Conformational Analysis of *meso*-2,3,4,5-Tetramethylhexane and Some of Its Derivatives[‡]

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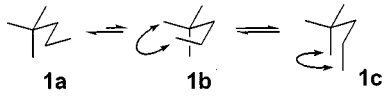
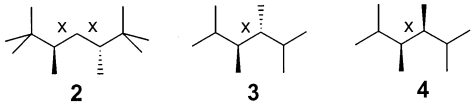
Compounds **12**–**15**, *meso*-type 2,3,4,5,6,7-hexasubstituted octane derivatives, have been synthesized using solely substrate-based asymmetric induction. Thanks to the specific relative configurations at the six stereogenic centres, these compounds have a high tendency to populate the conformation with a fully extended zig-zag backbone chain.

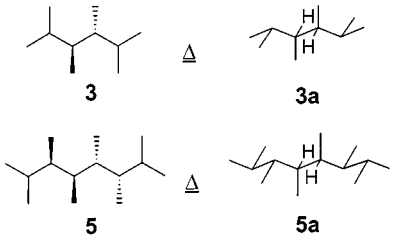
We are interested in compounds with flexible molecular backbones that adopt a single distinct conformation.[2] Such properties should result when every rotatable bond in the compound in question has only a single low-energy local conformation and when all undesired conformations are of substantially higher energy. In the case of saturated alkane chains, this could come about as a result of a substituent pattern that creates destabilizing *syn*-pentane interactions in each of the undesired conformers. The underlying principle can be illustrated with reference to 2,2-dimethylpentane (**1**), considering rotation about the C-3/C-4 bond.[3] Of the three diamond lattice type conformations, only conformation **1a** is free of *syn*-pentane interactions, whereas the conformers **1b** and **1c** are destabilized by a *syn*-pentane interaction.



Such a *syn*-pentane interaction results in a destabilization of 1.8 to 2.5 kcal mol^{-1}, depending on how readily it can relax into a non-diamond lattice conformation.[4] Adoption of a single conformation at a rotatable bond causes a decrease in entropy, which has to be compensated by an enthalpy penalty. The enthalpy penalty of a single destabilizing *syn*-pentane interaction for forming an undesired rotamer may be sufficient to control the conformation of molecules such as **1**, with one or two rotatable bonds. When it comes to larger molecules, however, this enthalpy penalty may not be high enough to control the conformation at several rotatable bonds simultaneously, or, put another way, to enforce a high population of a single global conformation. For this reason, we were interested in identification of alkane chain substituent patterns that would penalize undesired rotamers with a higher enthalpy penalty, such as by simultaneous creation of *two* *syn*-pentane interactions. Other groups[5] and we ourselves[6–8] have identified some substituent patterns for alkane chains (cf. **2**–**4**) which meet these criteria.



This holds, for example, for the central bond in *meso*-tetramethylhexane (**3**), the conformational properties of which are discussed in this paper. The considerations mentioned above made us anticipate that **3** should populate the conformation **3a** with high preference, since this is the only backbone conformation free of *syn*-pentane interactions.



However, force field calculations with the MM3* force field implemented in the Macromodel program[9] indicated that the conformational preference for **3a** should amount to only ca. 80%; the results are summarized in Table 1. The higher energy conformers are pair-wise degenerate for reasons of symmetry.

The low level of conformational preference can be attributed to the four methyl side groups present in **3**, which give rise to eight *gauche* interactions with the main chain even in the desired conformer **3a**. This results in a ca. 5 kcal destabilization of the low-energy conformation and so reduces the decisive energy gap between **3a** and the undesired higher energy conformations. For this reason it appeared futile to extend the concept to hexamethyloctane (**5**), in which the most stable conformation **5a** would have 12 destabilizing *gauche* interactions. It turned out, however, that Macromodel calculations predicted a higher conforma-

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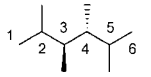
Table 1. Relative enthalpy, population (25 °C) and backbone dihedral angles for *meso*-2,3-dimethylbutane conformers calculated by MM3*

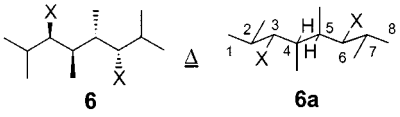


3

enthalpy (kJ/mol)	population (%)	dihedral angles (degrees) 1-2-3-4	2-3-4-5	3-4-5-6
84.6	80.3	171.2	180.0	–171.2
91.3	5.3	150.1	–63.0	–52.5
91.3	5.3	52.5	63.1	–150.1
92.8	2.8	55.8	82.7	–58.9
92.8	2.8	59.0	–82.6	–55.8
95.6	0.9	–45.2	175.8	–170.5
95.5	0.9	170.5	–175.5	45.2

tional preference (88%) for **5** than for **3**. Apparently, the steric crowding is felt more strongly in the bent conformers of the larger molecule **5** than in those of **3**.

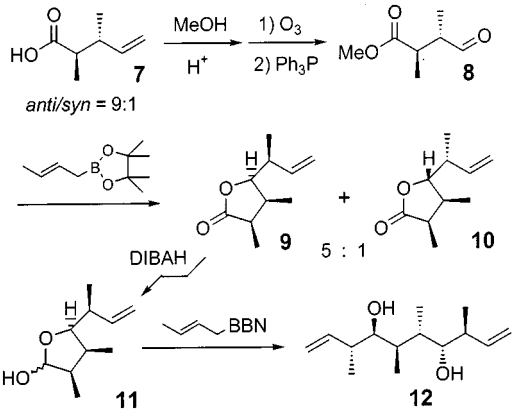
A further improvement of the conformational preference appeared possible in view of the magnitude of the individual destabilizing *gauche* interactions. While *gauche* interactions between alkyl groups are quite substantial, those between an alkyl group and smaller heteroatom groups are of significantly reduced magnitude.[10] Thus, modification of **5** to a dihetero-substituted analogue **6**, in which X is a group sterically less demanding than a methyl group, should reduce the magnitude of six of the twelve unfavourable *gauche* interactions present in the desired conformer **6a**. We therefore initiated a study of compounds **6**, in which the X group is an oxygen functionality such as an ether or an ester moiety.



6 **6a**

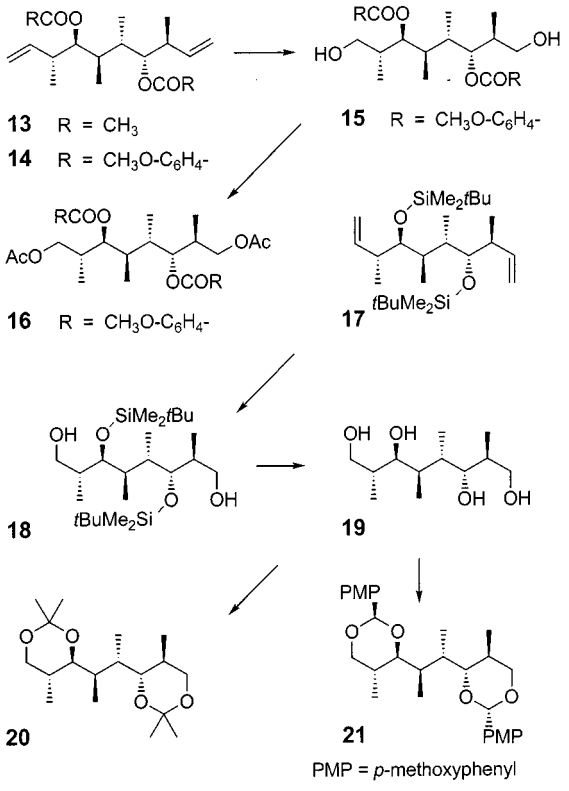
Synthesis

Since compound **6** is a *meso* compound, the generation of the stereogenic centres has to rely on substrate-based asymmetric induction only. Because of the symmetry of **6**, a bidirectional approach appeared attractive. However, any attempts along these lines met with failure, since the reacting ends of the synthetic intermediates were too close to one another and interacted with one another. We were therefore forced to use a stepwise approach, starting from the unsymmetrically substituted core structure **7**. The starting material **7** was obtained as a 9:1 *anti*/*syn* mixture from a Claisen rearrangement.[11]



7 **8** **9** **10** **11** **12**

Acid **7** was esterified (85%) and the alkene was ozonized to give the aldehyde **8** (92%). Treatment of **8** with the (*E*)-crotylboronate, followed by hydrolysis of the ester, furnished the lactones **9** and **10** in a 5:1 ratio. At this point, the major diastereomer **9** could be obtained (74%) diastereomerically pure by chromatography. The relative configuration of **9** could not be established at this stage, but it was assumed[12–14] to be the Cram product, a fact later shown to be correct. The lactone group in **9** was reduced with DIBAH to the lactol **11**. Since only a minute amount of free aldehyde is in equilibrium with the lactol, the more reactive (*E*)-crotyl-9-BBN[15] was chosen[16] to effect the second allylmetallation. This produced a single diol in 72% yield. The ^{13}C NMR spectrum proved it to have the symmetrical structure **12**.



13 R = CH_3
14 R = CH_3O-C_6H_4-
15 R = CH_3O-C_6H_4-
16 R = CH_3O-C_6H_4-
17 **18** **19** **20** **21**

The key compound **12** was converted into the diacetate **13** and the bis(*p*-methoxybenzoate) **14**. Ozonolysis of **14** with reductive workup furnished the diol **15**, which was converted into the diacetate **16.** A similar sequence led from **12**, through the silylated compounds **17** and **18**, to the tetraol **19**. This last was converted into the bis-1,3-dioxane **20**, and the bis(*p*-methoxybenzylidene acetal) **21**.

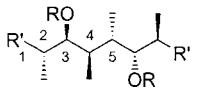
Conformational Analyses

Conformational analyses of the derivatives of **6** is based on $^3J_{H,H}$ coupling constants along the molecular backbone; a large degree of alteration (large/small/large) is characteristic[17] of a preponderant population of the conformation **6a**. The coupling constants 2-H/3-H = 6-H/7-H and 3-H/4-H = 5-H/6-H can be directly derived from the spectra to ±0.1 Hz. Protons 4-H and 5-H are enantiotopic. Since they are coupled across the symmetry centre of the molecule, they give rise to a higher order multiplet, not amenable to direct coupling constant analysis. One way to determine the coupling constant between 4-H and 5-H is by inspection of the ^{13}C sidebands of the ^1H NMR signal of 4-H = 5-H. Since the latter signal is overlapped with the ^1H NMR signal of 2-H = 7-H, a special ^{13}C editing technique (SELINCOR)[18] had to be used to record the unobscured ^1H NMR signal of 4-H = 5-H. To simplify the coupling patterns further we used a SELINCOR experiment in which the ^1H NMR signal of the methyl groups at positions 4 and 5 were homodecoupled. The coupling constants for 4-H, 5-H listed in Table 2 were acquired in this manner, but because of line broadening their accuracy is ± 0.3 Hz at best.

The simplest system is provided by compound **20**, in which rotation about the C-2/C-3 and the C-6/C-7 bonds is constrained by incorporation into the ring systems. The coupling constants 3-H/4-H (< 1 Hz) and 4-H/5-H (9.4 Hz) alternate and correspond to the values calculated (Macromodel) for the conformation corresponding to **6a**. In order to check whether the predominant conformation is populated to > 95%, we looked at the temperature dependence of the coupling constants. Indeed, the alteration of the coupling constants increased slightly on lowering the temperature. (The accuracy of the coupling constants determined at −70 °C is lower, due to line broadening.) We therefore assume that at room temperature compound **20** has a ca. 90% preference for the fully extended conformation of the **6a** type. The *p*-methoxybenzylideneacetal **21** showed coupling constants rather similar to those of the acetonide **20**.

In compounds **20** and **21**, the X groups (cf. **6**) are ether oxygen atoms. On going to compounds **15** and **16**, the X groups are modified to ester-type oxygen atoms, which have a stronger tendency to adopt positions lateral to the main chain,[10] and therefore should reinforce the tendency to populate the **6a** conformation. Indeed, the alteration of the coupling constants 3-H/4-H and 4-H/5-H found for compounds **15** and **16** is still somewhat larger than that found for **20**. There is, moreover, a substantial conformational preference in the outer segments to adopt the conformation

Table 2. Vicinal coupling constants [Hz] along the backbone of compounds **12** to **19**



Compound	Solvent	Temp. (°C)	J_{H2-H3}	J_{H3-H4}	J_{H4-H5}
20	$CDCl_3$	25	10.1	< 0.8	9.4
		–40	10.2	< 1.8	9.6
		–70	10.5	< 1.0	10.6
21	$CDCl_3$	25	9.8	<1.9	9.8
15	$CDCl_3$	25	10.5	< 1.0	10.0
16	$CDCl_3$	25	9.5	< 1.0	9.8
13	$CDCl_3$	25	8.8	1.7	8.4
14	$CDCl_3$	25	8.5	1.8	8.8
12	$CDCl_3$	25	9.3	< 2.0	9.5
	CD_3OD	25	8.5	1.5	9.0
	$[D_6]DMSO$	25	10.5	1.5	9.5

6a, as the coupling constants 2-H/3-H assume large values. The latter coupling constants are higher for the diol **15** than for the diacetate **16**. As the X-ray structure of **15** indicates (cf. Figure 1), the diol might adopt an internally hydrogen-bonded arrangement, further stabilizing the conformation corresponding to **6a**. When the backbone dihedral angles found in the X-ray structure of **15** are used, Macromodel calculates the following coupling constants: 10.7 Hz, 1.1 Hz, and 12.4 Hz (J_{H2-H3}, J_{H3-H4}, J_{H4-H5}), in close agreement with those found (cf. Table 3). For **16**, no such assistance from formation of internal hydrogen bonds is possible, and this might be the reason for the differences in the coupling constants between **16** and **15**. In Table 3 there is a comparison of the backbone dihedral angles found in the crystal structure and those calculated with the MM3* force field.

For the derivatives **12**, **13**, and **14**, with terminal vinyl groups, a somewhat lower preference for the conformation corresponding to **6a** was found. This holds for the local conformer preference at any of the skeletal bonds C-2/C-3, C-3/C-4, and C-4/C-5. This can be ascribed to the fact that a vinyl group does not have a high preference for positioning itself in the end-of-chain position, as it would have to be in the conformation corresponding to **6a** (Figure 2). In model compounds related to the halves of compound **12**, the vinyl group is oriented about 50% end-of-chain

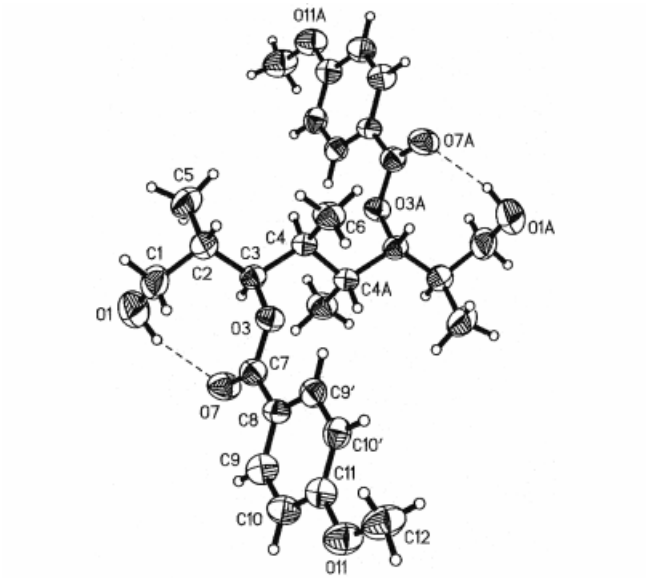
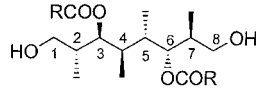


Figure 1. X-ray crystal structure of compound **15**

Table 3. Conformer population (25 °C) and backbone dihedral angles for compound **15** calculated with MM3* compared to data from the X-ray crystal structure



15 R = CH_3O-C_6H_4-

population (%)	1-2-3-4 5-6-7-8	2-3-4-5 4-5-6-7	3-4-5-6
crystal:	–175.2 175.2	–173.2 173.2	180.0
80	–177.6 –179.3	–177.4 177.6	176.3
18	–177.8 –178.9	–161.4 –167.6	71.8

and 50% lateral to the chain.[19] In view of this, the conformational preferences found for compounds **12**, **13**, and **14** are surprisingly high, and show that these compounds also have molecular backbones that probably populate the extended conformation at more than 80%. The conformational preference of the diol **12** should be sensitive to solvation effects; solvation changes the effective size of a polar group and, hence, the enthalpy term of *gauche* interactions involving this group. For this reason, we determined the coupling constants for **12** both in hydrogen bond donating and in hydrogen bond accepting solvents (cf. Table 2). Thus, there was a decrease in the conformational preference in methanol, whereas in DMSO the conformational preference was reinforced. These solvent effects remained small, however. In this study we have shown that derivatives **6** of hexamethyloctane (**5**), with the two methyl groups at C-3 and C-6 replaced by "slimmer" oxygen functionalities, have a marked tendency to adopt the fully extended conformation **6a**.

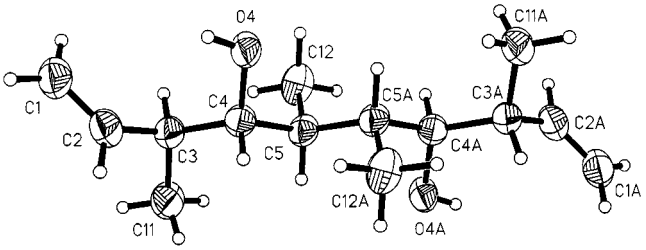


Figure 2. X-ray crystal structure of compound **12**

Experimental Section

General Remarks: All temperatures quoted are uncorrected. – ^{1}H NMR, ^{13}C NMR: Bruker ARX 200, AC 300, AMX 500. – Boiling range of petroleum ether: 40–60 °C. – Flash chromatography: SI 60 silica gel, E. Merck KGaA, Darmstadt, 40–63 μm. Buffer (pH = 7): $NaH_2PO_4 \cdot 2\,H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4\,H_2O$ (213.6 g) made up to 1 L with water. Conformer populations were estimated on the basis of force field calculations, using the MM3* force field implemented in the MACROMODEL[9] program, versions 4.5 and 6.5. Conformers with energies of < 25 kJ above the minimum energy conformer were subjected to Boltzmann averaging for 298 K to predict the conformer population.

1. Methyl (2*R,3*S**)-2,3-Dimethyl-4-pentenoate:** *p*-Toluenesulfonic acid monohydrate (608 mg, 3.20 mmol) was added to a solution of (2*R**,3*S**)-2,3-dimethyl-4-pentenoic acid (**7**)[11] (87:13 diastereomer mixture, 9.26 g, 72.3 mmol) in anhydrous methanol (50 mL). The mixture was maintained under reflux for 12 h. Saturated aqueous $NaHCO_3$ solution (15 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Distillation of the residue (11.3 g) at 40 mbar provided the product (9.06 g, 88%) as a colourless liquid of b.p. 61 °C, 40 mbar. The diastereomer ratio was determined from the ^{1}H NMR spectrum as 87:13. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 2.25–2.46 (m, 2 H), 3.65 (s, 3 H), 5.00–5.04 (m, 2 H), 5.55–5.67 (m, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 18.5, 41.2, 45.0, 51.5, 115.1, 141.0, 176.5. – $C_8H_{14}O_2$ (142.2): Calcd. C 67.56, H 9.92; found C 67.54, H 9.96.

2. (3*S,4*R**,5*R**)-3,4-Dimethyl-5-[(1*R**)-1-methylprop-2-enyl]-4,5-dihydrofuran-2(3*H*)-one (9):** A stream of ozone in oxygen was passed through a solution of methyl (2*R**,3*S**)-dimethylpentenoate (4.30 g, 30.2 mmol) in dichloromethane (50 mL) at –78 °C. After the solution had taken on a slight blue colour, excess ozone was purged with nitrogen and triphenylphosphane (11.9 g, 45.4 mmol) was added at –78 °C. After the mixture had reached room temperature, the solvents were removed in vacuum and the residue was subjected to flash chromatography on silica gel (30 g) with pentane to give crude **8** (4.1 g, 95%), which was taken up in anhydrous THF (15 mL). – (*E*)-2-Butene (8.40 g, 150 mmol) was added at –78 °C, by cannula, to a solution of potassium *tert*-butoxide (5.03 g, 45.0 mmol) in THF (80 mL). After the mixture had been stirred for 15 min, a solution of *n*-butyllithium (1.53 M in hexane, 29.0 mL, 45.0 mmol) was added slowly over 2 h at –78 °C. After this mixture had been stirred for 45 min at this temperature, *B*-isopropoxy-4,4,5,5-tetramethyl-1,3-dioxaborolane (9.30 g, 50.0 mmol) was ad-

ded over 1 h at −78 °C. $BF_3{\cdot}OEt_2$ (6.73 mL, 55.0 mmol) was then added rapidly, followed by the solution of the aldehyde **8** prepared above. The solution was stirred for 12 h at −78 °C. After reaching room temperature, the mixture was poured into a buffer solution (pH = 7, 80 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phases were dried and concentrated to give crude **9** (3.90 g). The material was added to a solution of LiOH (4.20 g, 101 mmol) in dimethoxyethane/water (5:3, 150 mL) and was stirred for 30 min. The mixture was acidified by addition of aqueous hydrochloric acid (2 N, 45 mL), stirred for 5 min and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 35 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated to give a 5:1 mixture of **9** and **10**. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 20:1 furnished 2.07 g (60%) of **9**. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.09 (d, *J* = 7.2 Hz, 3 H), 2.30−2.46 (m, 1 H), 2.47 (quintd, *J* = 7.0 and 4.0 Hz, 1 H), 2.74 (quint, *J* = 7.1 Hz, 1 H), 3.91 (dd, *J* = 10.6 and 4.1 Hz, 1 H), 5.01 (d, *J* = 10.4 Hz, 1 H), 5.05 (dt, *J* = 17.3 and 1.2 Hz, 1 H), 5.82 (ddd, *J* = 17.3, 10.4, and 6.7 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.9, 9.8, 14.8, 36.8, 37.2, 41.2, 84.9, 115.1, 134.0, 178.9. − $C_{10}H_{16}O_2$ (168.2): calcd. C 71.39, H 9.59; found C 71.11, H 9.47.

3. (3*S,4*R**,5*R**)-3,4-Dimethyl-5-[(1*R**)-1-methylprop-2-enyl]tetrahydrofuran-2-ol (11):** A solution of diisobutylaluminium hydride (1 M) in petroleum ether (13 mL) was added dropwise at −78 °C to a solution of **9** (2.07 g, 12.3 mmol) in anhydrous THF (50 mL). After the mixture had been stirred for 1 h at −78 °C, methanol (10 mL) was added. The mixture was allowed to come to room temperature and saturated aqueous NH_4Cl solution (40 mL) was added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated, and the crude product (2.18 g) was purified by flash chromatography with pentane/*tert*-butyl methyl ether = 5:1 to give **11** as a colourless liquid (1.72 g, 82%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 1.99−2.29 (m, 3 H), 3.87 (dd, *J* = 10.3 and 3.3 Hz, 1 H), 3.98 (d, *J* = 3.8 Hz, 1 H), 5.02 (ddd, *J* = 10.3, 1.8, and 0.8 Hz, 1 H), 5.09 (ddd, *J* = 17.3, 1.8, and 0.9 Hz, 1 H), 5.80 (ddd, *J* = 17.4, 7.5, and 10.0 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.2, 12.0, 16.4, 38.6, 39.2, 45.5, 85.5, 103.8, 114.0, 142.4. − $C_{10}H_{18}O_2$ (exact mass): calcd. for [M + H] 171.1386, found 171.1377.

4. (3*R,4*R**,5*R**,6*S**,7*S**,8*S**)-3,5,6,8-Tetramethyl-1,9-decadiene-4,7-diol (12):** Precooled (*E*)-2-butene (4.50 g, 65.0 mmol) was added at −88 °C by cannula to a solution of potassium *tert*-butoxide (2.47 g, 22.0 mmol) in anhydrous THF (40 mL). *n*-Butyllithium in hexane (1.53 M, 14.4 mL, 22.0 mmol) was added dropwise over 1.5 h at −78 °C. A solution of *B*-methoxy-9-borabicyclononane (1 M in THF, 22.0 mL) was then added dropwise at −78 °C over 45 min. After the mixture had been stirred for 30 min, $BF_3{\cdot}OEt_2$ (2.65 mL, 25.0 mmol) was added rapidly. Finally, a solution of **11** (1.67 g, 9.8 mmol) in anhydrous THF (15 mL) was added at −88 °C. After stirring for 12 h, the mixture was allowed to come to room temperature. Aqueous NaOH (3 N, 50 mL) and aqueous H_2O_2 (30%, 17 mL) were added, and the mixture was refluxed for 1 h and cooled. Brine (20 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product (6.0 g) was purified by flash chromatography with pentane/*tert*-butyl methyl ether = 10:1 to give **12** as a single diastereomer (1.59 g, 72%) of m.p. 84 °C.[20] − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.5 Hz, 6 H), 0.95 (d, *J* = 6.6 Hz, 6 H), 1.73−1.76 (m, 2 H), 2.27 (tq, *J* = 8.8 and 6.8 Hz, 2 H), 3.42 (dd, *J* = 9.3 and 1.2 Hz, 2 H), 5.12 (dd, *J* = 10.2 and 1.8 Hz, 2 H), 5.15 (dd, *J* = 17.1 and 1.7 Hz, 2 H), 5.71 (ddd, *J* = 17.2, 10.1, and 8.8 Hz, 2 H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0, 16.6, 36.3, 43.2, 74.3, 116.6, 142.5. − $C_{14}H_{26}O_2$ (226.4): calcd. C 74.29, H 11.58; found C 74.10, H 11.42.

5. (3*R,4*R**,5*R**,6*S**,7*S**,8*S**)-4,7-Diacetoxy-3,5,6,8-tetramethyl-1,9-decadiene (13):** A solution of *n*-butyllithium (1.44 M in hexane, 320 μL, 0.46 mmol) was added dropwise to a solution of the diol **12** (50 mg, 0.22 mmol) in anhydrous THF (1 mL). Acetyl chloride (33 μL, 0.46 mmol) was added after 15 min and the mixture was stirred for 5 h. Saturated aqueous NH_4Cl solution (2 mL) and aqueous hydrochloric acid (2 M, 1 mL) were added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 5:1 furnished **13** (28 mg, 45%) as a colourless solid of m.p. 87.5 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 6 H), 0.88 (d, *J* = 6.4 Hz, 6 H), 1.49−1.60 (m, 2 H), 2.00 (s, 6 H), 2.34−2.47 (m, 2 H), 4.86 (dd, *J* = 8.8 and 1.7 Hz, 2 H), 4.88 (dd, *J* = 10.1 and 1.8 Hz, 2 H), 4.92 (dd, *J* = 17.1 and 1.5 Hz, 2 H), 5.54 (ddd, *J* = 17.0, 10.0, and 8.9 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 17.1, 21.4, 36.5, 41.7, 76.9, 115.2, 141.1, 170.9. − $C_{18}H_{30}O_4$ (310.4): calcd. C 69.64, H 9.74; found C 69.56, H 9.61.

6. (3*R,4*R**,5*R**,6*S**,7*S**,8*S**)-4,7-Bis(*p*-methoxybenzoyloxy)-3,5,6,8-tetramethyl-1,9-decadiene (14)**: *n*-Butyllithium (1.54 M in hexane, 1.20 mL, 1.86 mmol) was added at 0 °C to a solution of the diol **12** (200 mg, 0.88 mmol) in anhydrous THF (3 mL). After the mixture had been stirred for 5 min at 0 °C, *p*-methoxybenzoyl chloride (252 μL, 1.86 mmol) was added, stirring was continued for 30 min at room temperature and saturated aqueous NH_4Cl solution (2 mL) and aqueous hydrochloric acid (2 M, 1 mL) were added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 4:1 furnished compound **14** (416 mg, 95%) as a slightly yellowish solid of m.p. 143 °C. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.0 Hz, 6 H), 1.11 (d, *J* = 6.3 Hz, 6 H), 1.65−1.79 (m, 2 H), 2.44−2.63 (m, 2 H), 3.86 (s, 6 H), 4.85 (dd, *J* = 10.1 and 1.9 Hz, 2 H), 4.93 (dd, *J* = 17.5 and 2.3 Hz, 2 H), 5.19 (dd, *J* = 8.5 and 1.8 Hz, 2 H), 5.70 (ddd, *J* = 17.1, 10.0, and 8.8 Hz, 2 H), 6.89−6.96 (m, 4 H), 7.94−8.01 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 17.2, 37.1, 41.7, 55.5, 77.2, 113.7, 115.3, 123.2, 131.7, 140.7, 163.3, 165.9. − $C_{30}H_{38}O_6$ (494.6): calcd. C 72.85, H 7.74; found C 72.55, H 7.59.

7. (2*R,3*S**,4*R**,5*S**,6*R**,7*S**)-3,6-Bis(*p*-methoxybenzoyloxy)-2,4,6,7-tetramethyloctane-1,8-diol (15):** A stream of ozone in oxygen was passed at −45 °C through a solution of **14** (500 mg, 1.0 mmol) in dichloromethane (5 mL) and methanol (5 mL). After the blue colour persisted, excess ozone was purged with nitrogen. The mixture was cooled to −78 °C and $NaBH_4$ (255 mg, 6.72 mmol) was added. After the mixture had reached room temperature, aqueous hydrochloric acid (2 M, 6 mL) was added and the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 2:1 furnished compound **15** (160 mg, 33%) as a colourless solid of m.p. 174 °C.[20]

– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 6 H), 1.10 (broad d, *J* = 5.8 Hz, 6 H), 1.62–1.73 (m, 2 H), 1.83–1.91 (m, 2 H), 3.39 (dd, *J* = 12.2 and 2.5 Hz, 2 H), 3.51 (dd, *J* = 12.2 and 2.8 Hz, 2 H), 3.86 (s, 6 H), 5.23 (broad d, *J* = 10.5 Hz, 2 H), 6.94–6.97 (m, 4 H), 7.98–8.01 (m, 4 H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.2, 14.1, 36.7, 37.4, 55.6, 63.9, 75.5, 114.0, 122.0, 132.0, 164.0, 167.8. – $C_{28}H_{38}O_8$ (exact mass): calcd. 502.2566, found 502.2532.

8. (2*R,3*S**,4*R**,5*S**,6*R**,7*S**)-1,8-Diacetoxy-3,6-bis(*p*-methoxybenzoyloxy)-2,4,5,7-tetramethyloctane (16):** Acetic anhydride (38 μL, 0.40 mmol) was added dropwise to a solution of **15** (50 mg, 0.10 mmol) in dichloromethane (3 mL). 4-Dimethylaminopyridine (ca. 3 mg) was added and the mixture was stirred for 16 h. Saturated aqueous $NaHCO_3$ solution (3 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 1:2 furnished **16** (38 mg, 60%) as a colourless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.0 Hz, 6 H), 1.14 (d, *J* = 6.0 Hz, 6 H), 1.59–1.73 (m, 2 H), 1.88 (s, 6 H), 3.86 (s, 6 H), 2.10–2.31 (m, 2 H), 3.94 (d, *J* = 5.5 Hz, 2 H), 3.97 (d, *J* = 4.5 Hz, 2 H), 5.27 (d, *J* = 9.5 Hz, 2 H), 6.89–6.96 (m, 4 H), 7.95–8.02 (m, 4 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.6, 14.4, 20.9, 35.4, 37.1, 55.6, 66.8, 75.5, 113.8. 122.6, 131.8, 163.6, 165.9, 171.1. – $C_{32}H_{42}O_{10}$ (exact mass): calcd. 586.2778; found 586.2774.

9. (3*R,4*R**,5*R**,6*S**,7*S**,8*S**)-4,7-Bis(*tert*-butyldimethylsilyloxy)-3,5,6,8-tetramethyl-1,9-decadiene (17):** 2,6-Lutidine (290 μL, 2.5 mmol) was added under nitrogen to a solution of **12** (227 mg, 1.0 mmol) in dichloromethane (5 mL). After the mixture had been stirred for 10 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (700 μL, 3.0 mmol) was added dropwise. After this mixture had been stirred for 3 h, saturated aqueous $NaHCO_3$ solution (3 mL) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 20:1 furnished compound **17** (489 mg, 100%) as a colourless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.20 (s, 6 H), 0.89 (d, *J* = 5.5 Hz, 6 H), 0.90 (s, 18 H), 0.96 (d, *J* = 6.9 Hz, 6 H), 1.49–1.53 (m, 2 H), 2.32 (quint, q, *J* = 6.9 Hz, 2 H), 3.66 (d, *J* = 6.2 Hz, 2 H), 4.93–5.00 (m, 4 H), 5.78 (ddd, *J* = 17.1, 10.5, and 7.7 Hz, 2 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.9, 1.2, 12.7, 16.9, 26.4, 38.3, 44.1, 55.9, 76.3, 114.3, 142.8. – $C_{26}H_{54}O_2Si_2$ (454.9): calcd. C 68.65, H 11.97; found C 68.50, H 11.78.

10. (2*R,3*S**,4*R**,5*S**,6*R**,7*S**)-3,6-Bis(*tert*-butyldimethylsilyloxy)-2,4,5,7-tetramethyloctane-1,8-diol (18):** A stream of ozone in oxygen was passed at –25 °C through a solution of **17** (150 mg, 0.33 mmol) in dichloromethane (1 mL) and methanol (1 mL). When the blue colour persisted, excess ozone was purged with a stream of nitrogen. The mixture was cooled to –80 °C and $NaBH_4$ (100 mg, 2.64 mmol) was added. After the mixture had reached room temperature, silica gel (4 g) was added, and the suspension was concentrated. The material was placed on a chromatography column and eluted with pentane/*tert*-butyl methyl ether = 5:1 to furnish **18** (126 mg, 82%) as a colourless solid of m.p. 113 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.12 (s, 6 H), 0.88–0.93 (m, 30 H), 1.46–1.48 (m, 2 H), 1.74–1.83 (m, 2 H), 2.08 (broad s, 2 H), 3.54 (dd, *J* = 10.7 and 5.1 Hz, 2 H), 3.66 (dd, *J* = 10.7 and 5.8 Hz, 2 H), 3.76 (d, *J* = 7.5 Hz, 2 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.9, –3.3, 12.5, 14.9, 18.7, 26.3, 39.0, 40.9, 66.2, 76.0. – $C_{24}H_{54}O_4Si_2$ (462.8): calcd. C 62.28, H 11.76; found C 62.33, H 11.78.

11. (4*S,5*R**)-2,2,5-Trimethyl-4{(1*R**,2*S**)-1-methyl-2-[(4*R**,5*S**)-2,2,5-trimethyl-1,3-dioxan-4-yl]propyl}-1,3-dioxane (20):** HF (5% in acetonitrile, 15 mL) was added to **18** (600 mg, 1.30 mmol) and the resulting solution was stirred for 30 min. Saturated aqueous $NaHCO_3$ solution (5 mL) and sodium chloride (10 g) were added and the solution was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue (450 mg) was taken up in THF (2 mL). 2-Methoxypropene (500 μL, 5.0 mmol) and *p*-toluenesulfonic acid (ca. 5 mg) were added. After the mixture had been stirred for 12 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 10:1 furnished compound **20** (40 mg, 10%) as a colourless solid of m.p. 113–114 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.7 Hz, 6 H), 0.86 (d, *J* = 6.4 Hz, 6 H), 1.34 (s, 6 H), 1.41 (s, 6 H), 1.63 (m, 2 H), 1.82–1.91 (m, 2 H), 3.50 (t, *J* = 11.2 Hz, 2 H), 3.63 (d, *J* = 10.1 Hz, 2 H), 3.69 (dd, *J* = 11.5 and 4.8 Hz, 2 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5, 12.5, 19.0, 29.9, 31.0, 34.9, 66.8, 75.4, 98.1. – $C_{18}H_{34}O_4$ (314.5): calcd. C 68.75, H 10.90; found C 68.85, H 11.01.

12. (4*S,5*R**)-2-(*p*-Methoxyphenyl)-5-methyl-4-{(1*R**,2*S**)-1-methyl-2-[(4*R**,5*S**)-2-(*p*-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-propyl}-1,3-dioxane (21):** HF (5% in acetonitrile, 2 mL) was added to **18** (80 mg, 0.17 mmol). After the mixture had been stirred for 30 min, saturated aqueous $NaHCO_3$ solution (1 mL) and sodium chloride (1 g) were added. The phases were separated and the aqueous phase was extracted with diethyl ether (6 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to leave the crude tetraol **19** as a yellowish liquid (57 mg), which was taken up in THF (5 mL). To this solution were added *p*-methoxybenzaldehyde dimethyl acetal (210 μL, 1.02 mmol) and *p*-toluenesulfonic acid (ca. 5 mg). After the mixture had been stirred for 12 h, saturated aqueous $NaHCO_3$ solution (1 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/diethyl ether = 10:1 furnished **21** (30 mg, 38%) as a colourless solid of m.p. 185 °C. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 5.7 Hz, 6 H), 1.07 (d, *J* = 6.5 Hz, 6 H), 1.87–1.90 (m, 2 H), 2.10–2.14 (m, 2 H), 3.52 (t, *J* = 11.1 Hz, 2 H), 3.63 (d, *J* = 9.7 Hz, 2 H), 3.83 (s, 6 H), 4.14 (dd, *J* = 11.2 and 4.7 Hz, 2 H), 5.45 (s, 2 H), 6.90–6.93 (m, 4 H), 7.42–7.44 (m, 4 H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 12.3, 30.9, 35.2, 55.4, 73.5, 83.8, 101.1, 113.6, 127.4, 131.9, 160.4. – $C_{28}H_{38}O_6$ (exact mass): calcd. 470.2668; found 470.2674.

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[1] R. W. Hoffmann, R. Göttlich, U. Schopfer, *Eur. J. Org. Chem.*, **2001**, 1865–1871.
[2] R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134–2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054–2070.
[3] This conformational preference in **1** is commonly referred to as the *tert*-butyl effect.[5,21–23]

[4] S. Tsuzuki, L. Schäfer, H. Goto, E. D. Jemmis, H. Hosoya, K. Siam, K. Tanabe, E. Osawa, *J. Am. Chem. Soc.* **1991**, *113*, 4665−4671.
[5] R. W. Alder, P. R. Allen, D. Hnyk, D. W. H. Rankin, H. E. Robertson, B. A. Smart, R. J. Gillespie, I. Bytheway, *J. Org. Chem.* **1999**, *64*, 4226−4232.
[6] R. W. Hoffmann, M. Stahl, U. Schopfer, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 559−566.
[7] R.W. Hoffmann, B. C. Kahrs, J. Schiffer, J. Fleischhauer, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407−2414.
[8] T. Trieselmann, R. W. Hoffmann, *Org. Lett.* **2000**, *2*, 1209−1212.
[9] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440−467.
[10] R. W. Hoffmann, D. Stenkamp, T. Trieselmann, R. Göttlich, *Eur. J. Org. Chem.* **1999**, 2915−2927.
[11] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877.
[12] R. W. Hoffmann, U. Weidmann, *Chem. Ber.* **1985**, *118*, 3966−3979.
[13] R. W. Hoffmann, H. Brinkmann, G. Frenking, *Chem. Ber.* **1990**, *123*, 2387−2394.
[14] H. Brinkmann, R. W. Hoffmann, *Chem. Ber.* **1990**, *123*, 2395−2401.
[15] G. W. Kramer, H. C. Brown, *J. Organomet. Chem.* **1977**, *132*, 9−27.
[16] A. L. Smith, C.-K. Hwang, E. Pitsinos, G. R. Scarlato, K. C. Nicolaou, *J. Am. Chem. Soc.* **1992**, *114*, 3134−3136.
[17] R. Göttlich, B. C. Kahrs, J. Krüger, R. W. Hoffmann, *Chem. Commun.* **1997**, 247−251.
[18] T. Fäcke, S. Berger, *Magn. Reson. Chem.* **1995**, *33*, 144−148.
[19] R. Göttlich, U. Schopfer, M. Stahl, R. W. Hoffmann, *Liebigs Ann./Recueil* **1997**, 1757−1764.
[20] Crystallographic data (excluding structure factors) for compounds **12** and **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-160450 (**12**) and -160451 (**15**) (Klaus Harms, 2001). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[21] S. Pucci, M. Aglietto, P. L. Luisi, *J. Am. Chem. Soc.* **1967**, *89*, 2787−2788.
[22] S. Cauwberghs, P. J. De Clercq, *Tetrahedron Lett.* **1988**, *29*, 2493−2496.
[23] R. W. Alder, C. M. Maunder, A. G. Orpen, *Tetrahedron Lett.* **1990**, *31*, 6717−6720.

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