Conformation of Isobutyl, 2,2-Dibromoethyl, and 2-Methoxypropyl Side Chains on Cyclohexane and Tetrahydropyran Ring Systems[‡]

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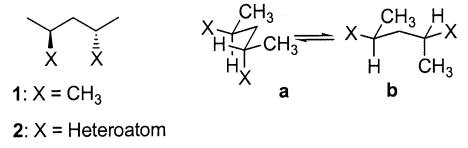
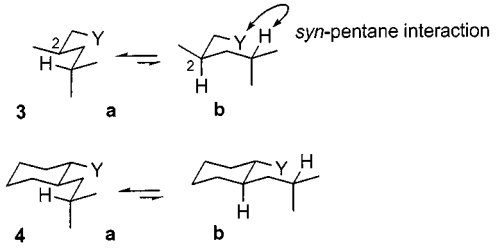
An isobutyl group placed equatorially in the 2-position of a 1-equatorially substituted cyclohexane adopts a preferred conformation (cf. **5**). This also holds when it is placed in the 2-position on a 3-equatorially substituted tetrahydropyran (cf. **6**). The same conformational preference is found for 2-methoxypropyl residues in the 2-position of 3-substituted tetrahydropyrans (cf. **8** and **10**). The latter compounds chelate lithium cations as analogues of 1,2-dimethoxyethane. Through this complexation, it is possible to effect a change in the side chain conformation.

Introduction

2,4-Dimethylpentane (**1**) populates two enantiomorphous conformations, **1a** and **1b**, equally.[2−5] In the heteroatom analogs **2**,[6,7] the conformer equilibrium may be shifted to favor the **a** conformer on the basis of steric or polar effects.



Another potential way to influence the conformer equilibrium of **1** is to introduce an "inductor" group, which selectively destabilizes one of the two conformers **1a** and **1b**.[8,9] For instance, placement of a substituent Y antiperiplanar to the C-2-methyl group in **3** will only slightly destabilize conformer **3a**, through a single *gauche* interaction, but will destabilize conformer **3b** by creating a *syn*-pentane interaction. Therefore, the conformer equilibrium should be shifted in favor of **3a**, due to the presence of the inductor group.

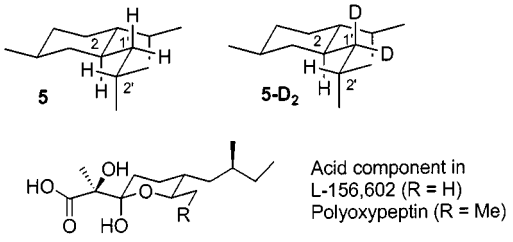


One way to guarantee the spatial arrangement of the inductor group antiperiplanar to the C-2-methyl group in unit **3** is to use the anullated ring system **4**. To evaluate the magnitude and scope of this conformational induction, we studied a number of derivatives of **4**. The results of these studies are reported in this paper.

Results

Derivatives of Isobutylcyclohexane and 2-Isobutyltetrahydropyran

Synthetic accessibility inclined us to study the hydrocarbon **5** (available from menthone, see below) rather than the simple hydrocarbon **4**. In order to evaluate the folding of the isobutyl side chain (cf. **4a** and **4b**), the vicinal coupling constants between the diastereotopic protons at C-1′ and the tertiary protons at C-2 and C-2′ had to be determined. As the relevant signals are obscured by overlaying in the ^{1}H NMR spectrum of **5**, we intended to extract the characteristic coupling constants using the SELINCOR technique,[10] with the aid of the ^{13}C NMR signal of C-2′.



In the ^{13}C NMR spectrum of **5**, signals for carbon atoms carrying two hydrogen atoms appear at δ = 24.4, 35.4, 41.4, and 42.7; one of these must be the signal of C-1′. In order to identify this, the deuterated compound **5-D$_2$** was prepared. The deuterium substitution significantly lessened the intensity of the signal at δ = 42.7, which we therefore assign to C-1′. Using the SELINCOR technique,[10] the ^{1}H NMR signal of the protons attached to C-1′ were recorded. One of these protons resonated at δ = 0.82 as a ddd (J = 13.0,

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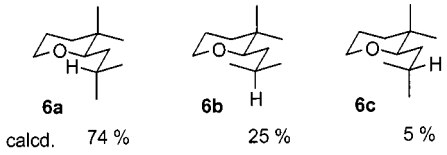
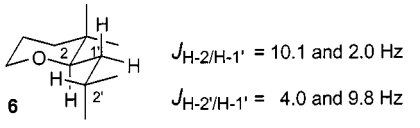
10.4, and 3.3 Hz). The other proton signal appeared at δ = 1.33, also as a ddd (J = 12.9, 10.4, and 4.0 Hz). The vicinal coupling constants 10.4 and 3.3 Hz, together with 10.4 and 4.0 Hz, demonstrate the substantial preference for a distinct conformation of the isobutyl side chain in **5**. We infer this to be the one depicted, since force-field calculations for compound **4** predicted a 89% preference for conformation **4a**.[8] Nature uses this type of conformational preorganization of side chains in certain acid components of antibiotics such as L-156,602[11] or polyoxypeptin,[12] whereby a hydrophobic part of the pharmacophore is held in a distinct shape.

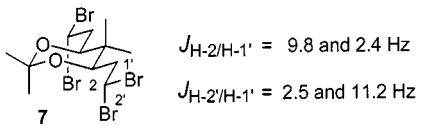
It therefore appeared worthwhile to investigate the behavior of an oxygen analog of **4**. We chose the tetrahydropyran derivative **6**. The change from cyclohexane to tetrahydropyran allows conformers such as **6b** and **6c**, involving a 1,3-parallel arrangement[13] between the side chain methyl group and the oxygen atom, to be significantly populated, since an oxygen substituent is smaller than a CH_2 group. Compound **6** additionally contains an axial methyl group. This has a small conformation-reinforcing effect, as it destabilizes some of the higher energy conformers of the side chain even further.[9,14] Thus, MACROMODEL[15] predicts the following conformer population.





The synthesis of **6** was straightforward (see below). The relevant $^3J_{H,H}$ coupling constants show the alteration characteristic of the presence of a predominant conformer. The larger difference between the coupling constants along the C-2−C-1′ bond, compared to the C-1′−C-2′ bond, is in line with a minor presence of conformer **6b** in the equilibrium.

Another compound, **7**, related to **6**, was available from a previous study. In compound **7** a 2,2-dibromoethyl group takes the position of the isobutyl side chain in **6**.[16] Because of the similar sizes of a methyl group and a bromine substituent, the effects on the conformer population should be similar. Since the ^{1}H NMR spectra of **7** showed a higher order splitting, due to an accidental coincidence of the chemical shifts of the 1′-H protons, the coupling constants had to be approximated by simulation of the splitting pattern.



The $^3J_{H,H}$ coupling constants obtained are in line with the presence of a single conformer, which should be the one shown in **7**. This corresponds to the conformation found in the crystal structure of **7** (Figure 1).

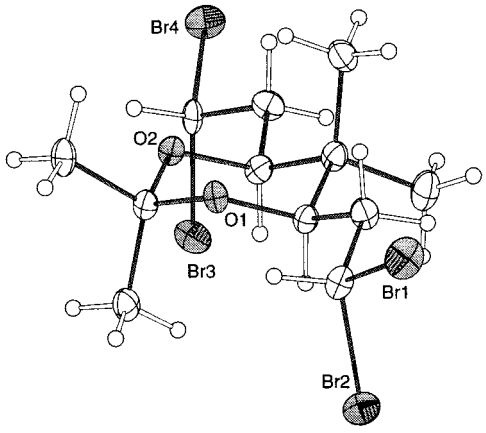
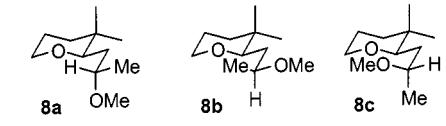


Figure 1. X-ray crystal structure of compound **7**

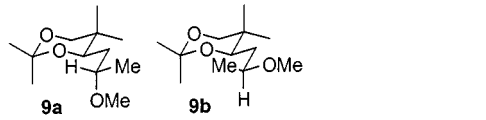
The change from the pure hydrocarbon **5** to the monooxygenated analog **6** resulted in a (small) decrease in the population of the preferred conformation **6a**, and increased populating of conformation **6b**. One might expect on this basis that introduction of a further oxygen atom, as in compound **8**, should diminish the conformer preference further. However, force-field calculations predict a high (92%) preference for populating the conformation **8a**. Conformation **8b** should be rather sparsely populated (5%), while conformation **8c** should contribute only marginally to the conformer equilibrium. Therefore, the force-field calculations suggest that the conformer preference in **8** should be increased relative to that in **6**, probably as a consequence of polar interactions.[7]



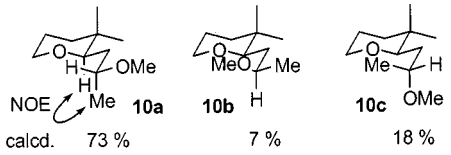
Solvent	$J_{H-2/H-1'}$		$J_{H-2'/H-1'}$		(Hz)
$C_6H_5CH_3$	10.4	1.1	2.8	9.6	
$CHCl_3$	10.5	1.5	2.8	9.7	
CH_3NO_2	10.3	1.5	3.1	9.4	
CH_3CN	10.5	1.9	3.6	10.3	

This is indeed borne out by the coupling constants recorded for **8**. The possible contribution by polar interactions suggests that the conformer population might depend on the solvent polarity. The coupling constants recorded for solutions of **8** in various solvents, however, show that there are only minor changes on going from toluene to acetonitrile.

The related dioxane derivative **9** was studied as well. It showed coupling constants (in toluene) very similar to those found for **8**.



Since the polar and steric effects may act in concert to give high conformer preferences in **8** and **9**, the diastereomeric compound **10** might then be expected to be a mismatched system. In fact, force-field calculations predict a significantly reduced preference for conformation **10a**, with attendant higher contributions of the conformations **10b** and **10c** in the conformer equilibrium.



Solvent	$J_{H-2/H-1'}$		$J_{H-2'/H-1'}$		(Hz)
$C_6H_5CH_3$	10.6	1.8	3.2	10.0	
$CHCl_3$	10.6	1.9	3.5	9.5	
CH_3NO_2	10.4	1.9	3.0	-	
C_5H_5N	10.5	1.8	3.3	10.5	

Nevertheless, the NMR spectra of **10** show vicinal coupling constants which again indicate a strong preference for a single conformation. Moreover, the data show that this preference does not depend on the polarity of the solvent. That conformer **10a**, and not conformer **10c**, is the preferred one follows from a strong NOE contact between 3′-CH_3 and 2-H.

As a common feature in the set of compounds **6**−**10**, we anticipated that the *gem*-dimethyl inductor group of the THP ring would guarantee a high preference for an antiperiplanar orientation [17−20] of C-2′ to the *gem*-dimethyl group. Regarding the C-1′−C-2′-bond, the conformer preference was in all cases found to be higher than that calculated by the MM3* force-field. When comparing compounds **6**−**10** with 2,4-dimethoxypentane, which has only a low conformational preference,[21] the high conformational preference found for the compounds **8**−**10** is gratifying.

Complexation Studies

The fact that the conformational preferences calculated for compounds **8**−**10** are high (ca. 90%), but not exceedingly high, opens up the possibility of changing the conformer population by external action. We imagined that complexation with a bidentate Lewis acid should lead to a change in the conformer population. Complexation-induced changes in the conformation of ligands have been the object of many investigations; for some recent examples, see refs.[22−25] A case related to the systems **8**−**10** is given in the complexation of C-sucrose with Ca ions.[26] Such complexation-induced conformational changes are of interest in the context of signal transduction across membranes.[27]

For this reason, we looked at the interaction of compound **8** with Li cations. NMR titration of **8** with $LiBPh_4$ in CD_3NO_2 revealed significant changes in the ^{13}C NMR chemical shifts, as well as in the splitting pattern of the ^1H NMR signal of 2′-H (cf. Figure 2). The change in the major conformer from **8a** to **8c** attendant with Li ion complexation is most easily seen with an NOE experiment: Uncomplexed **8** shows no NOE between 2-H and 3′-CH_3, but such an NOE effect is observed upon addition of 1.6 equiv. of $LiBPh_4$.

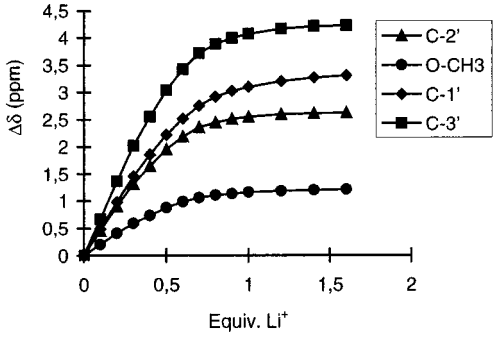
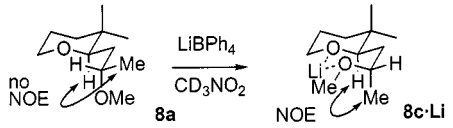
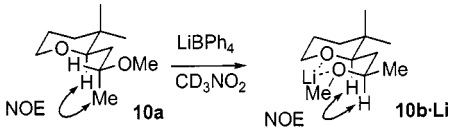


Figure 2. NMR titration of compound **8** with $LiBPh_4$; changes in the ^{13}C NMR chemical shifts



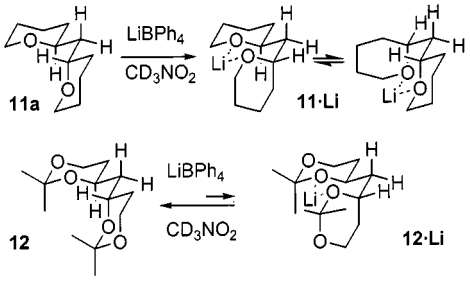
The changes in the ^{13}C NMR chemical shifts induced by the addition of $LiBPh_4$ (cf. Figure 2) can be reproduced by numerical simulation,[28] suggesting complexation constants of ca. 580 $L{\cdot}mol^{-1}$ for an **8**·Li complex and of ca. 30 $L^2{\cdot}mol^{-2}$ for an $(\mathbf{8})_2$·Li complex.

We then initiated a similar study with the diastereomeric ligand **10**. Again, addition of $LiBPh_4$ to a solution of **10** in CD_3NO_2 resulted in significant changes in the ^1H and ^{13}C NMR spectra. In this case, however, complexation was accompanied by considerable line broadening of the NMR signals, precluding an NMR titration of sufficient quality to allow the determination of complexation constants. That complexation to Li cations induced a conformation change from **10a** to **10b** could, nevertheless, be established by resorting to NOE experiments.



Uncomplexed **10** (= **10a**) shows an NOE contact between 2-H and 3′-CH_3 and no NOE contact between 2-H and 2′-H. Upon addition of ca. 5 equiv. of $LiBPh_4$, the former NOE contact vanishes, while a new one appears between 2-H and 2′-H.

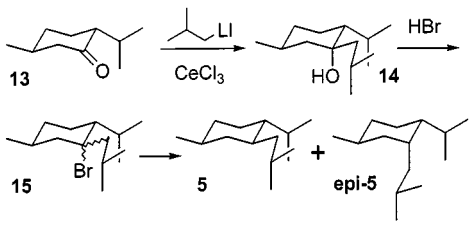
Encouraged by these results, we took a brief look at the complexation behavior of the bis(tetrahydropyranyl)methane **11**.[14] Initial experiments with **11** in toluene solution showed that the $^3J_{H,H}$ coupling constants characteristic of **11a** (9.4 and 2.7 Hz) changed to 8.0 and 3.5 Hz upon addition of $LiClO_4$. NMR titration with $LiBPh_4$ in CD_3NO_2 was complicated by the precipitation of a complex − probably the (**11**)$_2$·Li complex − in an intermediate concentration range. The complex redissolved upon further addition of $LiBPh_4$. The complexation constant for the formation of the **11**·Li and (**11**)$_2$·Li complexes have been approximated by simulation and turned out to be of the same magnitude as the complexation constants found for **8**.



Finally, when the bis(dioxane) compound **12**[29] was treated with $LiBPh_4$ in CD_3NO_2, only very small (< 0.5 ppm, but systematic) changes occurred in the ^{13}C NMR chemical shifts. These show that the complexation constants are only of the order of 1−2 L·mol^{-1}. This is in line with the reduced basicity of oxygen atoms in acetals, compared to those in an ether function.[30] Kishi reported[26] a related observation concerning the complexing abilities of O-sucrose versus C-sucrose towards Ca ions. These results are noteworthy in that very similar structural entities, such as **11** and **12**, can be activated (**11**) or deactivated (**12**) towards conformational switching by cation complexation.

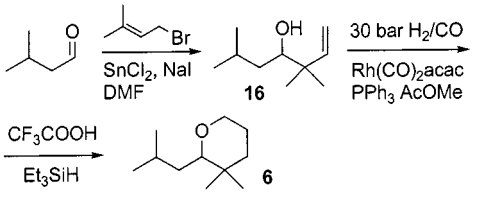
Syntheses

The synthesis of **5** started from menthone. Addition of isobutyllithium in the presence of $CeCl_3$ at −78 °C furnished 54% of the alcohol **14**. A single diastereomer was isolated. We assume that the hydroxy group in **14** is in the axial position, but this is not proven. When ionic reduction (Ph_3SiH, CF_3COOH; or Et_3SiH, CF_3COOH) was used to convert **14** into **5**, product mixtures of **5** and **epi-5** were obtained, with **epi-5** predominating. The assignment is based on the ^{13}C NMR spectra, in which we attribute the set of signals with a larger number of signals shifted upfield in the δ = 20−50 range to **epi-5**, which bears an axial isobutyl group.[31] Moreover, only one of these compounds shows a methyl signal at δ = 15 (i.e. < 20), diagnostic of an isopropyl group flanked by an equatorial substituent.[32]

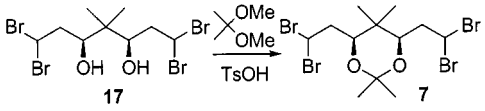


We then transformed **14** into the tertiary bromo compound **15**[31] (77%). Reduction with Bu_3SnH and AIBN gave a 1.4:1 mixture of **5**/**epi-5**. The highest ratio of **5** to **epi-5** (3.6:1) was reached when **15** was reduced with sodium metal in refluxing THF followed by protonation with methanol at −78 °C. The mixture of **5**/**epi-5** obtained (93%) was used as such to determine the characteristic NMR data of **5**.

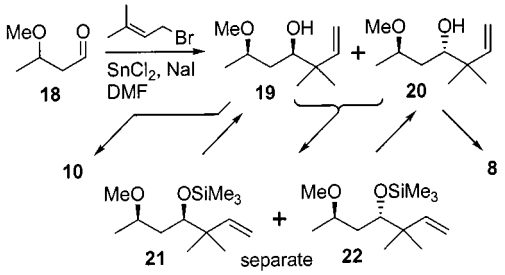
For the synthesis of **6**, isovaleraldehyde was converted[33] into the homoallylic alcohol **16** (74%). The latter compound was subjected to hydroformylation, followed by ionic reduction of the tetrahydropyranol intermediate. This sequence furnished the tetrahydropyran **6** in 87% yield.



The acetonide **7** was obtained by acetalization of the diol **17**, available from another study.[34]

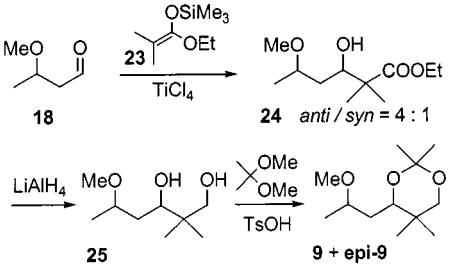


The synthesis of **8** and **10** began with the prenylation[33] of β-methoxybutyraldehyde (**18**).[35] This produced a 1:2 mixture of the epimeric alcohols **19** and **20**. Separation of the epimers by flash chromatography was possible, but we found it more convenient to convert **19** and **20** into the silyl ethers **21** and **22**, which allowed for easy chromatographic separation.



The alcohols **19** and **20** were then obtained individually by hydrolysis of the separated silyl ethers **21** and **22**. The relative configurations of **19** and **20** were assigned on the basis of chemical shift values of the oxygen-bearing carbon atoms [δ = 78.5, 78.6 (*syn*); 74.3, 74.8 (*anti*)].[36] The homoallylic alcohol **19** was converted into the tetrahydropyran **10** (82%) by a sequence of hydroformylation and ionic reduction. Likewise, the alcohol **20** furnished 66% of **8**.

Finally, for the synthesis of **9** the aldehyde **18** was allowed to react with the ketene acetal **23**[37] under $TiCl_4$ catalysis.[38] This furnished the hydroxy ester **24** with a 4:1 *anti*/*syn* selectivity. Diastereomer assignment was again based on the ^{13}C NMR signal positions[36] [δ = 75.5, 77.5 (*syn*); 72.4, 73.9 (*anti*)].



The mixture of esters **24** was reduced to a mixture of diastereomeric diols **25**, which were immediately converted into the acetonides **9** and **epi-9**. Flash chromatography provided **9** in 57% yield.

Experimental Section

General Remarks: All temperatures quoted are uncorrected. − ^1H NMR, ^{13}C NMR: Bruker ARX-200, AC-300, WH-400, AM-400, AMX 500. − Boiling range of petroleum ether: 40−60 °C. − Flash chromatography: SI 60 silica gel, Merck KGaA, Darmstadt, 40−63 μm. Conformer populations were estimated on the basis of force-field calculations using the MM3* force-field implemented in the MACROMODEL[15] 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. (1*R*,2*R*,5*S*)-1-Isobutyl-2-isopropyl-5-methylcyclohexanol (14): $CeCl_3$ (2.52 g, 9.83 mmol) was dried at 10^{-3} Torr and 140 °C for 1.5 h. The material was subsequently suspended in THF (30 mL). The suspension was cooled to −78 °C and a solution of isobutyllithium (12.6 mL, 0.72 M in Et_2O, 9.43 mmol) was added dropwise. After the mixture had been stirred for 1 h, (*R*,*R*)-menthone (1.12 g, 7.25 mmol) was added and the suspension was stirred for a further 1.5 h at −78 °C. Saturated aqueous NH_4Cl solution (10 mL) was added, and after the mixture had reached room temperature, water was added until a homogenous solution resulted. The phases were separated and the aqueous phase was extracted with dichloromethane (5 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. To reduce residual menthone, the remaining yellowish oil was added at 0 °C to a solution of $NaBH_4$ (70 mg) in methanol (8 mL). After the mixture had been stirred at room temperature overnight, water (5 mL) was added, the phases were separated, and the aqueous phase was extracted with dichloromethane (5 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue, using petroleum ether/*tert*-butyl methyl ether (25:1), furnished **14** as a colorless oil (0.831 g, 54%). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.75−1.15 (m, 19 H), 1.25−1.55 (m, 4 H), 1.55−1.85 (m, 4 H), 2.12 (qd, *J* = 7.0 and 1.8 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 20.6, 22.6, 23.6, 23.7, 24.6, 25.3, 25.5, 28.1, 35.1, 47.0, 49.4, 49.8, 75.5. − $[\alpha]_D^{20}$ = −10.0 (*c* = 1.55, diethyl ether). − $C_{14}H_{28}O$ (212.4): calcd. C 79.18, H 13.29; found C 78.91, H 13.05.

2. (1*R*,2*RS*,4*S*)-2-Isobutyl-1-isopropyl-4-methylcyclohexane (5): A stream of hydrogen bromide was slowly introduced into a flask containing (1*R*,2*R*,5*S*)-1-isobutyl-2-isopropyl-5-methylcyclohexanol (**14**) (167 mg, 0.79 mmol). After ca. 45 min, two phases formed. TLC indicated that the reaction was complete after 1.5 h. The mixture was diluted with ether (8 mL). The resulting solution was washed with aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The solution was dried ($MgSO_4$) and concentrated to give a colorless oil (167 mg), which appeared to be a single diastereomer. − ^{13}C NMR (50 MHz, C_6D_6): δ = 17.6, 20.7, 22.3, 23.2, 25.2, 25.4, 32.4, 32.7, 33.5, 37.4, 38.1, 40.9, 42.7, 89.6. − The bromo compound obtained (50 mg, ca. 0.18 mmol) was taken up in THF (1.5 mL) and sodium (122 mg, 5.3 mmol) was added in small pieces. This mixture was heated to reflux for 2 h and cooled to room temperature. The remaining sodium pieces were removed and the solution was cooled to −78 °C. Methanol (0.5 mL) was added slowly over 1 h. The mixture was allowed to come to room temperature and was extracted with pentane (3 × 4 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with petroleum ether furnished **5** and **epi-5** (33 mg, 93%) as a colorless oil. The diastereomer ratio was estimated to be 3.6:1 by integrating the ^{13}C NMR signals at δ = 47.9 and 48.3. − **5**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 21.3, 21.7, 22.9, 24.4, 24.5, 24.8, 26.2, 32.8, 35.4, 36.6, 41.4, 42.7, 47.9. − HRMS: $C_{14}H_{28}$: required for [M^+] 196.2191, found 196.2197.

3. 3,3,6-Trimethyl-1-hepten-4-ol (16): Prenyl bromide (12.5 g, 83.6 mmol), sodium iodide (20.9 g, 139 mmol), and $SnCl_2{\cdot}2H_2O$ (23.6 g, 104 mmol) were added slowly to a solution of isovaleraldehyde (6.00 g, 69.7 mmol) in dimethylformamide (140 mL) at 0 °C in such a manner that the temperature did not rise above 30 °C. The resulting suspension was stirred for 2 d. The mixture was poured into aqueous NH_4F solution (15%, 100 mL), the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Distillation of the residue furnished **16** (15.35 g, 74%) as a colorless liquid of b.p. 69 °C/30 mbar. − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.99 (s, 6 H), 1.24 (m, 2 H), 1.76 (m, 1 H), 3.47 (m, 1 H), 5.0 (m, 2 H), 5.81 (m, 1 H). These data correspond to those given in ref.[39]

4. 2-Isobutyl-3,3-dimethyltetrahydropyran (6): Triphenylphosphane (2.4 g, 9.0 mmol) was added to a solution of (acetylacetonato)-dicarbonylrhodium (31 mg, 0.12 mmol) in methyl acetate (2 mL), resulting in a strong gas evolution. After stirring for 30 min, this solution was transferred into an autoclave which contained a solution of 3,3,6-trimethyl-1-hepten-4-ol (**16**) (1.0 g, 6.0 mmol) in methyl acetate (23 mL). The contents of the autoclave were stirred for 48 h at 100 °C under 30 bar of CO/H_2. The contents of the autoclave were concentrated and the residue was taken up in pentane/ethyl acetate (4:1) (50 mL) and filtered through silica gel (50 g). The filtrate was concentrated and the residue was taken up in dichloromethane (20 mL). Triethylsilane (1.3 mL, 8.0 mmol) and trifluoroacetic acid (1.3 mL, 17 mmol) were added at 0 °C. The

solution was heated to reflux for 18 h. Aqueous ammonia (25%) was added until the mixture was basic. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether (9:1) furnished 0.89 g (87%) of **6** as a colorless liquid. − ^{1}H NMR (500 MHz, CD_3NO_2): δ = 0.80 (s, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.16 (ddd, *J* = 14.0, 10.1, and 2.0 Hz, 1 H), 1.24 (ddd, *J* = 14.0, 10.1, and 2.0 Hz, 1 H), 1.36 (m, 2 H), 1.46 (m, 1 H), 1.73 (m, 2 H), 3.03 (dd, *J* = 10.1 and 2.0 Hz, 1 H), 3.31 (ddd, *J* = 12.5, 11.1, and 2.4 Hz, 1 H), 3.88 (dddd, *J* = 11.1, 4.9, 1.7, and 1.7 Hz, 1 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 21.5, 23.2, 23.9, 24.7, 27.6, 32.6, 38.8, 39.3, 68.8, 83.7. − $C_{11}H_{22}O$ (170.3): calcd. C 77.58, H. 13.02; found C 77.30, H 12.60.

5. (4*R,6*S**)-4,6-Bis(2′,2′-dibromoethyl)-2,2,5,5-tetramethyl-1,3-dioxane (7):** *p*-Toluenesulfonic acid (40 mg, 0.20 mmol) was added to a solution of (3*S**,5*R**)-1,1,7,7-tetrabromo-3,5-dihydroxy-4,4-dimethylheptane (**17**) (683 mg, 1.44 mmol) in 2,2-dimethoxypropane (10 mL). After the mixture had been stirred for 1 d, triethylamine (5 drops) was added and the mixture was concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether (10:1) furnished **7** (682 mg, 92%) as a colorless solid of m.p. 162−165 °C[40] − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (s, 3 H), 0.89 (s, 3 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 2.35−2.51 (m, 4 H), 3.71−3.78 (m, 2 H), 5.69−5.76 (m, 2 H). Simulation of the spectrum is compatible with the following assignments: δ = 2.425 (ddd, *J* = 14.4, 11.2, and 2.4 Hz, 1 H), 2.448 (ddd, *J* = 14.4, 9.8, and 2.5 Hz, 1 H), 3.74 (ddd, *J* = 9.8, 2.4, and −0.2 Hz, 1 H), 5.72 (ddd, *J* = 11.2, 2.5, and −0.2 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.3, 20.0, 29.8, 34.6, 43.7 (2C), 45.1 (2C), 76.2 (2C), 99.3. − $C_{12}H_{20}Br_4O_2$ (515.9): calcd. C 27.94, H 3.91; found C 28.04, H 3.84.

6. 6-Methoxy-3,3-dimethyl-4-trimethylsilyloxy-1-heptenes (21 and 22): 3-Methoxybutanal (**18**)[35] (10.0 g, 97.9 mmol), prenyl bromide (17.52 g, 117.6 mmol), and sodium iodide (30.0 g, 200 mmol) were dissolved in dimethylformamide (200 mL). $SnCl_2 \cdot 2H_2O$ (33.0 g, 146 mmol) was added under nitrogen, in such a manner that the temperature did not exceed 30 °C. The mixture was stirred for 2 d, aqueous NH_4F solution (20%, 600 mL) was added, the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 200 mL). The combined organic phases were concentrated. Zinc powder (ca. 100 mg) was added and the suspension was stirred for 10 min. *tert*-Butyl methyl ether (200 mL) was added, together with $MgSO_4$ (ca. 0.5 g). The suspension was filtered and the filtrate was concentrated. Distillation furnished a ca. 2:1 mixture of the alcohols **19** and **20** as a colorless liquid of b.p. 60−64 °C at 1 mbar. Separation of the mixture by flash chromatography is possible, using diethyl ether/pentane (1:1). The mixture of **19** and **20** (5.35 g, 31.1 mmol) was taken up in dichloromethane (150 mL). Triethylamine (5.8 mL, 42 mmol), 4-(dimethylamino)pyridine (ca. 100 mg), and chlorotrimethylsilane (4.0 g, 37 mmol) were added at 0 °C. The mixture was stirred for 12 h at room temperature. Water (100 mL) and ether (150 mL) were added. The phases were separated and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with petroleum ether/dichloromethane (1:1) furnished **22** (4.20 g, 55%) and **21** (1.81 g, 24%) as colorless liquids.

(4*R,6*R**)-6-Methoxy-3,3-dimethyl-4-trimethylsilyloxy-1-heptene (21):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9 H), 0.95 (s, 6 H), 1.10 (d, *J* = 6.0 Hz, 3 H), 1.40 (ddd, *J* = 13.4, 9.3, and 2.3 Hz, 1 H), 1.72 (ddd, *J* = 13.4, 9.3, and 4.2 Hz, 1 H), 3.25−2.34 (m, 5 H), 4.95 (dd, *J* = 17.2 and 1.4 Hz, 1 H), 4.97 (dd, *J* = 11.1 and 1.4 Hz, 1 H), 5.80 (dd, *J* = 17.2 and 11.1 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.86, 18.9, 22.5, 24.1, 39.9, 41.9, 55.8, 75.1, 77.5, 111.9, 145.8. − $C_{13}H_{28}O_2Si$ (244.4): calcd. C 63.88, H 11.55, found C 63.70, H 11.69.

(4*R,6*S**)-6-Methoxy-3,3-dimethyl-4-trimethylsilyloxy-1-heptene (22):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9 H), 1.03 (s, 6 H), 1.08 (d, *J* = 6.0 Hz, 3 H), 1.27 (ddd, *J* = 14.3, 10.2, and 2.3 Hz, 1 H), 1.53 (ddd, *J* = 14.3, 10.3, and 1.6 Hz, 1 H), 3.28 (s, 3 H), 3.35−3.49 (m, 1 H), 3.66 (dd, *J* = 10.2 and 1.6 Hz, 1 H), 4.87−4.99 (m, 2 H), 5.73−5.91 (m, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.95, 19.1, 22.7, 24.1, 40.8, 41.5, 55.1, 72.9, 76.6, 111.6, 146.1. − $C_{13}H_{28}O_2Si$ (244.4): calcd. C 63.88, H 11.55, found C 63.89, H 11.72.

7. (4*R,6*R**)-4-Hydroxy-6-methoxy-3,3-dimethyl-1-heptene (19):** (4*R**,6*R**)-6-Methoxy-3,3-dimethyl-4-trimethylsilyloxy-1-heptene (**21**) (1.58 g, 6.45 mmol) in ethanol (30 mL) was stirred with aqueous NH_4F solution (15%, 20 mL) for 12 h. The mixture was extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with petroleum ether/ether (1:1) furnished **19** (945 mg, 85%) as a colorless oil. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 6 H), 1.15 (d, *J* = 6.0 Hz, 3 H), 1.40−1.58 (m, 2 H), 3.33 (s, 3 H), 3.47 (ddd, *J* = 10.1, 1.5, and 1.5 Hz, 1 H), 3.47−3.56 (m, 1 H), 3.73 (d, *J* = 1.5 Hz, 1 H), 4.99 (dd, *J* = 17.3 and 1.5 Hz, 1 H), 5.00 (dd, *J* = 11.1 and 1.5 Hz, 1 H), 5.86 (dd, *J* = 17.3 and 11.1 Hz, 1 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 22.0, 23.2, 38.3, 41.2, 55.8, 78.5, 78.6, 112.1, 145.7. − $C_{10}H_{20}O_2$ (172.3): calcd. C 69.72, H 11.70; found C 69.52, H 11.84.

8. (4*R,6*S**)-4-Hydroxy-6-methoxy-3,3-dimethyl-1-heptene (20):** (4*R**,6*S**)-6-Methoxy-3,3-dimethyl-4-trimethylsilyloxy-1-heptene (**22**) (3.12 g, 12.8 mmol) was deprotected as described under 7 to give **20** as a colorless oil (1.93 g, 88%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 3 H), 1.00 (s, 3 H), 1.17 (d, *J* = 6.2 Hz, 3 H), 1.43−1.57 (m, 2 H), 2.44 (broad s, 1 H), 3.31 (s, 3 H), 3.56−3.66 (m, 2 H), 5.01 (dd, *J* = 17.5 and 1.5 Hz, 1 H), 5.04 (dd, *J* = 10.9 and 1.5 Hz, 1 H), 5.84 (dd, *J* = 17.5 and 10.9 Hz, 1 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 22.5, 22.8, 37.4, 41.2, 56.2, 74.3, 74.8, 112.8, 145.5. − $C_{10}H_{20}O_2$ (172.3): calcd. C 69.72, H 11.70; found C 69.66, H 11.72.

9. (2*R,2′*S**)-2-(2′-Methoxypropyl)-3,3-dimethyltetrahydropyran (8):** Compound **20** (1.03 g, 6.00 mmol) was transformed essentially as described for compound **6**, to give **8** as a colorless oil (734 mg, 66%). − ^{1}H NMR (500 MHz, CD_3NO_2): δ = 0.80 (s, 3 H), 0.87 (s, 3 H), 1.08 (d, *J* = 6.2 Hz, 3 H), 1.23 (ddd, *J* = 14.4, 10.3, and 3.1 Hz, 1 H), 1.30−1.40 (m, 2 H), 1.42−1.49 (m, 1 H), 1.54 (ddd, *J* = 14.4, 9.4, and 1.5 Hz, 1 H), 1.68−1.82 (m, 1 H), 3.15 (dd, *J* = 10.3 and 1.5 Hz, 1 H), 3.26 (s, 3 H), 3.32 (ddd, *J* = 12.3, 11.1, and 2.1 Hz, 1 H), 3.43 (m, 1 H, decoupling at δ = 1.08 revealed dd, *J* = 9.4 and 3.1 Hz), 3.88 (dddd, *J* = 11.1, 4.9, 1.6, and 1.6 Hz, 1 H). − ^{13}C NMR (100 MHz, CD_3NO_2): δ = 19.5, 20.2, 24.4, 28.1, 33.5, 38.8, 40.3, 56.5, 69.6, 75.2, 83.3. − $C_{11}H_{22}O_2$ (186.3): calcd. C 70.92, H 11.90; found C 70.80, H 11.65.

10. (2*R,2′*R**)-2-(2′-Methoxypropyl)-3,3-dimethyltetrahydropyran (10):** Compound **19** (1.0 g, 6.0 mmol) was converted into the tetrahydropyran as described for compound **6**, to give **10** (0.92 g, 82%) as a colorless liquid. − ^{1}H NMR (500 MHz, CD_3NO_2): δ = 0.81 (s, 3 H), 0.90 (s, 3 H), 1.10 (d, *J* = 6.1 Hz, 3 H), 1.30−1.41 (m, 3 H), 1.44−1.50 (m, 1 H), 1.62 (ddd, *J* = 13.9, 10.4, and 3.0 Hz, 1 H), 1.70−1.83 (m, 1 H), 3.00 (dd, *J* = 10.4 and 1.9 Hz, 1 H), 3.25

(s, 3 H), 3.29 (ddd, J = 12.2, 11.1, and 2.2 Hz, 1 H), 3.36−3.45 (m, 1 H), 3.86 (dddd, J = 11.1, 4.8, 1.7, and 1.7 Hz, 1 H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7, 19.0, 23.0, 27.5, 32.6, 35.9, 39.1, 55.8, 68.7, 74.7, 82.5. − $C_{11}H_{22}O_2$ (186.3): calcd. C 70.92, H 11.90, found C 70.62, H 11.84.

11. Ethyl 3-Hydroxy-5-methoxy-2,2-dimethylhexanoate (24): A solution of 3-methoxybutanal (**18**)[35] (2.16 g, 21.2 mmol) in dichloromethane (30 mL) was stirred for 20 min with molecular sieves (4 Å, 1 g). The solution was cooled to −78 °C. $TiCl_4$ (2.4 mL, 22 mmol) was added. After the mixture had been stirred for 15 min, 1-ethoxy-2-methyl-1-trimethylsilyloxy-1-propene (**23**)[37] (4.02 g, 21.4 mmol) was added dropwise. After stirring for 2 h at −78 °C, the mixture was allowed to come to 0 °C. Water (10 mL) and ether (50 mL) were added, the phases were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), and concentrated. Bulb-to-bulb distillation of the residue at 60 °C/1 mbar furnished the ester **24** (2.62 g, 57%) as a diastereomer mixture. − $C_{11}H_{22}O_4$ (218.3): calcd. C 60.52, H 10.16; found C 60.44, H 10.30. − **Major Diastereomer (*anti*):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94−1.16 (m, 12 H), 1.30−1.40 (m, 2 H), 3.20 (s, 3 H), 3.44−3.58 (m, 1 H), 3.70 (broad s, 1 H), 3.76−3.88 (m, 1 H), 3.94−4.08 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.5, 20.3, 21.4, 38.1, 46.5, 55.8, 60.2, 72.4, 73.9, 177.3. − **Minor Diastereomer (*syn*):** The following signals could be recorded. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.21 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 20.5, 38.2, 46.7, 55.5, 60.1, 75.5, 77.5, 176.8.

12. (2′*R,4*S**)-4-(2′-Methoxypropyl)-2,2,5,5-tetramethyl-1,3-dioxane (9):** Compound **24** (2.40 g, 11.0 mmol) was added to a solution of $LiAlH_4$ (0.50 g, 13 mmol) in THF (20 mL) under argon. After 15 h of reflux, the mixture was cooled to 0 °C. Excess $LiAlH_4$ was decomposed by the dropwise addition of saturated aqueous NH_4F solution (20 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography of the residue with petroleum ether/ethyl acetate (1:2) furnished the mixture of the diastereomeric diol **25** (592 mg, 31%) as a colorless oil. − **Major Diastereomer (*anti*):** ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 18.8, 22.2, 37.4, 37.9, 56.0, 71.9, 74.7, 75.0. − **Minor Diastereomer (*syn*):** ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 19.0, 22.3, 37.9, 38.0, 55.6, 71.3, 78.6, 79.4. − The diols obtained (570 mg, 3.23 mmol) were taken up in dichloromethane (10 mL). 2,2-Dimethoxypropane (1.3 mL) and camphorsulfonic acid (ca. 50 mg) were added. The mixture was stirred for 3 h at room temperature and poured into saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography with dichloromethane/ethyl acetate (10:1) furnished the major diastereomer **9** (401 mg, 57%) as a colorless oil. − ^{1}H NMR (500 MHz, [D_8]toluene): δ = 0.530 (s, 3 H), 1.009 (s, 3 H), 1.023 (d, J = 6.2 Hz, 3 H), 1.314 (ddd, J = 13.9, 10.3, and 2.6 Hz, 1 H), 1.364 (s, 1 H), 1.459 (ddd, J = 13.9, 10.0, and 1.4 Hz, 1 H), 1.477 (s, 1 H), 3.181 (s, 3 H), 3.192 (d, J = 10.7 Hz, 1 H), 3.40−3.49 (m, 2 H), 3.845 (dd, J = 10.3 and 1.4 Hz, 1 H). − ^{13}C NMR (125 MHz, [D_8]toluene): δ = 18.3, 19.1, 19.5, 21.5, 30.1, 32.5, 37.9, 56.1, 72.3, 73.1, 73.5, 98.6. − $C_{12}H_{24}O_3$ (216.3): calcd. C 66.63, H 11.18, found C 66.65, H 11.24.

13. Complexation of 8 with Lithium Tetraphenylborate: Compound **8** (19.1 mg, 1.02 μmol) was dissolved in 0.5 mL of CD_3NO_2. NMR spectra of this solution were recorded and new spectra measured after each addition of 20 μL of a 0.708 M solution of lithium tetraphenylborate in CD_3NO_2. The chemical shifts recorded were plotted against the equivalents of lithium tetraphenylborate added. The resulting curves were simulated by considering formation of 1:1 and 2:1 ligand/lithium complexes. This provided an approximation of the equilibrium constants.

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[1] R. W. Hoffmann, D. Stenkamp, *Tetrahedron* **1999**, *55*, 7169−7176.
[2] S. Sykora, *Collect. Czech. Chem. Commun.* **1968**, *33*, 3514−3527.
[3] P. L. Luisi, *Naturwissenschaften* **1977**, *64*, 569−574.
[4] W. C. Still, D. Cai, D. Lee, P. Hauck, A. Bernardi, A. Romero, *Lect. Heterocycl. Chem.* **1987**, *9*, S33−S42.
[5] G. Quinkert, E. Egert, C. Griesinger, *Aspekte der Organischen Chemie*, VCH, **1995**, vol. 1, p. 131.
[6] R. Göttlich, B. C. Kahrs, J. Krüger, R. W. Hoffmann, *Chem. Commun.* **1997**, 247−251.
[7] R. W. Hoffmann, D. Stenkamp, T. Trieselmann, R. Göttlich, *Eur. J. Org. Chem.* **1999**, 2915−2927.
[8] R. W. Hoffmann, M. Stahl, U. Schopfer, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 559−566.
[9] R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134−2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054−2070.
[10] T. Fäcke, S. Berger, *Magn. Reson. Chem.* **1995**, *33*, 144−148.
[11] P. Durette, F. Baker, P. L. Barker, J. Boger, S. S. Bondy, M. L. Hammond, T. J. Lanza, A. A. Pessolano, C. G. Caldwell, *Tetrahedron Lett.* **1990**, *31*, 1237−1240.
[12] K. Umezawa, K. Nakazawa, T. Uemura, Y. Ikeda, S. Kondo, H. Naganawa, N. Kinoshita, H. Hashizume, M. Hamada, T. Takeuchi, S. Ohba, *Tetrahedron Lett.* **1998**, *39*, 1389−1392.
[13] E. Kleinpeter, R. Meusinger, C. Duschek, R. Borsdorf, *Magn. Reson. Chem.* **1987**, *25*, 990−995.
[14] R.W. Hoffmann, B. C. Kahrs, J. Schiffer, J. Fleischhauer, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407−2414.
[15] 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.
[16] For the conformational preference of other 2-(2,2-dibromoethyl)tetrahydropyrans, see: R. W. Hoffmann, H.-C. Stiasny, J. Krüger, *Tetrahedron* **1996**, *52*, 7421−7434.
[17] S. Cauwberghs, P. J. De Clercq, *Tetrahedron Lett.* **1988**, *29*, 2493−2496.
[18] R. W. Alder, C. M. Maunder, A. G. Orpen, *Tetrahedron Lett.* **1990**, *31*, 6717−6720.
[19] 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.
[20] R. W. Alder, P. R. Allen, K. R. Anderson, C. P. Butts, E. Khosravi, A. Martin, C. M. Maunder, A. G. Orpen, C. B. St. Purcain, *J. Chem. Soc., Perkin Trans. 2* **1998**, 2083−2107.
[21] K. Matsuzaki, K. Sakota, M. Okada, *J. Polym. Sci., Part A* **1969**, *7*, 1444−1449.
[22] M. Raban, D. L. Burch, E. R. Hortelano, D. Durocher, D. Kost, *J. Org. Chem.* **1994**, *59*, 1283−1287.
[23] B. König, H. Hollnagel, B. Ahrens, P. G. Jones, *Angew. Chem.* **1995**, *107*, 2763−2765; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2538.
[24] O. Reany, S. Blair, R. Kataky, D. Parker, *J. Chem. Soc., Perkin Trans. 2* **2000**, 623−630.
[25] A. Szuma, D. T. Gryko, J. Jurczak, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1553−1558.

[26] D. O'Leary, Y. Kishi, *J. Org. Chem.* **1994**, *59*, 6629−6636.
[27] W. Krauss, H.-G. Weinig, M. Seydack, J. Bendig, U. Koert, *Angew. Chem.* **2000**, *112*, 1905−1908; *Angew. Chem. Int. Ed.* **2000**, *39*, 1835−1837.
[28] R. W. Hoffmann, I. Münster, *Liebigs Ann./Recueil* **1997**, 1143−1150.
[29] R. W. Hoffmann, B. C. Kahrs, *Tetrahedron Lett.* **1996**, *37*, 4479−4482.
[30] A. Kankaanperä, *Acta Chem. Scand.* **1969**, *23*, 1723−1727.
[31] W. Damm, B. Giese, T. Hartung, T. Hasskerl, K. N. Houk, O. Hüter, H. Zipse, *J. Am. Chem. Soc.* **1992**, *114*, 4067−4079.
[32] J. Firl, G. Kresze, T. Bosch, V. Arndt, *Justus Liebigs Ann. Chem.* **1978**, 87−97.
[33] T. Imai, S. Nishida, *Synthesis* **1993**, 395−399.
[34] H. C. Stiasny, *Synthesis* **1996**, 259−264.
[35] F. Büttner, *Justus Liebigs Ann. Chem.* **1953**, *583*, 184−190.
[36] R. W. Hoffmann, U. Weidmann, *Chem. Ber.* **1985**, *118*, 3980−3992.
[37] N. Slougui, G. Rousseau, *Synth. Commun.* **1987**, *17*, 1−11.
[38] M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542−555; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556−569.
[39] B. M. Mikhailov, Y. N. Bubnov, A. V. Tsyban, M. S. Grigoryan, *J. Organomet. Chem.* **1978**, *154*, 131−145.
[40] Crystallographic data (excluding structural factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-157271. 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].

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