Flexible molecules with defined shape. Part 3.[1] Conformational analysis of bis(tetrahydropyran-2-yl)methanes

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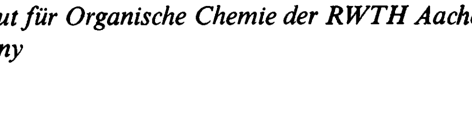
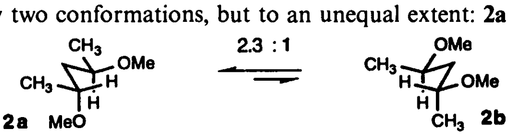
(*R*,*R*)-Bis(tetrahydropyran-2-yl)methane 4 along with its racemate have been synthesized. MM3 calculations suggest that the conformer 4a should be populated to *ca.* 85% in the conformer equilibrium. Analysis of the ^{1}H NMR coupling constants show that one conformer predominates by about 9 : 1. That this is the conformer 4a is shown by various NMR techniques, as well as by comparison of calculated with measured CD spectroscopic data. The study is extended to the methyl-substituted bis(tetrahydropyranyl)methanes 21 and 23 which show, as predicted from MM3 calculations, essentially mono-conformational behaviour.

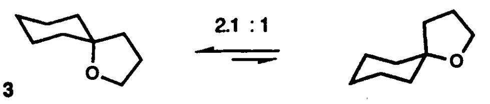
Conformation design[2] aims at the recognition and synthesis of segments of molecular backbones, which are conformationally flexible, but populate predominantly (*i.e.* >90%) a single conformation. The starting point for the considerations is a multi-conformational carbon chain. A mono-conformational structure should result if destabilizing interactions could be introduced by structural modification into all but one of the low energy conformations. For instance, pentane has five low energy conformations (E_{rel} < 3 kcal mol^{-1}†) available.[3] Introduction of two methyl groups into the 2 and 4 position reduces the conformational diversity to a bi-conformational situation,[4] as 2,4-dimethylpentane (1) populates just two enantiomorphic



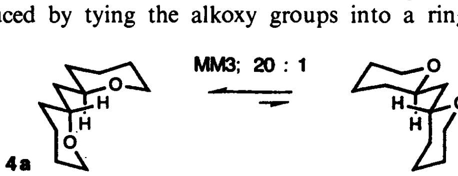
conformations. All other diamond lattice conformations of 1 suffer from destabilizing g^+g^--interactions and are hence of higher energy.

Introduction of further alkyl substituents may not be an appropriate way to create a mono-conformational situation, because such further substituents will destabilize the low energy conformation as well. Rather, the conformational degeneracy of 1 could be lifted by changing to non-alkyl substituents. For instance, 2,4-dimethoxypentane 2 has been found to populate mainly two conformations, but to an unequal extent: 2a being





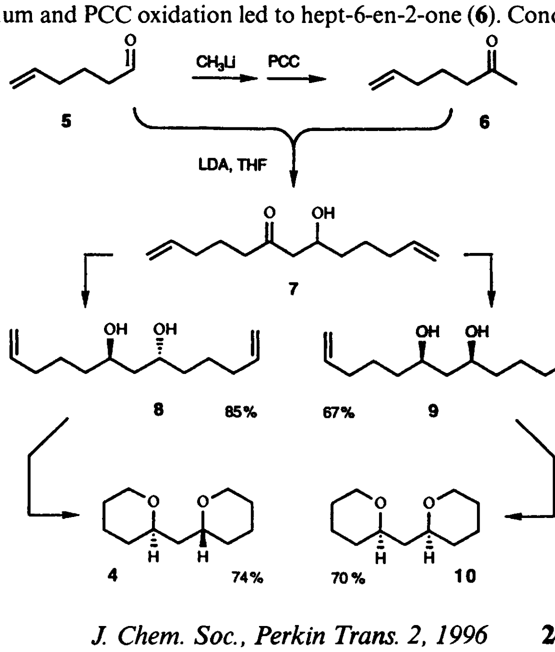
favoured by a margin of approximately 2 : 1,[5] because the *O*-methyl group is slimmer than the methyl group, *cf.* the *A* values (OMe = 0.75 and Me = 1.74 kcal mol^{-1}) or the conformer equilibrium of the spiro compound 3.[6] In other words, the 1,3-parallel interactions between a C–H bond and a methyl group are more destabilizing than the similar interactions between a C–H bond and a methoxy group.[7] With respect to the compound 2, this effect on the conformer equilibrium is probably counteracted to some extent by the different restriction in conformational freedom experienced by the methoxy groups in 2a and 2b: *i.e.* 2a has only four low energy methoxy rotamers accessible, whereas 2b has nine rotamers available. This statistical advantage of the skeletal arrangement 2b can be reduced by tying the alkoxy groups into a ring. Hence,



the conformational equilibrium of 4 should be further on the side of 4a. MM2 calculations predicted[1] a 4 : 1, and MM3*-calculations an 11 : 1, preference for 4a. This induced us to synthesize the bis(tetrahydropyranyl)methane 4 and related compounds, and to study their conformational properties.

Synthesis of bis(tetrahydropyranyl)methanes

The synthesis of the C_2-symmetric bis(tetrahydropyranyl)-methane 4 started from hex-5-enal[8] (5) (generated by Cope-rearrangement from hexa-1,5-dien-3-ol[9]). Addition of methyllithium and PCC oxidation led to hept-6-en-2-one (6). Conden-



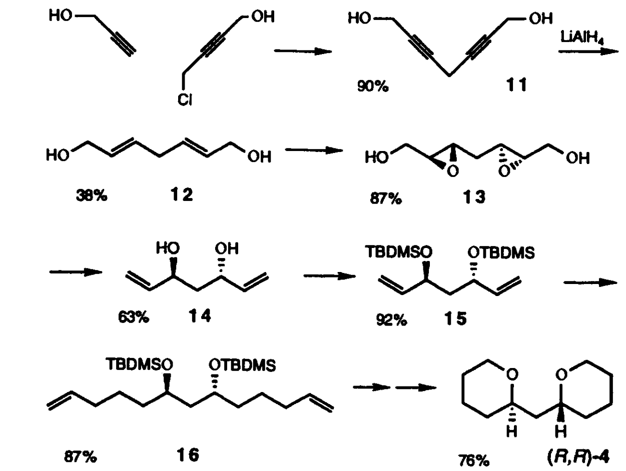
† 1 cal = 4.184 J.

sation of **5** and **6** provided the aldol **7**, which was reduced with tetramethylammonium triacetoxyborohydride to furnish the racemic *anti*-diol **8** with a diastereoselectivity (ds) of 92% according to the ^{13}C NMR spectrum. Ozonolysis of **8** followed by reduction of the resulting bis-lactol gave the desired bis-(tetrahydropyranyl)methane **4**.

Likewise, reduction of the aldol **7** by diethylmethoxyborane–$NaBH_4$ gave the *meso*-diol **9** which was converted by ozonolysis and reduction of the bis-lactol to the *meso*-bis(tetrahydropyranyl)methane **10**.

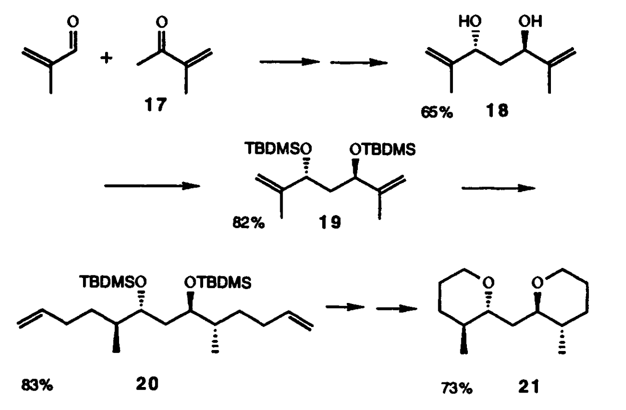
Conformational analysis of bis(tetrahydropyranyl)methanes can be carried out with racemic compounds, such as **4**. Yet, conformational preferences should also be reflected in the chiroptical properties. For a study of the latter, enantiomerically pure material is required. We therefore embarked on a synthesis of (*R*,*R*)-**4** using a bidirectional strategy.

The starting point is the symmetrical heptadiynediol **11**, which could be obtained from prop-2-ynol and the 4-chlorobut-2-ynol in 90% yield.[10] Lithium aluminium hydride reduction of **11** led to the (*E*,*E*)-heptadienediol **12** in moderate yield (38%).



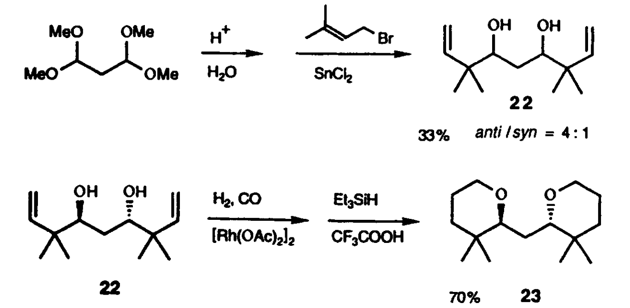
Sharpless epoxidation of the latter furnished the diepoxide **13**, which could be converted to the (*S*,*S*)-heptadienediol **14** in 63% yield. Silylation with *tert*-butyldimethylsilyl chloride to give **15** set the stage for a chain extension based on Knochel's transmetallation reactions.[11] Thus, hydroboration of **15** by 9-BBN (9-borabicyclo[3.3.1]nonane) was followed by boron–zinc exchange, followed again by a copper–zinc exchange and terminated by coupling with allyl iodide. This one-pot procedure provided 78% of the tridecadiene **16**. The latter was deprotected to furnish (*R*,*R*)-**7** (89%) which was then converted to (*R*,*R*)-**4** as described above.

Of further interest, as detailed below, were bis(tetrahydropyranyl)methanes which carry methyl substituents in the 3- and 3′-positions, such as **21** and **23**. The synthesis of **21** commenced



from 2-methylprop-2-enal and the α,β-unsaturated ketone **17**. Aldol condensation[12] followed by triacetoxyborohydride reduction led to the *anti*-diol **18** (ds 94%). This was converted to the bis-silyl derivative **19**. Creation of the next two stereogenic centres was effected by stereoselective hydroboration with 9-BBN.[13] The resulting alkylborane was again subjected to a chain extension by Knochel transmetallation[11] leading to the tridecadiene **20** in good yield. Further conversion into the bis(tetrahydropyranyl)methane **20** followed the routes used in the preparation of **4** and **10**.

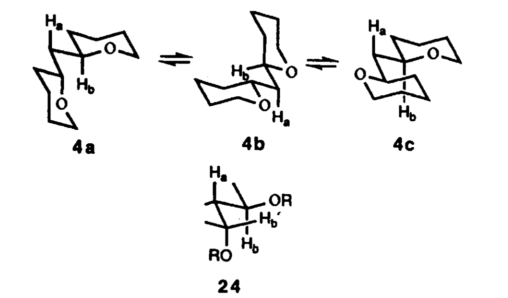
Synthesis of the tetramethyl derivative **23** was based on a bidirectional chain extension[14] of malonaldehyde bis(dimethyl acetal). This was effected by the reaction with 4-bromo-2-methylbut-2-ene and tin(II) chloride[15] in DMF resulting in a 4:1 (±)/*meso* mixture of the diols **22**. The *anti*-diol **22** could



be crystallized (20% yield) from this mixture. It was easily converted into the bis(tetrahydropyranyl)methane **23** by regioselective hydroformylation followed by reduction of the bis-lactol as before.

Analysis of the conformer populations

According to MM3 calculations the bis(tetrahydropyranyl)-methane **4** should populate mainly three conformations **4a**, **4b** and **4c** in an 85:4:10 ratio. Since individual pairs of vicinal



protons have different couplings in the different conformers, (*e.g.* the coupling constant between the protons H_a and H_b should be large in **4a** and small in **4b**) the conformer population will be reflected in the apparent vicinal coupling constants of the protons in the CH_2 bridge in **4**. The measured coupling constant is an average value weighted by the conformer population, *i.e.* for a 1:1 conformer population of **4a** and **4b** the average coupling constant would be approximately 6–7 Hz. If one conformer predominates in the equilibrium two couplings, one >6 Hz and one <6 Hz should be observed. If one conformer is populated to >90%, the coupling constants would reflect those of the specific conformer. Coupling constants for the individual conformers of **4** can be predicted on the basis of model compounds, a routine implemented in the MACROMODEL[16] program. For instance, coupling constants of 9.4 and 2.7 Hz were predicted this way for **4a**.

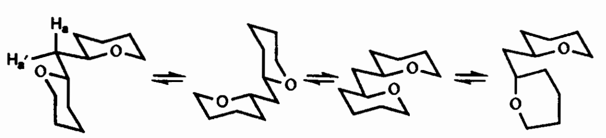
In order to see whether one conformer is substantially favoured in the conformer equilibrium of **4** we had to determine the coupling constants for the protons of the bridge of **4**. The ^{1}H NMR spectra were recorded in [$^2H_8$]toluene, which resulted in better resolved coupling patterns. Since compound **4** has C_2

Table 1 $^3J_{HH}$ Coupling constants (±0.2 Hz) for the protons H_a and H_a' in **4**

T/°C	J_{H_a,H_b}	$J_{H_a,H_b'}$
−30	2.4	9.9
+27	2.7	9.4
+50	3.0	9.0

symmetry, H_a and H_a', as well as H_b and H_b', *cf.* **24**, are homotopic. The spectra are therefore of higher order and the coupling constants can only be estimated by simulation of the spectra. Simulation was carried out with the program CALM.[17] The results are compiled in Table 1. The alteration of the apparent coupling constants shows that one conformer of **4** predominates in the conformer equilibrium, yet the temperature dependence shows that the equilibrium does not lie completely on one side. The preferred conformer can be either **4a** or **4b**, but not **4c**, since a predominance of **4c** should lead to coupling constants around 6 Hz. The large coupling constants in the individual conformers **4a**, **4b** and **4c** can be assumed[5] to be about 10.2 Hz and the small ones about 1.5 Hz. If, for example, the conformer **4a** predominates, a 10% population of **4b** or a 20% population of **4c** would reduce the apparent coupling constants to 9.3 and 2.2 Hz, respectively. In view of the uncertainty (±0.2 Hz) of the experimentally derived coupling constants it is justified to combine the contributions from the minor conformers without weighting that of **4b** as twice that of **4c**. This then leads to the qualitative statement that the population of the major conformer should be around 85% at 27 °C and >90% at −30 °C. When comparing these values to the data reported for **2** it becomes evident that tying the loose methoxy groups into a ring has a substantial effect on the conformer population.

While **4** is a C_2 symmetrical molecule, the consequence of this fact for the conformational preferences becomes apparent when comparing it to its σ-symmetric *meso*-analogue **10**. According

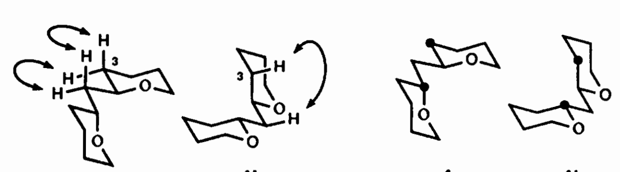


10a **10a′** **10b** **10c**

to MM3* calculations, **10** should populate mainly (78%) two chiral enantiomorphs, and hence isoenergetic, conformations **10a** and **10a′**. The remainder falls to the conformations **10b** and **10c**. The equal population of the two enantiomorphous conformations is manifest in the coupling constants of the diastereotopically distinct protons H_a and H_b to their respective neighbours: both H_a and H_b show an average coupling constant of 7 Hz, in line with an essential bi-conformational situation.

Identity of the predominant conformer

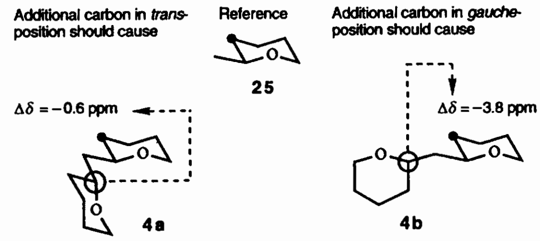
The coupling constants show that in the case of **4** one conformer is substantially favoured, but do not indicate whether this is **4a**, as predicted by the force field calculations, or perhaps **4b**. In the following we report several observations, which in concert suggest that **4a** is the preferred conformer. The first indications came from NOE experiments. NOE contacts were found from the protons of the methylene bridge to both diastereotopic protons on C-3 as expected for **4a**. If **4b** were to predominate, an NOE only to the axial proton on C-3 would be expected.



4a **4b** **4a** **4b**

Next, by a GRECCO experiment,[18] the $^3J_{C,C}$ coupling between the carbons marked was investigated. In **4a** the carbons are arranged in a *trans*-disposition, in **4b** in a *gauche*-disposition. The $^3J_{C,C}$ coupling constant was determined to 3.4 Hz, which while being small for a *trans*-coupling, matches the *trans*-coupling constants found in certain cyclohexane derivatives.[19]

^{13}C-Chemical shifts are conformation dependent, a fact that has been applied to conformational analysis by Whitesell *et al.*[20] Following his reasoning, the chemical shift of the marked carbon in **4a** and **4b** can be predicted in relation to an appropriate



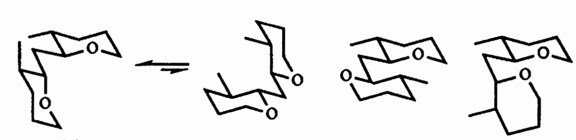
reference structure **25**. To determine the difference in chemical shifts for C-3 in **25** and **4** the ^{13}C NMR spectrum was measured for a mixture of the two compounds. The Δδ for C-3 was found to be −0.9 ppm, in line with a 9 : 1 preference of **4a** over **4b**.

Finally, the conformers **4a** and **4b** should have different chiroptical properties. However, there were no data for model compounds on which to base predictions as to the sign and magnitude of the Cotton effect for **4a** and **4b**. For this reason, we calculated the CD spectra of **4a** and **4b** based on the MM3 geometries using the program package DZDO/MCD3SP,[21] which allows the calculation of excitation energies and rotational strengths for a given molecular geometry. We chose the semiempirical method CNDO/2S,[22] which had been previously used by us for the calculation of the CD spectra of some biaryl systems.[23] The CI (configuration interaction) calculations were performed with 196 single excitations. The wavelengths obtained for the four lowest energy transitions and the corresponding rotational strengths are given in Table 2. As one can see, the rotational strengths of the two conformers differ markedly. As is usual for $\sigma \longrightarrow \sigma^*$ and $n \longrightarrow \sigma^*$ transitions investigated by semiempirical methods, the calculated wavelengths are much too small, when compared to the experimental absorptions, but this holds equally for both conformers allowing a comparison of their calculated optical properties.

We then multiplied all the rotational strengths with Gaussians centred at the respective wavelengths using an empirical bandwidth at half height of 7 nm and constructed the CD spectra for **4a** and **4b** (see Fig. 1). One can see that the first significant CD band of **4a** and **4b**, which corresponds to the one which is observable with normal instrumentation, differs in sign. As (*R*,*R*)-**4** was found to have a negative Cotton effect, $\Delta\varepsilon = -2.94$, this further strengthens our conclusion that the predominant conformer of **4** is the conformer **4a**.

Methyl-substituted bis(tetrahydropyranyl)methanes

The change from compound **2** to compound **4** led to an increase in the population of the preferred conformer from 70% to about 90%. In order to approach a mono-conformational situation, we intended to introduce substituents, which should selectively destabilize the minor conformers **4b** and **4c** with an



21a **21b** **21c** **21d**

J = 10.1 and 2.0 Hz

Table 2 Wavelengths and rotational strengths for the four lowest energy transitions of **4a** and **4b**

	Transition 1		Transition 2		Transition 3		Transition 4	
	λ/nm	$R[^{DBM}_{100}]$ [a]	λ/nm	$R[^{DBM}_{100}]$	λ/nm	$R[^{DBM}_{100}]$	λ/nm	$R[^{DBM}_{100}]$
4a	121.9	7.5	121.5	−132.2	119.6	73.7	119.6	51.5
4b	122.2	−460.8	122.0	447.9	119.8	206.6	119.8	−160.9

[a] DBM = Debye–Bohr magneton.

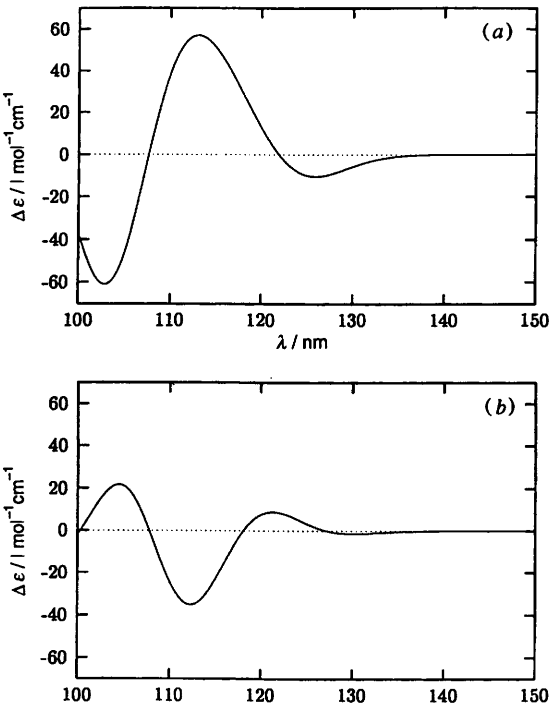
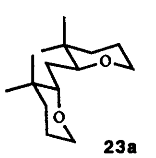


Fig. 1 The calculated CD spectrum of (*a*) **4a** and (*b*) **4b**

attendant increase in the population of the **4a** type conformer. This could be realized with the dimethyl-substituted system **21**. While the two methyl substituents are in a comfortable position in **21a**, they would suffer *syn*-pentane interactions in **21b** or **21c**. The coupling constants determined for **21** (J = 10.1 and 2.0 Hz) reflect an increase in the conformer population of **21a** to >95%. MM3* calculations suggest that in addition conformation **21d** should be populated to about 2%. Introduction of two further methyl substituents as in **23** should selectively destabilize the conformer of the **21d** type. Hence, the conformation **23a** should

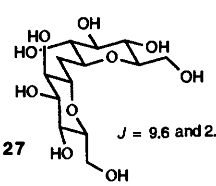


23a

J = 10.2 and 1.3 Hz

26

27



J = 9.6 and 2.4 Hz

be populated to an even larger extent. The coupling constants determined for **23**, J = 10.2 and 1.5 Hz, signal that **23** is an essentially mono-conformational entity. The predominance of the conformation **23a** can be considered as a consequence of the *tert*-butyl effect, whereby in 2,2,6,6-tetramethylheptane (**26**) each of the central bonds should be of the *trans*-conformation.[24] The evolution of the structure from compound **1** over **2** and **4**, to **23** shows how a bi-conformational backbone (**1**) can be 'converted' to a mono-conformational one (**23**) by conformation design. These structures, the bis(tetrahydropyranyl)methanes, investigated are by no means unique: *C*-β,β-trehalose (**27**) is a compound related to **4**, whose tendency to populate a single conformation (J = 9.6 and 2.4 Hz)[25] is in between that of **4** and **21**. Moreover, *C*-glycosides in general are likewise bis(tetrahydropyranyl)methanes. Again, the substituent pattern may lead to marked conformational preferences, which have been improved by judicious conformation design.[26]

Experimental

All reactions have been carried out in flame dried glassware under dry nitrogen. All temperatures quoted are not corrected. ^{1}H NMR, ^{13}C NMR: Bruker AC 300 and AMX 500. J values are given in Hz. Polarimetry: Perkin-Elmer 241. CD-spectra: Spectrometer AVIV 62 DS. Boiling range of light petroleum: 40–60 °C. Column chromatography: Kieselgel 60 (0.063–0.200 mm, Merck, Darmstadt). Flash chromatography: Kieselgel 60 (0.040–0.063 mm, Merck, Darmstadt). $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Hept-6-en-2-ol

The aldehyde **5**[8] (4.94 g, 50.3 mmol) in 20 ml of diethyl ether was added at −78 °C to 35 ml of a 1.6 M solution of methyllithium in diethyl ether (56 mmol). The reaction was allowed to reach room temperature and was hydrolysed at 0 °C by addition of 20 ml of saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted three times with 30 ml of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated. The residue was purified by bulb-to-bulb distillation at 0.1 mbar, 30 °C (water bath) to give 5.53 g (96%) of the desired alcohol as a colourless liquid. δ_H (300 MHz, $CDCl_3$) 1.15 (d, J 6.2, 3 H), 1.32–1.53 (m, 4 H), 1.79 (s, 1 H), 1.96–2.10 (m, 2 H), 3.68–3.84 (m, 1 H), 4.84–5.02 (m, 2 H), 5.77 (dddd, J 16.9, 10.3, 6.7 and 6.7, 1 H); δ_C(75 MHz, $CDCl_3$) 23.4, 25.0, 33.3, 38.7, 67.9, 114.5 [$C_7H_{14}O$ (M, 114.2): calc. C 73.63, H 12.36; found C 73.53, H 12.30%].

Hept-6-en-2-one 6

Hept-6-en-2-ol (5.12 g, 44.8 mmol) was added at 0 °C to a suspension of 14.0 g (65 mmol) of pyridinium chlorochromate and 14 g of silica gel in 100 ml of anhydrous dichloromethane. After stirring for 2 h at room temperature 150 ml of diethyl ether were added, the mixture was filtered over silica gel followed by washing with 100 ml of diethyl ether. The combined filtrates were concentrated under normal pressure and the residue was purified by bulb to bulb distillation to give 4.15 g (86%) of **6** as a colourless liquid. The NMR data agreed with those given in ref. 27.

8-Hydroxytrideca-1,12-dien-6-one 7

A 1.4 M solution of butyllithium in hexane (11.8 ml, 16.5 mmol) was added at −78 °C to a solution of 3.0 ml (21 mmol) of anhydrous diisopropylamine in 40 ml of anhydrous THF. The mixture was allowed to reach 0 °C and was cooled again to −78 °C. The ketone **6** (1.846 g, 16.4 mmol) was added and after 15 min stirring, 1.643 g (16.4 mmol) of the aldehyde **5** was added. The reaction was quenched after 7 min by addition of 1.2 ml (20 mmol) of acetic acid. After reaching room temperature 20 ml of water was added and the phases were separated. The aqueous phase was extracted three times with 50 ml each of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with diethyl ether–light petroleum (1 : 3) furnished 1.95 g (56%) of the aldol **7** as a slightly yellowish oil. δ_H(300 MHz, $CDCl_3$) 1.29–1.74 (m, 6 H), 1.92–2.12 (m, 4 H), 2.26–2.64 (m, 4 H), 3.05 (s, 1 H), 3.92–4.08 (m, 1 H), 4.86–5.06 (m, 4 H), 5.64–5.86 (m, 2 H); δ_C(75 MHz, $CDCl_3$) 22.6, 24.7, 33.0, 33.5, 35.9, 42.7, 49.1, 67.5, 114.7, 115.4, 137.8, 138.5, 212.0 [$C_{13}H_{22}O_2$ (*M*, 210.3): calc. C 74.24, H 10.54; found C 74.19, H 10.35%].

(6*R,8*R**)-Trideca-1,12-diene-6,8-diol 8**

Tetramethylammonium triacetoxyborohydride[28] (18.5 g, 70 mmol) was added slowly under nitrogen to a mixture of 40 ml of acetonitrile and 40 ml of acetic acid. After stirring for 30 min the solution was cooled to −40 °C and a solution of 1.845 g (8.7 mmol) of the aldol **7** in 12 ml of acetonitrile was added. The mixture was stirred for 36 h at −40 °C. A solution of 1 M aqueous potassium sodium tartrate (105 ml) was added followed by 45 ml of 25% aqueous ammonia, to render the mixture alkaline. The phases were separated and the aqueous phases extracted four times with 100 ml of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue with *tert*-butyl methyl ether–light petroleum (1 : 1) furnished 1.58 g (85%) of the diol **8** as a colourless viscous oil in 92% diastereomeric purity according to the ^{13}C NMR spectrum. δ_H(300 MHz, $CDCl_3$) 1.28–1.71 (m, 10 H), 1.95–2.17 (m, 4 H), 2.49 (br s, 2 H), 3.87–4.01 (m, 2 H), 4.89–5.07 (m, 4 H), 5.80 (dddd, *J* 16.9, 10.3, 6.7 and 6.7, 2 H); δ_C(75 MHz, $CDCl_3$) 25.0, 33.6, 36.9, 42.4, 69.3, 114.7, 138.6 [$C_{13}H_{24}O_2$ (*M*, 212.3): calc. C 73.54, H 11.39; found C 73.50, H 11.59%].

(*R,*R**)-Bis(tetrahydropyran-2-yl)methane 4**

A stream of ozone in oxygen was introduced at −78 °C into a solution of 609 mg (2.87 mmol) of the diol **8** in 20 ml of anhydrous dichloromethane until the blue colour persisted. The excess of ozone was removed by a stream of anhydrous nitrogen. A solution of 1.58 g (6.0 mmol) of triphenylphosphine in 5 ml of dichloromethane was added and the mixture was allowed to reach room temperature. The solvents were removed *in vacuo* at 0.1 mbar, 4 h. The residue was taken up in 20 ml of dichloromethane. Triethylsilane (2.3 ml, 14 mmol) and trifluoroacetic acid (1.4 ml, 19 mmol) were added. After heating to reflux for 6 h the mixture was allowed to stand for 12 h. 25% Aqueous ammonia (3 ml) was added. The phases were separated and the aqueous phase was extracted twice with 20 ml of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with diethyl ether–light petroleum (1 : 4) furnished 73 mg (14%) of a diastereomeric mixture followed by 393 mg (74%) of diastereomerically pure **4** as a colourless liquid. δ_H(500 MHz, [$^2H_8$]toluene) 1.14–1.27 (m, 4 H), 1.34 (qt, *J* 12.7 and 3.8, 2 H), 1.39–1.50 (m, 4 H), 1.54 (ddd, *J* 14.0, 9.4 and 2.7, 2 H), 1.60–1.68 (m, 2 H), 3.31 (td, *J* 11.4 and 2.3, 2 H), 3.60 (m, *J* 10.9, 9.4, 2.7 and 1.9, 2 H), 3.89 (dddd, *J* 11.4, 4.0, 1.7 and 1.7 Hz, 2 H); δ_C(125 MHz, [$^2H_8$]toluene) 24.2, 26.7, 33.2, 44.8, 68.3, 74.3 [$C_{11}H_{20}O_2$ (*M*, 184.3): calc. C 71.70, H 10.94; found C 71.65, H 10.88%].

(6*R,8*S**)-Trideca-1,12-diene-6,8-diol 9**

A 15% solution of triethylborane in hexane (4.8 ml, 5.0 mmol) was added to a solution of 0.2 ml of methanol and of 4 mg of pivalic acid in 5 ml of anhydrous THF. After 1 h the mixture was diluted with 20 ml of THF and cooled to −78 °C. Methanol (8 ml) and a solution of 789 mg (3.75 mmol) of the aldol **7** in 3 ml of THF were added slowly. After 30 min, 0.20 g (5.3 mmol) of sodium borohydride were added and the mixture was stirred for 8 h at −78 °C. After reaching room temperature, 20 ml of saturated aqueous NH_4Cl were added, the phases separated and the aqueous phase extracted four times with 50 ml each of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with light petroleum–diethyl ether (1 : 2) furnished 532 mg (67%) of the diol **9** as a colourless oil in 95% diastereomeric purity according to the ^{13}C NMR spectrum. δ_H(300 MHz, $CDCl_3$) 1.30–1.62 (m, 10 H), 1.98–2.10 (m, 4 H), 3.34 (br s, 2 H), 3.76–3.90 (m, 2 H), 4.88–5.04 (m, 4 H), 5.79 (dddd, *J* 16.9, 10.3, 6.7 and 6.7, 2 H); δ_C(75 MHz, $CDCl_3$) 24.6, 33.6, 37.6, 42.8, 72.9, 114.6, 138.6 [$C_{13}H_{24}O_2$ (*M*, 212.3): calc. C 73.54, H 11.39; found C 73.36, H 11.21%].

***meso*-Bis(tetrahydropyran-2-yl)methane 10**

The diol **9** (228 mg, 1.07 mmol) was ozonolysed and reductively cyclized as described in the preparation of **4** to give 139 mg (70%) of **10** as a colourless oil. δ_H(500 MHz, [$^2H_8$]toluene) 1.14–1.35 (m, 6 H), 1.40–1.52 (m, 5 H), 1.60–1.70 (m, 2 H), 2.01 (ddd, *J* 13.8, 7.0 and 7.0 Hz, 1 H), 3.23 (ddd, *J* 11.3, 2.1 and 2.1, 2 H), 3.39–3.47 (m, 2 H), 3.87 (ddd, *J* 11.3, 2.2 and 2.2, 2 H); δ_C(125 MHz, [$^2H_8$]toluene) 23.0, 26.7, 32.3, 43.8, 68.3, 74.6 [$C_{11}H_{20}O_4$ (*M*, 184.3): calc. C 71.70, H 10.94; found C 71.53, H 11.15%].

Hepta-2,5-diyne-1,7-diol 11

Into 100 ml of anhydrous dimethylformamide were added under stirring sequentially 20.0 g (0.15 mol) of powdered potassium carbonate, 22 g (0.15 mol) of anhydrous sodium iodide, 14 g (74 mmol) of copper iodide and 7.0 g (0.13 mol) of prop-2-ynol. After stirring for 30 min, 7.32 g (70 mmol) of 4-chloro-2-butynol were added and the mixture was stirred for 6 h under nitrogen. The solvents were removed at 0.1 mbar with the bath temperature being held below 40 °C. The residue was dissolved in 250 ml of ethyl acetate and was filtered through 2 cm of Kieselguhr. The filtrate was concentrated and 400 ml of water were added to the residue. The precipitate formed was filtered. The water was removed from the filtrate by freeze drying. The residue was taken up in 250 ml of ethyl acetate, 100 g of neutral alumina were added, the suspension was thoroughly mixed and the solvent was removed *in vacuo*. The residue was placed in two charges on top of a chromatography column with 300 g of silica gel each. Chromatography with ethyl acetate–light petroleum (1 : 1) furnished 7.85 g (90%) of the diol **11** as a light yellow solid, mp 87 °C. δ_H(300 MHz, [$^2H_6$]acetone) 3.29 (s, 2 H), 4.19 (s, 6 H); δ_C(75 MHz, [$^2H_6$]acetone) 9.7, 50.6, 79.0, 80.5 [$C_7H_8O_2$ (*M*, 124.1): calc. C 67.73, H 6.50; found C 67.48, H 6.44%].

(*E*,*E*)-Hepta-2,5-diene-1,7-diol 12

2-Methoxyethanol (17.4 ml, 0.22 mol) was added at 0 °C to a solution of 5.0 g (0.13 mol) of $LiAlH_4$ in 100 ml of anhydrous THF. After cooling to −30 °C a solution of 3.00 g (24.2 mmol) of the diol **11** in 20 ml THF was added dropwise. The mixture was stirred at 0 °C (1 h) and room temperature (14 h). THF (100 ml) was added, the mixture cooled to −78 °C and hydrolysed by addition of 11 ml of water. The pasty mixture was filtered and the residue was washed with 150 ml of THF and 100 ml of ethanol. The filtrates were concentrated *in vacuo*. Flash chromatography of the residue with ethyl acetate furnished 1.17 g (38%) of the diol **12** as a colourless oil. δ_H(500 MHz, $CDCl_3$) 2.72 (t, *J* 5.8, 2 H), 3.35 (s, 2 H), 3.98 (d, *J* 5.1, 4 H), 5.54 (td, *J* 15.5 and 5.1, 2 H), 5.60 (td, *J* 15.5 and 5.8, 2 H); δ_C(125 MHz, $CDCl_3$) 34.6, 63.9, 129.9, 130.0 [$C_7H_{12}O_2$ (*M*, 128.2): calc. C 65.60, H 9.44; found C 65.49, H 9.30%].

(2*S*,3*S*,5*S*,6*S*)-2,3:5,6-Diepoxyheptane-1,7-diol 13

Powdered molecular sieves (4 Å, 1.5 g) were suspended in 30 ml of dichloromethane and 10 ml of chloroform. At −10 °C, 277 mg (1.34 mmol) of (2*R*,3*R*)-(+)-diethyl tartrate, 255 mg (0.90 mmol) of titanium tetraisopropoxide and 4.5 ml (27 mmol) of a 6 M solution of *tert*-butyl hydroperoxide in decane were added sequentially. After stirring for 30 min the mixture was cooled to −30 °C. A solution of 1.150 g (8.97 mmol) of the diol **12** in 10 ml of chloroform was added. The mixture was stirred for 1 h at −30 °C and stored in a deep freeze for 36 h at −25 °C. A solution of 192 mg (0.91 mmol) of citric acid monohydrate in 3 ml of acetone and 20 ml of diethyl ether was added at this temperature. After reaching room temperature, the mixture was filtered and the residue was washed with 30 ml of THF and 80 ml of acetonitrile. The combined filtrates were discarded. The residue was washed with 80 ml of water to extract the product. The solution was concentrated by freeze drying to give 1.26 g (87%) of the diol **13** as a colourless powder, mp 161 °C. The ee was determined to be 98% by Mosher analysis of the monosilyl derivative of **14**. $[\alpha]_D^{20}$ −49.8 (c 0.64, H_2O); δ_H(300 MHz, D_2O, relative to HDO at δ 4.80) 1.93 (t, J 5.6, 2 H), 3.14–3.26 (m, 4 H), 3.56 (dd, J 13.0 and 5.4, 2 H), 3.91 (dd, J 13.0 and 2.7, 2 H); δ_C(125 MHz, D_2O relative to CH_3OD at δ 47.5) 31.5, 52.5, 57.5, 59.6.

(3*R*,5*R*)-Hepta-1,6-diene-3,5-diol 14

A solution of 1.98 g (7.8 mmol) of iodine in 10 ml of THF was added under nitrogen and cooling to a solution of 2.06 g (7.9 mmol) of triphenylphosphine in 40 ml of THF maintaining the temperature around 20 °C by external cooling. After stirring for 5 min, 0.60 g (8.8 mmol) of imidazole and 600 mg (3.75 mmol) of the epoxy alcohol **13** were added. After stirring for 40 min at room temperature the mixture was cooled to 0 °C and 2.0 g of zinc–copper couple were added. The mixture was held for 2 h under reflux; 0.5 ml of water was added and the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography with light petroleum–ethyl acetate (1 : 1) to give 302 mg (63%) of **14** as a colourless oil. $[\alpha]_D^{20}$ +17.2 (c 1.31, methanol); δ_H(300 MHz, $CDCl_3$) 1.69 (t, J 5.8, 2 H), 3.60 (s, 2 H), 4.38 (br td, J 5.8 and 5.4, 2 H), 5.07 (ddd, J 10.4, 1.4 and 1.4, 2 H), 5.22 (ddd, J 17.2, 1.4 and 1.4, 2 H), 5.85 (ddd, J 17.2, 10.4 and 5.4, 2 H); δ_C(75 MHz, $CDCl_3$) 42.0, 70.0, 114.4, 140.4 [$C_7H_{12}O_2$ (M, 128.2): calc. C 65.60, H 9.44; found C 65.52, H 9.31%].

(3*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)hepta-1,6-diene 15

4-Dimethylaminopyridine (*ca.* 50 mg) and 273 mg (2.1 mmol) of the diol **14** were added to a solution of 0.5 g (7 mmol) of imidazole and of 0.9 g (6 mmol) of *tert*-butyldimethylchlorosilane in 2 ml of anhydrous DMF. After stirring for 2 d at room temperature 20 ml of saturated aqueous NH_4Cl were added. The phases were separated and the aqueous phase was extracted three times with 50 ml each of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue with light petroleum furnished 698 mg (92%) of the product **15** as a colourless liquid. $[\alpha]_D^{20}$ +6.6 (c 6.98, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 0.02 (s, 6 H), 0.05 (s, 6 H), 0.88 (s, 18 H), 1.68 (t, J 6.5, 2 H), 4.17 (td, J 7.0 and 6.5, 2 H), 5.02 (ddd, J 10.3, 1.7 and 1.1, 2 H), 5.11 (ddd, J 17.2, 1.1 and 1.1, 2 H), 5.80 (ddd, J 17.2, 10.3 and 7.0, 2 H); δ_C(75 MHz, $CDCl_3$) −4.6, −3.9, 18.2, 25.9, 47.4, 71.3, 114.1, 141.9 [$C_{19}H_{40}O_2Si_2$ (M, 356.7): calc. C 63.98, H 11.30; found C 64.16, H 11.25%].

(6*R*,8*R*)-6,8-Bis(*tert*-butyldimethylsilyloxy)trideca-1,12-diene 16

To a solution of 690 mg (1.9 mmol) of the diene **15** in 5 ml of THF were added 9.0 ml (4.5 mmol) of a 0.5 M solution of 9-BBN in THF. After heating for 8 h under reflux the mixture was cooled to 0 °C and 14.0 ml (14.0 mmol) of a 1 M solution of diethylzinc in light petroleum was added. The solution was concentrated at 0 °C and 0.1 mbar by condensation of all volatiles into a liquid nitrogen trap. The residue was taken up in 30 ml of THF and the solution was cooled to −78 °C. A solution of 2.51 g (28.0 mmol) of copper cyanide and 2.37 g (56.0 mmol) of lithium chloride in 20 ml of THF were added dropwise. The mixture was allowed to reach 0 °C and was cooled again to −78 °C. 5.0 ml (54 mmol) of iodine-free allyl iodide were added dropwise. The mixture was allowed to reach room temperature over 2 h with stirring. The solvents were removed *in vacuo* and the residue was absorbed on 10 g of silica gel. The product was extracted by washing with 200 ml of light petroleum. Concentration of the solution followed by flash chromatography with light petroleum furnished 665 mg (78%) of the bis(silyl ether) **16** as a colourless oil. $[\alpha]_D^{20}$ −3.5 (c 10.75, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 0.04 (s, 6 H), 0.05 (s, 6 H), 0.88 (s, 18 H), 1.36–1.46 (m, 8 H), 1.55 (t, J 6.1, 2 H), 1.97–2.08 (m, 4 H), 3.66–3.78 (m, 2 H), 4.88–5.04 (m, 4 H), 5.75 (dddd, J 16.9, 10.3, 6.6 and 6.6, 2 H); δ_C(75 MHz, $CDCl_3$) −4.2, −4.0, 18.1, 24.3, 26.0, 33.9, 37.4, 45.4, 70.1, 114.4, 138.9.

(2*R*,2′*R*)-Bis(tetrahydropyran-2-yl)methane (*R*,*R*)-4

A suspension of 1.7 g (40 mmol) of sodium fluoride in 20 ml of diethyl ether was placed into a polyethylene vial. 6.7 ml (45 mmol) of trifluoroacetic acid and 640 mg (1.45 mmol) of the bis(silyl ether) **16** were added. After 6 d at room temperature 5 ml of methanol and 6.0 g of potassium hydroxide were added with cooling. After reaching room temperature 20 ml of water were added, the phases were separated and the aqueous phase was extracted three times with 50 ml of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with *tert*-butyl methyl ether–light petroleum (1 : 1) furnished 274 mg (89%) of (6*R*,8*R*)-trideca-1,12-diene-6,8-diol, which showed identical spectra to the material obtained in the synthesis of **8** {$[\alpha]_D^{20}$ −5.5 (c 3.51, $CHCl_3$)}. Triphenylphosphine (408 mg, 1.56 mmol), triethylsilane (0.6 ml, 3.7 mmol) and trifluoroacetic acid (0.4 ml, 4.5 mmol) were used to convert 157 mg of the diol obtained in 10 ml of anhydrous dichloromethane into (*R*,*R*)-**4** as described in the synthesis of **4**. $[\alpha]_D^{20}$ −24.1 (c 1.98, $CHCl_3$); −50.0 (c 2.26, methanol); −94.7 (c 1.85, benzene); $[\theta]_{182}^{20}$ -0.97×10^4 (c 7.27, perfluorooctane).

(3*R,5*R**)-2,6-Dimethylhepta-1,6-diene-3,5-diol 18**

2,6-Dimethyl-5-hydroxyhepta-1,6-dien-3-one[12] (2.12 g, 13.8 mmol) was reduced with 29.1 g (0.11 mol) of tetramethylammonium triacetoxyborohydride as described in the synthesis of **8**. Flash chromatography with ethyl acetate–light petroleum (1 : 3) furnished 2.00 g (93%) of the diol **18** as a colourless oil in 94% diasteroselectivity according to the ^1H and ^{13}C NMR spectra. δ_H(300 MHz, $CDCl_3$) 1.70 (s, 6 H), 1.78 (t, J 5.6, 2 H), 2.94 (s, 2 H), 4.28 (t, J 5.6, 2 H), 4.85 (s, 2 H), 5.02 (s, 2 H); δ_C(75 MHz, $CDCl_3$) 18.5, 38.5, 72.7, 110.3, 147.0 [$C_9H_{16}O_2$ (M, 156.2): calc. C 69.19, H 10.32; found C 69.31, H 10.45%].

(3*R,5*R**)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2,6-dimethylhepta-1,6-diene 19**

The diol **18** (1.60 g, 10.3 mmol) was silylated with 2.4 g (35 mmol) of imidazole and 4.4 g (29 mmol) of *tert*-butyldimethylchlorosilane as described in the synthesis of **15** to give 3.26 g (82%) of **19** as a colourless oil. δ_H(300 MHz, $CDCl_3$) −0.02 (s, 6 H), 0.04 (s, 6 H), 0.88 (s, 18 H), 1.65 (br t, J 6.2, 2 H), 1.67 (s, 6 H), 4.07 (t, J 6.2, 2 H), 4.72–4.77 (m, 2 H), 4.81 (s, 2 H); δ_C(75 MHz, $CDCl_3$) −5.0, −4.4, 16.5, 18.2, 25.9, 43.9, 74.3, 111.3, 147.8 [$C_{21}H_{44}O_2Si_2$ (M, 384.8): calc. C 65.56, H 11.53; found C 65.47, H 11.64%].

(5*R,6*S**,8*S**,9*R**)-6,8-Bis(*tert*-butyldimethylsilyloxy)-5,9-dimethyltrideca-1,12-diene 20**

A 0.5 M solution of 9-BBN in THF (11.6 ml, 5.8 mmol) was added to a solution of 1.01 g (2.6 mmol) of the diene **19** in 10 ml of THF. After 5 d at room temperature the mixture was cooled to 0 °C, and 17.4 ml (17.4 mmol) of a 1 M solution of diethylzinc in light petroleum was added. Subsequent reaction with 3.47 g (38.7 mmol) of copper cyanide, 3.29 g (77.5 mmol) of lithium chloride and 5.0 ml (87 mmol) of iodine-free allyl iodide followed by flash chromatography was carried out as described in the preparation of **16**, furnishing 1.02 g (83%) of **20** as a colourless oil. δ_H(300 MHz, $CDCl_3$) 0.03 (s, 6 H), 0.05 (s, 6 H), 0.83 (d, J 6.9, 6 H), 0.87 (s, 18 H), 1.04–1.42 (m, 6 H), 1.54–1.71 (m, 2 H), 1.86–2.20 (m, 4 H), 3.62–3.78 (m, 2 H), 4.87–5.05 (m, 4 H), 5.75 (dddd, J 16.9, 10.3, 6.6 and 6.6, 2 H); δ_C(75 MHz, $CDCl_3$) −4.2, −3.9, 13.7, 18.1, 25.9, 31.7, 32.2, 34.3, 38.7, 73.3, 114.3, 139.1 [$C_{27}H_{56}O_2Si_2$ (*M*, 468.9): calc. C 69.16, H 12.04; found C 69.28, H 11.96%].

(5*R,6*R**,8*S**,9*R**)-5,9-Dimethyltrideca-1,12-diene-6,8-diol**
Silyl ether **20** (444 mg, 0.95 mmol) was desilylated with 1.2 g (29 mmol) of sodium fluoride and 3.5 ml (45 mmol) of trifluoroacetic acid as described in the preparation of (*R*,*R*)-**4**. Flash chromatography with light petroleum–diethyl ether 1:1 furnished 205 mg (90%) of the product as a colourless liquid. δ_H(300 MHz, $CDCl_3$) 0.85 (d, *J* 6.7, 6 H), 1.05–1.20, 1.30–1.75 (m, 8 H), 1.75–2.25 (m, 4 H), 2.87 (br s, 2 H), 3.65–3.75 (m, 2 H), 4.80–5.02 (m, 4 H), 5.70–5.80 (m, 2 H); δ_C(75 MHz, $CDCl_3$) 15.0, 31.2, 31.6, 35.4, 38.3, 72.8, 114.3, 138.9 [$C_{15}H_{28}O_2$ (*M*, 240.4): calc. C 74.95, H 11.74; found C 74.76, H 11.75%].

(2*R,3*S**,2′*S**,3′*R**)-Bis(3-methyltetrahydropyran-2-yl)methane 21**
The 5,9-dimethyltrideca-1,12-diene-6,8-diol (153 mg, 0.64 mmol) was subjected to ozonolysis followed by reductive silylation as described in the preparation of **4** to give 118 mg (87%) of **21** as a colourless oil. δ_H(500 MHz, [$^2H_8$]toluene) 0.81 (d, *J* 6.6, 6 H), 0.95–1.06 (ddd, *J* 12.0, 12.0 and 4.0, 2 H), 1.20–1.30 (m, 4 H), 1.49–1.63 (m, 4 H), 1.69 (sextet, *J* 14.0, 10.1 and 2.0, 2 H), 3.27 (ddd, *J* 12.2, 11.1 and 2.2, 2 H), 3.35 (decet, *J* 10.1, 9.6 and 2.0, 2 H), 3.94 (dddd, *J* 11.1, 4.6, 2.1 and 1.8, 2 H); δ_C(125 MHz, [$^2H_8$]toluene) 18.4, 27.4, 33.5, 36.4, 38.3, 68.1, 79.6 [$C_{13}H_{24}O_2$ (*M*, 212.3): calc. C 73.54, H 11.39; found C 73.29, H 11.28%].

(4*R,6*R**)-3,3,7,7-Tetramethylnona-1,8-diene-4,6-diol 22**
Stirring of 44.2 g (0.27 mol) of 1,1,3,3-tetramethoxypropane in 270 ml of 1 M aqueous hydrochloric acid led to a homogenous solution. After 45 min at 30 °C the mixture was cooled to 0 °C. A solution of 21.5 g (0.54 mol) of sodium hydroxide in 100 ml of water was added. The deep red mixture was concentrated *in vacuo*, the residue was dried at 0.1 mbar and was suspended in 600 ml of dimethylformamide. At 0 °C, 20.6 ml (0.27 mol) of trifluoroacetic acid were added, followed by 135 g (0.90 mol) of sodium iodide, 95.0 g (0.64 mol) of 1-bromo-3-methylbut-2-ene and 190 g (0.84 mol) of tin dichloride dihydrate. The temperature was monitored and not allowed to exceed 30 °C. After stirring for 4 d at room temperature under nitrogen the mixture was poured into 0.8 l of a 15% aqueous NH_4F solution. The phases were separated and the aqueous phase was extracted four times with 150 ml each of *tert*-butyl methyl ether. The combined organic phases were washed with 50 ml of 30% aqueous K_2CO_3 and concentrated. The solid residue was dissolved in 100 ml of *tert*-butyl methyl ether and was stirred with *ca.* 200 mg of zinc powder for 30 min. The mixture was diluted with 200 ml of *tert*-butyl methyl ether and dried with $MgSO_4$. Concentration of the solution led to a residue which was bulb to bulb distilled at 110 °C and 1 mbar to give 19.1 g (33%) of a 1:4 *syn*:*anti* mixture (according to the ^{13}C NMR spectrum) of **22**. Recrystallisation from toluene furnished 10.4 g of the *anti*-diol **22**. From the mother liquor another 1.06 g could be obtained to furnish a total of 11.5 g (20%) of **22**, mp 122 °C. δ_H(500 MHz, $CDCl_3$) 1.04 (s, 6 H), 1.05 (s, 6 H), 1.45 (sextet, *J* 14.0, 10.8 and 1.8, 2 H), 1.77 (d, *J* 5.1, 2 H), 3.63 (decet, *J* 14.0, 10.8, 5.1 and 1.8, 2 H), 5.09 (dd, *J* 17.6 and 1.4, 2 H), 5.12 (dd, *J* 10.8 and 1.4, 2 H), 5.85 (dd, *J* 17.6 and 10.8, 2 H); δ_C(75 MHz, $CDCl_3$) 22.2, 23.2, 32.6, 41.5, 74.5, 113.4, 145.3 [$C_{13}H_{24}O_2$ (*M*, 212.3): calc. C 73.54, H 11.39; found C 73.68, H 11.50%].

(2*R,2′*S**)-Bis(3,3-dimethyltetrahydropyran-2-yl)methane 23**
Into a steel autoclave was placed a solution of 2.12 g (10 mmol) of the diol **22**, 2.0 g (7.6 mmol) of triphenylphosphine in 10 ml of ethyl acetate. 40 mg of rhodium diacetate were added and the autoclave was pressurized to 35 bar with a 1:1 mixture of carbon monoxide and hydrogen. The autoclave was heated to 110 °C for 12 h during which time the reaction mixture was stirred. After cooling, the resulting mixture was concentrated and the residue was taken up in 50 ml of dichloromethane, and the mixture was filtered over 200 g of silica gel. The column was washed with 400 ml of a 10:1 mixture of dichloromethane and diethyl ether. The filtrates were discarded. The product **23** was eluted from the column with 800 ml of ethyl acetate. Solvents were removed *in vacuo* and the residue was taken up in 50 ml of dichloromethane. Reductive cyclization was effected with 4.8 ml (30 mmol) of triethylsilane and 4.6 ml (60 mmol) of trifluoroacetic acid as described in the preparation of **4**. Flash chromatography with light petroleum–diethyl ether (10:1) furnished 1.68 g (70%) **23** as colourless crystals, mp 53 °C. δ_H(500 MHz, [$^2H_8$]toluene) 0.82 (s, 6 H), 0.94 (s, 6 H), 1.09 (br d, *J* 13.2, 2 H), 1.22 (ddd, *J* 13.2, 13.2 and 4.2, 2 H), 1.26–1.34 (m, 2 H), 1.48 (sextet, *J* 14.0, 10.2 and 1.3, 2 H), 1.69 (qt, *J* 13.2 and 4.5, 2 H), 3.27 (ddd, *J* 13.2, 11.8 and 2.4, 2 H), 3.36 (sextet, *J* 10.2 and 1.3, 2 H), 3.91 (m, 2 H); δ_C(125 MHz, [$^2H_8$]toluene) 19.2, 23.8, 27.8, 31.0, 32.8, 39.7, 68.8, 82.0 [$C_{15}H_{28}O_2$ (*M*, 240.4): calc. C 74.95, H 11.74; found C 74.87, H 11.80%].

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