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Conformation Preferences in 2,4,6-Trisubstituted Heptanes[1]

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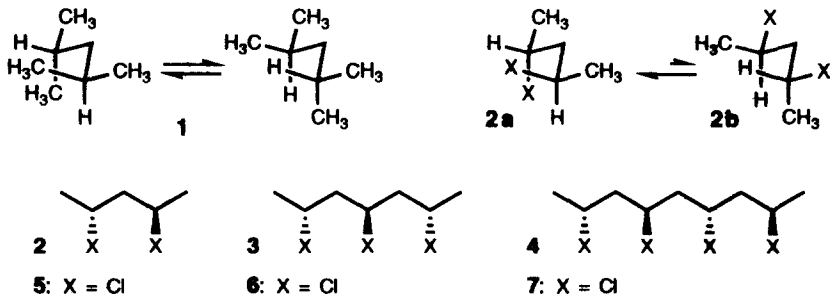
Abstract: The preference of (2R*,4r*,6S*)-2,4,6-trichloroheptane (**6**) for populating the fully extended conformation mirrors the local conformational preferences of the 2,4-dichloropentane subunits. Likewise, the preference of (2R*,4r*,6S*)-2,6-dichloro-4-methyl-heptane (**9**) to populate the extended conformation mirrors that of the 2-chloro-4-methyl-heptane subunits. There is therefore no cooperative effect (neither positive nor negative) between the 2,4-disubstituted pentane subunits in determining the conformer preferences of the 2,4,6-trisubstituted heptanes studied.

Key-Words: Conformation / Local conformer populations / *syn*-Pentane interactions.

Introduction

Conformation control of flexible molecules [2] is both of intellectual and practical interest. The former refers to the challenge of identifying novel modes of conformation control beyond those used by nature in compounds derived of polypropionate biogenetic origin [3]. The latter refers to the synthesis of peptidomimetics [4], in which conformational preorganization may facilitate binding to the targeted binding site. Once, small backbone segments, with high conformational preferences are identified, a combination of such building blocks might allow a modular approach to larger molecular backbones with a good level of conformational preorganization [5]. Small backbone segments with conformational preferences may be derived from 2,4-dimethylpentane (**1**), which populates just two low energy conformations [6,7,8], because all other backbone conformations are destabilized by syn-pentane interactions. Substitution of one or two of the methyl groups by other groups, i.e. going from **1** to **2** breaks the symmetry of the system and lifts the energetic degeneracy of the conformers. A previous study [9] showed that substituents such as chlorine, bromine, azido, or phthalimido lead to moderate or even high conformational preferences in compounds of the general structure **2**.



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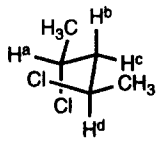
Conceptually, combination of the segments **2** with one another should generate larger systems **3** and **4** with four and six rotatable bonds respectively. We would like to address here the question, to what extent conformation control is possible in these extended systems.

Dichloro-pentane **5** shows a sizeable (> 10 : 1) preference to populate the conformer **5a** with the chlorine atoms in the sterically more encumbered position [9,10,11,12,13,14]. This preference is attributed both to steric and stereoelectronic effects. Conformational analysis of the trichloro-heptane **6** would then reveal whether the conformational preferences of the two local segments of the type **2** are simply additive or whether there is some positive or negative cooperativity. The conformational behaviour of **6** had been addressed before, since **6** is a model compound for syndiotactic polyvinyl chloride. Based on IR and NMR data, it had been estimated that the preference for compound **6** to populate the conformation **6a** is in the order of 85% [15]. Predictions based on the rotational isomeric state model suggested for compound **6** a 93% preference for the conformer **6a** [16,17].

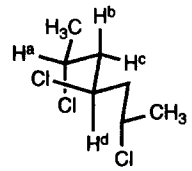
Results and Discussion

We were interested in a direct comparison of the ^{1}H NMR coupling constants of compounds **5** and **6**, since these coupling constants reflect the position of the conformer equilibria. For this reason, compound **6** was synthesized in a stereospecific manner as detailed below. The following $^3J_{H,H}$ coupling constants could be recorded for compound **6**:



$J_{a,b} = J_{c,d} = 2.2$ Hz

$J_{a,c} = J_{b,d} = 10.6$ Hz



$J_{a,b} = 2.5$ Hz

$J_{a,c} = 10.8$ Hz

$J_{c,d} = 2.3$ Hz

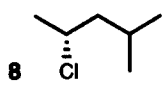
$J_{b,d} = 10.8$ Hz

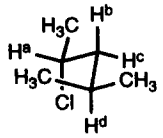
5a = preferred conformer of **5**

6a = preferred conformer of **6**

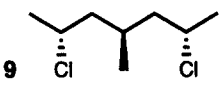
The coupling constants of **6** match those recorded for **5**. Therefore, the conformational preference in the individual dichloropentane segments of **6** (ca. 92 : 8) is the same as that prevailing in **5**. Knowledge of the local conformer preferences (0.92) in the individual segments of the trichloro compound **6** allows then to estimate the overall preference for populating the fully extended, conformation **6a**, which should be the most stable one: Multiplication of the local conformer preferences (0.92 x 0.92 = 0.85) leads to a value which is in good agreement with predictions made earlier. Along the same line, the preference of the tetrachloro compound **7** to populate the most stable conformation may be estimated to be $(0.92)^3 = 0.78$. If we set a limit of a conformational preference of > 80% as being meaningful in conformation design, it follows, that the trichloro compound **6** meets this criterium, but that longer carbon chains with multiple chlorine substitutions in 2,4,6,.. position, such as **7** or syndiotactic polyvinyl chloride, will have only a short persistence length of conformational preference of ca. four consecutive rotatable bonds.

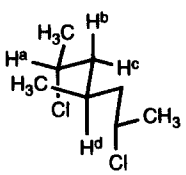
The conformational control in **5** and **6** is likely governed to a significant extent by polar and stereoelectronic effects. To get a feeling of how large the contribution by an individual chlorine atom is, we investigated the system **9** in which the central chlorine atom has been replaced by a nonpolar methyl group. The vicinal $^3J_{H,H}$ coupling constants of **9** could easily be determined as shown below.





$J_{a,b}$ = 4.8 Hz
$J_{a,c}$ = 9.3 Hz





$J_{a,b}$ = 4.4 Hz
$J_{a,c}$ = 9.8 Hz
$J_{c,d}$ = 4.9 Hz
$J_{b,d}$ = 9.0 Hz

8a = preferred conformer of **8**

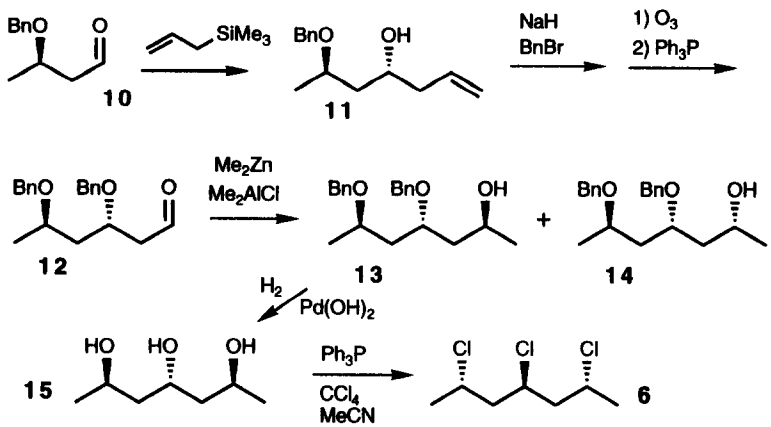
9a = preferred conformer of **9**

Comparison of the coupling constants of **9** with those of **6** reveals that the conformational bias in **9** is not as marked as in **6**. But with respect to **8** as a reference compound, it is clear that again the conformational preferences found in the individual segments of **9** match by and large that found in **8** [9].

The additivity of the local conformational preferences of the individual backbone segments, i.e. the absence of any cooperative effects, when going from a simple 2,4-disubstituted pentane unit to compounds with two and more adjacent units of this type renders conformational control of more extended structures of the type **4** with six or more rotatable structure bonds unrewarding, unless the conformational preferences of the individual segments exceed a value of 0.95.

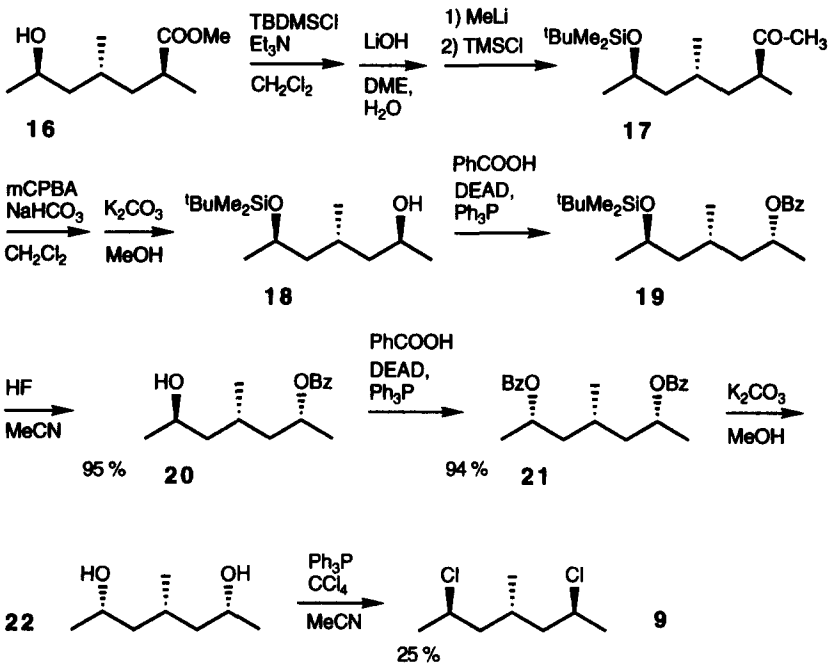
Syntheses

The synthesis of the trichloro compound **6** was based on a chelation controlled [18] allylation reaction of the aldehyde **10** developed by Reetz [19]. The reported high diastereoselectivity (>98:2) in the generation of **11** was attained only, if the concentration of the aldehyde **10** was kept below 0.04 M.



Subsequent conversion to the homologous aldehyde **12** proceeded as described previously [19]. When treating the aldehyde **12** as described by Reetz with dimethylzinc and titanium tetrachloride to give the alcohol **13**, we could reproduce the high diastereoselectivity (9:1), but did not attain yields in excess of 20%. We therefore turned to the system of dimethylzinc and dimethylaluminium chloride, which provided a 2.8:1 mixture of **13** and its epimer **14** in 72% yield. Debenzylation of the mixture afforded a mixture of triols from which the desired major diastereomer **15** was easily obtained pure by crystallization. The triol **15** was then converted to the trichloro compound **6** (83%), presumably with inversion of configuration [20].

The synthesis of the dichloro-compound **9** started with the ε-hydroxy ester **16** [21,22], which had three stereogenic centers with a defined configuration. Further elaboration into **9** required, however, twofold configurational inversion at two of the stereocenters.



First, the secondary hydroxyl group in **16** was TBS-protected (80%). The ester was then saponified with LiOH (98%) and the carboxylic acid was converted [23] with methyllithium into the methyl ketone **17** (93%). Baeyer-Villiger oxidation of the latter (78%) followed by hydrolysis of the acetate function gave the monoprotected diol **18** (89%).

Simultaneous Mitsunobu inversion of two stereogenic centers starting from the meso-diol (not shown) corresponding to **18** was low yielding. Therefore sequential Mitsunobo reactions were carried out: The first one furnished the benzoate **19** in 88% yield. Cleavage of the TBS-group by HF/acetonitrile (95%) set the stage for the next Mitsunobu reaction to give the dibenzoate **21** in 94% yield. The latter was saponified with methanolic potassium carbonate (94%) and converted to the dichloro compound **9** as described for **6**. The low yield (25%) obtained in a single experiment was not optimized.

EXPERIMENTAL

All temperatures quoted are not corrected. - Reactions were carried out under dry nitrogen or argon. - ^1H and ^{13}C NMR: Bruker AC 300 and AMX-500 spectrometers. - pH7-Buffer: 56.2 g of NaH_2PO_4. $2H_2O$ and 213.2 g $Na_2HPO_4.2H_2O$ in 1.0 l of water. Flash chromatography: Silica gel Si60 (40 - 63 μm. - E. Merck AG, Darmstadt).

1. *(2S*,4R*,6R*)-4,6-Dibenzyloxy-2-heptanol* (**13**): A solution of *(3S*,5R*)*-3,5-dibenzyloxy-hexanal (**12**) (2.8 g, 8.9 mmol) in dichloromethane (250 ml) was stirred at -100°C with molecular sieves Å4 for 15 min. A solution of dimethylaluminium chloride (1.0 M in hexane, 22.3 mmol) was added dropwise. After stirring for further 15 min at -100°C a solution of dimethylzinc (2.0 M in toluene, 11 mmol) was added dropwise. The colorless solution was stirred for 1.5 h at -100°C and was quenched via canula into pH7

buffer solution (200 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/methyl *tert.*-butyl ether 4:1 to 2:1 furnished 406 mg of diastereomerically pure **13**, 1.32 g of a 3.5 : 1 mixture of **13** and **14** and 375 mg of a 1.0 : 2.2 mixture of **13** and **14**. **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.2 Hz, 2 H), 1.23 (d, J = 6.1 Hz, 3 H), 1.52 (ddd, J = 14.6, 5.0, and 2.6 Hz, 1 H), 1.68 (ddd, J = 14.4, 9.2, and 3.7 Hz, 1 H), 1.89 - 1.80 (m, 2 H), 2.92 (s, 1 H, OH), 3.73 (m, 1 H), 3.94 (m, 1 H), 4.11 (m, 1 H), 4.29 (d, J = 11.5 Hz, 1 H), 4.36 (d, J = 11.2 Hz, 1 H), 4.58 (d, J = 11.6 Hz, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 7.36 - 7.27 (m, 10 H). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8, 23.7, 41.4, 42.2, 64.7, 70.3, 71.6, 71.7, 74.7, 127.5, 127.7, 127.8, 128.0, 128.3, 128.4, 138.0, 138.7.

2. *(2R*,4r*,6S*)-2,4,6-Heptanetriol* (**15**): Palladium hydroxide on carbon (20%, 55 mg, 0.04 mmol) was added into a solution of a 3.5:1 mixture of **13** and **14** (1.31 g, 4.0 mmol) in methanol (10 ml). The mixture was stirred for 2 h under hydrogen and was filtered over Kieselgur. Concentration of the filtrate resulted in an oil (590 mg), which was recrystallized from methyl *tert*-butyl ether (10 ml) and methanol (0.5 ml) to give **15** (375 mg, 82%) as colorless crystals, m.p. 90°C. - ^{1}H NMR (300 MHz, CD_3OD): δ = 1.17 (d, J = 6.3 Hz, 6 H), 1.49 (m, 4 H), 3.99 (m, 3 H), 4.88 (s, 3 H). - ^{13}C NMR (75 MHz, CD_3OD): δ = 22.7, 46.2, 64.0, 65.1. - $C_7H_{16}O_3$ (148.2): calcd. C 56.73, H 10.88; found: C 56.72, H 10.91.

3. *(2R*,4r*,6S*)-2,4,6-Trichloroheptane* (**6**): Triphenylphosphine (1.06 g, 4.05 mmol) was added into a solution of (2R*,4r*,6S*)-2,4,6-heptanetriol (**15**) (150 mg, 1.01 mmol) in acetonitrile (3.0 ml) and CCl_4 (3.0 ml). After stirring for 15 h at room temperature silica gel (2.0 g) was added and the solvents were removed i. vac.. Flash chromatography of the residual material over silica gel with pentane followed by pentane and 1 % methyl *tert*-butyl ether furnished **6** (170 mg, 83%) as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (d, J = 6.6 Hz, 6 H), 2.00 (m, 4 H), 4.37 (m, 2 H), 4.50 (m, 1 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 48.9, 55.1, 58.2. - $C_7H_{13}Cl_3$ (203.5): calcd. C 41.31, H 6.44; found: C 41.40, H 6.29.

4. *Methyl (2R*,4S*,6S*)-6-tert-Butyldimethylsilyloxy-2,4-dimethyl-heptanoate*: Triethylamine (11.9 ml, 85.1 mmol), 4-dimethylaminopyridine (416 mg, 3.4 mmol) and *tert*-butyl-chloro-dimethylsilane (50% in toluene, 18.0 g, 59.6 mmol) were added sequentially into a solution of methyl (2R*,4S*,6S*)-6-hydroxy-2,4-dimethyl-heptanoate (**16**) [21,22]. After stirring for 1 d at room temperature saturated aqueous $NaHCO_3$ solution (50 ml) was added, the phases were separated and the aqueous phase was extracted with methyl *tert*-butyl ether (3 x 100 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (13.1 g) over silica gel with petroleum ether/methyl *tert*-butyl ether varying from 100 : 1 to 70 : 1 furnished the product (11.1 g, 86%) as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.84 - 0.88 (m, 3 H), 0.86 (s, 9 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 0.97 - 1.20 (m, 2 H), 1.42 (ddd, J = 13.5, 8.7, and 4.0 Hz, 1 H), 1.60 (m, 2 H), 2.54 (m, 1 H), 3.63 (s, 3 H), 3.85 (m, 1 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.8, -4.1, 17.6, 18.0, 19.5, 24.5, 25.9, 27.1, 37.2, 42.0, 47.3, 51.4, 66.1, 177.4. - $C_{16}H_{34}O_3Si$ (302.5): calcd. C 63.52, H 11.33; found C 63.52, H 11.31.

5. *(2R*,4S*,6S*)-6-tert-Butyldimethylsilyloxy-2,4-dimethyl-heptanoic acid*: Lithium hydroxide (1.32 g, 55.0 mmol) was added into a solution of methyl (2R*,4S*,6S*)-6-*tert*-butyldimethylsilyloxy-2,4-dimethyl-heptanoate (11.2 g, 36.7 mmol) in 1,2-dimethoxyethane (150 ml) and water (150 ml). After stirring for 9 h at 40°C saturated aqueous $NaHCO_3$ solution (150 ml) was added and the phases were separated. The aqueous phase was acidified with hydrochloric acid (1 M) and the solution was extracted with methyl *tert*-butyl ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$) and concentrated to leave the desired acid (10.4 g, 98%) analytically pure. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 0.89 (d, J = 6.4 Hz, 3 H), 1.05 (ddd, J = 13.3, 9.0, and 3.9 Hz, 1 H), 1.10 (d, J = 6.1 Hz, 3 H), 1.16 (d, J = 6.9 Hz, 3 H), 1.13 - 1.19 (m, 1 H), 1.44 (ddd, J = 13.5, 8.8, and 3.9 Hz, 1 H),

1.67 (m, 2 H), 2.56 (m, 1 H), 3.87 (m, 1 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.8, -4.1, 17.4, 18.0, 19.6, 24.5, 25.9, 27.0, 37.1, 41.6, 47.3, 66.1, 183.5. - $C_{15}H_{32}O_3Si$ (288.5): calcd. C 62.45, H 11.18; found C 62.30, H 11.09.

6. *(3R*,5S*,7S*)-7-tert-Butyldimethylsilyloxy-3,5-dimethyl-2-octanone* (**17**): A solution of methyllithium (1.6 M in ether, 11.6 mmol) was added at -30°C into a solution of (2R*,4S*,6S*)-6-*tert*-butyldimethylsilyloxy-2,4-dimethyl-heptanoic acid (1.11 g, 3.9 mmol) in THF (26 ml). After stiring for 2 h at -30°C chlorotrimethylsilane (6.4 ml, 50 mmol) were added dropwise. The solution was stirred for 2 min and poured into precooled (0°C) pH7-buffer solution (150 ml). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 70 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (1.16 g) over silica gel with pentane/*tert*-butyl methyl ether varying from 100:1 to 10:1 furnished the product **17** (1.03 g, 93%) as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.85 (s, 9 H), 0.85 (m, 3 H), 0.97 (ddd, J = 13.2, 9.2, and 3.7 Hz, 1 h), 1.04 (d, J = 6.9 Hz, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.11 (m, 1 H), 1.41 (ddd, J = 13.5, 8.9, and 3.5 Hz, 1 H), 1.51 - 1.62 (m, 2 H), 2.09 (s, 3 H), 2.59 (m, 1 H), 3.85 (m, 1 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.8, -4.1, 16.7, 18.0, 19.9, 24.6, 25.9, 27.0, 27.8, 41.0, 44.8, 47.0, 66.0, 212.8. - $C_{16}H_{34}O_2Si$ (286.5): calcd. C 67.07, H 11.96; found C 66.80, H 12.18.

7. *(2R*,4S*,6S*)-2-Acetoxy-6-tert-butyldimethylsilyloxy-4-methyl-heptane*: A solution of (3R*,5S*,7S*)-7-*tert*-butyldimethylsilyloxy-3,5-dimethyl-2-octanone (**17**) (1.50 g, 5.3 mmol) in dichloromethane (8 ml) was added dropwise into a solution of meta-chloroperbenzoic acid (70%, 2.59 g, 10.5 mmol) and $NaHCO_3$ (1.01 g, 12.1 mmol) in dichloromethane (45 ml) at 0°C. The solution was allowed to reach room temperature and was stirred for 17 d. 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 x 40 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel with pentane/*tert*-butyl methyl ether varying from 100:1 to 10:1 furnished the product (1.20 g, 76%) as a colorless oil. The product was contaminated by impurities having aromatic proton signals in the NMR. In order to obtain a sample for analysis, the crude ester was saponified and reacetylated. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (m, 12 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.03 - 1.12 (m, 1 H), 1.18 (d, J = 6.2 Hz, 3 H), 1.15 - 1.22 (m, 1 H), 1.43 (ddd, J = 13.6, 9.1, and 4.2 Hz, 1 H), 1.58 (ddd, J = 13.8, 9.1, and 5.0 Hz, 1 H), 1.69 (m, 1 H), 1.98 (s, 3 H), 3.85 (m, 1 H), 5.00 (m, 1 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.9, 4.1, 18.0, 19.1, 20.6, 21.3, 24.6, 25.7, 25.9, 44.1, 47.5, 66.1, 68.9, 170.7. - $C_{16}H_{34}O_3Si$ (302.5): calcd. C 63.52, H 11.33; found C 63.47, H 11.26.

8. *(2R*,4S*,6S*)-6-tert-Butyldimethylsilyloxy-4-methyl-2-heptanol* (**18**): Potassium carbonate (770 mg, 5.57 mmol) was added to a solution of crude (2R*,4S*,6S*)-2-acetoxy-6-*tert*-butyldimethylsilyloxy-4-methyl-heptane (1.20 g, 4.0 mmol) in methanol (20 ml). After stirring for 1 d at room temperature saturated aqueous $NaHCO_3$ solution (30 ml) was added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 80 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (1.04 g) with petroleum ether/*tert*-butyl methyl ether varying from 100:1 to 10:1 furnished **18** (0.92 g, 89%) as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.80 (s, 9 H), 0.90 (d, J = 6.6 Hz, 3 H), 1.11 (d, J = 6.1 Hz, 3 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.07 - 1.23 (m, 2 H), 1.38 - 1.53 (m, 3 H, contains OH signal), 1.76 (m, 1 H), 3.87 (m, 2 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.7, -4.1, 18.1, 19.9, 24.0, 24.5, 25.9, 26.2, 47.4, 47.7, 66.1, 66.5. - $C_{14}H_{32}O_2Si$ (260.5): calcd C 64.55, H 12.38; found C 64.34, H 12.46.

9. *(2S*,4S*,6S*)-2-Benzoyloxy-6-tert-butyldimethylsilyloxy-4-methyl-heptane* (**19**): Benzoic acid (328 mg, 2.69 mmol) and triphenylphosphine (670 mg, 2.55 mmol) were added into a solution of (2R*,4S*,6S*)-6-*tert*-butyldimethylsilyloxy-4-methyl-2-heptanol (**18**) (500 mg, 1.92 mmol) in THF (7.7 ml). The mixture

was cooled to -30°C and diethyl azodicarboxylate (393 µl, 2.50 mmol) was added dropwise. The solution was allowed to reach room temperature and was stirred for 14 h. 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 200 : 1 to 50 : 1 furnished a mixture of the product **19** and triphenylphosphine as a colorless oil. This mixture was taken up in THF (10 ml). A solution of *tert*-butylhydroperoxide (5.0 M in dichloromethane, 1.00 ml) was added and the mixture was stirred for 30 min at room temperature. Saturated aqueous $NaHCO_3$ solution (10 ml) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 ml). The combined organic phases were washed with brine (10 ml), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether varying from 200 : 1 to 80 : 1 furnished the product **19** (616 mg, 88%) as a colorless oil. - ^1H NMR (500 MHz, $CDCl_3$): d = -0.01 (s, 3 H), 0.01 (s, 3 H), 0.80 (s, 9 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.0 Hz, 3 H), 1.05 - 1.13 (m, 1 H), 1.32 (d, J = 6.2 Hz, 3 H), 1.50 (dt, J = 13.6 and 6.4 Hz, 1 H), 1.55 (ddd, J = 13.4, 9.0, and 4.0 Hz, 1 H), 1.66 (dt, J = 13.7 and 7.4 Hz, 1 H), 1.80 (m, 1 H), 3.87 (m, 1 H), 5.23 (m, 1 H), 7.41 (m, 2 H), 7.53 (m, 1 H), 8.03 (m, 2 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.9, -4.1, 18.0, 19.6, 20.1, 24.5, 25.8, 26.1, 44.0, 47.4, 66.0, 70.2, 128.2, 129.5, 131.0, 132.6, 166.1. - $C_{21}H_{36}O_3Si$ (364.6): calcd. C 69.18, H 9.95; found C 69.35, H 9.86.

10. *(2S*,4R*,6S*)-6-Benzoyloxy-4-methyl-2-heptanol* (**20**): (2S*,4S*,6S*)-2-Benzoyloxy-6-*tert*-butyldimethylsilyloxy-4-methyl-heptane (**19**) (661 mg, 1.81 mmol) was dissolved in a solution of HF in acetonitrile (5%, 9.0 ml). After stirring for 35 min saturated aqueous $NaHCO_3$ solution (40 ml) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 70 ml). The combined organic phases were washed with brine (30 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (484 mg) with pentane/*tert*-butyl methyl ether = 1:1 furnished the product **20** (433 mg, 95%) as a colorless oil. - ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.4 Hz, 3 H), 1.12 (d, J = 6.2 Hz, 3 H), 1.07 - 1.16 (m, 1 H), 1.28 (d, J = 6.2 Hz, 3 H), 1.44 - 1.68 (m, 5 H contains OH), 3.79 (m, 1 H), 5.24 (m, 1 H), 7.36 (m, 2 H), 7.46 (m, 1 H), 7.97 (m, 2 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 20.4, 24.6, 26.4, 44.2, 46.5, 65.4, 69.9, 128.2, 129.5, 130.7, 132.7, 166.4. - $C_{15}H_{22}O_3$ (250.3): calcd. C 71.97, H 8.86; found C 71.74, H 8.79.

11. *(2R*,4s*,6S*)-2,6-Dibenzoyloxy-4-methyl-heptane* (**21**): Benzoic acid (294 mg, 2.40 mmol), and triphenylphosphane (599 mg, 2.28 mmol), **20** (430 mg, 1.72 mmol) and diethyl azodicarboxylate (0.35 ml, 2.23 mmol) were allowed to react as described under 9. to give the product **21** (570 mg, 94%) as a colorless oil. - ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.0 Hz, 3 H), 1.28 (d, J = 6.2 Hz, 6 H), 1.66 (m, 5 H), 5.27 (m, 2 H), 7.42 (m, 4 H), 7.54 (m, 2 H), 8.03 (m, 4 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 20.3, 27.0, 43.0, 69.9, 128.3, 129.5, 130.8, 132.7, 166.1. - $C_{22}H_{26}O_4$ (354.5): calcd. C 74.55, H 7.39; found C 74.49, H 7.37.

12. *(2R*,4s*,6S*)-4-Methyl-2,6-heptanediol* (**22**): Potassium carbonate (878 mg, 8.35 mmol) was added into a solution of (2R*,4s*,6S*)-2,6-dibenzoyloxy-4-methyl-heptane (**21**) (563 mg, 1.59 mmol) in methanol (3.2 ml). After stirring for 3 d at room temperature saturated aqueous NH_4Cl solution (30 ml) was added, the phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 50 ml). The combined organic phases were washed with brine (30 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether varying from 2 : 1 to 1 : 3 furnished **22** (218 mg, 94%) as a colorless oil. - ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, J = 6.8 Hz, 3 H), 1.17 (d, J = 6.1 Hz, 6 H), 1.30 - 1.47 (m, 4 H), 1.76 (m, 1 H), 1.90 (broad s, 2 H, OH), 3.93 (m, 2 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 23.8, 26.3, 46.6, 66.2. - $C_8H_{18}O_2$ (146.2): calcd. C 65.71, H 12.41; found C 65.51, H 12.27.

13. *(2R*,4r*,6S*)-2,6-Dichloro-4-methyl-heptane* (**9**): Triphenylphosphane (596 mg, 2.27 mmol) was added at 0°C into a solution of (2R*,4s*,6S*)-4-methyl-2,6-heptanediol (**22**) (123 mg, 0.84 mmol) in acetonitrile (1.7 ml) and CCl_4 (1.7 ml). The mixture was allowed to reach room temperature and was stirred for 18 h. Silica gel (1.0 g) was added and the solvents were removed i. vac. Flash chromatography of the residue with pentane furnished the product **9** (39 mg, 25%) as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, J = 6.5 Hz, 3 H), 1.53 (ddd, J = 14.1, 9.0, and 4.4 Hz, 2 H), 1.53 (d, J = 6.5 Hz, 6 H), 1.73 (ddd, J = 14.1, 9.7, and 4.9 Hz, 2 H), 2.06 (m, 1 H), 4.11 (m, 2 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.8, 28.2, 47.7, 56.3. - $C_8H_{16}Cl_2$ (183.1): calcd. C 52.47, H 8.81; found C 52.48, H 8.81.

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