Conformational Analysis of Axially Substituted 4,4′-Bi-1,3-dioxanyls[‡]

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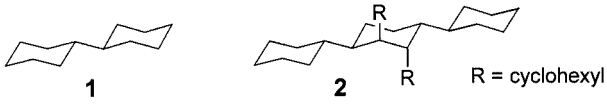
Keywords: Conformational analysis / Oxygen heterocycles

In contrast to the simple 4,4′-bi-1,3-dioxanyl derivative **6**, which has no conformational preference at the inter-ring bond, the derivatives **9** and **10**, which have two strategically placed axial methyl groups, show conformational preferences exceeding 95 %. This is related to the conformational preference found in one of the substructures of the natural product prymnesin.

Introduction

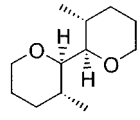
The constitution of a molecule does not necessarily define its shape because rotation about single bonds generates a multitude of different possible conformations. However, the shape of a molecule will be defined when, for certain reasons, only a single conformation at each rotateable bond is populated. The structural element of bicyclohexyl (**1**) is seemingly unspectacular in this respect, although Biali[2] has shown that certain bicylohexyl derivatives, such as **2**, populate preferred conformations not only in the six-membered rings, but also at the inter-ring bonds, in order to avoid *syn*-pentane interactions.[3]



1 **2**

In **2** it is the axial substituents R on the central ring that control the conformations at the inter-ring bonds. Related bi-tetrahydropyranyl systems of the type **3** have been studied by W. C. Still.[4] In that case, methyl substituents are placed in equatorial positions and, considering the inter-ring bond, they destabilize the conformers **3b** and **3c** by *syn*-pentane interactions such that conformer **3a** is populated almost exclusively.

With the intention of designing flexible molecules with defined shape we prepared the acetals **4** and **5** related to the compound **3**. Determination of the $^3J_{H,H}$ coupling constants across the inter-ring bond revealed that these compounds populate a single conformation **4a** or **5a** to



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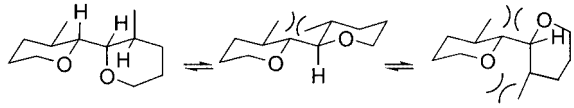
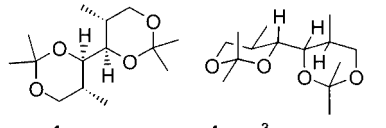
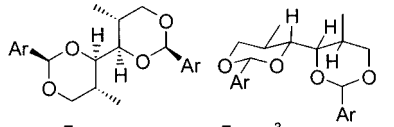


3a **3b** **3c**

> 90%.[5] The effect of the equatorial methyl groups on the conformational preference becomes evident when comparing these coupling constants with those of compound **6**. The absence of the conformation-controlling methyl groups renders conformation **6a** as just one of several low energy conformations.

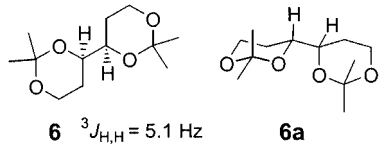


4 **4a** $^3J_{H,H}$ = 2.6 Hz



5 **5a** $^3J_{H,H}$ = 2.4 Hz

Ar = *p*-MeOC$_6$H$_4$-



6 $^3J_{H,H}$ = 5.1 Hz **6a**

[‡] Flexible Molecules with Defined Shape, XX. Part XIX: Ref.[1]

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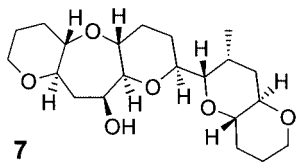

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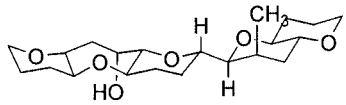
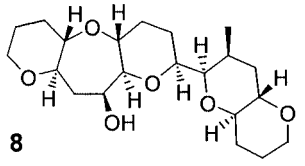


7a $^3J_{H,H}$ = 7.8 Hz



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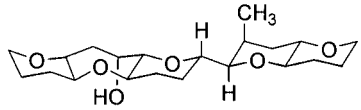


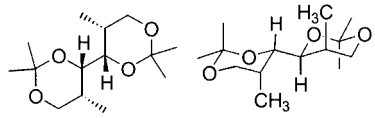
8a $^3J_{H,H}$ = 9.0 Hz

In compounds **3** to **5** the conformational restriction is imposed by a methyl group placed equatorially on the ring. As compound **2** illustrates, a similar conformational restriction should be possible also by a substituent in an axial position. This was demonstrated[6] recently in a study dealing with the structure of prymnesin. In that study, model compounds **7** and **8** were prepared.

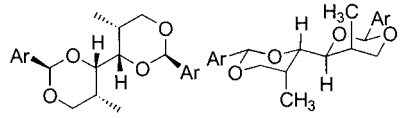
The $^3J_{H,H}$ coupling constants across the inter-ring bond demonstrate a distinct conformational preference for **7a** in the case of compound **7** and an even higher conformational preference for **8a** in the case of the diastereomeric compound **8**. Prymnesin (not shown), which contains substructure **8**, has a $^3J_{H,H}$ coupling constant of 8.5 Hz.

Clearly the single axial methyl group is capable of controlling the conformation at the inter-ring bonds of **7**, **8**, and of prymnesin to favour a single distinct conformation. This must be essential for the biological function of prymnesin (which has not been established), because this methyl group is the only methyl branch in this huge (C_{90}) natural product with a linear carbon chain probably derived from a polyketide of biogenetic origin. The exchange of a single gene cassette (propionate for acetate) at this position must have imparted a significant advantage for the modified molecule during evolution. The introduction of this methyl group controls the folding at a flexible hinge of prymnesin to give the molecule a distinct shape, optimal for its biological function.

The study of compounds **7** and **8** demonstrated the control of conformation at an inter-ring bond between two tetrahydropyran rings by an axial methyl substituent.[6] This stimulated us to perform and report related studies which we carried out on 4,4′-bi-1,3-dioxolan-4-yl compounds **9** and **10**, which contain axial methyl groups.



9 **9a**



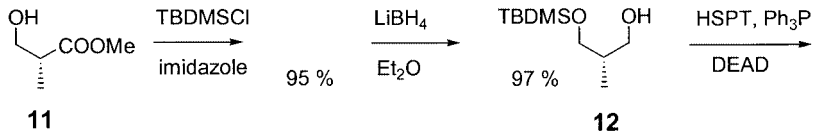
10 **10a**

Ar = *p*-MeOC$_6$H$_4$-

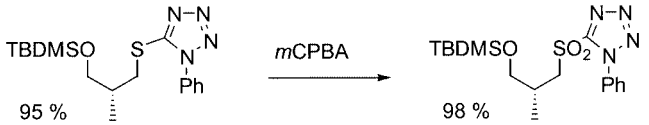
According to the considerations delineated above, we were convinced that compounds **9** and **10** should display a high preference for population of the conformations **9a** and **10a**, respectively.

The synthesis of **9** commenced with the commercially available methyl (*R*)-(−)-hydroxyisobutyrate (**11**). Silylation and reduction following literature precedent[7] gave the alcohol **12**.

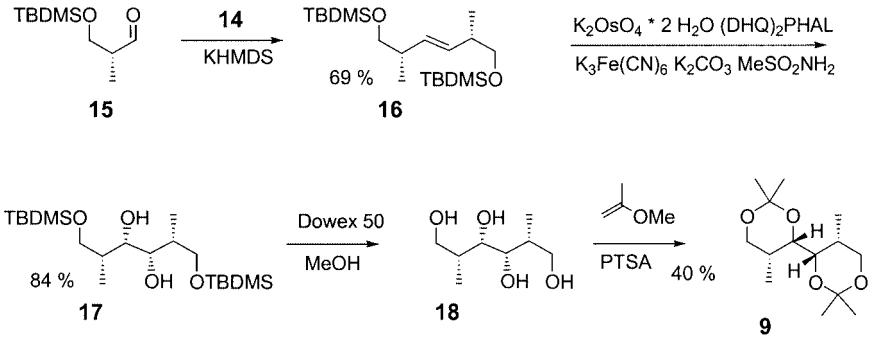
The latter was converted into the phenyltetrazolyl sulfide **13**, which was subsequently oxidised to the sulfone **14** in order to initiate a Julia/Lythgoe olefination using the Kocienski variant.[8] Consequently, the alcohol **12** was oxidized to the aldehyde **15**.[9]



11 **12**



13 **14**

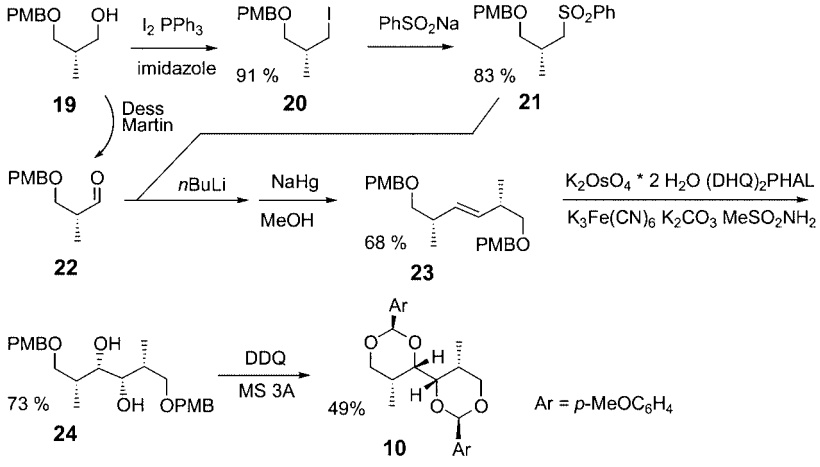


Olefination gave **16** in 69% yield. **16** was obtained as the pure (*E*) diastereomer. This followed from the coupling constant of 15.7 Hz between the olefinic hydrogen atoms.[10]

At this stage, the two remaining stereogenic centres were introduced by an asymmetric dihydroxylation[11] using the $(DHQ)_2PHAL$ ligand[12] and 2 mol% osmate. The reaction provided the diol **17** as a single diastereomer in 84% yield. If the dihydroxylation had unexpectedly occurred at the other face of the double bond, the reaction sequence would have led to the known compound **4**[5] instead of **9**. The *tert*-butyldimethylsilyl groups of **17** could be readily removed by treatment with Dowex 50 in MeOH. However, acetonisation of the resulting tetraol **18** was problematic. There is a strong tendency for formation of a mono-acetonide at the two internal hydroxy groups under equilibrating conditions. We therefore resorted to a kinetically controlled acetonisation with methoxypropene.[13] This furnished the desired 4,4′-bi-1,3-dioxolanyl **9** in moderate yield.

The corresponding *p*-methoxyphenyl derivative **10** was prepared using similar methods. Given the difficulties encountered in converting the tetraol **18** into a bi-1,3-dioxanyl, we wanted to introduce the *p*-methoxybenzyl group at an early stage. Thus, our synthesis started from the known alcohol **19** and aldehyde **22.**[14] First, the alcohol **19** was converted into the sulfone **21** via the iodo compound **20**.[15] On Julia−Lythgoe olefination with the aldehyde **22**, the sulfone **21** gave the alkene **23** as a 13:1 (^{1}H NMR) mixture of geometric isomers, in 68% yield. The (*E*) isomer was predominant according to the ^{13}C NMR chemical shifts. The presence of the (*Z*) diastereomer was neglected since only the (*E*) isomer reacted[16] to give the diol **24** in the subsequent asymmetric dihydroxylation,[12] in 73% yield. In the event of an unexpected dihydroxylation at the other face of the double bond, the reaction sequence would have led to the known[5] compound **5** instead of **10**. The reaction sequence was completed by a DDQ oxidation,[17] which provided directly the desired bi-1,3-dioxanyl **10**.

Next, we turned to the conformational analysis of **9** and **10**. Initial force field calculations with the MM3* force field implemented in the MACROMODEL program package[18] indicated a 96% preference for **9** to populate conformation **9a** and a 99% preference for conformation **10a** in the case of compound **10.**[19] We wanted to substantiate this by determination of the $^3J_{H,H}$ coupling constants across the inter-ring bond. Due to the C_2 symmetry of **9** and **10** the relevant hydrogen atoms at the ring junction are homotopic. In order to measure the coupling constants the symmetry had to be broken in a SELINCOR experiment.[20] This revealed coupling constants of 8.6 Hz and 9.2 Hz for compounds **9** and **10**, respectively, indicating that the conformers **9a** and **10a** are indeed populated to a > 90% extent. In fact, the conformational preference is more marked in the case of **10** in line with the predictions made on the basis of the force field calculations. The high conformational preference for a single conformation at the inter-ring bond demonstrates the effect that can be attained by



(two) axially placed methyl groups. This underscores the interpretation regarding the conformation controlling effect of the axial methyl group in prymnesin,[6] alluded to above.

Experimental Section

General Remarks: All temperatures quoted are uncorrected. ^{1}H NMR, ^{13}C NMR: Bruker ARX-200, AC-300, WH-400, AM-400, AMX-500. Boiling range of petroleum ether: 40−60 °C. Flash chromatography: Silica gel SI 60, E. Merck KGaA, Darmstadt, 40−63 μm. pH7-buffer: $NaH_2PO_4 \cdot 2\,H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4\,H_2O$ (213.6 g) made up to 1 L using water. Conformer populations were estimated on the basis of force field calculations using the MM3* force field implemented in the MACROMODEL[18] program, version "maestro 4.1". 5000 starting structures were generated with a Monte Carlo procedure and energy minimized ($CHCl_3$ environment). Conformers having energies of < 6 kcal·mol^{-1} above the minimum energy conformer were subjected to a Boltzmann averaging for 298 K to predict the conformer population.

(2*R*)-5-[3-(*tert*-Butyldimethylsilyloxy)-2-methylpropylsulfanyl]-1-phenyl-1*H*-tetrazole (13): Diethyl azodicarboxylate (1.045 g, 6.00 mmol) was added dropwise at 0 °C to a solution of (2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropanol[7] (**12**, 1.022 g, 5.00 mmol) and triphenylphosphane (1.574 g, 6.00 mmol) in THF (20 mL). After stirring at room temperature for 1.5 h silica gel (ca. 5 g) was added and the solvent was removed in vacuo. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 30:1, furnished the product **13** (1.725 g, 95%) as a colourless oil. $[\alpha]_D^{20} = +2.2$ ($c = 3.43$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.02 (s, 6 H), 0.85 (s, 9 H), 1.01 (d, $J = 6.8$ Hz, 3 H), 2.06−2.16 (m, 1 H), 3.34 (dd, $J = 12.8$, 6.6 Hz, 1 H), 3.47 (dd, $J = 12.8$, 6.7 Hz, 1 H), 3.49 (dd, $J = 10.0$, 5.6 Hz, 1 H), 3.61 (dd, $J = 10.0$, 4.8 Hz, 1 H), 7.50−7.57 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 (2 C), 16.2, 18.3, 25.9 (3 C), 35.7, 37.0, 66.4, 123.9 (2 C), 129.7 (2 C), 130.0, 133.2, 157.4 ppm. $C_{17}H_{28}N_4OSSi$ (364.58): calcd. C 56.00, H 7.74, N 15.37; found C 55.95, H 7.65, N 15.47.

(2*R*)-5-[3-(*tert*-Butyldimethylsilyloxy)-2-methylpropane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (14): *m*-Chloroperbenzoic acid (3.357 g, 13.62 mmol) was added in small portions at 0 °C to a solution of the sulfide **13** (826 mg, 2.27 mmol) in dichloromethane (20 mL). The resulting white suspension was stirred for 18 h at room temp. Aqueous NaOH (10%, 30 mL) was added, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 4:1, furnished the product **14** (886 mg, 98%) as a colourless oil. $[\alpha]_D^{20} = -5.5$ ($c = 6.23$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.10 (s, 6 H), 0.84 (s, 9 H), 1.10 (d, $J = 6.9$ Hz, 3 H), 2.37−2.47 (m, 1 H), 3.45 (dd, $J = 10.0$, 5.6 Hz, 1 H), 3.50 (dd, $J = 14.7$, 7.7 Hz, 1 H), 3.67 (dd, $J = 10.0$, 4.6 Hz, 1 H), 3.99 (dd, $J = 14.7$, 4.9 Hz, 1 H), 7.50−7.55 (m, 3 H), 7.61−7.65 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.7, −5.6, 18.7, 18.2, 25.8 (3 C), 31.2, 58.6, 66.1, 125.1 (2 C), 129.6 (2 C), 131.3, 133.1, 154.0 ppm. $C_{17}H_{28}N_4O_3SSi$ (396.58): calcd. C 51.49, H 7.36, N 14.14; found C 51.63, H 7.36, N 13.86.

(2*S*,5*S*,3*E*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-2,5-dimethyl-3-hexene (16): A solution of KHMDS (0.50 M in DME, 3.40 mL, 1.7 mmol) was added at −55 °C to a solution of the sulfone **14**[7] (674 mg, 1.70 mmol) in DME (7 mL). The resulting yellow-orange solution was stirred for 1 h at this temp. Aldehyde **15** (241 mg, 1.19 mmol) was added and the mixture was allowed to reach room temperature over 12 h. Water (15 mL) was added, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 9:1, furnished the product **16** (307 mg, 69%) as a colourless oil. In addition, some (150 mg, 0.38 mmol) of the sulfone **14** was recovered. **16:** $[\alpha]_D^{20} = -4.4$ ($c = 3.30$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.15 (s, 12 H), 0.86 (s, 18 H), 0.93 (d, $J = 6.8$ Hz, 6 H), 2.20−2.26 (m, 2 H), 3.32 (dd, $J = 9.8$, 7.2 Hz, 2 H), 3.45 (dd, $J = 9.8$, 6.0 Hz, 2 H), 5.24−5.40 (m_c, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.6 (4 C), 16.7 (2 C), 18.3 (2 C), 25.9 (6 C), 39.4 (2 C), 68.3 (2 C), 132.4 (2 C) ppm. HRMS (ESI) [M^+ + Na] ($C_{20}H_{44}O_2Si_2Na$): calcd. 395.2778; found 395.2827.

(2*R*,3*S*,4*S*,5*R*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-2,5-dimethylhexane-3,4-diol (17): The alkene **16** (363 mg, 0.97 mmol) was added to a mixture of potassium osmate(VI) dihydrate (7.0 mg, 0.02 mmol), $(DHQ)_2PHAL$[12] (40 mg, 0.05 mmol), potassium hexacyanoferrate(III) (958 mg, 2.91 mmol), potassium carbonate (402 mg, 2.91 mmol), and methanesulfonamide (92 mg, 0.97 mmol) in water/*tert*-butyl alcohol (1:1, 8 mL). After stirring at room temperature for 12 h, sodium sulfite (3.5 g) was added and stirring was continued for 1 h. Water (20 mL) was added, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (6 × 10 mL). The combined organic layers were washed with aqueous KOH (0.5 N, 10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 9:1→ 5:1, furnished the product **17** (329 mg, 84%) as a colourless oil, which crystallised upon storage in a refrigerator. M.p. 48 °C. $[\alpha]_D^{20} = -4.8$ ($c = 2.49$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 12 H), 0.83 (s, 18 H), 0.87 (d, $J = 7.0$ Hz, 6 H), 1.66−1.72 (m, 2 H), 3.12 (d, $J = 3.5$ Hz, 2 H), 3.54 (dd, $J = 10.0$, 6.0 Hz, 2 H), 3.62 (dd, $J = 10.0$, 4.2 Hz, 2 H), 3.65−3.68 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.9 (4 C), 11.2 (2 C), 18.2 (2 C), 25.9 (6 C), 37.6 (2 C), 66.4 (2 C), 72.9 (2 C) ppm. $C_{20}H_{46}O_4Si_2$ (406.75): calcd. C 59.06, H 11.40; found C 58.85, H 11.58.

(4*S*,5*R*,4*S*′,5*R*′)-2,2,5,2′,2′,5′-Hexamethyl-4,4′-bi-1,3-dioxanyl (9): Dowex 50 ion exchange resin (ca 20 mg) was added to a solution of the diol **17** (107 mg, 0.26 mmol) in MeOH (2 mL) and the mixture was stirred for 18 h at room temp. The mixture was filtered, the resin was washed with MeOH (2 mL) and the combined filtrates were concentrated. The residue was taken up in THF (1.5 mL). 2-Methoxypropene (75 mg, 1.04 mmol) and pyridinium *p*-toluenesulfonate (ca 20 mg) were added at 0 °C. After stirring for 1 h at this temperature, saturated aqueous $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with *tert*-butyl methyl ether (4 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 3:1 containing 1% of triethylamine, furnished the product **9** (26 mg, 40%) as a colourless solid of m.p. 98 °C. $[\alpha]_D^{20} = -7.3$ ($c = 1.23$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, $J = 6.8$ Hz, 6 H), 1.41 (s, 6 H), 1.43 (s, 6 H), 1.48−1.53 (m, 2 H), 3.55 (dd, $J = 11.5$, 1.5 Hz, 2 H), 3.82 (ps, 2 H), 4.10 (dd, $J = 11.5$, 2.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5 (2 C), 19.0 (2 C), 28.3 (2 C), 29.7 (2 C), 67.0 (2 C), 72.1 (2 C), 98.9 (2 C) ppm. $C_{14}H_{26}O_4$ (258.36): calcd. C 65.09, H 10.14; found C 64.94, H 10.03.

(2*R*)-1-Methoxy-4-[2-methyl-3-(phenylsulfonyl)propoxymethyl]-benzene (21): A mixture of (2*R*)-1-iodo-3-(4-methoxybenzyloxy)-2-methylpropane[15] (**20**) (1.456 g, 4.55 mmol) and sodium benzene-

sulfinate (2.595 g, 15.81 mmol) in DMF (15 mL) was heated for 12 h to 60 °C. Water (100 mL) was added and the mixture was extracted with *tert*-butyl methyl ether (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1.5:1→ 1:1, furnished the product **20** (1.259 g, 83%) as a colourless oil. $[\alpha]_D^{20} = -5.2$ ($c = 1.15$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$):[21] δ = 1.10 (d, $^3J = 6.9$ Hz, 3 H), 2.32−2.42 (m, 1 H), 2.91 (dd, $^3J = 7.9$, $^2J = 14.2$ Hz, 1 H), 3.27 (dd, $^3J = 6.5$, $^2J = 9.4$ Hz, 1 H), 3.35−3.42 (m, 2 H), 3.79 (s, 3 H), 4.32 (d, $^2J = 11.7$ Hz, 1 H), 4.36 (d, $^2J = 11.7$ Hz, 1 H), 6.84−6.88 (m, 2 H), 7.16−7.20 (m, 2 H), 7.52−7.57 (m, 2 H), 7.61−7.67 (m, 1 H), 7.90−7.92 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 29.3, 55.2, 59.3, 72.5, 73.2, 113.7 (2 C), 127.8 (2 C), 129.1 (2 C), 129.2 (2 C), 130.1, 133.4, 140.1, 159.2 ppm. $C_{18}H_{22}O_4S$ (334.12): calcd. C 64.65, H 6.63; found C 64.38, H 6.72.

(2*S*,3*E*,5*S*)-1,6-Bis(4-methoxybenzyloxy)-2,5-dimethyl-3-hexene (23): A solution of *n*BuLi (1.55 M in hexane, 1.30 mL, 2.00 mmol) was added dropwise at −78 °C to a solution of the sulfone **20** (758 mg, 2.27 mmol) in anhydrous THF (10 mL). After stirring for 1 h a solution of the aldehyde **22**[14] (218 mg, 1.05 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 2 h at −78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1.5:1, furnished a diastereomeric mixture of hydroxysulfones (548 mg, 96%) as a colourless oil (together with recovered sulfone **20** (415 mg, 1.24 mmol)). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.73 (d, $^3J = 7.1$ Hz, 3 H), 0.77 (d, $^3J = 6.8$ Hz, 3 H), 1.87−2.32 (m, 2 H), 2.46 (br. s, 1 H), 3.26−3.37 (m, 1 H), 3.42−3.50 (m, 2 H), 3.67 (s, 6 H), 3.73−3.81 (m, 2 H), 4.08−4.16 (m, 1 H), 4.23−4.35 (m, 4 H), 6.75−6.79 (m, 5 H), 7.05−7.19 (m, 3 H), 7.29−7.53 (m, 3 H), 7.74−7.84 (m, 1 H), 7.65−7.70 (m, 1 H) ppm.

Na_2HPO_4 (903 mg, 6.36 mmol) and Na/Hg (6%, 4.6 g, ca. 12 mmol) were added at −35 °C to a solution of the hydroxy-sulfones (486 mg, 0.90 mmol) in MeOH/EtOAc (2:1, 12 mL). After stirring for 1 h at this temperature, water (10 mL) was added and the liquid was decanted from the residual mercury. The solution was extracted with *tert*-butyl methyl ether (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 9:1→ 2:1, furnished the alkene **23** as a colourless oil. $[\alpha]_D^{20} = +3.7$ ($c = 1.91$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, $^3J = 6.8$ Hz, 6 H), 2.41−2.46 (m, 2 H), 3.22 (dd, $^3J = 7.3$, $^2J = 9.1$ Hz, 2 H), 3.33 (dd, $^3J = 6.2$, $^2J = 9.1$ Hz, 2 H), 3.76 (s, 6 H), 4.42 (s, 4 H), 5.37−5.44 (m, 2 H), 6.86 (d, $J = 8.7$ Hz, 4 H), 7.24 (d, $J = 8.7$ Hz, 4 H) ppm. Integration of the olefinic proton signals revealed an *E*/*Z*-ratio of 13:1. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.2 (2 C), 36.8 (2 C), 55.2 (2 C), 72.5 (2 C), 75.2 (2 C), 113.7 (4 C), 129.1 (4 C), 130.8 (2 C), 132.4 (2 C), 159.0 (2 C) ppm. $C_{24}H_{32}O_4$ (384.51): calcd. C 74.97, H 8.39; found C 75.04, H 8.21.

(2*R*,3*S*,4*S*,5*R*)-1,6-Bis(4-methoxybenzyloxy)-2,5-dimethylhexane-3,4-diol (24): The alkene **23** (58 mg, 0.15 mmol) was added to a mixture of potassium osmate(VI) dihydrate (0.7 mg, 2.7 μmol), $(DHQ)_2PHAL$[12] (5.0 mg, 6.4 μmol), potassium hexacyanoferrate-(III) (148 mg, 0.45 mmol), potassium carbonate (62 mg, 0.45 mmol), and methanesulfonamide (14 mg, 0.15 mmol) in water/*tert*-butyl alcohol (1:1, 1.5 mL). After stirring at room temperature for 16 h, sodium sulfite (113 mg, 0.90 mmol) was added and stirring was continued for 1 h. Water (2 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (6 × 2 mL). The combined organic layers were washed with aqueous KOH (0.5 N, 5 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 1:1→ 0:1, furnished the diastereomerically pure product **24** (46 mg, 73%) as a colourless oil together with (2*S*,3*Z*,5*S*)-1,6-bis(4-methoxybenzyloxy)-2,5-dimethyl-3-hexene (4 mg, 0.01 mmol, 7%).

24: $[\alpha]_D^{20} = +13.5$ ($c = 1.52$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, $^3J = 7.0$ Hz, 6 H), 1.84−2.02 (m, 2 H), 3.07 (br. s, 2 H), 3.41−3.50 (m, 2 H), 3.60−3.64 (m, 4 H), 3.79 (s, 6 H), 4.43 (s, 4 H), 6.84−6.99 (m, 4 H), 7.22−7.28 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (2 C), 36.1 (2 C), 55.2 (2 C), 72.9 (2 C), 73.1 (2 C), 73.2 (2 C), 113.8 (4 C), 129.2 (4 C), 130.2 (2 C), 159.9 (2 C) ppm.

(2*S*,3*Z*,5*S*)-1,6-Bis(4-methoxybenzyloxy)-2,5-dimethyl-3-hexene (*Z*-23): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, $^3J = 6.7$ Hz, 6 H), 2.78−2.82 (m, 2 H), 3.18−3.32 (m, 4 H), 3.80 (s, 6 H), 4.40−4.47 (m, 4 H), 5.16−5.23 (m, 4 H), 7.22−7.26 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (2 C), 32.8 (2 C), 55.2 (2 C), 72.5 (2 C), 75.0 (2 C), 113.7 (4 C), 129.0 (4 C), 133.0 (2 C), 158.7 (2 C) ppm.

(2*S*,2′*S*,5*R*,5′*R*)-2,2′-Bis(4-methoxyphenyl)-5,5′-dimethyl-4,4′-bi-1,3-dioxanyl (10): The diol **24** (262 mg, 0.63 mmol) and molecular sieves (3 Å, 600 mg, freshly powdered) were stirred in dichloromethane (10 mL) for 1 h and the suspension was cooled to −30 °C. Dichlorodicyanoquinone (316 mg, 1.39 mmol) was added and stirring was continued while the temperature increased to 0 °C over 5 h. The colour changed from green over deep red to pink. The mixture was filtered and saturated aqueous $NaHCO_3$ solution (10 mL) was added to the filtrate. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether, 2:1, containing 1% of triethylamine, furnished the product **10** (128 mg, 49%) as a colourless solid of m.p. 178 °C. $[\alpha]_D^{20} = +68.5$ ($c = 0.73$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (d, $^3J = 6.8$ Hz, 6 H), 1.68 (pq, $J = 6.9$ Hz, 2 H), 3.80 (s, 6 H), 3.99−4.02 (m, 4 H), 4.08−4.11 (dd, $^3J = 2.3$, $^2J = 11.2$ Hz, 2 H), 5.51 (s, 2 H) 6.86−6.89 (m, 4 H), 7.42−7.45 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 (2 C), 28.4 (2 C), 55.3 (2 C), 77.6 (2 C), 79.7 (2 C), 101.6 (2 C), 113.5 (4 C), 127.4 (4 C), 131.3 (2 C), 159.9 (2 C) ppm. Compound **10** was characterized by the spectroscopic data only.

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[1] R. W. Hoffmann, G. Mas, T. Brandl, *Eur. J. Org. Chem.* **2002**, 3455−3464.
[2] [2a] I. Columbus, S. Cohen, S. E. Biali, *J. Am. Chem. Soc.* **1994**, *116*, 10306−10307. [2b] I. Columbus, R. E. Hoffman, S. E. Biali, *J. Am. Chem. Soc.* **1996**, *118*, 6890−6896.
[3] R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134−2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054−2070.

[4] [4a] T. Iimori, S. D. Erickson, A. L. Rheingold, W. C. Still, *Tetrahedron Lett.* **1989**, *30*, 6947−6950. [4b] G. Li, W. C. Still, *J. Org. Chem.* **1991**, *56*, 6964−6966. [4c] X. Wang, S. D. Erickson, T. Iimori, W. C. Still, *J. Am. Chem. Soc.* **1992**, *114*, 4128−4137. [4d] S. D. Erickson, M. H. J. Ohlmeyer, W. C. Still, *Tetrahedron Lett.* **1992**, *33*, 5925−5928. [4e] G. Li, W. C. Still, *Tetrahedron Lett.* **1992**, *33*, 5929−5932. [4f] G. Li, W. C. Still, *Tetrahedron Lett.* **1993**, *34*, 919−922. [4g] S. Tang, W. C. Still, *Tetrahedron Lett.* **1993**, *34*, 6701−6704. [4h] M. T. Burger, A. Armstrong, F. Guarnieri, D. Q. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1994**, *116*, 3593−3594.

[5] T. Brandl, R. W. Hoffmann, *Eur. J. Org. Chem.* **2002**, 2613−2623.

[6] M. Sasaki, M. Ebine, H. Takagi, H. Takakura, T. Shida, M. Satake, Y. Oshima, T. Igarashi, T. Yasumoto, *Org. Lett.* **2004**, *6*, 1501−1504.

[7] K. Mori, K. Koseki, *Tetrahedron* **1988**, *44*, 6013−6020.

[8] P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morely, *Synlett* **1998**, 26−28.

[9] S. D. Burke, J. E. Cobb, K. Takeuchi, *J. Org. Chem.* **1990**, *55*, 2138−2151.

[10] As the olefinic hydrogen atoms in **16** are homotopic due to the C_2 symmetry of the molecule, this value had to be determined by a SELINCOR experiment.[20]

[11] Cf.: [11a] L. Sun, W. Zhou, X. Pan, *Tetrahedron: Asymmetry* **1991**, *2*, 973−976. [11b] G. Oddon, D. Uguen, A. De Clan, J. Fischer, *Tetrahedron Lett.* **1998**, *39*, 1149−1152.

[12] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2769−2771.

[13] M. L. Wolfrom, A. B. Diwadkar, J. Gelas, D. Horton, *Carbohydr. Res.* **1974**, *35*, 87−96.

[14] [14a] R. D. Walkup, J. D. Kahl, R. R. Kane, *J. Org. Chem.* **1998**, *63*, 9113−9116. [14b] M. G. Organ, J. Wang, *J. Org. Chem.* **2003**, *68*, 5568−5574.

[15] T. Heckrodt, J. Mulzer, *Synthesis* **2002**, 1857−1866.

[16] D. Xu, G. A. Crispino, K. B. Sharpless, *J. Am. Chem. Soc.* **1992**, *114*, 7570−7572.

[17] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885−888.

[18] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440−467.

[19] For the bis(acetonide) corresponding to **9** (having only one axial methyl group) the preference to populate a conformation corresponding to **9a** was calculated to be 88%.

[20] T. Fäcke, S. Berger, *Magn. Reson. Chem.* **1995**, *33*, 144−148.

[21] cf. the data in: P. M. Smith, E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3541−3566.

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