Synthesis and Conformational Analysis of Bis(1,3-dioxan-5-yl)ethane Derivatives[‡]

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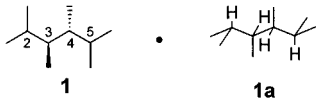
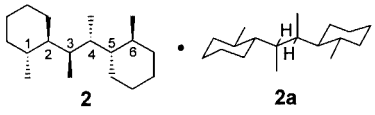
Keywords: Conformational analysis / Force-field calculations / Heterocycles

Bis(1,3-dioxan-5-yl)ethanes **4**, **30**, **32**, and **33** were synthesized in order to verify the high conformational preferences of their flexible backbones predicted by force-field calculations. Conformational analysis based on $^3J_{H,H}$ coupling constants gave results different from expectations based on the force-field calculations. The MM3* force-field of MACROMODEL was apparently not parametrized suitably to deal with the double-*gauche* interactions occurring along the backbones of compounds **30**, **32**, and **33**.

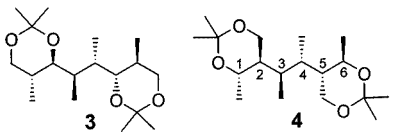
Many of the natural products of polyketide biogenetic origin have conformational preferences, be it global ones or local ones in certain segments of the molecule.[2] This is assumed to be the result of an evolutionary process, optimizing the binding properties of these molecules to their corresponding receptors. Over the last few years we have been interested in learning how conformational preferences are attained in the flexible open-chain structures used by nature. We are interested in identifying principles that might be applicable in the design of flexible molecules with preferred conformations, molecules not necessarily patterned after the polypropionate structures found in nature.[3] A general search identified some substituent patterns for alkane chains that should give rise to preferred backbone conformations.[4] One such substituent pattern is shown in **1**, for which a conformation with an extended chain should be favored, because all the other (undesired) conformations are of higher energy.[4,5] Rotation about the C-2/C-3 bond in **1** generates conformations with a *syn*-pentane interaction. These conformers relax to a non-diamond lattice conformation, calculated to be +1.6 and +2.0 kcal·mol^{-1} higher in energy than conformation **1a**.[5] Similarly, rotation about the central C-3/C-4 bond generates conformations +2.6 kcal·mol^{-1} higher in energy than **1a**. Because there are three rotatable bonds, the overall conformation preference for **1** is calculated to be only 80%.





One way to improve on this would be to introduce further substituents into **1** in such a manner that the undesired conformations would be destabilized by two simultaneous *syn*-pentane interactions. This might be achieved by the presence of two additional methyl groups at C-1 and C-6. The proper orientation of these two additional (methyl) groups in space could be attained by annelation of a six-membered ring to the C-1/C-2 and C-5/C-6 bonds.[4] The resulting compound **2** had a calculated overall conformational preference of > 99%.[4]

Compound **2** itself would not be not suited for conformational analysis by NMR spectroscopy, because complete signal overlap in the ^{1}H NMR spectrum would prevent the assignment and the determination of the vicinal $^3J_{H,H}$ coupling constants along the backbone, the basis for a conformational analysis. In a preliminary investigation, we synthesized and studied compounds of type **3**, which were found to have overall conformational preferences of ca. 90% at room temperature.[5]



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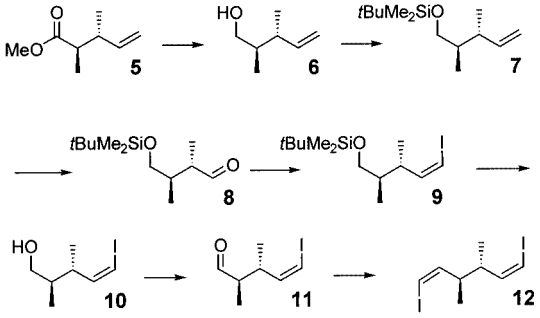
This result fell short of the optimum calculated for **2** because the undesired conformers of **3** involved *syn*-pentane interactions between an oxygen atom and a CH_2 group, interactions less destabilizing[6] than the *syn*-pentane interactions between two CH_2 groups that would prevail in the undesired conformers of **2**. We therefore turned our attention to compound **4**, which would match the situation prevalent in **2** in this respect, but should still be expected to permit conformational analysis by NMR spectroscopy. We report here on the synthesis of **4** and related model compounds, their conformational analyses, and some unexpected results from the latter.

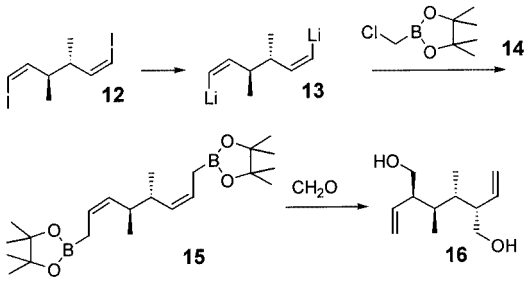
Synthesis

The synthesis of compound **4**, with six contiguous stereocenters, was anything but trivial. The task was even more challenging since **4** is a *meso* compound, and so only substrate-based asymmetric induction could be applied once a bi-directional approach[7,8] was adopted. We envisaged a synthesis that would start from a core structure **5**,[5] with two stereogenic centers of appropriate relative configuration. Compound **5** was produced by means of an Ireland−Claisen rearrangement of crotyl propionate.[9]

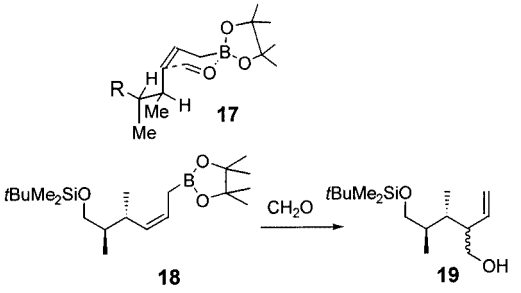


The ester **5** was reduced with $LiAlH_4$ (99%) to afford the known[10] alcohol **6**. Silylation to give **7** (95%) was effected with *tert*-butylchlorodimethylsilane and imidazole in dichloromethane. The double bond in **7** was ozonized to give the aldehyde **8**, which was immediately subjected to a Wittig reaction, furnishing the *Z* iodo alkene **9** in 77% overall yield. Desilylation to give **10** (90%) could be achieved with HF in acetonitrile. Swern oxidation of **10** to the aldehyde **11** was immediately followed by a Wittig reaction to give the symmetrical diiodo alkene **12** (78%). From this point on we pursued a bidirectional approach to reach the target structure **4**. Our plan was to homologate **12** to give the bis-allylboronate **15**, which upon treatment with formaldehyde was intended to give the diol **16**.

The conversion of a vinyl iodide into an allylboronate is a well established reaction,[11] which we had used successfully before.[12,13] Iodine/lithium exchange with *n*-butyllithium in THF to give **13**, followed by addition of the α-chloromethyl boronate **14**, gave **15** in unsatisfactory yields of below 50%. Success was eventually achieved by carrying out the iodine/lithium exchange under the conditions described by Bailey[14] (*tert*-butyllithium in ether/pentane mixtures), resulting in **15** in yields exceeding 80%.



The next step, the allylboration of **15** to give **16**, established two new stereogenic centers. There was no precedent for asymmetric induction resulting from stereogenic centers in the δ-position of an allylboronate in an allylboration reaction. Thanks to the *Z* double bond in **15**, however, avoidance of A[1,3] strain should result in distinct conformational preorganization of **15**,[15] which should direct the attack of formaldehyde to the less shielded face of the allylboronate moiety (cf. **17**). This should give rise to the diol **16** with the proper relative configuration.



The other problem to be addressed was how formaldehyde could be used in an allylboration reaction. Model studies were carried out with the allylboronate **18**. Treatment with aqueous formaldehyde in acetonitrile at room temperature furnished a 71% yield of **9**, which was obtained, however, as a 2:1 diastereomer mixture. Introduction of gaseous formaldehyde into a THF solution of **18** at −20 °C in THF or the use of formyl-trimethylsilane[16] brought no advantage. We then resorted to solutions of monomeric formaldehyde in THF.[17] Treatment of **18** with a tenfold excess of this solution at −78 °C in THF afforded **19** in 7:1 diastereomer ratio and in 62% yield. This selectivity could be increased to 8:1 by use of a THF/ether solvent mixture. These conditions were then applied to the treatment of **5** to give the bis-formylated product in 50−60% yield as a diastereomer mixture. The desired symmetrical diastereomer **16** was readily identifiable in the mixture by the number of ^{13}C NMR signals. Compound **16** dominated in the mixture by 3.5:1 and could be isolated as a pure diastereomer by flash chromatography. While the ^{13}C NMR spectrum established the symmetrical nature of **16**, it did not establish whether **16** had the desired relative configuration at the two new stereogenic centers. Such evidence was

obtained after conversion of **16** to the bis-Boc derivative **20**, the stereostructure of which was verified by X-ray crystal structure analyses (Figure 1).

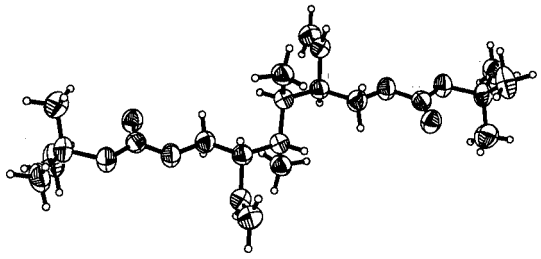
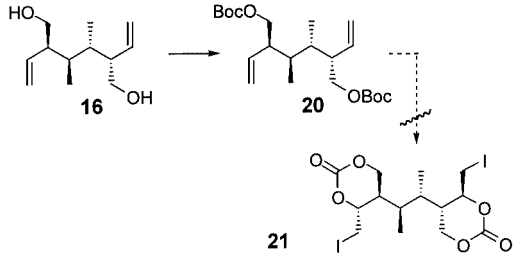
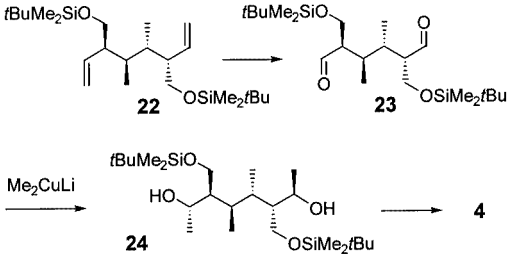


Figure 1. X-ray crystal structure of compound **20**



The Boc derivative **20** had been prepared with the goal of generating the remaining two stereogenic centers in an iodolactonization reaction.[18] This reaction could readily be performed with model substrates, but failed with the bis-alkene **20**. We therefore had to devise another approach to generate the final two stereogenic centers with substrate-based asymmetric induction. To this end, diol **16** was bis-silylated to give **22** (97%), which was ozonized to afford the dialdehyde **23** (98%). To obtain compound **24**, it was necessary to achieve stereoselective addition of a methyl anion to each of the two aldehyde functions in **23**. Precedent for asymmetric induction in the desired direction had been reported by W. C. Still[19] with lithium dimethyl cuprate as nucleophile. Treatment of **23** with this reagent at −78° furnished a single diastereomer of a diol, for which we were later able to establish the structure **24**.



At this point the stereochemical challenges associated with the synthesis of **4** had been overcome. Desilylation of **24** with tetrabutylammonium fluoride in THF, followed by acetalization with 2-methoxypropene, then furnished the target compound **4** in 66% yield. An X-ray crystal structure analysis of **4** secured the relative configuration as that shown (Figure 2).

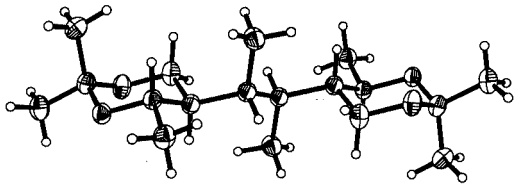
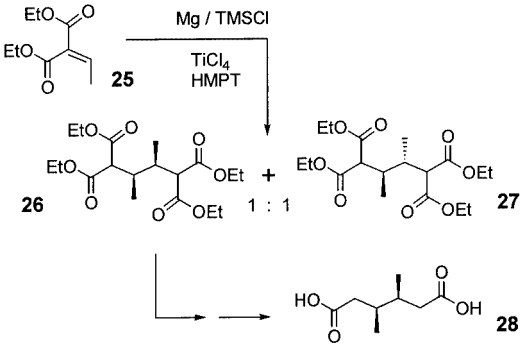


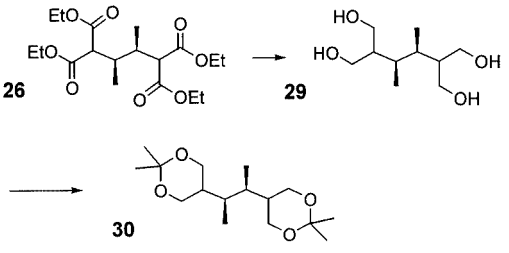
Figure 2. X-ray crystal structure of compound **4**

This study was undertaken in order to elucidate the extent to which the methyl substituents at C-1 and C-6 in **2** reinforced the preference to populate a fully extended conformation. For comparison, this logically required the corresponding compounds lacking these substituents, and so we needed compound **32** in order to compare its conformational behavior with that of **4**. The synthesis of **32** took advantage of the fact that compound **27**, with the carbon skeleton of **32**, is readily available.



Reductive coupling of the ethylidenemalonate **25** furnished a 1:1 mixture of the dimers *rac*-**26** and *meso*-**27**,[20] which could be separated by chromatography. We saponified the diastereomer of lower R_f (**26**) and heated the resulting tetraacid to provide 3,4-dimethylacetic acid **28**. Since both diastereomers of this acid had been characterized,[21] this allowed us to assign the D,L configurations to **28** and **26**, establishing **27** as the *meso* compound.

Tetraester **26** was reduced with $LiBH_4$ to the corresponding tetraol **29**. Treatment of the latter with 2,2-dimethoxypropane and camphorsulfonic acid furnished the acetonide **30**. The diastereomeric tetraester **27** was converted similarly to the acetonide **32**.



As conformational analysis of **30** and **32** produced results (see below) that were in clear contrast to our expectations, we then wanted to study a further compound in this series. For this reason the diol **31** was converted into the bis-dioxane **33**. In order to secure its stereostructure beyond any doubt, we subjected compound **33** to X-ray structure analysis (cf. Figure 3).

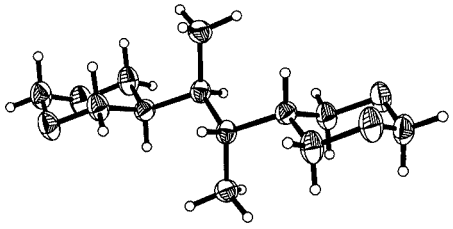
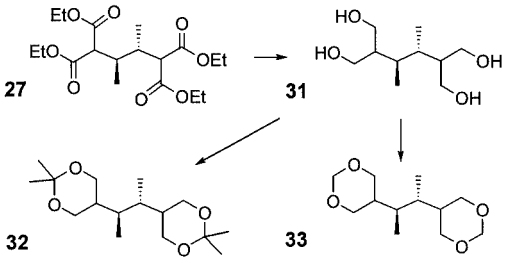


Figure 3. X-ray crystal structure of compound **33**



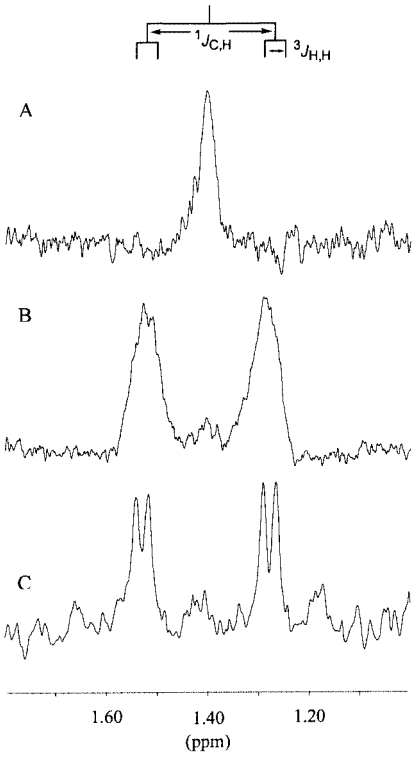


Figure 4. Determination of the $^3J_{H,H}$ coupling constant for 3-H in the ^{1}H NMR spectrum of compound **4**; ^{1}H NMR traces of 3-H in compound **4**; spectrum A: simple SELINCOR; spectrum B: ^{13}C-coupled SELINCOR; spectrum C: ^{13}C-coupled SELINCOR with ^{1}H-homo-decoupling of the methyl protons

Conformational Analysis

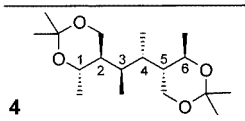
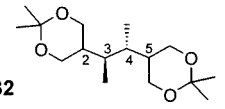
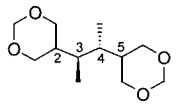
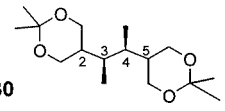
The conformational analysis of **4** was based on vicinal $^3J_{H,H}$ coupling constants along the molecular backbone. The proton signal of 1-H was readily identified in the ^{1}H NMR spectrum. The 1-H/2-H coupling constants could be determined after decoupling of the C-1−CH_3 protons. The signal of 3-H (= 4-H) was overlayed, and so the signal was recorded by the SELINCOR technique.[22] This procedure essentially gives a ^{13}C-coupled ^{1}H NMR spectrum of 3-H, corresponding to recording the ^{13}C-satellites in the ^{1}H NMR spectrum of 3-H, a technique necessary to break the symmetry of compound **4**, in order to determine the 3-H/4-H coupling constant across the symmetry element of the compound. Homo-decoupling of the protons of C-3−CH_3 simplified the pattern to the point (cf. Figure 4) that the coupling constants of interest − 3-H/2-H and 3-H/4-H − could be read directly from the spectrum.

The data for **4** in Table 1 show an extreme variation in the values of the coupling constants $J_{2\text{-H/3-H}}$ and $J_{3\text{-H/4-H}}$ (1.4 and 12.2 Hz), as would be expected[23] for the prevalence of a single preferred conformation. This preferred conformation (cf. **2a**) should correspond to that found in the solid state. If the backbone dihedral angles found in the X-ray crystal structure were taken, MACROMODEL[24] calculated the vicinal coupling constants as 3.7 and 11.7 Hz. If the geometry of the X-ray structure of **4** was minimized by the MM3* force-field implemented in MACROMODEL, the coupling constants were calculated as 2.4 and 11.7 Hz. A Monte Carlo search of the conformations available to **4**, followed by a Boltzmann distribution (300 K) of the conformers ≤ 6 kcal·mol^{-1} above the minimum energy structure, indicated that the minimum energy conformation corresponding to **2a** should be 99% populated.

Calculations and NMR spectra thus gave a consistent result: that compound **4** should show a large preference for populating the conformation corresponding to the X-ray crystal structure at room temperature. The high preference was attributable to the presence of the two methyl groups at C-1 and C-6. This should be evident on comparison of the conformational preference of **4** with that of compound **32**, without those two methyl groups. Force-field calculations predicted that the conformation corresponding to **2a** should be only 80% populated for compound **32**, resulting in Boltzmann-averaged coupling constants of 3.3 and 9.6 Hz. The experimentally determined values of 6.2 and 4.0 Hz (cf. Table 1), however, were in clear disagreement with those predictions.

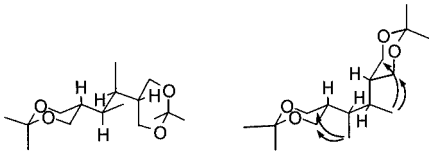
This motivated us to study an additional compound, **33** (the simple methylene acetal), and to secure the stereostructure of this compound by X-ray crystal structure analysis. For compound **33**, the same conformational preferences (and hence the same coupling constants) were calculated as for the bis-acetonide **32**. Experimentally, we similarly determined the same coupling constants for compound **33** as for the bis-acetonide **32**. It therefore became clear that the con-

Table 1. $^3J_{H,H}$ Coupling constants [Hz] along the backbones of the compounds **4**, **30**, **32**, and **33** at 300 K

		$^3J_{H\text{-}2/H\text{-}3}$	$^3J_{H\text{-}3/H\text{-}4}$
 **4**	Exptl.	1.4	12.2
	Calcd.*	2.4	11.7
 **32**	Exptl.	6.2	4.0
	Calcd.*	3.3	9.6
 **33**	Exptl.	6.2	4.0
	Calcd.*	3.3	9.6
 **30**	Exptl.	10.4	2.7
	Calcd.*	9.6	4.4

After Boltzmann averaging over the MM3 energies of the conformers

former preference prevalent in **32** and **33** was much smaller than that calculated or expected on the basis of qualitative considerations. Apparently there had to be some further factor affecting the relative conformer energies in the bis(dioxanyl)ethanes **32** and **33**. This made us curious about the conformational preferences of the diastereomeric D,L-compound **30**. Compound **30** was able to adopt two backbone conformations, **30a** and **30b**, free of *syn*-pentane interactions. Force-field calculations suggested that conformation **30a** should be 65% populated, and **30b** 32%.

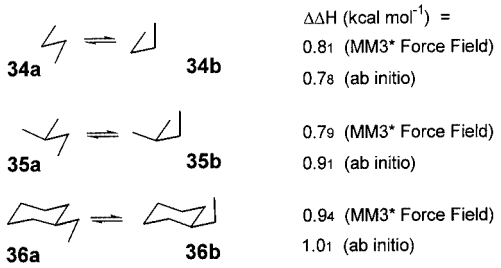


30a **30b**

The coupling constants after Boltzmann averaging were predicted to be 9.6 and 4.4 Hz. The experimentally determined coupling constants (10.4 and 2.7 Hz) revealed a stronger than calculated preference for population of conformation **30a**. Clearly, there again had to be an additional energy term that, in this case, would destabilize **30b** relative to **30a**.

Since both conformers **30a** and **30b** were free of *syn* pentane interactions, the energy difference between **30a** and **30b** should be determined by the number of *gauche* interactions along the molecular backbone, and to and between the methyl groups. All these *gauche* interactions were between C−H groups in 1,4-relationships. Conformation **30a** had seven such *gauche* interactions, **30b** had eight. A *gauche* interaction between two C−H groups in butane should correspond to an enthalpy difference of 0.83 kcal·mol^{-1}.[25,26] MM3* force-field calculations placed the enthalpy difference between **30a** and **30b** at 0.76 kcal·mol^{-1}. Since the conformer preference as derived from the NMR coupling constants indicated a larger enthalpy difference between **30a** and **30b**, there was the question of whether the enthalpy term for a *gauche* interaction was by and large constant, or whether it depended significantly on the substituent pattern and the nature of the carbon backbone. Some indication that this is so may be found in ref.[25,26]

In view of this, we carried out ab initio calculations (RIDFT with BP86 density functionals implemented in TURBOMOLE 5.3, TZVB basis set) to estimate the *trans*/*gauche* energy differences for compounds **34**, **35**, and **36**.



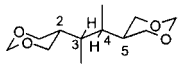
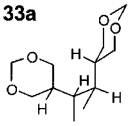
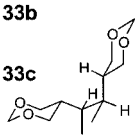
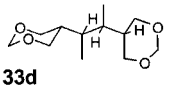
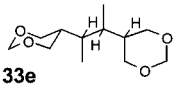
It could be seen that the enthalpy term for creation of a "double *gauche*" orientation in **35b** was indeed larger (by 0.1 kcal·mol^{-1}) than that for creation of a single *gauche* interaction in **34b**, a fact not reproduced by the force-field calculations. The steric interactions created in **35b** could apparently not be relaxed as easily as those in **34b**. A conceivable mode of relaxation, among other factors,[25,26] would be the widening of the angle between the two geminal methyl groups. This would become even more difficult on going to **36**. Calculations showed that **36b** was now higher in energy than **36a** by 1.0 kcal·mol^{-1}, a clear sign that the relaxation of a double *gauche* interaction was even more difficult in **36b** than in **35b**, without an annelated ring. It therefore appeared that the MM3* force-field underestimated the double *gauche* interaction by 0.1 kcal·mol^{-1}.

To return to the unusual conformational preferences found in the bis(dioxanyl)ethanes **30**, **32**, and **33**, the situation present in **36b** was present twice in conformation **30b**, but not in conformation **30a**. Hence, **30b** should be destabilized relative to **30a** by an additional quantity of ca. 0.2 kcal·mol^{-1} relative to the value calculated by the MM3* force-field, resulting in an increased conformational preference for **30a**, as found experimentally.

The unexpected situation found with compounds **32** and **33** is more involved. The five lowest-energy conformations of **33** are depicted schematically in Table 2. Structures **33b**−**e** are shown as diamond-lattice conformations, but they relax to non-diamond-lattice conformations due to the presence of a *syn*-pentane interaction. The calculations took this into account.

Only **33a** is free of *syn*-pentane interactions, whilst **33b**−**e** each have one (relaxed) *syn*-pentane interaction. Conformer **33a** has two double *gauche* interactions of the type **36b**. Conformers **33c**−**e** each have one such interaction, con-

Table 2. Steric interactions and $^3J_{H,H}$ coupling constants for the low-energy conformers of **33**

	Number of *syn*-pentane interactions	Number of double-*gauche* interactions	Relative energy* (kcal mol^{-1})	Calcd* [Hz] $^3J_{H\text{-}2/H\text{-}3}$	Calcd* [Hz] $^3J_{H\text{-}3/H\text{-}4}$
 **33a**	0	2	0	2.1	11.7
 **33b**	1	0	1.8	12.3	0.8
 **33c**	1	1	1.5	6.3	2.5
 **33d**	1	1	3.0	1.4	11.7
 **33e**	1	1	3.5	5.1	11.7

* Calculations refer to the individual conformers, which were relaxed to the nearest-energy minimum with the MM3* force field. Coupling constants were symmetry-averaged in conformers **b-e**.

former **33b** has none. Given the fact that the MM3* force-field underestimated destabilization by a double *gauche* interaction by about 0.1 kcal·mol^{-1}, the MM3* energy level of **33a** should be raised by 2 × 0.1 kcal·mol^{-1}, and those of **33c** to **33e** by 1 × 0.1 kcal·mol^{-1}, to approximate the real situation. Hence, conformers **33c**−**e**, and especially **33b**, should be more highly populated than predicted by the MM3* force-field.

The coupling constants calculated for the individual (relaxed) conformers are listed in Table 2. They showed that a higher population of **33b** should increase the averaged value of $^3J_{2\text{-}H/3\text{-}H}$ and decrease that of $^3J_{3\text{-}H/4\text{-}H}$ with reference to the values calculated for the most stable conformation **33a**. This would indeed account for the difference between the experimentally obtained coupling constants and those calculated with the MM3* force-field for compounds **32** and **33**.

The idea that a double *gauche* interaction would produce an additional destabilization of 0.1 kcal·mol^{-1} relative to two "simple" *gauche* interactions allows the initially surprising observations made regarding the conformer populations of the bis-dioxanyl-ethanes **30**, **32**, and **33** to be accounted for qualitatively. This does not, of course, prove that this explanation is correct.

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): $NaH_2PO_4 \cdot 2H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4H_2O$ (213.6 g) made up to 1 L with water. Conformer populations were estimated on the basis of force-field calculations with the MM3* force-field implemented in the MACROMODEL[24] program, versions 4.5 and 6.5. Conformers with energies < 6 kcal·mol^{-1} above the minimum energy conformer were subjected to Boltzmann averaging for 298 K to predict the conformer population.

1. (2*R,3*R**)-2,3-Dimethylpent-4-enone (6):** Methyl (2*R**,3*R**)-dimethylpentenoate (**5**, diastereomeric purity 90%, 15.0 g, 106 mmol) in THF (20 mL) was added at 0 °C to a suspension of lithium aluminium hydride (10.0 g, 263 mmol) in THF (250 mL). The mixture was then heated to reflux for 1 h. After the mixture had cooled to 0 °C, saturated aqueous potassium sodium tartrate solution (500 mL) was added dropwise. The mixture was vigorously stirred for 12 h. The phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (5 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 5:1, furnished compound **6** (10:1 diastereomer mixture, 11.9 g, 99%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 7.0 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 1.49−1.68 (m, 1 H), 2.11−2.35 (m, 2 H), 3.39 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.52 (dd, *J* = 10.5, 6.2 Hz, 1 H), 4.92−5.01 (m, 2 H), 5.70 ppm (ddd, *J* = 17.6, 9.4, and 8.4 Hz, 1 H). These data differ from those reported in ref.,[10] which account for only 11 of the 14 hydrogen atoms. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.9, 17.7, 39.3, 40.5, 66.3, 114.3, 141.7 ppm. These data match those reported in ref.[10]

2. (2*R,3*R**)-1-*tert*-Butyldimethylsilyloxy-2,3-dimethyl-4-pentene (7):** Imidazole (4.1 g, 60 mmol) and a solution of *tert*-butylchlorodimethylsilane (50% in hexane, 18 mL, 60 mmol) were added to a solution of the alcohol **6** (6.20 g, 54 mmol) in dichloromethane (100 mL). The mixture was stirred for 30 min at room temperature and poured into saturated aqueous $NaHCO_3$ solution (50 mL). The phases were separated, and the aqueous phase was extracted with pentane (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 100:1, furnished compound **7** (11.7 g, 95%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.82 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.48−1.66 (m, 1 H), 2.20−2.40 (m, 1 H), 3.40 (dd, *J* = 9.6, 6.6 Hz, 1 H), 3.50 (dd, *J* = 9.8, 6.3 Hz, 1 H), 4.93 (s, 1 H), 4.98−5.00 (m, 1 H), 5.72 ppm (ddd, *J* = 17.8, 9.6, and 8.1 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.2, 13.1, 18.0, 18.5, 26.1, 39.0, 40.7, 66.5, 114.0, 141.9 ppm. $C_{12}H_{26}OSi$ (214.2): calcd. C 67.22, H 12.22; found C 66.79, H 12.60.

3. (2*R,3*S**,4*Z*)-1-(*tert*-Butyldimethylsilyloxy)-5-iodo-2,3-dimethylpent-4-ene (9):** A stream of ozone in oxygen was passed at −78 °C through a solution of the alkene **7** (diastereomeric purity 10:1, 6.86 g, 30.0 mmol) in dichloromethane (100 mL). When the blue color persisted, triphenylphosphane (9.83 g, 37 mmol) was added, and the mixture was allowed to come to room temperature. The solution was concentrated, and the residue was adsorbed onto silica gel (20 g). Flash chromatography with pentane furnished the aldehyde **8** (7.00 g, 99%) as a colorless liquid.

A solution of sodium hexamethyldisilazide (2 M in THF, 16.2 mL, 32.4 mmol) was added dropwise to a suspension of (iodomethyl)triphenylphosphonium iodide (18.6 g, 35 mmol) in THF (90 mL). The mixture was cooled to −78 °C and HMPT (525 μL, 3.2 mmol) was added. The aldehyde obtained above was added dropwise at −78

°C. After stirring for 45 min, the mixture was allowed to come to room temperature and poured into brine (50 mL). The phases were separated and the aqueous phase was extracted with pentane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane furnished **9** (diastereomeric purity 10:1, 8.3 g, 78%) as a slightly yellowish liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.61−1.69 (m, 1 H), 2.54−2.63 (m, 1 H), 3.43 (dd, *J* = 9.9, 6.5 Hz, 1 H), 3.56 (dd, *J* = 9.9, 5.4 Hz, 1 H), 6.05 (dd, *J* = 9.2, 7.3 Hz, 1 H), 6.15 ppm (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.2, 14.2, 17.0, 18.5, 26.1, 40.6, 41.2, 66.3, 81.2, 145.0 ppm. $C_{13}H_{27}IOSi$ (354.4): calcd. C 44.06, H 7.68; found C 44.20, H 7.53.

4. (2*R,3*S**,4*Z*)-2,3-Dimethyl-5-iodopent-4-enol (10):** A solution of HF in acetonitrile (5%, 15 mL) was added to compound **9** (1.45 g, 4.1 mmol), and the mixture was stirred for 30 min. Saturated aqueous $NaHCO_3$ solution (100 mL) was added, 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, 10:1, furnished compound **10** (diastereomeric purity 10:1, 0.95 g, 90%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.49−1.76 (m, 1 H and OH), 2.63−2.70 (m, 1 H), 3.45 (dd, *J* = 10.9, 6.1 Hz, 1 H), 3.54 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.09 (dd, *J* = 9.4, 7.3 Hz, 1 H), 6.19 ppm (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 17.3, 40.6, 66.6, 81.8, 144.3 ppm. $C_7H_{13}O_2I$ (exact mass): calcd. 239.9986; found 240.0011.

5. (1*Z*,3*R,4*S**,5*Z*)-1,6-Diiodo-3,4-dimethylpenta-1,5-diene (12):** Dimethyl sulfoxide (6.20 mL, 87.4 mmol) was added dropwise at −78 °C to a solution of oxalyl chloride (3.7 mL, 43 mmol) in dichloromethane (130 mL). After this had been stirred for 15 min, a solution of compound **10** (8.73 g, 36.2 mmol) in dichloromethane (15 mL) was added dropwise, and the mixture was stirred for 45 min. Triethylamine (18.0 mL, 130 mmol) was added, and the mixture was allowed to come to room temperature. Water (60 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 10:1, furnished the aldehyde **11** (8.59 g, 99%) as a colorless liquid.

A solution of sodium hexamethyldisilazide (2 M in THF, 20.0 mL, 40.0 mmol) was added at room temperature to a suspension of iodomethyl-triphenyl-phosphonium iodide (23.0 g, 43.4 mmol) in THF (110 mL). The mixture was cooled to −60 °C and HMPT (650 μL, 4.00 mmol) was added. After the mixture had then been cooled to −78 °C, a solution of the aldehyde **11** obtained above in THF (10 mL) was added, and stirring was continued for 45 min. The mixture was allowed to come to room temperature, and brine (60 mL) was added. The phases were separated and the aqueous phase was extracted with pentane (3 × 10 mL). 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 **12** (diastereomeric ratio 91:9, 10.2 g, 78%) as a slightly pink liquid. The reaction itself and the chromatographic purification were both carried out in vessels wrapped with aluminum foil, in order to minimize photolytic decomposition of the product. The product was stored in a refrigerator over copper turnings. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.4 Hz, 6 H), 2.44−2.61 (m, 2 H), 5.91−6.04 (m, 2 H), 6.21 ppm (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 44.0, 82.1, 144.7 ppm. $C_8H_{12}I_2$ (HRMS, EI): calcd. 361.9028; found 361.9015.

6. (3*R,4*R**,5*S**,6*S**)-3,6-Bis(hydroxymethyl)-4,5-dimethylocta-1,6-diene (16):** A solution of *tert*-butyllithium in pentane (1.7 M, 55.3 mL, 94.1 mmol) was added over 2 h at −78 °C to a solution of the diiodo-alkene **12** (8.10 g, 22.4 mmol) in ether (300 mL) and petroleum ether (170 mL). 2-Chloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[27] (8.30 g, 47.0 mmol) was added dropwise over 1 h in such a manner that the forming precipitate redissolved before the next drop was added. The mixture was stored for 7 h at −78 °C and allowed to come to room temperature. Buffer solution (pH 7, 150 mL), brine (50 mL), and water (50 mL) were added, the phases were separated, and the aqueous phase was extracted with pentane (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude **15** (9.90 g) had the following spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.3 Hz, 6 H), 1.21 (s, 24 H), 1.64 (dd, *J* = 8.1, 1.1 Hz, 4 H), 2.15−2.21 (m, 2 H), 5.19 (tdd, *J* = 10.8, 9.5, and 1.3 Hz, 2 H), 5.45 ppm (td, *J* = 10.8, 8.1 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9, 24.9, 37.2, 83.2, 123.2, 135.0 ppm.

A solution of monomeric formaldehyde (ca. 0.6−0.8 M) in THF (300 mL) was generated according to ref.[17] This solution was added dropwise to a solution of the bis-allylboronate obtained above in ether (300 mL). The mixture was stirred for 3 days at −55 °C and allowed to come to room temperature. Brine (100 mL) was added, the phases were separated, and the aqueous phase was extracted with ether (4 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with dichloromethane/*tert*-butyl methyl ether, 10:1, furnished the diol **16** (diastereomer ratio 3.5:1, 2.44 g, 58%) as a colorless solid.

Repeated flash chromatography with dichloromethane/*tert*-butyl methyl ether furnished diastereomerically pure **16**, m.p. 76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.0 Hz, 6 H), 1.52−1.68 (m, 4 H), 2.34 (tdd, *J* = 9.2, 7.6, and 3.7 Hz, 2 H), 3.30 (td, *J* = 9.9, 1.7 Hz, 2 H), 3.68 (td, *J* = 9.8, 4.0 Hz, 2 H), 5.13 (dd, *J* = 17.3, 2.0 Hz, 2 H), 5.21 (dd, *J* = 10.3, 1.6 Hz, 2 H), 5.67 ppm (ddd, *J* = 17.1, 10.0, and 9.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 38.3, 49.4, 63.0, 118.1, 140.5 ppm. $C_{12}H_{22}O_2$ (exact mass): calcd. for M + Na 221.1548; found 221.1518.

7. (2*R,3*S**,4*R**)-1-*tert*-Butyldimethylsilyloxy-4-(hydroxymethyl)-2,3-dimethyl-5-hexene (19):** Compound **9** (4.90 g, 13.8 mmol) was converted as described under 6. into the allylboronate **8** (5.55 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.88 (s, 12 H), 1.24 (d, *J* = 7.3 Hz, 3 H), 1.26 (s, 9 H), 1.27 (d, *J* = 7.3 Hz, 3 H), 1.72−1.87 (m, 3 H), 2.21−2.34 (m, 1 H), 3.37 (dd, *J* = 9.8, 6.5 Hz, 1 H), 3.48 (dd, *J* = 9.8, 6.3 Hz, 1 H), 4.89−4.99 (m, 1 H), 5.69 ppm (ddd, *J* = 17.8, 9.6, and 8.1 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.2, 13.1, 18.0, 18.4, 24.5, 26.1, 39.0, 40.6, 66.4, 84.3, 114.0, 141.9 ppm.

The material was allowed to react with monomeric formaldehyde as described under 6. to give compound **19** (diastereomer ratio 8:1, 2.90 g, 77%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 6 H), 0.83 (d, *J* = 7.1 Hz, 3 H), 0.85 (s, 9 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 1.40−1.49 (m, 1 H), 1.68−1.79 (m, 1 H), 1.96 (broad s, OH), 2.27 (qd, *J* = 8.8, 3.9 Hz, 1 H), 3.34 (t, *J* = 9.3 Hz, 2 H), 3.56 (dd, *J* = 9.8, 5.1 Hz, 1 H), 3.67 (dd, *J* = 10.5, 4.2 Hz, 1 H), 5.11 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.18 (dd, *J* = 10.4, 1.3 Hz, 1 H), 5.65 ppm (ddd, *J* = 17.2, 10.0, and 9.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3, 12.7, 16.2, 18.3, 26.0, 37.4, 37.5, 50.3,

63.2, 74.9, 117.8, 140.2 ppm. $C_{15}H_{32}O_2Si$ (exact mass): calcd. for M + Na 295.2078; found 295.2069.

8. (3*R,4*R**,5*S**,6*S**)-3,6-Bis(*tert*-butoxycarbonyloxymethyl)-4,5-dimethylocta-1,7-diene (20):** A solution of *n*-butyllithium in hexane (1.63 M, 1.80 mL, 2.94 mmol) was added dropwise at −78 °C to a solution of the diol **16** (255 mg, 1.34 mmol) in THF (10 mL). After the mixture had been stirred for 10 min, di-*tert*-butyl dicarbonate (1.26 mL, 5.88 mmol) was added. Stirring was continued for 1 h, and saturated aqueous NH_4Cl solution (10 mL) was added carefully. The phases were separated and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane furnished compound **20** (336 mg, 63%) as a colorless solid of m.p. 71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 6 H), 1.45 (s, 18 H), 1.61−1.70 (m, 2 H), 2.53−2.61 (m, 2 H), 4.01 (dd, *J* = 10.5, 9.3 Hz, 2 H), 4.09 (dd, *J* = 10.7, 4.4 Hz, 2 H), 5.05 (dd, *J* = 11.7, 0.7 Hz, 2 H), 5.10 (dd, *J* = 5.1, 0.7 Hz, 2 H), 5.74 ppm (ddd, *J* = 17.1, 10.4, and 8.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 27.9, 38.6, 44.3, 67.2, 82.0, 116.6, 139.4, 153.8 ppm. $C_{22}H_{38}O_6$ (398.5) calcd. C 66.30, H 9.61; found C 66.01, H 9.45.

Crystallographic data[28] for **20**: crystal size 0.30 × 0.25 × 0.05 mm^3, monoclinic, space group $P2_1/c$, *a* = 17.385(4), *b* = 6.0278(12), *c* = 11.228(3) Å, β = 97.233(19)°, *V* = 1167.2(5) $Å^3$, D_c = 1.134 g·cm^{-3} for *Z* = 2, *F*(000) = 436, μ = 0.081 mm^{-1}, STOE IPDS image plate diffractometer, λ = 0.71069 Å, *T* = 193(2) K, 5673 reflections, θ_{max} = 25°, 1973 independent (R_{int} = 0.0511) and 1233 observed reflections [$F \geq 4\sigma(F)$], no absorption correction, direct methods, anisotropic refinement, hydrogens located and isotropically refined, 203 refined parameters, *R* = 0.0599 (observed data), wR^2 = 0.1775 (independent data).

9. (3*R,4*R**,5*S**,6*S**)-3,6-Bis(*tert*-butyldimethylsilyloxymethyl)-4,5-dimethylocta-1,7-diene (24):** Imidazole (410 mg, 6.00 mmol) and a solution of *tert*-butylchlorodimethylsilane in hexane (50%, 1.50 mL, 6.00 mmol) were added to a solution of the diol **16** (250 mg, 1.26 mmol) in dichloromethane (2 mL). After the mixture had been stirred for 30 min, saturated aqueous $NaHCO_3$ solution (10 mL) was added and the phases were separated. The aqueous phase was extracted with pentane (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 10:1, furnished compound **24** (482 mg, 90%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 12 H), 0.87 (s, 18 H), 0.92 (d, *J* = 6.8 Hz, 6 H), 1.68−1.77 (m, 2 H), 2.27−2.36 (m, 2 H), 3.56 (dd, *J* = 9.8, 6.6 Hz, 2 H), 3.64 (dd, *J* = 9.8, 4.6 Hz, 2 H), 4.97−5.04 (m, 4 H), 5.79 ppm (ddd, *J* = 17.0, 10.6, and 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.2, 14.5, 18.5, 26.1, 38.1, 48.0, 64.1, 115.1, 141.8 ppm. $C_{24}H_{50}O_2Si_2$ (426.8): calcd. C 67.54, H 11.80; found C 67.58, H 11.81.

10. (2*R,3*R**,4*R**,5*S**,6*S**,7*S**)-3,6-Bis(*tert*-butyldimethylsilyloxymethyl)-4,5-dimethyloctane-2,7-diol (24):** The diene **22** (826 mg, 1.93 mmol) was ozonized as described under 3. Flash chromatography with pentane/*tert*-butyl methyl ether, 100:1, furnished the dialdehyde **23** (827 mg, 99%) as a colorless liquid, which was used as obtained.

A solution of methyllithium in pentane (5%, 5.50 mL, 12.5 mmol) was added at −20 °C to a suspension of copper iodide (Merck, 1.21 g, 6.36 mmol) in ether (3 mL). The resulting yellow solution was cooled to −90 °C and a solution of **23** (336 mg, 0.79 mmol) in ether (3 mL) was added. After stirring for 1 h at −90 °C, the mixture was poured into saturated aqueous NH_4Cl solution (10 mL). The phases were separated, and the aqueous phase was extracted with 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, 10:1, furnished the diol **24** (274 mg, 75%) as a colorless solid of m.p. 65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.09 (s, 6 H), 0.83 (d, *J* = 6.6 Hz, 6 H), 0.89 (s, 18 H), 1.18 (d, *J* = 6.1 Hz, 6 H), 1.53−1.63 (m, 4 H), 3.78 (dd, *J* = 10.0, 8.3 Hz, 2 H), 3.86 (dd, *J* = 10.2, 3.4 Hz, 2 H), 4.02 (dq, *J* = 6.8, 6.6 Hz, 2 H), 4.10 ppm (broad s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.5, 13.3, 18.2, 21.7, 25.9, 35.4, 47.2, 63.7, 71.7 ppm. $C_{24}H_{54}O_4Si_2$ (462.8): calcd. C 62.28, H 11.76; found C 62.04, H 11.53.

11. (4*R,5*S**)-2,2,4-Trimethyl-5-{(1*R**,2*S**)-1-methyl-2-[(4*S**,5*R**)-2,2,4-trimethyl-1,3-dioxan-5-yl]propyl}-1,3-dioxane (4):** A solution of tetrabutylammonium fluoride in THF (1 M, 1.5 mL, 1.5 mmol) was added to a solution of the diol **24** (90 mg, 0.19 mmol) in THF (2 mL). After the mixture had been stirred for 2 h at room temperature, *p*-toluenesulfonic acid monohydrate (350 mg, 1.84 mmol) was added, followed by 2-methoxypropene (0.40 mL, 6.1 mmol). After the mixture had been stirred for 2 h, saturated aqueous $NaHCO_3$ solution was added (10 mL), the phases were separated, and the aqueous phase was extracted with ether (3 × 3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with *tert*-butyl methyl ether furnished compound **4** (39 mg, 66%) as a colorless solid of m.p. 162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.1 Hz, 6 H), 1.14 (d, *J* = 6.4 Hz, 6 H), 1.37 (s, 6 H), 1.41−1.42 (m, 2 H), 1.43 (s, 6 H), 1.69 (tdd, *J* = 10.4, 4.9, and 1.4 Hz, 2 H), 3.63 (dd, *J* = 11.8, 4.9 Hz, 2 H), 3.77 (dd, *J* = 11.4, 11.1 Hz, 2 H), 4.01 ppm (dq, *J* = 9.7, 6.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6. 19.6, 19.9, 29.6, 33.4, 42.1, 59.2, 67.9, 98.2 ppm. $C_{18}H_{34}O_4$ (314.5): calcd. C 68.75, H 10.90; found C 68.54, H 10.67.

Crystallographic data[28] for **4**: crystal size 0.54 × 0.42 × 0.21 mm^3, monoclinic, space group $P2_1/n$, *a* = 7.2387(11), *b* = 17.7725(18), *c* = 7.5135(12) Å, β = 112.485(11)°, *V* = 893.1(2) $Å^3$, D_c = 1.169 g·cm^{-3} for *Z* = 2, *F*(000) = 348, μ = 0.080 mm^{-1}, STOE IPDS-II image plate diffractometer, λ = 0.71069 Å, *T* = 193(2) K, 8410 reflections, θ_{max} = 26°, 1688 independent (R_{int} = 0.0355) and 1561 observed reflections [$F \geq 4\sigma(F)$], empirical absorption correction (multiscan method), direct methods, anisotropic refinement, hydrogens located and isotropically refined, 169 refined parameters, *R* = 0.0304 (observed data), wR^2 = 0.0786 (independent data).

12. Tetraethyl 2,3-Dimethylbutane-1,1,4,4-tetracarboxylate (26, 27): Diethyl ethylidenemalonate (**25**, 3.71 g, 19.9 mmol) was added dropwise to a suspension of magnesium powder (722 mg, 30.8 mmol) in HMPT (14.2 g, 39.6 mmol), chlorotrimethylsilane (6.48 g, 59.7 mmol), and $TiCl_4$ (4 drops). After stirring for 16 h at 45 °C, the mixture was poured onto ice. Concd. hydrochloric acid (8 mL) was added and the phases were separated. The organic phase was washed with hydrochloric acid (2 M, 2 × 10 mL) and water (10 mL). The combined aqueous phases were extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 10:1, furnished a 1:1 mixture of **26** and **27** (2.01 g, 54%). Renewed flash chromatography furnished **27** (diastereomer ratio 10:1, 858 mg) and **26** (diastereomer enrichment 3:1, 916 mg) as slightly yellowish liquids.

Compound 26 (d,l): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 6 H), 1.26 (t, *J* = 7.1 Hz, 6 H), 1.28 (t, *J* = 6.8 Hz, 6 H), 2.14−2.36 (m, 2 H), 3.31 (d, *J* = 10.1 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 4 H), 4.21 ppm (q, *J* = 7.1 Hz, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.2, 14.8 (2C), 35.4, 57.3, 62.0, 62.2, 168.8, 169.1 ppm.

Compound 27 (*meso*): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.6 Hz, 6 H), 1.25 (t, *J* = 7.1 Hz, 6 H), 1.26 (t, *J* = 7.1 Hz, 6 H), 2.21−2.37 (m, 2 H), 3.47 (d, *J* = 6.3 Hz, 2 H), 4.18 ppm (q, *J* = 7.1 Hz, 8 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.7, 14.8, 15.3, 37.2, 54.7, 61.9, 62.2, 169.3, 169.7 ppm. $C_{18}H_{30}O_8$ (374.4): calcd. C 57.74, H 8.08; found C 57.80, H 7.83.

13. (3*R,4*R**)-3,4-Dimethylhexanedioic Acid (28):** Aqueous potassium hydroxide solution (18.6 M, 200 μL) was added to a solution of **26** (200 mg, 0.53 mmol) in ethanol (1.5 mL). After having been heated at reflux for 6 h, the solution was concentrated. The residue was added dropwise to aqueous hydrochloric acid (2 M, 1 mL). The phases were separated and the aqueous phase was extracted with ether (4 × 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue (106 mg) was heated at 160 °C for 6 h. The residue had the following ^{13}C NMR spectroscopic data (75 MHz, [D_6]acetone): δ = 15.2, 34.8, 39.6, 174.4 ppm. The data corresponded to those given in ref.[21]

14. 5-[(1*R,2*R**)-2-(2,2-Dimethyl-1,3-dioxan-5-yl)-1-methylpropyl]-2,2-dimethyl-1,3-dioxane (30):** $LiBH_4$ (120 mg, 5.40 mmol) was added to a solution of a 3:1 mixture of **26** and **27** (336 mg, 0.90 mmol) in ether (3 mL). The exothermic reaction was moderated by cooling with an ice bath. After the mixture had stood for 14 h at room temperature, ethanol (4 mL) was added, and the mixture was heated under reflux for 15 min. Conc. hydrochloric acid (1 mL) was added to the hot reaction mixture and, after standing for 8 h, the solution was concentrated. The residue was taken up in THF (2 mL), and *p*-toluenesulfonic acid (ca. 10 mg) was added, followed by 2,2-dimethoxypropane (6.50 mL, 65 mmol). After the mixture had been stirred for 16 h, triethylamine (0.5 mL) was added, and the mixture was poured into brine (10 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 3:1, furnished a 3:1 mixture of **30** and **32** (42 mg, 16%) as a colorless solid of melting range 88−90 °C.

Compound 30: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.6 Hz, 6 H), 1.37 (s, 6 H), 1.39 (s, 6 H), 1.32−1.41 (m, 2 H), 1.66−1.73 (m, 2 H), 3.58 (dd, *J* = 11.5, 9.7 Hz, 2 H), 3.60 (dd, *J* = 11.5, 9.5 Hz, 2 H), 3.85 (ddd, *J* = 11.7, 4.4, and 1.4 Hz, 2 H), 3.89 ppm (ddd, *J* = 11.6, 4.6, and 1.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.4, 20.5, 27.6, 31.7, 36.6, 63.6, 64.1, 97.7 ppm. $C_{16}H_{30}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 66.81, H 10.55.

15. 5-[(1*R,2*S**)-2-(2,2-Dimethyl-1,3-dioxan-5-yl)-1-methylpropyl]-2,2-dimethyl-1,3-dioxane (32):** $LiBH_4$ (177 mg, 8.0 mmol) was added to a solution of **27** (500 mg, 1.34 mmol) in ether (4 mL). The exothermic reaction was moderated by cooling with an ice bath. After the mixture had stood for 14 h, ethanol (4 mL) was added and the mixture was heated under reflux for 15 min. Conc. hydrochloric acid (1 mL) was added and after standing for 8 h the solution was concentrated. The residue was extracted with dichloromethane (5 × 5 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated to leave a brownish, viscous liquid (324 mg). Flash chromatography with *tert*-butyl methyl ether, followed by dichloromethane, followed by methanol, furnished in the latter fractions the tetraol **31** (175 mg, 64%) as a colorless solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.4 Hz, 6 H), 1.37−1.54 (m, 2 H), 1.83−2.14 (m, 2 H), 3.74−4.05 ppm (m, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 35.0, 37.8, 64.8, 66.8 ppm.

Compound **31** (200 mg, 0.97 mmol) was dissolved in 2,2-dimethoxypropane (1.70 g, 16.3 mmol), and camphor-10-sulfonic acid (70 mg, 0.30 mmol) was added. After the mixture had been stirred for 16 h, triethylamine (0.5 mL) was added and the mixture was poured into brine (10 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with petroleum ether/*tert*-butyl methyl ether, 3:1, furnished compound **32** (64 mg, 25%) as a colorless solid of m.p. 88−90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.0 Hz, 6 H), 1.35 (s, 6 H), 1.39 (s, 6 H), 1.23−1.39 (dq, *J* = 7.0, 4.4 Hz, 2 H), 1.87−1.92 (m, 2 H), 3.70 (dd, *J* = 11.2, 10.1 Hz, 4 H), 3.76 (ddd, *J* = 11.5, 5.0, and 1.7 Hz, 2 H), 3.83 ppm (ddd, *J* = 11.6, 4.8, and 1.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 20.1, 28.1, 35.5, 35.8, 63.0, 64.3, 97.8 ppm. $C_{16}H_{30}O_4$ (286.4): calcd. C 67.10, H 10.56; found C 66.58, H 10.84.

16. 5-[(1*R,2*S**)-2-(1,3-Dioxan-5-yl)-1-methylpropyl]-1,3-dioxane (33):** $LiBH_4$ (353 mg, 16.0 mmol) was added to a solution of **27** (1.00 g, 2.67 mmol) in ether (15 mL). After the mixture had been stirred for 2 h, ethanol (3 mL) was added and the mixture was heated under reflux for 3 h. Aqueous hydrochloric acid (2 N, 3 mL) was added, and the mixture was again heated under reflux for 12 h. The pH was brought to 3 by addition of aqueous hydrochloric acid (2 N, ca. 8 mL), and the solution was concentrated. One half of the residue was taken up in dimethoxymethane (1.72 mL, 19.6 mmol). LiBr (17 mg, 0.20 mmol), and *p*-toluenesulfonic acid monohydrate (18 mg, 0.11 mmol) were added. The mixture was stirred for 12 h and poured into brine (3 mL). The phases were separated and the aqueous phase was extracted with ether (5 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography with pentane/*tert*-butyl methyl ether, 4:1, furnished compound **33** (44 mg, 14%) as a colorless solid of m.p. 70 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.9 Hz, 6 H), 1.25−1.41 (m, 2 H), 1.91−2.08 (m, 2 H), 3.48 (dd, *J* = 11.2, 2.7 Hz, 2 H), 3.53 (dd, *J* = 11.1, 2.5 Hz, 2 H), 3.95−4.13 (m, 4 H), 4.59 (d, *J* = 6.1 Hz,. 2 H), 4.97 ppm (d, *J* = 6.1 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 35.7, 36.6, 70.4, 71.5, 94.3 ppm. $C_{12}H_{22}O_4$ (exact mass): calcd. for M + Na 253.1452; found 253.1416.

Crystallographic data[28] for **33**: crystal size 0.54 × 0.45 × 0.10 mm^3, monoclinic, space group $P2_1/c$, *a* = 6.4912(9), *b* = 8.3470(14), *c* = 11.0834(15) Å, β = 99.509(11)°, *V* = 592.27(15) $Å^3$, D_c = 1.291 g·cm^{-3} for *Z* = 2, *F*(000) = 252, μ = 0.095 mm^{-1}, STOE IPDS-II image plate diffractometer, λ = 0.71069 Å, *T* = 193(2) K, 4365 reflections, θ_{max} = 26°, 1131 independent (R_{int} = 0.0399) and 977 observed reflections [$F \geq 4\sigma(F)$], no absorption correction, direct methods, anisotropic refinement, hydrogens located and isotropically refined, 117 refined parameters, *R* = 0.0321 (observed data), wR^2 = 0.0870 (independent data).

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