Flexible Molecules with Defined Shape XI[+]

Conformer Equilibria in 2,4-Disubstituted Pentane Derivatives

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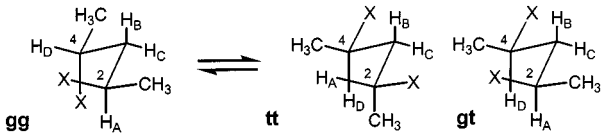
Keywords: Conformational analysis / Conformational isomerism / Isotopic labeling / 2,4-Disubstituted pentanes

2,4-Disubstituted pentanes are molecules which adopt essentially only two conformations. Substituents have been varied in order to find those which lead to a strong preference of the conformer equilibrium. Studying 2-substituted 4-methylpentanes **3** and 4-benzyloxypentanes **12**, it has been shown that substituent effects on the conformer equilibria are not additive, as would be expected on the grounds of steric effects alone. Rather, interactions between polar groups reinforce the bias of the conformer equilibria. When applied to 2,4-disubstituted pentanes, substituents such as chloro or phthalimido shift the conformer equilibrium to the side of the *gg* conformer with preferences exceeding 90%.

Many examples of compounds which have a flexible molecular backbone but nevertheless adopt certain preferred conformations are found in nature.[2] Local segments in some of these compounds can be identified as derivatives of 2,4-dimethylpentane (**1**), which itself has two enantiomorphous low energy conformations comprising > 90% of the conformer population.[3] Conformation design[4] (by nature or by man) could be based on structural modifications of **1**, i.e. the introduction of heteroatom substituents X, cf. **2**. This should shift the conformer equilibrium of the 2,4-disubstituted pentane skeleton to one side, hopefully rendering the skeleton "monoconformational".



1 X = CH_3

2 X ≠ CH_3

Scheme 1

For instance, for (*R**,*R**)-2,4-dimethoxypentane (**2**, X = OCH_3), the equilibrium favors the *gg* conformer.[5] The shift in the conformer equilibrium is attributed to the fact that the methoxy group in **2** has a smaller van der Waals radius than a methyl group.[6] The destabilizing interaction between the hydrogen atom H_A at C-2 and the methoxy group at C-4 in the *gg* conformer is therefore smaller than the interaction between H_A at C-2 and the methyl group at C-4 in the *tt* conformer. This favors the *gg* conformer in the equilibrium. But aside from this purely steric argument, there may be other factors influencing the conformer equilibria.[7] In order to learn more on how substituents affect the conformer equilibrium of **2**, the present study was undertaken. We hoped to identify in this manner, substituents X which most strongly influence the conformer equilibrium of **2**.

Determinations of the position of the conformer equilibrium of **2** are based on vicinal $^1H,^1H$-NMR coupling constants. The measured $^3J_{H,H}$ coupling constants for the protons H_AH_B, H_AH_C, H_BH_D, H_CH_D represent the population weighted average of the values for the individual (low energy) conformers of **2**. MM3* calculations were carried out in order to identify the low energy conformers, and to predict conformer populations. E.g. for (*R**,*R**)-dimethoxypentane (**2,** X = OCH_3) the calculations predict the ratio of the *gg*; *tt*; *gt* conformer populations to be 80:7:9, i.e. there should be a significant contribution of the *gt* conformer to the conformer population, in addition to the expected *gg* and *tt* conformers. The *gt* conformer is destabilized relative to the most stable *gg* conformer by a 1,3-parallel oxygen/methyl interaction[7] amounting to 0.8 kcal·mol^{-1}. It is at present not clear whether the *gt* conformer really contributes towards the conformer equilibrium to such a large extent, or whether this prediction is merely a reflection of an inadequate parameterization of the force field. Vicinal coupling constants for the individual conformers of **2** (*gg*, *tt*, *tg*) were calculated based on a Karplus relationship implemented in the MACROMODEL program.[8] This routine takes into account effects of the electronegativity of the substituents X on the size of the individual coupling constants. Interpolation[9] of the measured coupling constants between the values calculated for the *gg* and *tt* conformers of **2** then allows for a crude estimate of the position of the conformer equilibrium.[4] In this manner the *gg*/*tt* conformer ratio for (*R**,*R**)-2,4-dimethoxypentane (**2,** X = OCH_3) is estimated to be 2.3:1.

2-Substituted 4-Methylpentanes

The steric effects of substituents on the conformer equilibria can easily be assessed by studying the conformer popu-

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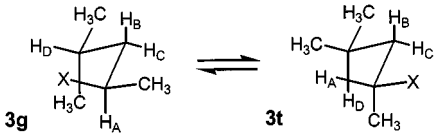
lations of 2-substituted 4-methylpentanes **3**, in which dipole−dipole interactions may be neglected. A qualitative analysis of the steric effects reveals two limiting cases: If the substituent X in **3** is a methyl group, i.e., the situation present in **1**, a 1:1 conformer equilibrium prevails; if the substituent is reduced in size (it may not become smaller than a hydrogen atom, i.e. **3,** X = H), MM3* calculations predict a conformer ratio of 4:1. Substituents that have a size inbetween that of a hydrogen atom and a methyl group should then lead to conformer preferences for the *g* conformer which fall between the values 1:1 and 4:1. If the substituent X in **3** becomes larger than a methyl group, the *t* conformer of **3** should be favored.

We previously reported data[10] for compounds **3** in which the substituent X is a vinyl, phenyl, formyl or alkoxycarbonyl group. These compounds showed moderate conformer preferences of up to 2:1 for the *g* conformer. This is in line with the idea[11] that sp^2-hybridized carbon atoms are smaller than methyl groups. Here we consider compounds **3**, in which the substituent X is a heteroatom.

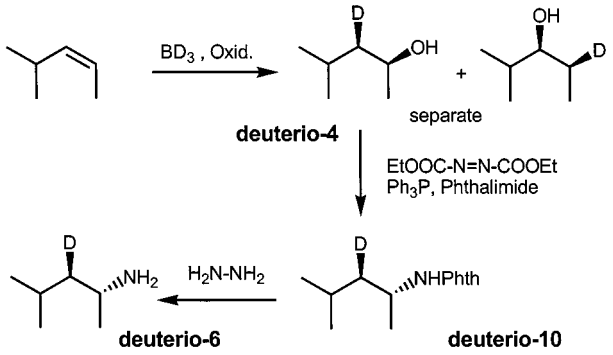


Scheme 2

There are already some reports regarding the conformer preferences of hetero-substituted compounds of the type **3**: For the chloro compound **11** (and the corresponding bromo compound), IR studies[12] indicate a clear preference for the *gauche* conformer.

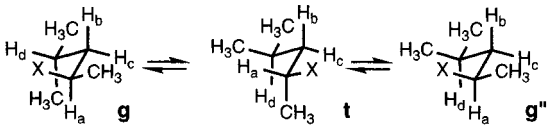
For the alcohol **4**, lanthanide-induced shifts in the NMR spectra have been interpreted in terms of a preference for the *t* conformation.[13] MM3* calculations suggest, however, a preference for the *g* conformation. This discrepancy could be explained by the fact that oxygen coordinated to europium is larger than a methyl group, whereas a hydroxy group is not.[11]

In order to get a clear picture, we calculated the conformer populations and measured the NMR coupling constants for the compounds **4**−**11**, cf. Table 1. In order to avoid any ambiguities in identifying the predominant conformer, in several instances we assigned the individual coupling constants by specific deuterium labeling. To this end, (*Z*)-4-methyl-2-pentene was hydroborated with BD_3 to give **deuterio-4** and the regioisomer, which were separated by chromatography.



Scheme 3

Table 1. Experimentally derived and calculated conformer populations for 2-substituted 4-methylpentanes



	X =	contribution of the **g**, **t**, **g"** conformers to the total conformer population (%) calculated with MM3* [a]	NMR coupling constants (Hz) H_aH_b	H_aH_c	H_bH_d	H_cH_d		Solvent	**g** : **t** estimated from NMR
4	OH	53 : 24 : 15	8.2	4.9	6.0	8.2	b) c)	$CDCl_3$	1.6 : 1
			8.2	4.9	6.0	8.2		DMSO	1.6 : 1
5	OMe	47 : 28 : 12	7.4	5.6	6.4	7.4	c)	$CDCl_3$	1.4 : 1
6	NH_2	50 : 34 : 7	7.8	5.9	6.4	7.8	b)	DMSO	1.4 : 1
7	NH_3^+ AcO^-	39 : 54 : -	5.9	8.6	8.2	6.2	b)	DMSO	1 : 1.7
8	NHMe	54 : 32 : 10	5.7	7.7	8.0	6.0		DMSO	1 : 1.6
			6.3	7.4	7.9	6.5		$CDCl_3$	1 : 1.3
9	NMe_2	58 : 31 : 8	7.1	7.1	7.1	7.1	b)	DMSO	1 : 1
			5.7	8.0	7.9	6.3		$CDCl_3$	1 : 1.5
10	NPhth	78 : 7 : 10	9.9	4.8	4.8	10.3	b)	C_6D_6	3.7 : 1
11	Cl	63 : 29 : 4	9.3	4.8	5.4	8.6		$CDCl_3$	2.2 : 1

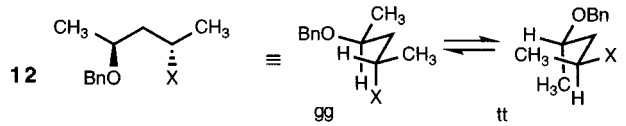
a) The numbers do not add up to 100%, due to the presence of conformations not corresponding to **g**, **t** or **g″**. For the force field used in MACROMODEL see ref.[32] − b) Coupling constants have been assigned by specific deuterium labeling. − c) The calculated (MACROMODEL) gauche coupling constants involving the hydrogen atom α to oxygen for the individual conformers depended on the spatial arrangement of the OR group. These couplings were not used when estimating the gg:tt ratios.

The deuterated alcohol was then converted into the phthalimide (**deuterio-10**), which was the precursor to the specifically deuterated amines **6** and **9**.

Inspection of the data in Table 1 shows that the conformer preferences are small. The alcohol **4** displays a preference for the *gauche* conformer **4g**. In view of the similarity of the coupling constants, we believe that this also holds for the methoxy compound **5**. MM3* predicted a preference for the *gauche* conformation for all the amines **6**, **8**, and **9**. This, however, is contradicted by the NMR spectra recorded for the dimethylamino compound **9**. Here, the *trans* conformer was found to be favored. MM3* correctly predicted the shift of the preferred conformation from *gauche* to *trans* on protonation of the amine **6**. From both the MM3* calculations and the NMR spectra, it can be concluded that the phthalimido compound **10** has the strongest preference for the *g* conformation of all the compounds studied. This is not surprising, since the sp^2-hybridized nitrogen atom of the phthalimido group should be smaller than the sp^3-hybridized nitrogen atom in the amines **6**, **8**, and **9**.

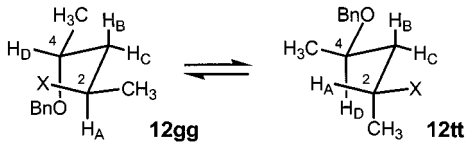
But with more polar substituents, steric effects may not be the only factor affecting the conformer equilibria. It appears that polar effects may be of similar importance in favoring the *gauche* conformer, since 1-halopropanes[14] and 1-propanol[15] prefer a conformation, in which the C−X bond is *gauche* to the C−C-bond, a situation not induced by steric effects. This finding has been attributed to a stabilizing $\sigma_{C-H} - \sigma^*_{C-X}$ interaction, for which an antiperiplanar arrangement of the interacting orbitals is a prerequisite.[16] This interaction would be possible in **3g** but not in **3t**, provided that a C−H bond is a better σ-donor than a C−C bond.[17] The conformational preferences in the halopropanes has also been discussed in terms of induced dipole−dipole interactions.[18][19]

Table 2. Experimentally derived and calculated conformer populations for 2-substituted 4-benzyloxypentanes



12	X =	$^3J_{H,H}$ (Hz)	gg : tt from NMR[a)]	gg : tt : others from MM3* [b)]
a	OMe	9.0 3.6 9.0 3.6	3.2 : 1	84 : 4 : 12
b	SPh	9.6 4.7 9.2 3.6	3.1 : 1	93 : 2 : 5
c	Cl	10.7 2.8 10.0 2.6	8.9 : 1	89 : 3 : 8
d	Br	10.4 3.2 9.4 3.0	6.3 : 1	90 : 4 : 6
e	$CH=CH_2$	9.5 4.9 8.9 4.0	2.6 : 1	90 : 3 : 7
f	$C(CH_3)=CH_2$	9.3 5.3 8.5 4.1	2.4 : 1	91 : 3 : 6
g	$C(O)-CH_3$	8.9 4.5 8.7 3.8	2.9 : 1	83 : 3 : 14
h	COOH	9.5 4.5 9.0 3.7	3.8 : 1	84 : 3 : 13
i	$COOCH_3$	9.7 4.4 8.9 3.7	3.4 : 1	87 : 2 : 11
j	NPhth	11.0 3.8 9.3 2.8	>10 : 1	63 : 1 : 37
k	N_3	10.3 3.0 9.8 3.4	≈4.5 : 1	
l	C≡CH	11.0 4.3 9.9 3.0	5.8 : 1	90 : 2 : 8
m	$C\equiv C-SiMe_3$	10.8 4.5 9.8 3.2	≈4.5 : 1	

a) The calculated (MACROMODEL) gauche coupling constants involving the hydrogen atom α to oxygen for the individual conformers depended on the spatial arrangement of the OR group. These couplings were not used when estimating the gg:tt ratios. b) For the force field used in MACROMODEL see ref.[32]



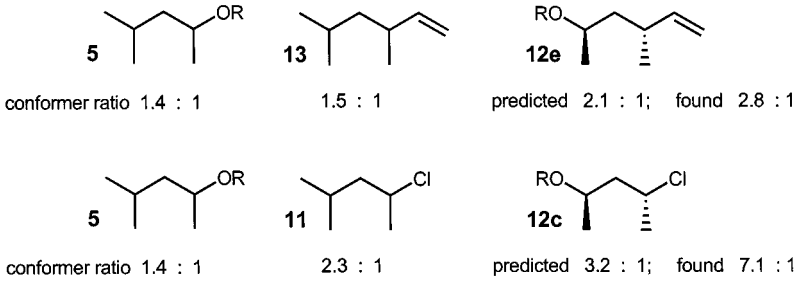
Scheme 4

2-Substituted 4-Benzyloxypentanes

We then addressed the question of whether substituent effects on conformer equilibria are additive on going from the monosubstituted derivatives **3**, to disubstituted derivatives **2**. For simplicity, we first studied a series of compounds **12** in which we kept one substituent (the benzyloxy group) constant. The results compiled in Table 2 show moderate to marked conformational preferences. The predominance of the *gg* conformer was ascertained for **12b**, **12c**, and **12l** by determination of $^3J_{C,H}$ coupling constants.[20] In the other cases, the assignment of the predominant conformer is tentative, and is based on MM3* calculations.

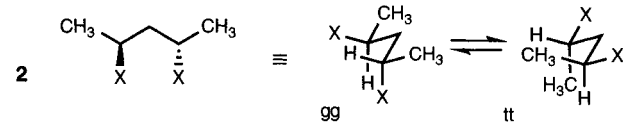
With the aid of the results in Table 2, we may now evaluate whether the substituent effects recorded for monosubstituted pentanes **3** may be used to predict the position of the conformer equilibria of the disubstituted pentanes **12**. Two examples will be given: Multiplication of the conformer ratios found for the disubstituted pentanes **5** and **13** (which is equivalent to adding the ΔG values of the conformer equilibria) leads to a predicted value for the position of the conformer equilibrium in the disubstituted pentane **12e** which is in fair agreement with the NMR-derived result. In the second example, two polar substituents are involved. When the conformer ratios of **5** and **11** are multiplied, the conformer ratio predicted for **12c** is clearly smaller than the experimentally derived value. This difference can be attributed to a mutual interaction between the substituents in **12c** which affects the position of the conformer equilibrium.

In previous studies on 1,3-difluoropropane[19] and (*R**,R*)-2,4-dichloropentane,[21] the nature of this interaction has been ascribed to 1,3-dipole−dipole interactions,



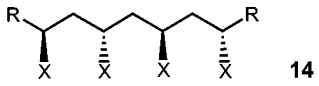
Scheme 5

Table 3. Experimentally derived and calculated conformer populations for 2,4-disubstituted pentanes



2	X^1 =	X^2 =	$^3J_{H,H}$ (Hz)	gg : tt from NMR	gg : tt : others from MM3* [a]
a	OMe	OMe	7.8 4.6 [b]	2.3 : 1 [d]	80 : 7 : 13
b	OAc	OAc	9.0 3.8 [c]	≈3.5 : 1 [d]	86 : 2 : 12
c	Cl	Cl	10.6 2.2	>10 : 1	92 : 5 : 3
d	Br	Br	10.9 2.4	>10 : 1	89 : 9 : 2
e	NPhth	NPhth	11.8 4.5	>10 : 1	90 : 1 : 9
f	N_3	N_3	10.5 3.0	8.0 : 1	
g	C≡C-SiMe$_3$	C≡C-SiMe$_3$	10.6 4.3	≈4.5 : 1	96 : 0 : 4 [e]
h	NPhth	Cl	10.7 2.9 10.9 4.0	8.1 : 1	88 : 2 : 10
i	NPhth	N_3	10.3 2.9 10.8 4.1	≈8.5 : 1	

[a] For the force field used in MACROMODEL see ref.[32] − [b] Values from ref.[5] − [c] Values from ref.[22] − [d] The calculated (MACROMODEL) gauche coupling constants involving the hydrogen atom α to oxygen for the individual conformers depended on the spatial arrangement of the OR group. These couplings were not used when estimating the gg:tt ratios. − [e] Calculated for −C≡C−C(CH$_3$)$_3$ substituents.



Scheme 6

which would additionally stabilize the *gg* conformer of **12c** over the *tt* conformer.

Other 2,4-Disubstituted Pentanes

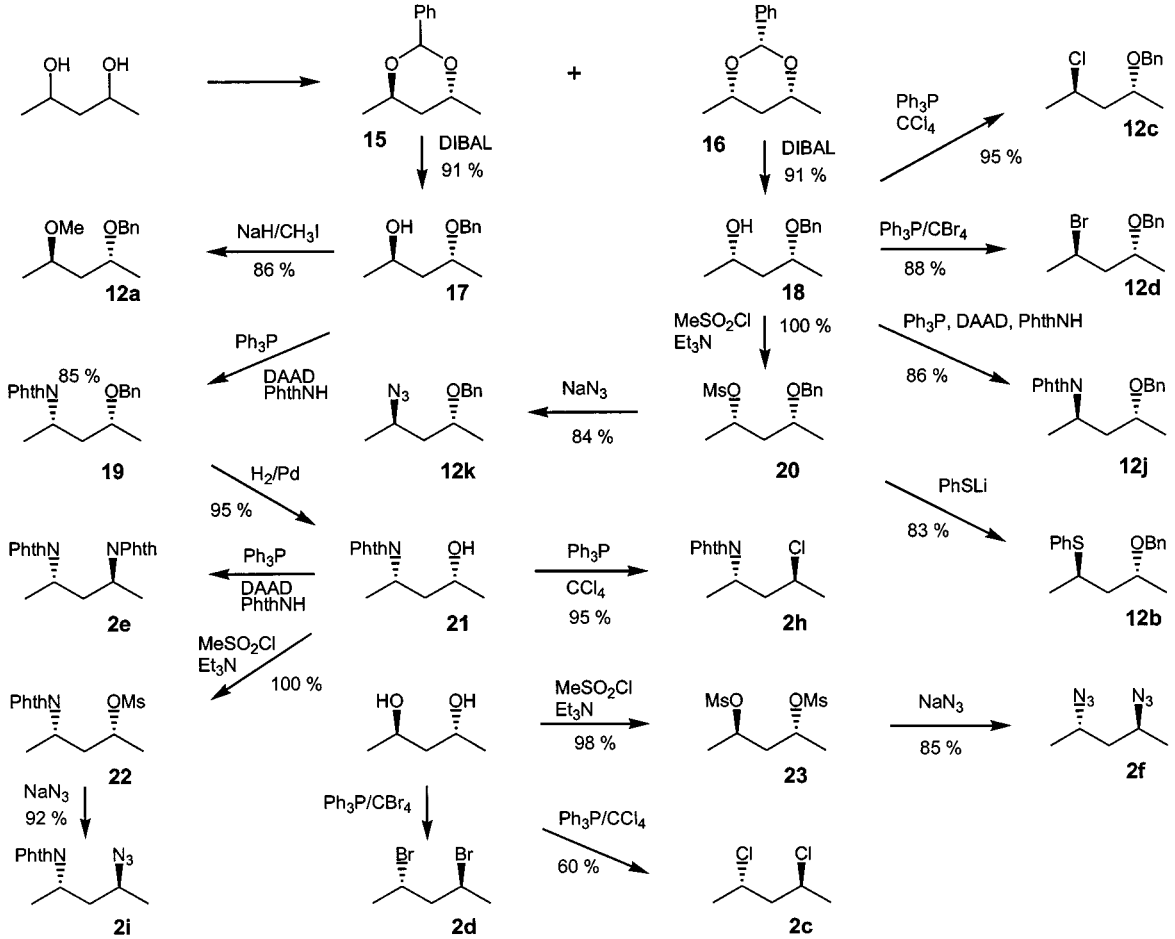
The finding that there are cooperative effects between substituents on the conformer equilibria in 2,4-disubstituted pentanes, is of importance for conformation design. The aim of this study was to identify specific substituents, which, when placed in the 2,4-positions of a pentane chain, would lead to a strong shift in the conformer equilibrium. The data collected in Table 1 and Table 2 suggest that the best candidates are chloro substituents, phthalimido groups, alkynes or azido groups. Therefore, the next round of experiments focussed on pentane derivatives having two of those substituents in the 2,4-positions. The compounds investigated, and the position of the conformer equilibria, as estimated from the ^{1}H-NMR coupling constants, are summarized in Table 3.

Since most of the compounds in Table 3 are C_2-symmetric, the relevant $^3J_{H,H}$ coupling constants could only be approximated by simulation[23] of the higher order multiplets. In turn, the accuracy of the values of the coupling constants is rather low (± 0.2 Hz). The predominance of the *gg* conformer has been established in the case of the dibromo compound **2d** by determining the $^3J_{C,C}$-coupling constant to be 3.8 Hz. Assignments in the other cases were made only on the basis of MM3* calculations.

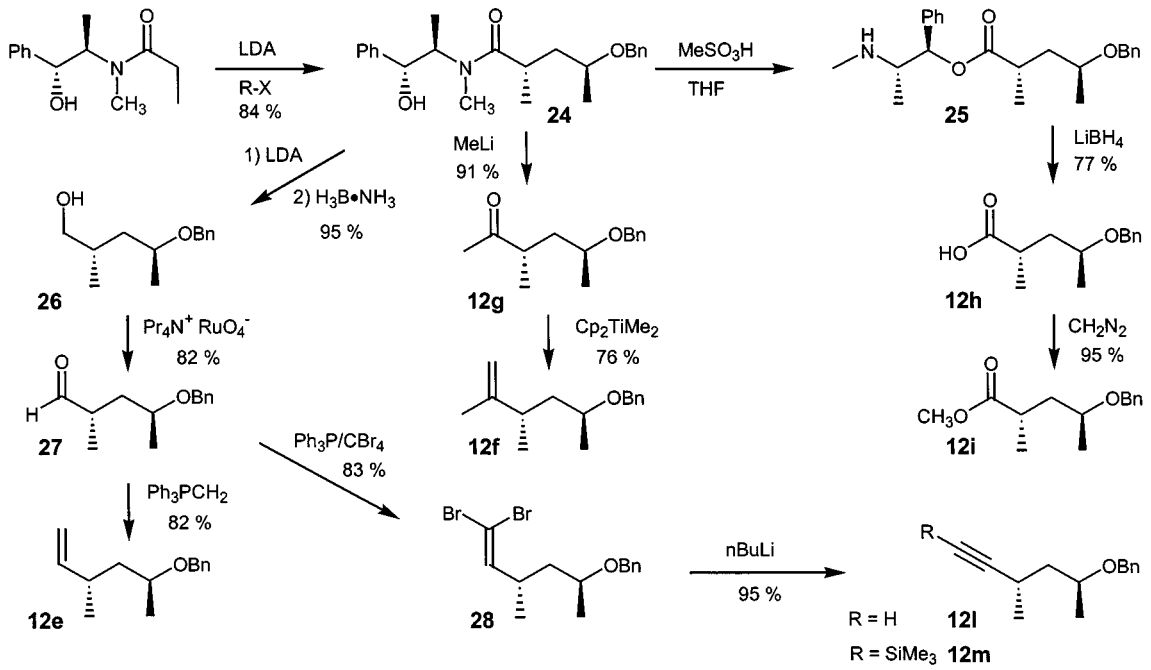
Our results for the dichloro **2c** and dibromo **2d** match those reported earlier in the literature.[24][25] The dichloro compound **2c**, especially has been the focus of attention as a model compound for the local conformations in syndiotactic polyvinyl chloride.[26]

Comparison of the data in Table 3 and Table 1 again shows that the effects of polar substituents on the conformer population are not additive. Thus, the dichloro compound **2c** shows a much larger conformational preference than predicted on the basis of the mono-halo compound **11** in Table 1.

Our aim was to identify substituents, which when placed in the 2,4-positions of pentane, led to a strong conformational preference of the pentane backbone. The dihalo compounds **2b**, **2c** and, most prominently, the diphthalimido compound **2e**, meet these criteria. It should therefore become possible to construct larger backbone sequences with a preferred conformation, such as **14,** based on these substituents.



Scheme 7

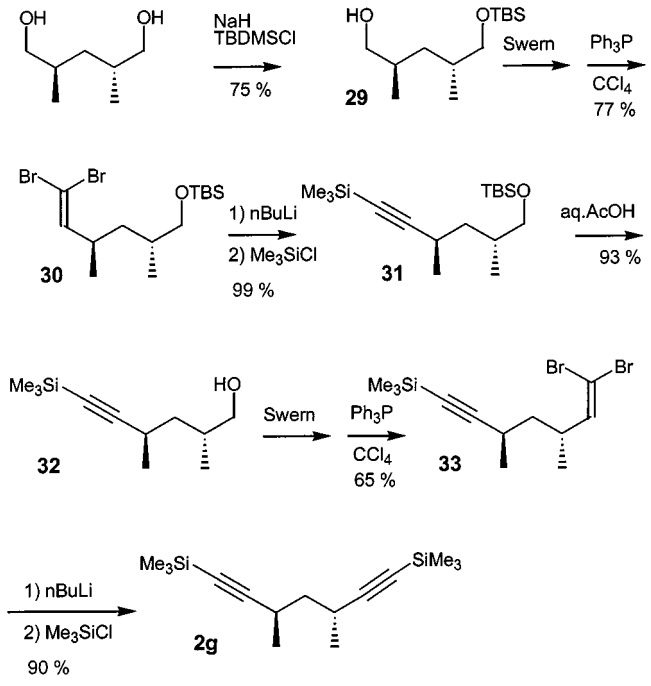


Scheme 8

Syntheses

The compounds referred to in Table 1 were partly commercially available and partly prepared by procedures given in the literature. The compounds referred to in Tables 2 and 3 were prepared following the routes outlined in Schemes 7 and 8.

In order to gain access to the bisalkyne **2g**, bidirectional routes were explored. Due to low yields, however, this approach was abandoned in favor of the more lengthy routes shown in Scheme 9.



Scheme 9

Experimental Section

All temperatures quoted are not corrected. − Reactions were carried out under dry nitrogen or argon. − Boiling range of petroleum ether: 40−60°C. − ^{1}H, ^{13}C NMR: Bruker AC 200, AC 300, AM 400, and AMX 500. Spectra were recorded at 20°C in $CDCl_3$ (99% D), which was also used as internal standard. − Buffer of pH = 7: $NaH_2PO_4 \times 2\ H_2O$ (56.2 g) and $Na_2HPO_4 \times 2\ H_2O$ (213.3 g) in 1.0 L of water. − Column chromatography: Silica gel Si60 (63−200 μm), E. Merck AG, Darmstadt. − Flash chromatography: Silica gel Si60 (40−63 μm), E. Merck AG, Darmstadt. − HPLC: Gilson/Abimed 305/306, LiChrosorb Si 60 (7 μm) Knauer, Berlin.

1. (2*S,3*R**)-3-Deuterio-4-methylpentan-2-ol (deuterio-4):** Sodium borodeuteride (600 mg, 14.4 mmol) was added to a solution of (*Z*)-4-methyl-2-pentene (1.5 mL, 12.0 mmol) in diethyl ether (50 mL). The suspension was cooled to −78°C and boron trifluoride−diethyl ether (2.2 mL, 18.0 mmol) was added slowly over 3 h. The mixture was allowed to reach room temperature. Aqueous NaOH (6 mL, 3 M) and H_2O_2 (6 mL, 30% in water) were slowly added and the mixture was stirred for 2 h. The phases were separated and the aqueous phase was extracted with ether (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with ether/pentane 1:4 to give the alcohol **deuterio-4** (185 mg, 15%) and its regioisomer. − **deuterio-4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 6 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 1.37 (m, 1 H), 1.40 (br. s, 1 H), 1.68 (m, 1 H), 3.84 (m, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.3, 23.1, 23.9, 24.8, 48.6 (triplet due to attached deuterium), 66.1. The undeuterated alcohol showed ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 1.14 (d, *J* = 6.2 Hz, 3 H), 1.19 (ddd, *J* = 13.6, 8.2, and 4.9 Hz, 1 H), 1.37 (ddd, *J* = 13.6, 8.2, and 4.9 Hz, 1 H), 1.70 (m, 1 H), 3.84 (m, 1 H).

2. (2*R,3*R**)-3-Deuterio-4-methyl-2-phthalimidopentane (deuterio-10): deuterio-4** and its regioisomer were prepared as above from $NaBD_4$ (100 mg, 2.4 mmol), BF_3−diethyl ether (370 μL, 3.0 mmol), and (*Z*)-4-methyl-2-pentene (750 μL, 6.0 mmol). The mix-

ture of alcohols obtained (207 mg, 2.0 mmol) was dissolved in THF (15 mL). Phthalimide (403 mg, 2.74 mmol) and triphenylphosphane (698 mg, 2.66 mmol) were added and the mixture was cooled to 0°C. Diethyl azodicarboxylate (456 mg, 2.62 mmol) was then added dropwise. After stirring at room temperature for 12 h, the mixture was concentrated and the residue was absorbed on silica gel (3 g). This was purified by flash chromatography, eluted with *tert*-butyl methyl ether/pentane 1:9 to give a 4:1 mixture of regio isomers (333 mg, 72%). This mixture was separated by preparative HPLC (2% *tert*-butyl methyl ether in pentane). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.2 Hz, 3 H), 0.84 (d, *J* = 6.0 Hz, 3 H), 1.37 (d, *J* = 7.0 Hz, 3 H), 1.38 (m, 2 H), 4.38 (m, 1 H), 7.61 (m, 2 H), 7.74 (m, 2 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0, 21.9, 22.9, 25.3, 42.2 (triplet due to the attached deuterium) 45.4, 123.0, 132.0, 133.7, 168.5. – $C_{14}H_{16}DNO_2$: M^+ found 232.1329, calcd. 232.1322. The undeuterated compound showed ^{1}H NMR (500 MHz, C_6D_6): δ = 0.88 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.42 (ddd, *J* = 13.9, 10.3, and 4.8 Hz, 1 H), 1.44 (d, *J* = 6.9 Hz, 3 H), 1.48 (m, 1 H), 2.30 (ddd, *J* = 13.9, 9.9, and 4.8 Hz, 1 H), 4.63 (m, 1 H), 6.05 (m, 2 H), 7.60 (m, 2 H).

3. (2*R,3*R**)-2-Amino-3-deuterio-4-methylpentane (deuterio-6):** Hydrazine hydrate (144 μL, 80% in water, 2.97 mmol) was added to a solution of **deuterio-10** (266 mg, 1.14 mmol) in methanol (3 mL). After heating under reflux for 5 h, the mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and absorbed onto an ion exchange column (Dowex H^+, 50 WX, 50–100 mesh). The resin was washed with water/methanol (1:1, 3 × 10 mL), and dichloromethane (3 × 10 mL). The amine was eluted with aqueous ammonia (12.5%, 3 × 10 mL). The combined ammonia solutions were extracted with dichloromethane (3 × 10 mL). Removal of the solvent led to the amine **deuterio-6** (85 mg, 73%). – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 0.82, (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.2 Hz, 3 H), 1.02 (m, 1 H), 1.63 (m, 1 H), 2.77 (m, 1 H). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 22.4, 23.0, 24.4, 25.0, 44.5, 49.8 (triplet due to attached deuterium). Undeuterated **6** showed ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 0.82 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.3 Hz, 3 H), 1.02 (ddd, *J* = 13.2, 7.8, and 5.9 Hz. 1 H), 1.11 (ddd, *J* = 13.2, 7.8, and 6.4 Hz, 1 H), 1.64 (m, 1 H), 2.78 (m, 1 H).

4. (2*R,3*R**)-2-(Dimethylamino)-3-deuterio-4-methylpentane (deuterio-9):** A solution of the deuterated amine **6** (128 mg, 0.93 mmol), formic acid (178 μL, 4.65 mmol), and formaldehyde (37% in water, 208 μL, 2.79 mmol) were stirred at 80°C for 17 h. After cooling to room temperature, hydrochloric acid (4 N, 5 mL) was added. The phases were separated and the aqueous phase was extracted with ether (5 mL). The ether phase was discarded and the aqueous phase was concentrated to leave a white solid. This was dissolved in water (5 mL), the solution was cooled to 0°C and solid NaOH was added to obtain a pH of 12. The solution was extracted with ether (4 × 2 mL) and the combined extracts were dried (K_2CO_3) and concentrated at 0°C, leaving the amine **deuterio-9** (91 mg, 75%). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.5 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.07 (m, 1 H), 1.55 (m, 1 H), 2.19 (s, 6 H), 2.59 (m, 1 H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 22.1, 23.3, 25.0, 40.1, 42.1 (triplet due to attached deuterium), 56.6. – ^{2}H NMR (61 MHz, $CDCl_3$): δ = 1.34 s. Undeuterated **9** showed ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.05 (ddd, *J* = 13.4, 8.0, and 5.7 Hz, 1 H), 1.30 (ddd, *J* = 13.4, 7.9, and 6.3 Hz, 1 H), 1.61 (m, 1 H), 2.37 (s, 3 H), 2.55 (m, 1 H), 5.26 (s, 6 H).

5. (2*R,4*R**)-4-Benzyloxy-2-pentanol (17):** A solution of diisobutylaluminium hydride (1.0 M in petroleum ether, 15.2 mmol) was added dropwise at 0°C to a solution of (4*R**,6*R**)-4,6-dimethyl-2-phenyl-1,3-dioxane (**15**)[27] (1.47 g, 7.6 mmol) in dichloromethane (15.0 mL). After stirring for 2 h at 0°C, and for one day at room temperature, ethyl acetate (50 mL) was added at 0°C. After stirring for 0.5 h, aqueous NaOH (3 M, 90 mL) and *tert*-butyl methyl ether (40 mL) were added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 40 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with mixtures of petroleum ether and *tert*-butyl methyl ether varying from 10:1 to 1:1 furnished **17** (1.35 g, 91%) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 4.63 (d, *J* = 11.6 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 4.13 (m, 1 H), 3.87 (m, 1 H), 2.85 (s, 1 H), 1.73–1.59 (m, 2 H), 1.27 (d, *J* = 6.2 Hz, 3 H), 1.19 (d, *J* = 6.3 Hz, 3 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 23.5, 44.5, 64.5, 70.5, 72.6, 127.5, 127.6, 128.3, 138.4. – $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 73.91, H 9.40.

6. (2*S,4*R**)-4-Benzyloxy-2-pentanol (18):** (2s*,4*R**,6*S**)-4,6-Dimethyl-2-phenyl-1,3-dioxane (**16**)[27] (1.96 g, 10.2 mmol) was allowed to react as described under 5. to give 1.57 g (79%) of the product as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.2 Hz, 3 H), 1.21 (d, *J* = 6.1 Hz, 3 H), 1.51 (dt, *J* = 14.5 and 9.5 Hz, 1 H), 1.68 (dt, *J* = 14.5 and 9.5 Hz, 1 H), 3.62 (s, 1 H), 3.78 (m, 1 H), 3.95 (m, 1 H), 4.39 (d, *J* = 11.4 Hz, 1 H), 4.63 (d, *J* = 11.5 Hz, 1 H), 7.23–7.32 (m, 5 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 23.4, 46.6, 67.5, 70.2, 75.7, 127.6, 127.7, 128.4, 138.0. – $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 73.91, H 9.47.

7. (2*R,4*R**)-2-Benzyloxy-4-methoxypentane (12a):** Sodium hydride (80% in white oil, 0.96 mmol) was added in small portions to a solution of (2*R**,4*R**)-4-benzyloxy-2-pentanol (**17**, 124 mg, 0.64 mmol) in dimethylformamide (1.6 mL) at 0°C. After stirring for 30 min, methyl iodide (0.89 mL, 9.6 mmol) was added dropwise and the suspension was stirred for 1.5 h at 0°C, and for 2 h at room temperature. Saturated aqueous $NaHCO_3$ solution (20 mL) was added; the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (138 mg) furnished the product **12a** (114 mg, 86%) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.2 Hz, 3 H), 1.20 (d, *J* = 6.1 Hz, 3 H), 1.57 (m, 2 H), 3.26 (s, 3 H), 3.53 (m, 1 H), 3.75 (m, 1 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.61 (d, *J* = 11.6 Hz, 1 H), 7.24–7.35 (m, 5 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 20.1, 45.3, 56.1, 70.8, 71.8, 73.6, 127.5, 127.9, 128.4, 139.1. – $C_{13}H_{20}O_2$ (208.3): calcd. C 74.96, H 9.68; found C 74.82, H 9.75.

8. (2*R,4*R**)-2-Benzyloxy-4-chloropentane (12c):** Triphenylphosphane (176 mg, 0.6 mmol) was added at room temperature to a solution of (2*S**,4*R**)-4-benzyloxy-2-pentanol (**18**) (97 mg, 0.5 mmol) in acetonitrile (0.5 mL) and CCl_4 (0.5 mL). After stirring for 5 h, saturated aqueous $NaHCO_3$ solution (3 mL) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane followed by 1% *tert*-butyl methyl ether in pentane furnished the product **12c** (101 mg, 95%) as a colorless oil. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.1 Hz, 3 H), 1.52 (d, *J* = 6.6 Hz, 3 H), 1.73 (ddd, *J* = 14.7, 10.7, and 2.6 Hz, 1 H), 1.88 (ddd, *J* = 14.7, 10.0, and 2.8 Hz, 1 H), 3.87 (m, 1 H), 4.36 (m, 1 H), 4.46 (d, *J* = 11.2 Hz, 1 H), 4.63 (d, *J* = 11.2 Hz, 1 H), 7.26–7.37 (m, 5 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 25.8, 48.2, 55.6, 71.2, 72.4,

127.5, 127.8, 128.3, 138.7. − $C_{12}H_{17}ClO$ (212.7): calcd. C 67.76, H 8.06; found C 67.49, H 7.76.

9. (2*R,4*R**)-2-Benzyloxy-4-bromopentane (12d):** CBr_4 (229 mg, 0.69 mmol) was added to a solution of (2*S**,4*R**)-4-benzyloxy-2-pentanol (**18**, 96 mg, 0.49 mmol) in dichloromethane (0.4 mL). The solution was cooled to −20°C and a solution of triphenylphosphane (181 mg, 0.69 mmol) in dichloromethane (1.0 mL) was added dropwise. After 1 d at room temperature, silica gel (0.7 g) was added and the mixture was concentrated. The residue was purified by flash chromatography using pentane and 0.7% *tert*-butyl methyl ether in pentane to furnish the product **12d** (105 mg, 88%) as a colorless oil. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.1 Hz, 3 H), 1.72 (d, *J* = 6.7 Hz, 3 H), 1.84 (ddd, *J* = 15.0, 10.4, and 3.0 Hz, 1 H), 1.90 (ddd, *J* = 15.0, 9.4, and 3.2 Hz, 1 H), 3.86 (m, 1 H), 4.45 (m, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.64 (d, *J* = 11.2 Hz, 1 H), 7.28−7.37 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 27.0, 48.9, 49.0, 71.3, 73.5, 127.6, 127.9, 128.4, 138.7. − $C_{12}H_{17}BrO$ (257.2): calcd. C 56.05, H 6.66; found C 56.34, H 6.70.

10. (2*R,4*R**)-2-Benzyloxy-4-phthalimidopentane (12j):** Phthalimide (106 mg, 0.72 mmol) and triphenylphosphane (180 mg, 0.68 mmol) were added sequentially at 0°C to a solution of (2*S**,4*R**)-4-benzyloxy-2-pentanol (**18**) (100 mg, 0.51 mmol) in THF (2.6 mL). After cooling to 0°C diethyl azodicarboxylate (105 μL, 0.67 mmol) was added dropwise, the mixture was allowed to reach room temperature. After 12 h, silica gel (0.7 g) was added and the suspension was concentrated. Flash chromatography of the residue with pentane and 10% *tert*-butyl methyl ether in pentane furnished the product **12j** (141 mg, 86%) as a colorless oil. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.1 Hz, 3 H), 1.45 (d, *J* = 7.0 Hz, 3 H), 1.79 (ddd, *J* = 14.6, 9.4, and 3.8 Hz, 1 H), 2.46 (ddd, *J* = 14.6, 11.0, and 2.8 Hz, 1 H), 3.40 (m, 1 H), 4.28 (d, *J* = 10.9 Hz, 1 H), 4.44 (d, *J* = 10.9 Hz, 1 H), 4.75 (m, 1 H), 7.18−7.34 (m, 5 H), 7.66 (m, 2 H), 7.78 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.25, 19.31, 40.5, 43.9, 70.8, 72.2, 122.9, 127.3, 127.9, 128.1, 132.0, 133.6, 138.4, 168.4. − $C_{20}H_{21}NO_3$ (323.4): calcd. C 74.28, H 6.55, N 4.33; found C 74.22, H 6.73, N 4.64.

11. (2*R,4*S**)-2-Benzyloxy-4-phthalimidopentane (19):** (2*S**,4*S**)-4-Benzyloxy-2-pentanol (**17**, 400 mg, 2.06 mmol) was allowed to react with phthalimide (424 mg, 2.88 mmol) and triphenylphosphane (718 mg, 2.74 mmol) essentially as described under 10. to give **19** (570 mg, 86%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.1 Hz, 3 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.84 (ddd, *J* = 14.1, 5.9, and 5.1 Hz, 1 H), 2.41 (ddd, *J* = 14.2, 8.8, and 7.9 Hz, 1 H), 3.51 (m, 1 H), 4.27 (d, *J* = 11.7 Hz, 1 H), 4.48 (d, *J* = 11.6 Hz, 1 H), 4.54 (m, 1 H), 7.08−7.16 (m, 5 H), 7.57−7.63 (m, 2 H), 7.67−7.73 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.6, 40.3, 44.8, 70.0, 72.9, 122.8, 127.0, 127.3, 128.0, 132.0, 133.5, 138.5, 168.3. − $C_{20}H_{21}NO_3$ (323.4): calcd. C 74.28, H 6.55, N 4.33; found C 74.19, H 6.46, N 4.57.

12. (1*R,3*S**)-3-Benzyloxy-1-methylbutyl Methanesulfonate (20):** Triethylamine (0.38 mL, 2.37 mmol) was added at −20°C to a solution of (2*S**,4*R**)-4-benzyloxy-2-pentanol (**18**) (408 mg, 2.10 mmol) in dichloromethane (8.4 mL). Methanesulfonyl chloride (0.19 mL, 2.42 mmol) was added and the solution was stirred for 25 min at room temperature. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL), the combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$). Concentration of the solution furnished the product **20** (572 mg, 100%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.1 Hz, 3 H), 1.37 (d, *J* = 6.3 Hz, 3 H), 1.67 (ddd, *J* = 14.1, 6.9, and 5.2 Hz, 1 H), 2.11 (ddd, *J* = 14.1, 7.7, and 6.4 Hz, 1 H), 2.92 (s, 3 H), 3.61 (m, 1 H), 4.39 (d, *J* = 11.7 Hz, 1 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.93 (m, 1 H), 7.25−7.34 (m, 5 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 21.1, 38.4, 43.6, 70.1, 71.1, 77.6, 127.5, 127.6, 128.3, 138.3. − $C_{13}H_{20}O_4S$ (272.4): calcd. C 57.33, H 7.40; found C 57.48, H 7.67.

13. (2*R,4*R**)-2-Azido-4-benzyloxypentane (12k):** Sodium azide (46 mg, 0.70 mmol) was added to a solution of (1*R**,3*S**)-3-benzyloxy-1-methyl-butyl methanesulfonate (**20**) (147 mg, 0.54 mmol) in dimethylformamide (1.8 mL). The mixture was stirred for 12 h at 50°C. Saturated aqueous $NaHCO_3$ solution (3 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (134 mg) with pentane and 1.5% *tert*-butyl methyl ether in pentane furnished the product **12k** (99 mg, 84%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.1 Hz, 3 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.39 (ddd, *J* = 14.4, 10.4, and 3.0 Hz, 1 H), 1.55 (ddd, *J* = 14.4, 9.9, and 3.3 Hz, 1 H), 3.66 (m, 2 H), 4.33 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 7.18−7.28 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 20.1, 44.3, 55.0, 70.8, 71.8, 127.6, 127.8, 128.3, 138.6. − $C_{12}H_{17}N_3O$ (219.3): calcd. C 65.73, H 7.81, N 19.16; found C 65.50, H 8.00, N 19.11.

14. (2*R,4*R**)-2-Benzyloxy-4-(phenylthio)pentane (12b):** *n*-Butyllithium (1.36 M in hexane, 0.86 mmol) was added dropwise at −78°C to a solution of thiophenol (103 μL, 1.0 mmol) in THF (2.0 mL). After stirring for 20 min at −78°C, a solution of (1*R**,3*S**)-3-benzyloxy-1-methylbutyl methanesulfonate (**20**) (151 mg, 0.58 mmol) in THF (1.0 mL) was added by means of a canula. The solution was allowed to stir for 36 h at room temperature. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane and 2% *tert*-butyl methyl ether in pentane furnished the product **12b** (137 mg, 83%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.0 Hz, 3 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 1.60 (ddd, *J* = 14.5, 9.6, and 3.6 Hz, 1 H), 1.81 (ddd, *J* = 14.5, 9.2, and 4.6 Hz, 1 H), 3.48 (m, 1 H), 3.89 (m, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 7.20−7.38 (m, 10 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 22.7, 40.5, 44.7, 70.8, 72.9, 126.6, 127.4, 127.8, 128.3, 128.7, 132.0, 135.3, 138.9. − $C_{18}H_{22}OS$ (286.4): calcd. C 75.48, H 7.74; found C 75.20, H 7.62.

15. (2*R,4*S**)-4-Phthalimido-2-pentanol (21):** Palladium hydroxide on carbon (20%, 13 mg) was added to a solution of (2*S**,4*R**)-2-benzyloxy-4-phthalimidopentane (**19**) (567 mg, 1.75 mmol) in methanol (17.5 mL). The mixture was stirred for 20 h under hydrogen. The mixture was filtered through a pad of Kieselgur and the filtrate was concentrated. The residue (408 mg) was purified by flash chromatography with gradients of petroleum ether and *tert*-butyl methyl ether varying from 4:1 to 1:2, giving the product **21** (387 mg, 95%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.2 Hz, 3 H), 1.43 (s, 1 H), 1.49 (d, *J* = 7.0 Hz, 3 H), 1.89 (ddd, *J* = 14.1, 6.3, and 4.7 Hz, 1 H), 2.18 (dt, *J* = 14.1 and 8.4 Hz, 1 H), 3.83 (m, 1 H), 4.53 (m, 1 H), 7.66−7.69 (m, 2 H), 7.78−7.81 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 24.1, 42.6, 45.0, 66.3, 123.0, 132.1, 133.8, 168.6. − $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.72, H 6.32, N 6.27.

16. (2*R,4*R**)-2,4-Bis(phthalimido)pentane (2e):** (2*R**,4*S**)-4-Phthalimido-2-pentanol (**21**, 125 mg, 0.54 mmol), phthalimide (118

mg, 0.80 mmol), triphenylphosphane, (187 mg, 0.71 mmol) and diethyl azodicarboxylate (110 μL, 0.70 mmol) were allowed to react as described under 10. Flash chromatography with pentane/*tert*-butyl methyl ether = 2:1 to 1.5:1 furnished the product **2e** (85 mg, 43%) followed by a 4:7 mixture of **2e** and diethyl azodicarboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.8 Hz, 6 H), 2.69 (m, 2 H), 4.24 (m, 2 H), 7.69−7.72 (m, 4 H), 7.78−7.82 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 36.4, 44.2, 123.0, 132.0, 133.8, 168.5. − $C_{21}H_{18}N_2O_4$ (362.4): calcd. C 69.60, H 5.01, N 7.73; found C 69.70, H 5.24, N 7.50.

17. (2*R,4*R**)-2-Chloro-4-phthalimidopentane (2h):** (2*R**,4*S**)-4-Phthalimido-2-pentanol (**21**, 96 mg, 0.41 mmol), CCl_4 (0.43 mL) and triphenylphosphane (157 mg, 0.60 mmol) were allowed to react as described under 8. resulting in the product **2h** (99 mg, 95%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.9 Hz, 3 H), 1.48 (d, *J* = 6.6 Hz, 3 H), 1.90 (ddd, *J* = 14.8, 10.7, and 4.0 Hz, 1 H), 2.74 (ddd, *J* = 14.8, 10.9, and 2.9 Hz, 1 H), 3.81 (m, 1 H), 4.69 (m, 1 H), 7.67−7.71 (m, 2 H), 7.78−7.81 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 25.5, 43.4, 44.9, 55.2, 123.1, 131.9, 133.9, 168.3. − $C_{13}H_{14}ClNO_2$ (251.7): calcd. C 62.03, H 5.61, N 5.56; found C 61.93, H 5.31, N 5.54.

18. (1*R,3*S**)-1-Methyl-3-phthalimidobutyl Methanesulfonate (22):** (2*S**,4*R**)-4-Phthalimido-2-pentanol (**21**, 90 mg, 0.39 mmol) and methanesulfonyl chloride (39 μL, 0.49 mmol) were allowed to react as described under 12. to give **22** (121 mg, 100%) as a colorless oil which was characterized only by the NMR spectra. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.3 Hz, 3 H), 1.47 (d, *J* = 6.9 Hz, 3 H), 2.09 (ddd, *J* = 14.4, 6.7, and 6.0 Hz, 1 H), 2.47 (dt, *J* = 14.4 and 7.8 Hz, 1 H), 2.94 (s, 3 H), 4.46 (m, 1 H), 4.75 (m, 1 H), 7.67−7.70 (m, 2 H), 7.76−7.80 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 21.3, 38.6, 40.3, 43.7, 77.1, 123.1, 131.8, 134.0, 168.2.

19. (2*R,4*R**)-2-Azido-4-phthalimidopentane (2i):** (2*S**,4*R**)-1-Methyl-3-phthalimidobutyl methanesulfonate (**22**) (121 mg, 0.39 mmol) and sodium azide (35 mg, 0.54 mmol) were allowed to react for 20 h at 40°C, as described under 13. to give the product **2i** (93 mg, 92%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.6 Hz, 3 H), 1.43 (d, *J* = 7.0 Hz, 3 H), 1.66 (ddd, *J* = 14.4, 10.3, and 4.1 Hz, 1 H), 2.35 (ddd, *J* = 14.3, 10.8, and 3.3 Hz, 1 H), 3.30 (m, 1 H), 4.55 (m, 1 H), 7.67−7.69 (m, 2 H), 7.77−7.81 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.5, 39.6, 44.3, 55.3, 123.1, 131.8, 133.9, 168.3. − $C_{13}H_{14}N_4O_2$ (258.3): calcd. C 60.45, H 5.46, N 21.69; found C 60.31, H 5.16, N 21.52.

20. (2*R,4*R**)-2,4-Diazido-pentane (2f):** (2*R**,4*R**)-2,4-Pentanediol (100 mg, 0.96 mmol) and methanesulfonyl chloride (0.17 mL, 2.2 mmol) were converted into the dimesylate **23** (244 mg, 98%) as described under 12. The latter was dissolved in DMF (3.0 mL) and sodium azide (156 mg, 2.4 mmol) was added. The mixture was held for 9 h at 50°C. Workup as described under 13. furnished the product **2f** (121 mg, 85%) which was characterized by the NMR spectra only in view of its high energetic nature. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.5 Hz, 6 H), 1.46 (m, 2 H), 3.66 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 43.1, 54.9.

21. (2*R,4*R**)-2,4-Dibromopentane (2d):** (2*S**,4*S**)-2,4-Pentanediol (120 mg, 1.15 mmol) was allowed to react with CBr_4 (1.07 g, 3.2 mmol) as described under 9. Flash chromatography with pentane and 1% *tert*-butyl methyl ether in pentane resulted in a 1:1 mixture of bromoform and the product **2d** (246 mg), and analytically pure product (77 mg) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 6.7 Hz, 6 H), 2.08 (m, 2 H), 4.35 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 49.7, 51.7, cf. ref.[28]

22. (2*R,4*R**)-2,4-Dichloropentane (2c):** (2*S**,4*S**)-2,4-Pentanediol (1.50 g, 14.4 mmol) and CCl_4 (9.0 mL) were allowed to react as described under 8. Distillation of the crude product at 14 mbar, 30°C furnished the product **2c** (1.21 g, 60%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 6.6 Hz, 6 H), 1.96 (m, 2 H), 4.32 (m, 2 H) cf. ref.[25] − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 50.5, 55.8.

23. (2*S*)-2-Benzyloxy-1-iodopropane: To a solution of triphenylphosphane (956 mg, 3.6 mmol) in dichloromethane (10 mL), were added imidazole (310 mg, 4.55 mmol), iodine (1.04 g, 4.10 mmol) and a solution of (2*S*)-2-benzyloxypropanol[29] (505 mg, 3.04 mmol) in dichloromethane (6 mL). After stirring for 1 d at room temperature, silica gel (6.0 g) was added. The mixture was concentrated and the residue was purified by flash chromatography with pentane/*tert*-butyl methyl ether varying from 80:1 to 40:1 to give the product (799 mg, 95%) as a colorless oil. − $[\alpha]_D^{20}$ = + 8.0 (*c* = 6.368, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.2 Hz, 3 H), 3.26 (m, 2 H), 3.50 (m, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 7.27−7.36 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 20.3, 70.9, 73.9, 127.7, 128.4, 138.1. − $C_{10}H_{13}IO$ (369.5): calcd. C 43.50, H 4.75; found C 43.58, H 4.93.

24. (2*S*,4*S*)-4-Benzyloxy-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2-dimethylpentanamide (24): A solution of diisopropylamine (9.2 mL, 65 mmol) in THF (47 mL) was added to dried lithium chloride (7.9 g, 190 mmol) and the mixture was cooled to −78°C. A solution of *n*-butyllithium (1.54 M in hexane, 61 mmol) was added dropwise. Stirring was continued for 10 min at −78°C, and for 15 min at 0°C. The mixture was recooled to −78°C and a solution of (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionic amide[33] (6.9 g, 31 mmol) in THF (108 mL) was added, and the yellow suspension was stirred for 1 h at −78°C, 20 min at 0°C and 5 min at room temperature. The mixture was cooled to 0°C and (2*S*)-2-benzyloxy-1-iodopropane (4.5 g, 16 mmol) was added dropwise. After stirring for 30 min at 0°C, and for 2 d at 45°C, the mixture was cooled to 0°C and hydrolyzed by the addition of aqueous semisaturated NH_4Cl solution (100 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (5 × 100 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (10.5 g) with mixtures of pentane and *tert*-butyl methyl ether varying from 2:1 to 1:10 furnished the product **24** (5.1 g, 84%) as a colorless oil. − $[\alpha]_D^{20}$ = −18.4 (*c* = 1.155, $CHCl_3$). − The NMR spectra were complex due to the presence of amide rotamers. − $C_{23}H_{31}NO_3$ (369.5): calcd. C 74.76, H 8.46, N 3.79; found C 74.60, H 8.74, N 3.92.

25. (2*S*,4*S*)-4-Benzyloxy-2-methylpentanol (26): *n*-Butyllithium (1.54 M in hexane, 16.2 mmol) was added dropwise at −78°C to a solution of diisopropylamine (2.5 mL, 17 mmol) in THF (17.4 mL). After stirring for 10 min at −78°C and 15 min at 0°C, borane−ammonia complex (90%, 0.57 g, 16.6 mmol) was added and the suspension was stirred for 15 min at 0°C. A solution of (2*S*,4*S*)-4-benzyloxy-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2-dimethylpentanoic amide (**24**) (1.54 g, 4.2 mmol) in THF (12.7 mL) was added slowly as the mixture was stirred for 2.5 h at room temperature. Hydrochloric acid (3 M, 140 mL) was added at 0°C and the solution was stirred for 30 min. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 70 mL). The combined organic phases were washed with hydrochloric acid (3 M, 20 mL), aqueous NaOH (2 M, 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (0.87 g) with pentane/*tert*-butyl methyl ether va-

rying from 4:1 to 1:1 furnished the product **26** (0.82 g, 95%) as a colorless oil. − $[\alpha]_D^{20}$ = + 28.4 (*c* = 3.830, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3 H), 1.23 (d, *J* = 6.2 Hz, 3 H), 1.56 (m, 2 H), 1.89 (m, 1 H), 2.55 (s, 1 H), 3.42 (m, 2 H), 3.70 (m, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 11.6 Hz, 1 H), 7.23−7.34 (m, 5 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 19.3, 32.2, 40.7, 68.0, 70.3, 72.9, 127.6, 127.7, 128.4, 138.4. − $C_{13}H_{20}O_2$ (208.3): calcd. C 74.96, H 9.68; found C 74.75, H 9.61.

26. (2*S*,4*S*)-4-Benzyloxy-2-methylpentanal (27): To a solution of (2*S*,4*S*)-4-benzyloxy-2-methylpentanol (**26**) (307 mg, 1.47 mmol) in dichloromethane (3.0 mL) was added molecular sieves (4 Å, 750 mg), *N*-methylmorpholine oxide (259 mg, 2.21 mmol) and tetra-*N*-propylammonium perruthenate (26 mg, 0.07 mmol). After stirring for 30 min at room temperature, the mixture was transferred to a chromatography column and purified by elution with pentane/*tert*-butyl methyl ether mixtures from 10:1 to 4:1. The product **27** (248 mg, 82%) was obtained as a colorless oil and immediately used in further transformations.

27. (3*S*,5*S*)-5-Benzyloxy-3-methylhexene (12e): *n*-Butyllithium solution (1.54 M in hexane, 0.48 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (187 mg, 0.52 mmol) in ether (2.0 mL). The resulting yellow suspension was cooled to −78°C, a solution of (2*S*,4*S*)-4-benzyloxy-2-methylpentanal (**27**) (83 mg, 0.40 mmol) in THF (1.0 mL) was slowly added and the mixture was allowed to reach room temperature overnight. Silica gel (0.35 g) was added and the mixture was concentrated. Flash chromatography of the residue with pentane followed by 1% of *tert*-butyl methyl ether in pentane furnished the product **12e** (67 mg, 82%) as a colorless oil. − $[\alpha]_D^{20}$ = + 72.0 (*c* = 1.495, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.8 Hz, 3 H), 1.19 (d, *J* = 6.1 Hz, 3 H), 1.31 (ddd, *J* = 14.0, 9.5, and 4.0 Hz, 1 H), 1.62 (ddd, *J* = 14.0, 8.9, and 4.9 Hz, 1 H), 2.42 (m, 1 H), 3.56 (m, 1 H), 4.39 (d, *J* = 11.4 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.88 (m, 1 H), 4.94 (m, 1 H), 5.64 (m, 1 H), 7.25−7.36 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.9, 21.0, 34.6, 44.5, 70.5, 73.0, 113.0, 127.4, 127.8, 128.3, 139.0, 144.4. − $C_{14}H_{20}O$ (204.3): calcd. C 82.30, H 9.87; found C 82.40, H 9.67.

28. (3*S*,5*S*)-5-Benzyloxy-1,1-dibromo-3-methylhexene (28): A solution of CBr_4 (564 mg, 1.70 mmol) in dichloromethane (0.7 mL) was added by means of a canula to a solution of triphenylphosphane (893 mg, 3.40 mmol) in dichloromethane (1.5 mL). After stirring for 50 min at 0°C, a solution of (2*S*,4*S*)-4-benzyloxy-2-methyl-pentanal (**27**) (180 mg, 0.87 mmol) in dichloromethane (1.0 mL) was added dropwise at −20°C. The suspension was allowed to reach room temperature. Silica gel (3.0 g) was added and the suspension was concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether varying from 100:1 to 20:1 furnished the product **28** (262 mg, 83%) as a colorless oil. − $[\alpha]_D^{20}$ = + 62.9 (*c* = 7.895, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.8 Hz, 3 H), 1.19 (d, *J* = 6.1 Hz, 3 H), 1.38 (ddd, *J* = 14.1, 9.8, and 3.4 Hz, 1 H), 1.65 (ddd, *J* = 14.1, 9.2, and 4.3 Hz, 1 H), 2.81 (m, 1 H), 3.47 (m, 1 H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 6.19 (d, *J* = 9.5 Hz, 1 H), 7.28−7.36 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7, 19.9, 35.2, 43.9, 70.7, 73.0, 87.6, 127.4, 127.8, 128.3, 138.7, 144.1. − $C_{14}H_{18}Br_2O$ (362.1): calcd. C 46.44, H 5.01; found C 46.56, H 5.01.

29. (3*S*,5*S*)-5-Benzyloxy-3-methylhexyne (12l): *n*-Butyllithium (1.54 M in hexane, 0.81 mmol) was added dropwise to a solution of (3*S*,5*S*)-5-benzyloxy-1,1-dibromo-3-methylhexene (**28**) (140 mg, 0.39 mmol) in THF (3.9 mL) at −78°C. After stirring for 3 h, water (0.2 mL) was added and the mixture was allowed to reach room temperature. Saturated aqueous $NaHCO_3$ solution (5 mL) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane followed by 2% *tert*-butyl methyl ether in pentane furnished the product **12l** (74 mg, 95%) as a colorless oil. − $[\alpha]_D^{20}$ = + 137.9 (*c* = 0.580, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 3 H), 1.22 (d, *J* = 6.1 Hz, 3 H), 1.49 (ddd, *J* = 13.7, 11.0, and 3.0 Hz, 1 H), 1.64 (ddd, *J* = 13.7, 9.9, and 4.3 Hz, 1 H), 2.02 (d, *J* = 11.3 Hz, 1 H), 2.80 (m, 1 H), 3.83 (m, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.62 (d, *J* = 11.3 Hz, 1 H), 7.26−7.37 (m, 5 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 21.4, 22.6, 44.7, 68.4, 71.1, 73.3, 88.8, 127.4, 127.8, 128.3, 138.9. − $C_{14}H_{18}O$ (202.3): calcd. C 83.12, H 8.97; found C 82.92, H 8.86.

30. (3*S*,5*S*)-5-Benzyloxy-3-methyl-1-trimethylsilylhexyne (12m): (3*S*,5*S*)-5-Benzyloxy-1,1-dibromo-3-methylhexene (**28**, 111 mg, 0.31 mmol) was allowed to react as described under 29. The mixture was quenched with chlorotrimethylsilane (0.16 mL, 1.23 mmol) and the solution was transferred by means of a canula to an aqueous pH7-buffer solution (10 mL). The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). After purification as described under 29. the product (**12m**, 78 mg, 93%) was obtained as a colorless oil. − $[\alpha]_D^{20}$ = + 147.2 (*c* = 1.130, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 9 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.14 (d, *J* = 6.1 Hz, 3 H), 1.39 (ddd, *J* = 13.6, 10.8, and 3.2 Hz, 1 H), 1.55 (ddd, *J* = 13.6, 9.8, and 4.5 Hz, 1 H), 2.75 (m, 1 H), 3.74 (m, 1 H), 4.38 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 7.18−7.30 (m, 5 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.26, 20.0, 21.3, 23.8, 44.8, 71.3, 73.7, 84.4. 111.7, 127.4, 127.8, 128.3, 139.0.

31. (3*S*,5*S*)-5-Benzyloxy-3-methyl-2-hexanone (12g): A solution of methyllithium (1.6 M in ether, 3.04 mmol) was slowly added at −78°C to a solution of (2*S*,4*S*)-4-benzyloxy-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2-dimethylpentanoic amide (**24**, 468 mg, 1.27 mmol) in ether (13.0 mL). After stirring for 15 min at −78°C, diisopropylamine (179 μL, 1.27 mmol) was added at 0°C and stirring was continued for 15 min. Acetic acid (20% in ether, 4.4 mL) was added, resulting in the formation of a white precipitate. Saturated aqueous NH_4Cl solution (20 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (305 mg) with pentane/*tert*-butyl methyl ether varying from 50:1 to 10:1 furnished the product **12g** (253 mg, 91%) as a colorless oil. − $[\alpha]_D^{20}$ = +51.6 (*c* = 4.350, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.2 Hz, 3 H), 1.19 (d, *J* = 6.1 Hz, 3 H), 1.55 (ddd, *J* = 14.1, 8.7, and 4.5 Hz, 1 H), 1.87 (ddd, *J* = 14.1, 8.9, and 3.8 Hz, 1 H), 2.05 (s, 3 H), 2.80 (m, 1 H), 3.50 (m, 1 H), 4.31 (d, *J* = 11.6 Hz, 1 H), 4.53 (d, *J* = 11.4 Hz, 1 H), 7.21−7.34 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.2, 19.7, 28.2, 40.2, 43.1, 70.4, 72.6, 127.5, 127.8, 128.3, 138.6, 212.5. − $C_{14}H_{20}O_2$ (208.3): calcd. C 76.33, H 9.15; found C 76.04, H 9.04.

32. (3*S*,5*S*)-5-Benzyloxy-2,3-dimethylhexene (12f): A solution of dimethyltitanocene (1.0 M in THF, 1.17 mmol) was added dropwise to a solution of (3*S*,5*S*)-5-benzyloxy-3-methyl-2-hexanone (**12g**, 103 mg, 0.47 mmol) in toluene (2.4 mL). The mixture was stirred in the dark for 16 h at 70°C. Silica gel (0.5 g) was added and the suspension was concentrated. Flash chromatography of the residue with pentane, followed by 2% *tert*-butyl methyl ether in pentane

furnished the product **12f** (77 mg, 76%) as a colorless oil. − $[\alpha]_D^{20}$ = + 38.3 (*c* = 2.940, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.0 Hz, 3 H), 1.18 (d, *J* = 6.1 Hz, 3 H), 1.46 (ddd, *J* = 14.1, 9.3, and 4.1 Hz, 1 H), 1.57 (ddd, *J* = 14.1, 8.5, and 5.3 Hz, 1 H), 1.63 (broad s, 3 H), 2.47 (m, 1 H), 3.47 (m, 1 H), 4.38 (d, *J* = 11.4 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.69 (m, 2 H), 7.24−7.35 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 19.9, 20.3, 37.8, 42.7, 70.6, 73.2, 110.0, 127.3, 127.7, 128.3, 139.1, 149.6. − $C_{15}H_{22}O$ (218.3): calcd. C 82.52, H 10.16; found C 82.20, H 10.35.

33. (2*S*,4*S*)-4-Benzyloxy-2-methylpentanoic Acid (12h): Methanesulfonic acid (69 μL, 1.07 mmol) was added dropwise to a solution of (2*S*,4*S*)-4-benzyloxy-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2-dimethylpentanoic amide (274 mg, 0.74 mmol) in THF (3 mL). After heating at reflux for 1 h, the mixture was cooled to 0°C and a solution of lithium tetrahydroboranate (24.0 mg, 1.11 mmol) in THF (1.6 mL) was added dropwise. Aqueous NaOH (1 M, 3.63 mmol) was added and the solution was stirred for 8 h at room temperature. Dichloromethane (20 mL) and water (20 mL) were added and the phases were separated. The aqueous phase was extracted with dichloromethane (20 mL) and acidified with hydrochloric acid (2 M) to pH = 2. The aqueous phase was extracted with dichloromethane (3 × 30 mL). The extracts were dried ($MgSO_4$) and concentrated to leave the acid **12h** (126 mg, 77%) as a colorless oil. − $[\alpha]_D^{20}$ = + 74.5 (*c* = 2.515, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.2 Hz, 3 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 1.63 (ddd, *J* = 14.2, 9.0, and 4.5 Hz, 1 H), 1.84 (ddd, *J* = 14.2, 9.5, and 3.7 Hz, 1 H), 2.78 (m, 1 H), 3.61 (m, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 7.26−7.33 (m, 5 H), 10.8 (broad s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9, 19.7, 36.0, 40.9, 70.7, 72.9, 127.4, 127.8, 128.3, 138.5, 183.1. − $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 70.28, H 8.31.

34. Methyl (2*S*,4*S*)-4-Benzyloxy-2-methylpentanoate (12i): A solution of diazomethane in ether (ca. 1.5 mL) was added to a solution of (2*S*,4*S*)-4-benzyloxy-2-methylpentanoic acid (**12h**) (81 mg, 0.36 mmol) in ether (2 mL) at 0°C until the yellow color persisted. The mixture was stirred for 1 h at 0°C. Saturated aqueous NH_4Cl solution (20 mL) was added and the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (99 mg) with pentane/*tert*-butyl methyl ether 10:1 to 4:1 furnished the ester **12i** (82 mg, 95%) as a colorless oil. − $[\alpha]_D^{20}$ = + 76.5 (*c* = 1.820, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (m, 6 H), 1.61 (ddd, *J* = 14.1, 8.9, and 4.4 Hz, 1 H), 1.84 (ddd, *J* = 14.1, 9.7, and 3.7 Hz, 1 H), 2.78 (m, 1 H), 3.53 (m, 1 H), 3.60 (s, 3 H), 4.37 (d, *J* = 11.4 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 7.25−7.34 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.0, 19.7, 35.9, 41.2, 51.4, 70.6, 72.9, 127.4, 127.8, 128.2, 138.7, 177.2. − $C_{14}H_{20}O_3$ (236.3): calcd. C 71.16, H 8.53; found C 70.97, H 8.66.

35. (2*R,4*R**)-2,4-Dimethyl-1,5-pentanediol:**[30] Borane−dimethyl sulfide (4.4 mL, 0.044 mol) was added dropwise at 0°C to a solution of (2*R**,4*R**)-dimethyl glutarate.[31] After stirring for 3 h at room temperature, methanol (10 mL) was added carefully at 0°C. After the vigorous reaction had ceased, the solvents were removed in vacuo. The residue was taken up in methanol (20 mL) and the solution was again concentrated in vacuo. The residue was partitioned between ether (20 mL) and aqueous saturated K_2CO_3 solution (20 mL). The phases were separated and the aqueous phase was extracted with ether (5 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with ether furnished the diol (2.45 g, 92%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.7 Hz, 6 H), 1.20 (t, *J* = 6.8 Hz, 2 H), 1.74 (sext, *J* = 6.6 Hz, 2 H), 2.08 (s, 2 OH), 3.44 (d, *J* = 6.6 Hz, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 32.8, 36.7, 68.8. − $C_7H_{16}O_2$ (132.2): calcd. C 63.60, H 12.20; found C 63.80, H 12.39

36. (2*R,4*R**)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentanol (29):** Sodium hydride (80% in white oil, 6.84 mmol) was added in small portions to a solution of (2*R**,4*R**)-2,4-dimethyl-1,5-pentanediol (861 mg, 6.51 mmol) in THF (10.9 mL) at 0°C. After stirring for 40 min at room temperature, *tert*-butylchlorodimethylsilane (50% in toluene, 6.84 mmol) was added and the mixture was stirred for 1 d. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 50 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (1.62 g) with pentane/*tert*-butyl methyl ether = 10:1 to 4:1 resulted in the product **29** (1.203 g, 75%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.83 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.87 (m, 3 H), 1.15 (m, 2 H), 1.70 (m, 2 H), 1.83 (s, 1 H), 3.41 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, 16.4, 16.6, 18.3, 25.9, 33.0, 33.1, 36.8, 68.9, 69.0. − $C_{13}H_{30}O_2Si$ (246.5): calcd. C 63.35, H 12.27; found C 63.11, H 12.28.

37. (3*R,5*R**)-1,1-Dibromo-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhexene (30):** A solution of dimethyl sulfoxide (1.33 mL, 18.7 mmol) in dichloromethane (7.0 mL) was added at −78°C to a solution of oxalyl chloride (0.80 mL, 9.4 mmol) in dichloromethane (8.0 mL). After stirring for 5 min a solution of (2*R**,4*R**)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanol (**29**, 1.54 g, 6.23 mmol) in dichloromethane (10 mL) was added and stirring was continued for 20 min at −78°C. Triethylamine (3.9 mL, 27 mmol) was added dropwise and the solution was allowed to reach 0°C over 2 h. Saturated aqueous NH_4Cl solution (50 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3 × 70 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Filtration of the residue with pentane/*tert*-butyl methyl ether, 12:1, over a short column of silica gel furnished the aldehyde (1.49 g, 98%) as a colorless oil. − A solution of CBr_4 (3.94 g, 11.9 mmol) in dichloromethane (5 mL) was added by means of a canula to a solution of triphenylphosphane (6.24 g, 23.8 mmol) in dichloromethane (10.9 mL). After stirring for 1 h at 0°C, this solution was cooled to −20°C and a solution of the above aldehyde (1.49 g, 6.1 mmol) in dichloromethane (6.5 mL) was added. The resulting suspension was stirred for 30 min at −20°C. Pentane (50 mL) was added and the solution was filtered through Kieselgur and concentrated. The residue was extracted with dichloromethane (3 × 20 mL) and pentane (20 mL). The extracts were filtered through Kieselgur and were concentrated. Flash chromatography of the residue with pentane followed by 1% *tert*-butyl methyl ether in pentane furnished the product **30** (1.89 g, 77%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.90 (s, 9 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 1.12 (dt, *J* = 13.5 and 7.5 Hz), 1 H), 1.43 (m, 1 H), 1.61 (m, 1 H), 2.53 (m, 1 H), 3.42 (m, 2 H), 6.19 (d, *J* = 9.4 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, 17.2, 18.3, 19.2, 26.0, 33.4, 36.1, 39.5, 67.6, 87.1, 144.7. − $C_{14}H_{28}Br_2OSi$ (400.3): calcd. C 42.01, H 7.05; found C 41.90, H 6.85.

38. (3*R,5*R**)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-1-trimethylsilyl-1-hexyne (31):** *n*-Butyllithium (1.95 M in hexane, 5.00 mmol) was added dropwise to a solution of (3*R**,5*R**)-1,1-di-

bromo-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhexene (**30**, 909 mg, 2.27 mmol) in THF (22.7 mL at −78°C). After stirring for 3 h, chlorotrimethylsilane (1.15 mL, 9.08 mmol) was added. The mixture was allowed to reach room temperature overnight, and was transferred by means of a canula to a pH7-buffer solution (80 mL). The phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 100 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane followed by 10% *tert*-butyl methyl ether in pentane furnished the product **31** (700 mg, 99%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.12 (s, 9 H), 0.88 (s, 9 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.26 (ddd, *J* = 13.4, 8.7, and 6.6 Hz, 1 H), 1.44 (m, 1 H), 1.81 (m, 1 H), 2.51 (m, 1 H), 3.39 (dd, *J* = 9.8 and 6.2 Hz, 1 H), 3.47 (dd, *J* = 9.8 and 5.2 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, 0.3, 17.4, 18.3, 21.2, 24.7, 26.0, 33.8, 40.7, 67.7, 83.8, 112.5. − $C_{17}H_{36}OSi_2$ (312.6): calcd. C 65.31, H 11.61; found C 65.56, H 11.79.

39. (3*R,5*R**)-3,5-Dimethyl-6-hydroxy-1-trimethylsilyl-1-hexyne (32):** Acetic acid (8.1 mL) was added to a solution of (3*R**,5*R**)-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethyl-1-trimethylsilyl-1-hexyne (**31**) (450 mg, 1.44 mmol) in THF (2.7 mL) and water (2.7 mL). After stirring for 18 h, saturated aqueous $NaHCO_3$ solution (50 mL) was added in small portions. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (570 mg), with pentane followed by 10% *tert*-butyl methyl ether in pentane furnished the product **32** (266 mg, 93%) as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.31−1.50 (m, 2 H), 1.66 (s, 1 H), 1.82 (m, 1 H), 2.53 (m, 1 H), 3.46 (dd, *J* = 10.7 and 5.9 Hz, 1 H), 3.53 (dd, *J* = 10.7 and 5.6 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 17.1, 21.1, 24.4, 33.6, 40.4, 67.5, 84.2, 112.3. − $C_{11}H_{22}OSi$ (198.4): calcd. C 66.60, H 11.18; found C 66.40, H 11.03.

40. (3*R,5*R**)-7,7-Dibromo-3,5-dimethyl-1-trimethylsilylhept-6-en-1-yne (33):** (3*R**,5*R**)-3,5-Dimethyl-6-hydroxy-1-trimethylsilyl-1-hexyne (**32**) (237 mg, 1.19 mmol) was converted into the dibromo compound (65%) as described under 37. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 1.37 (ddd, *J* = 13.4, 9.6, and 5.0 Hz, 1 H), 1.50 (ddd, *J* = 13.3, 10.1, and 4.6 Hz, 1 H), 2.44 (m, 1 H), 2.77 (m, 1 H), 6.15 (d, *J* = 9.5 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 19.5, 21.3, 25.1, 36.7, 43.5, 84.8, 88.2, 111.2, 143.6. − $C_{12}H_{20}Br_2Si$ (352.2): calcd. C 40.93, H 5.72; found C 40.99, H 5.83.

41. (3*R,5*R**)-3,5-Dimethyl-1,7-bis(trimethylsilyl)-1,6-heptadiyne (2g):** (3*R**,5*R**)-7,7-Dibromo-3,5-dimethyl-1-trimethylsilyl-hept-6-en-1-yne (**33**, 209 mg, 0.59 mmol) was converted into the bis(trimethylsilyl)alkyne (90%) as described under 39. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 18 H), 1.16 (d, *J* = 6.9 Hz, 6 H), 1.44 (m, 2 H), 2.68 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 21.4, 25.6, 44.5, 84.4, 111.4. − $C_{15}H_{28}Si_2$: calcd. C 264.1730: found 264.1731.

Acknowledgments

We thank the Volkswagenstiftung and the Fonds der Chemischen Industrie for support of this study. D. S. and R. G. are grateful to the latter institution for granting them fellowships. We thank also M. Dauber, T. Brandl, and A. Burton for help in the synthesis of the deuterium-labeled compounds.

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Received March 5, 1999
[O99128]