether) followed by evaporation and chromatography (petroleum ether to remove DBB, then 20% EtOAc) gave the product in 61% yield along with **6aα** and a trace of **4a**. NMR: see ref. 9a. MS: 185 (*M* − 1), 171 (*M* − Me), 169 (*M* − OH), 153 (*M* − Me − H_2O), 95.

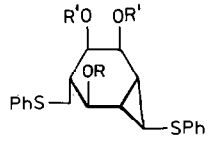
*scyllo-2,4,6-Tris(phenylthiomethyl)cyclohexane-1,3,5-triol (**1a**) and (DL)-(1α,2α, 3α,4β,5α,6α,7α)-7-phenylthio-4-phenylthiomethylbicyclo[4.1.0]heptane-2,3,5-triol (**23a**)*

A solution of 3.36 g 1,4-diazabicyclo[2.2.2]octane (30 mmol) and 3.52 ml thioanisole (30 mmol) in 45 ml THF was treated at 0°C with 17.5 ml n-BuLi solution (2.0 *M*, 35 mmol) then the mixture was stirred for 30 min at 0°C then 15 min at room temperature [13]. After recooling to 0°C the solution was added to a suspension of 1.26 g *cis*-benzene trioxide (10 mmol) [19] in 10 ml THF and 20 ml HMPA. The usual work-up (dilute H_2SO_4/ether) after 30 min at 0°C yielded a ~ 1/1 mixture of **1a** and **23a** (TLC, 40% EtOAc). These products can be separated by chromatography, but separation was more easily achieved after acetalation of **23a**, as follows: The mixture was concentrated, dissolved in 2,2-dimethoxypropane, and set aside overnight after addition of a catalytic amount *p*-toluenesulfonic acid, after which TLC showed complete conversion of **23a** to **23f** whereas **1a** was unchanged. Aqueous work-up (dilute Na_2CO_3/ether) and chromatography of the dried and concentrated mixture (20% EtOAc, then 50% EtOAc) gave 1.57 g **23f** (38%) as a colourless oil, then 2.10 g **1a** (42%) as colourless crystals, m.p. 126°C (CCl_4).

1a: NMR: 7.41–7.11 (m, 3Ph), 3.54 (br t, 1(3,5)-H), 3.32 (d, $3CH_2$), 2.51 (br s, 3OH), 1.77 (tt, 2(4,6)-H); $J_{1,2}$ 9.5, J_{2,CH_2} 4.5 Hz. IR: 3600–3200, 3050, 2890, 1580, 1479, 1436, 1425, 1084, 1060, 985, 737, 730, 684. Analysis: Found: C, 64.69; H, 6.05; S, 19.35. $C_{27}H_{30}O_3S_3$ calcd.: C, 65.03; H, 6.06; S, 19.29%.

23a: m.p. 158°C (acetone/EtOAc). NMR (acetone-d_6/$CDCl_3$): 7.35–7.02 (m, 2Ph), 4.25 (m, 2H), 4.00 (1H), 3.92 (d, 1OH), 3.50–3.20 (m, 4H), 2.1 (m, 4-H), 1.87 (t, 7-H), 1.62 (ddd, 1-H), 1.40 (ddd, 6-H); $J_{1,2}$ 2.5, $J_{2,3}$ 3, $J_{3,4}$ 10.5, $J_{4,5}$ 9, $J_{5,6}$ 0, $J_{1,6}$ 9, $J_{1,7}$ 4.4, $J_{6,7}$ 4.4, $J_{4,\alpha\text{-CH}}$ 4.5, $J_{4,\alpha\text{-CH}'}$ 4.5, $J_{\alpha\text{-CH},\alpha\text{-CH}'}$ 13 Hz. IR: 3600–3300, 1580, 1477, 1436, 1086, 1073, 1034, 741, 736, 689. Analysis: Found: C, 64.34; H, 5.98; S, 17.26. $C_{20}H_{22}O_3S_2$ calcd.: C, 64.14; H, 5.92; S, 17.12%

23f: NMR: 7.46–7.11 (m, 2Ph), 4.48 (d, 2-H), 3.73 (m, 3-H, 5-H), 3.37 (dd, A) and 3.04 (dd, B, α-CH_2), 2.96 (br d, OH), 1.97 (tdd, 4-H), 1.75 (m) and 1.57 (ddd, 1-H, 6-H, 7-H), 1.37 (s) and 1.35 (s, 2Me); $J_{1,2}$ 0*, $J_{2,3}$ 5*, $J_{3,4}$ 10, $J_{4,5}$ 10, $J_{1,6}$ 8, $J_{4,A}$ 4.5, $J_{4,B}$ 6, $J_{A,B}$ 13.5, $J_{5,OH}$ 6.7 Hz.



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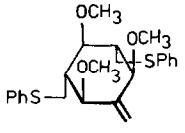

24b

(**a**: R = R′ = H;
f: R = H; R′,R′ = $C(CH_3)_2$)

*scyllo-1,3,5-Trimethoxy-2,4,6-tris(phenylthiomethyl)cyclohexane (**1b**) and (2α, 3β,4α,5β,6α)-2,4,6-trimethoxy-1-methylene-3,5-bis(phenylthiomethyl)cyclohexane (**24b**)*

A suspension of 1.3 g of powdered KOH in 4 ml DMSO was stirred with a solution of 504 mg **1a** (1.01 mmol) in 4 ml DMSO, and 0.7 ml MeI (11.2 mmol) was added [15]. After 20 h stirring aqueous work-up and chromatography (10% EtOAc) gave 52 mg crystalline **24b**, m.p. 123°C (CCl_4/petroleum ether), 12%, then 398 mg crystalline **1b**, m.p. 90°C (petroleum ether), 73%.

1b: NMR: 7.42–7.11 (m, 3Ph), 3.50 (s, 3OMe), 3.47 (t, 1(3,5)-H), 3.40 (d, $3CH_2$), 1.95 (tt, 2(4,6)-H); $J_{1,2}$ 10.5, J_{2,CH_2} 3.8 Hz. IR: 3060, 2930, 2895, 2815, 1580, 1569, 1477, 1434, 1365, 1084, 1022, 986, 735, 700, 688. Analysis: Found: C, 66.33; H, 6.72; S, 17.72. $C_{30}H_{36}O_3S_3$ calcd.: C, 66.63; H, 6.71, S, 17.79%.

24b: NMR: 7.48–7.12 (m, 2Ph), 5.08 ("t", C=CH_2), 3.67 (t, 4-H), 3.54 ("dd", 2(6)-H), 3.53 (dd, A) and 3.31 (dd, B, 2 α-CH_2), 3.42 (s, 4-OMe), 3.23 (s, 2(6)-OMe), 1.89 (tt, 3(5)-H); $J_{2,3}$ 10.5, $J_{3,4}$ 10.5, $J_{3,A}$ 3.5, $J_{3,B}$ 3.5, $J_{A,B}$ 12, $J_{2,olef} \leq 1$ Hz. IR: 3060, 2975, 2920, 2895, 2820, 1477, 1436, 1424, 1095, 1087, 1021, 998, 913, 734, 688. MS (CH_4): 431 (M + 1), 399 (M − MeOH + 1), 367, 335, 289. Analysis: Found: C, 66.98; H, 7.08; S, 14.89. $C_{24}H_{30}O_3S_2$ calcd.: C, 66.94; H, 7.02; S, 14.89%.

*scyllo-1,3,5-Trimethoxy-2,4,6-trimethylcyclohexane (**3bα**)*

A solution of 100 mg **1b** (0.18 mmol) in 1 ml THF was treated with LiDBB at −78°C. When the colour persisted an excess of H_2O was added. After the usual work-up (dilute NaOH/ether) TLC and Cap-GLC revealed the presence of only one product, which was isolated by flash distillation or by chromatography (10% EtOAc, then 20%) as a colourless volatile oil containing some solvent, yield 43 mg, 108%. A pure sample was obtained by preparative GLC (130°C). NMR: 3.33 (s, 3OMe), 2.36 (t, 1(3,5)-H), 1.56 (tq, 2(4,6)-H), 1.04 (d, 3Me); $J_{1,2}$ 10.5, $J_{2,Me}$ 7 Hz. MS (NH_3): 234 ($M + NH_4$), 217 (M + 1). When D_2O was used in place of H_2O, the product was found by MS to be D_3-**3bα** (≡ **3bβ**)/D_2-**3bα** ~ 2/1.

*scyllo-2,4,6-Trimethoxy-3,5-dimethyl-cyclohexane-1-acetic acid methylester (**7bδ**), scyllo-2,4,6-trimethoxy-5-methyl-cyclohexane-1,3-diacetic acid dimethylester (**8bδ**), and scyllo-2,4,6-trimethoxy-cyclohexane-1,3,5-triacetic acid trimethylester (**3bδ**)*

A solution of 54.1 mg **1b** (0.10 mmol) in 1 ml THF was treated at −78°C with a slight excess of LiDBB, then CO_2 was bubbled in until the colour had completely disappeared. After slow warming to room temperature HOAc was added until the mixture was neutral, then some MeOH and an excess of CH_2N_2 in ether were added. After evaporation to dryness the residue was transferred to the top of a column, and elution with petroleum ether gave the mineral oil and DBB, then elution with 50% EtOAc gave the products containing fraction, 12.5 mg (35%), by NMR and Cap-GLC a 1/3.5/3 mixture of **7bδ**, **8bδ**, and **3bδ**. The products can be separated by careful chromatography (40% EtOAc).

7bδ: NMR: 3.66 (s, CO_2Me), 3.36 (s, 4-OMe), 3.33 (s, 2(6)-OMe), 2.67 (t, 2(6)-H), 2.49 (d, CH_2), 2.40 (t, 4-H), 2.07 (m, 3(5)-H), 1.64 (m, 1-H), 1.09 (d, 2Me); $J_{1,2}$ 10.5, $J_{2,3}$ 10.5, $J_{3,4}$ 10.5, J_{1,CH_2} 5.6, $J_{3,Me}$ 7 Hz. MS (i-butane): 275 (M + 1), 243, 211.

8bδ: NMR: 3.66 (s, $2CO_2$Me), 3.33 (s, 4(6)-OMe), 3.29 (s, 2-OMe), 3.01 (t, 2-H), 2.71 (t, 4(6)-H), 2.45 (dd A) and 2.43 (dd B, $2CH_2$), 2.10 (m, 1(3)-H), 1.66 (m, 5-H), 1.10 (d, Me); $J_{1,2}$ 10.5, $J_{3,4}$ 10.5, $J_{4,5}$ 10.5, $J_{1,A}$ 5.6, $J_{1,B}$ 6.7, $J_{A,B}$ 16, $J_{5,Me}$ 7 Hz. MS (i-butane): 333 (M + 1), 301, 269.

3bδ: NMR: 3.66 (s, $3CO_2Me$), 3.28 (s, 3OMe), 3.06 (t, 2(4,6)-H), 2.51(d, $3CH_2$), 2.10 (tt, 1(3,5)-H); $J_{1,2}$ 10.5, J_{1,CH_2} 5.6 Hz. MS (i-butane): 391 ($M+1$), 359, 327.

*scyllo-2,4,6-Trimethoxy-5-phenylthiomethyl-cyclohexane-1,3-diacetic acid dimethylester (**9**)*

This was isolated by chromatography (40% EtOAc) as a colourless oil in 58% yield after the same procedure but using insufficient LiDBB to produce a persistent blue-green colour. NMR: 7.39–7.12 (m, Ph), 3.69 (s, $2CO_2Me$), 3.41 (s, 4(6)-OMe), 3.36 (5-CH_2), 3.32 (s, 2-OMe), 3.25 (t, 4(6)-H), 3.04 (t, 2-H), 2.63 (dd A) and 2.50 (dd B, 1(3)-CH_2), 2.12 (tt, 1(3)-H), 2.03 (tt, 5-H); $J_{1,2}=10.5$, $J_{3,4}$ 10.5, $J_{4,5}$ 10.5, $J_{1,A}$ 5.8, $J_{1,B}$ 5.8, $J_{A,B}$ 16, J_{5,CH_2} 2.5 Hz.

*scyllo-1,3,5-Trimethoxy-4,6-dimethyl-2-trimethylsilylmethylcyclohexane (**7bϵ**), scyllo-1,3,5-trimethoxy-6-methyl-2,4-bis(trimethylsilylmethyl)cyclohexane (**8bϵ**) and scyllo-1,3,5-trimethoxy-2,4,6-tris(trimethylsilylmethyl)cyclohexane (**3bϵ**)*

A solution of 54.5 mg **1b** (0.10 mmol) in 1 ml THF was treated at −78°C with a small excess of LiDBB, then 0.5 ml Me_3Si-OTf (2.75 mmol) was added. After 10 min at −78°C, 2 ml of a pH 7 buffer solution was added. After the usual work-up (dilute NaOH/ether) the mixture was evaporated to dryness and the residue transferred to the top of a column; elution with petroleum ether gave the mineral oil and DBB, and subsequent elution with 10% EtOAc gave a mixture of the three products. A known amount of *trans*-stilbene was added, and the yields of **7bϵ**, **8bϵ**, and **3bϵ** were determined by integrated NMR spectroscopy to be 2, 21 and 59%, respectively. The products can be separated by column chromatography; 5% EtOAc elutes **3bϵ**, then **8bϵ**, and 10% EtOAc then elutes **7bϵ**; all are colourless oils.

7bϵ: NMR: 3.36 (s, 2OMe), 3.35 (s, OMe), 2.46 (t, 1(3)-H), 2.40 (t, 5-H), 1.72–1.5 (m, 2-H, 4(6)-H), 1.07 (d, 2Me), 0.71 (d, CH_2), 0.03 (s, $SiMe_3$); $J_{1,2}$ 10.5, $J_{3,4}$ 10.5, $J_{4,5}$ 10.5, $J_{4,Me}$ 6.3, $J_{2,Me}$ 5Hz. MS (NH_3): 306 ($M+NH_4$), 289 ($M+1$), 257, 225.

8bϵ: NMR: 3.35 (s, 2OMe), 3.29 (s, OMe), 2.63 (t, 3-H), 2.49 (t, 1(5)-H), 1.70 (m, 2(4)-H), 1.57 (m, 6-H), 1.07 (d, Me), 0.77 (dd A) and 0.68 (dd B, 2 CH_2), 0.03 (s, $2SiMe_3$); $J_{1,2}$ 10.5, $J_{2,3}$ 10.5, $J_{5,6}$ 10.5, $J_{2,A}$ 4.2, $J_{2,B}$ 5.6, $J_{A,B}$ 14.5, $J_{6,Me}$ 6.3 Hz. MS (NH_3): 378 ($M+NH_4$), 361 ($M+1$), 329, 297.

3bϵ: NMR: 3.29 (s, 3OMe), 2.72 (t, 1(3,5)-H), 1.79 (tt, 2(4,6)-H), 0.75 (d, $3CH_3$), 0.04 (s, $3SiMe_3$); $J_{1,2}$ 10.5, J_{2,CH_2} 5.2 Hz. MS (NH_3): 450 ($M+NH_4$), 433 ($M+1$), 401, 369.

*scyllo-1-Ethyl-2,4,6-trimethoxy-3,5-dimethylcyclohexane (**7bη**), scyllo-1,3-diethyl-2,4,6-trimethoxy-5-methylcyclohexane (**8bη**), and scyllo-1,3,5-triethyl-2,4,6-trimethoxycyclohexane (**3bη**)*

A solution of 55 mg **1b** (0.10 mmol) in 1 ml THF was treated at −78°C with a small excess of LiDBB, then 0.15 ml Me-OTf (1.38 mmol) was added. After 15 min at −78°C, 2 ml of a pH 7 buffer solution was added. After the usual work-up (dilute NaOH/ether) the mixture was concentrated to dryness and the residue transferred to the top of a column. Elution with petroleum ether gave the mineral oil and DBB, and subsequent elution with 20% EtOAc gave a mixture of **7bη**, **8bη**, **3bη**, and **3bα** in 2.1/2.0/2.6/2.3 ratio (Cap-GLC). The products were separated by chromatography (5% EtOAc, then 10%); all are colourless oils.

7bη: NMR: 3.36 (s, OMe), 3.34 (s, 2OMe), 2.68 (t, 2(6)-H), 2.36 (t, 4-H), 1.62 (m,

1-H, 3(5)-H, CH_2), 1.08 (d, 2Me), 0.93 (t, CH_2Me); $J_{1,2}$ 10.5, $J_{2,3}$ 10.5, $J_{3,4}$ 10.5, $J_{3,Me}$ 7, J_{CH_2,CH_3} 7 Hz. MS (CH_4): 231 ($M+1$), 199, 167.
8bη: NMR: 3.37 (s, 2OMe), 3.34 (s, OMe), 2.96 (t, 2-H), 2.66 (t, 4(6)-H), 1.58 (m, 1(3)-H, 5-H, $2CH_2$), 1.09 (d, Me), 0.94 (t, $2CH_2Me$); $J_{1,2}$ 10.5, $J_{1,6}$ 10.5, $J_{4,5}$ 10.5, $J_{5,Me}$ 7, J_{CH_2,CH_3} 7 Hz. MS (CH_4): 245 ($M+1$), 213, 181.
3bη: NMR: 3.34 (s, 3OMe), 2.92 (t, 2(4,6)-H), 1.66 (m, 1(3,5)-H and $3CH_2$), 0.95 (t, $3CH_2Me$); $J_{1,2}$ 10.5, J_{CH_2,CH_3} 7 Hz. MS (CH_4): 259 ($M+1$), 227, 195.

*Rates of formation and decay of **2b***

*scyllo-1,3,5-Trimethoxy-2,4,6-tris(monodeuteriomethyl)cyclohexane (**3bβ**)*

A LiDBB solution was made during 4 h at 0°C from 174 mg Li dispersion (30% in mineral oil, 7.5 mmol) and 2.4 g DBB (9 mmol) in 23 ml THF (to which a few drops n-BuLi had been added to remove any water). Some of the solution was transfered via a canula at −78°C to a solution of 50 mg **1b** (0.09 mmol) in 0.5 ml THF until the blue-green colour persisted. This addition required a few seconds, then 0.5 ml D_2O was immediately added. The procedure was repeated 3 times but with the D_2O added after 2, 8, and 32 min reaction at −78°C, respectively. To each sample was added 0.4 ml of a solution of 113 mg n-$C_{16}H_{34}$ in 2 ml THF, i.e. 0.1 mmol in each case, as an internal standard. After the usual work-up (dilute NaOH/ether) the ether extracts were analysed by Cap-GLC with integration of the peaks of the product (8.90 min) and n-$C_{16}H_{34}$ (10.55 min retention time on 25 m OV-17, column 140°C, injector 180°C, 0.5 bar N_2). The ratios of product to standard determined by electronic integration were 0.48, 0.49, 0.53 and 0.54 for the 4 samples. Cap-GLC/MS (NH_3) showed the isotopic composition of the product molecular ion ($M+NH_4$) to be constant for all 4 samples; the intensity ratios of peak 237 to peak 236 were 3.62, 3.78, 3.25 and 3.40, respectively. Since the protonated sample **3bα** gives small peaks at m/z 233, 235 and 236 along with that at 234, this ratio is considered to indicate a ratio D_3-**3bα**/D_2-**3bα** of roughly 3/1. The samples were combined and the product was isolated by chromatography (10% EtOAc, then 20%) to give, after careful concentration, 71.8 mg of a colourless oil 0.33 mmol, 89%. To determine the response factor of the GLC integration this 71.8 mg sample was mixed with 72.9 mg n-$C_{16}H_{34}$ (0.323 mmol). Thus the true molar ratio of product to standard in the mixture was 1.016. The ratio found by GLC integration was 0.595, and so the response factor is 1.71. Using this factor the yields of product in the four samples were 89, 91, 98.5, and 100% respectively.

*scyllo-2,4,6-Trimethylcyclohexane-1,3,5-triol (**3aα**) and its triacetate **3dα***

Portions of a solution of 1.25 g **1a** (2.5 mmol) in 20 ml THF, and in turn small pieces of Na (totalling 400 mg, 16 mmol) were added alternately to ~70 ml liq. NH_3 at −78°C. Stirring was subsequently continued at −78°C for 30 min. The solution, which was dark blue, was then quenched by adding solid NH_4Cl until the mixture was colourless. The NH_3 was allowed to volatilize off then EtOH was added and the solution was filtered then concentrated. The product was freed from some PhSSPh by chromatography eluting first with EtOAc/petroleum ether/MeOH 5/5/1, then 1.5/1.5/1; yield 423 mg of colourless crystals, 97%. The substance does not melt, but sublimes above 200°C at 1 atm. For purification it was sublimed at 180°C/10^{-2} mmHg. NMR (CD_3OD, 400 MHz): 2.64 (t, 1(3,5)-H), 1.32 (m,

2(4,6)-H), 1.10 (d, 3 Me); $J_{1,2}$ 10.5, $J_{2,Me}$ 7 Hz. ^{13}C NMR: 77.86 (C-1(3,5)), 48.20 (C-2(4,6)), 15.84 (CH_3). IR: 3600–3200, 2980, 2963, 2875, 1464, 1448, 1365, 1158, 1082, 1010. MS: 138 ($M-2\ H_2O$), 123, 109. 98, 87. MS (NH_3): 192 ($M+NH_4$). Analysis: Found: C, 61.61; H, 10.41. $C_9H_{18}O_3$ calcd. C, 62.04; H, 10.41%.

The triol was treated with Ac_2O in pyridine to give the triacetate **3dα** which was purified by chromatography (20% EtOAc, then 30%) and sublimation (105°C/10^{-2} mmHg) to give colourless crystals, m.p. 138°C. NMR: 4.51 (t, 1(3,5)-H), 2.07 (s, 3OAc), 1.73 (m, 2(4,6)-H), 0.79 (d, 3 Me); $J_{1,2}$ 10.5, $J_{2,Me}$ 7 Hz. IR: 2975, 2930, 2915, 2885, 1740, 1376, 1245, 1220, 1170, 1147, 1019, 973, 940, 922. MS (NH_3): 318 ($M+NH_4$). Analysis: Found: C, 60.06; H, 7.96. $C_{15}H_{24}O_6$ calcd.: C, 59.98; H, 8.05%.

*scyllo-6-Methyl-2,4-bis(phenylthiomethyl)cyclohexane-1,3,5-triol triacetate (**12dα**), scyllo-4,6-dimethyl-2-phenylthiomethylcyclohexane-1,3,5-triol triacetate (**13dα**), and **3dα***

A solution of 50.3 mg **1a** (0.10 mmol) in 1 ml THF was treated for 7 min at −30°C with 0.20 ml of n-BuLi in hexane (2.0 *M*, 0.40 mmol). The solution was cooled to −78°C, then a LiDBB solution at the same temperature was added until the colour of the reagent was marked and persistent. After 3 min at −78°C 0.2 ml EtOH was added, to give a colourless mixture, and 2 ml pyridine and 2 ml Ac_2O were then added. The mixture was stirred at room temperature overnight, then evaporated to dryness at the pump. The solid mixture was transfered to the top of a column; petroleum ether eluted the mineral oil and DBB, then 20% EtOAc and 50% EtOAc eluted the acetate products (all three acetates have the same $R_f = 0.15$ in 20% EtOAc). The yields of products **12dα**, **13dα**, and **3dα** in this crude mixture were found by integrated NMR spectroscopy after addition of a known amount of *trans*-stilbene to be 17, 54, and 6%, respectively.

For analysing this NMR spectrum the spectra of the pure compounds were required. Pure **3dα** is available as described above, but **12dα** and **13dα** cannot be separated chromatographically. However, a mixture of the alcohols **12aα**, **13aα**, and **3aα** obtained as above but without the acetylation step was separated into the pure crystalline components by careful chromatography with EtOAc/petroleum ether/MeOH 5/5/1, R_f (**12aα**) = 0.3, R_f (**13aα**) = 0.15. The alcohols were acetylated in the usual way.

12dα: NMR: 7.37–7.13 (2Ph), 4.98 (t, 3-H), 4.77 (t, 1(5)-H), 2.90 ("d", $2CH_2$), 2.15 (m, 2(4)-H and 6-H), 2.08 (s, 1(5)-OAc), 2.03 (3-OAc), 0.84 (d, Me); $J_{1,2}$ 10.5, $J_{2,3}$ 10.5, $J_{5,6}$ 10.5, $J_{6,Me}$ 7 Hz.

13dα: NMR: 7.37–7.13 (m, Ph), 4.76 (t, 1(3)-H), 4.56 (t, 5-H), 2.89 (d, CH_2), 2.11 (s, 5-OAc), 2.08 (s, 1(3)-OAc), 2.1 (2-H), 1.80 (tq, 4(6)-H), 0.84 (d, 2Me); $J_{1,2}$ 10.5, $J_{3,4}$ 10.5, $J_{4,5}$ 10.5, J_{2,CH_2} 5.3, $J_{4,Me}$ 7 Hz. MS (NH_3): 426 ($M+NH_4$).

13aα: NMR (CD_3OD, 250 MHz): 7.41–7.07 (m, Ph), 3.45 (d, CH_2), 3.13 (t, 1(3)-H), 2.63 (t, 5-H), 1.74 (tt, 2-H), 1.36 (m, 4(6)-H); $J_{1,2}$ 10.5, $J_{3,4}$ 10.5, $J_{4,5}$ 10.5, J_{2,CH_2} 3.5, $J_{4,Me}$ 7Hz. MS (NH_3): 300 ($M+NH_4$), 283 ($M+1$), 265 ($M-H_2O+1$).

In all these experiments starting from **1a** a side product (10–15%) was produced, and it was isolated by chromatography (R_f 0.10 in 20% EtOAc) and identified as *(1α,2β,3α,4β,5α,8β)-3-methylbicyclo[3.2.1]octane-2,4,8-triol triacetate* (***14d***), colourless crystals, m.p. 86°C (petroleum ether). NMR: 4.74 (t, 8-H), 4.43 (d, 2(4)-H), 2.36 (2H), 2.29 (3-H), 2.12 (s, OAc). 2.06 (s, 2OAc), 1.85 (m, 2H), 1.58 (m, 2H), 1.06 (d, Me); $J_{1,2}$ 7.7*, $J_{2,3}$ 0*, $J_{1,8}$ 4.4, $J_{3,Me}$ 7 Hz. MS (NH_3): 316 ($M+NH_4$), 256.

D_2-13aα and $D_{2,5}$-3aα

1a was treated with n-BuLi, then with LiDBB as described above. After 10 h (30 h) at −70°C 0.1 ml D_2O was added. Acetylation, work-up and separation from DBB and mineral oil were carried out as before. NMR spectroscopy gave a ratio of D_n-**13dα**/D_n-**3dα**/D_n-**14d** = 4/1/1 (1/6.7/2) and a total yield of 61% (72%). **14d** was separated from the other two products by chromatography (20% EtOAc). The mixture of D_n-**13dα** and D_n-**3dα** was treated with MeONa in MeOH until saponification was complete. D_n-**13aα** and D_n-**3aα** were separated by chromatography (petroleum ether/EtOAc/MeOH 5/5/1). 250 MHz ^1H NMR (in CD_3OD) showed that D_n-**13aα** contained 0.7 D in the methyl positions, 0.9 D in the methylene positions and 0.4 D in the *ortho* positions (independent of the reaction time), and that D_n-**3aα** contained 2.5 D in the methyl positions (independent of the reaction time). The samples were evaporated to dryness and the residues dissolved in MeOH; this dissolution and evaporation were repeated twice to make sure that all OD had been replaced by OH. MS analysis was consistent with the NMR results: **13aα** was D_2 ($D_2/D_1 \geq 9/1$), **3aα** was $D_{2.5}$ ($D_3/D_2 \approx 1/1$).

The proton-decoupled ^{13}C NMR spectrum of $D_{2.5}$-**3aα** exhibited, along with the singlet at 15.82 ppm (CH_3), a triplet at 15.54 (CH_2D) and a quintet at 15.26 ppm (CHD_2), $^1J_{C,D}$ 19.5 Hz; likewise for C-2 along with the singlet at 48.17 ppm (CCH_3) two new singlets appeared at 48.09 and 48.01 ppm (CCH_2D and $CCHD_2$). Integration of these singlets gave a ratio $CH_3/CH_2D/CHD_2$ of 47/30/23 or 44/30/26 (two measurements).

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