Selective protection of spirocyclic diols. An unusual acetal opening by DIBAL-H

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The spirocyclic diols **1** and **2**, which possess two secondary hydroxyl groups, have been selectively protected as the monobenzyl ethers by a two-step procedure. Diols **1** and **2** were first transformed to their corresponding acetals **3** and **4**, and the regioselective opening of these acetals with DIBAL-H produced the desired monoprotected diols.

Selective synthetic transformations of diols require chemoselective protection of hydroxyl groups, which is especially problematic in the design and construction of polyfunctional molecules. Recently, we have synthesized the spirocyclic diols **1** and **2** (Scheme 1) with excellent regio- and diasteroselectivity from δ,ε-unsaturated α-alkyl β-hydroxy esters.[1] These synthons can be used for the synthesis of spiroketals present in various natural products.[2] As the spiroketals are differently substituted, it is necessary to differentiate the two secondary hydroxyl groups in **1** and **2**.

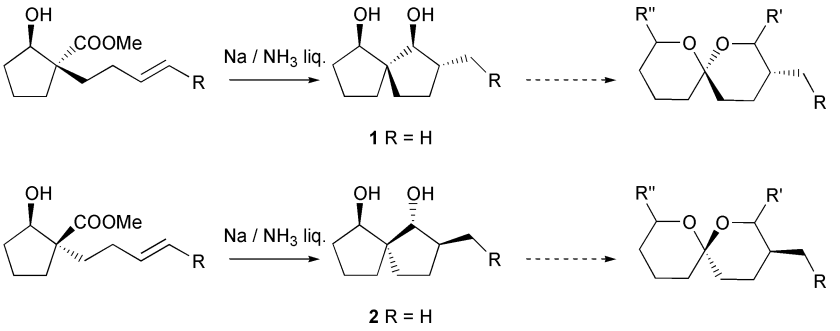
Results and discussion

Due to the non-selective nature of the benzylation reaction,[3] the regioselective reductive ring opening of the corresponding benzylidene acetal with DIBAL-H was studied. Acetalization of spiro diol **1** with benzaldehyde in the presence of PPTS in refluxing toluene led to the corresponding acetal **3** with total diastereoselectivity (yield = 90%; Scheme 2). Under the same conditions, the acetalization of **2** was not as selective as for **1**, as the two acetals **4** and **5** were obtained as an 80 : 20 mixture in 76% yield. The relative configurations of acetals **3**, **4** and **5** were determined by using ^{1}H NMR-nOe analysis (*cf. vide infra*).

The reduction of **3** by DIBAL-H in CH_2Cl_2 at 0 °C was highly regioselective as compound **6** was the only isolated monoprotected spiro diol (yield 98%; Scheme 3).[4] Furthermore, when acetal **4** was treated with DIBAL-H (CH_2Cl_2, 0 °C, 2 h), compounds **7** and **8** were isolated in 88% yield as a 98 : 2 mixture.

To explain the regioselectivity of the acetal cleavage in **3** and **4**, the conformation of these compounds was determined and the complexation of O(4) and O(6) by DIBAL-H was examined. The ^{1}H NMR-nOe analysis, combined with molecular modeling,[5] allowed the determination of the chair conformation of the acetal ring of **3** and its relative configuration at C(5), as nOe effects were observed between protons H(3a)–H(5), H(5)–H(6a) and H(3a)–H(6a) (Scheme 4). For compound **4,** the determination of a chair conformation of the acetal ring and the relative configuration at C(5) were also determined by combining ^{1}H NMR-nOe analysis and molecular modeling.[5] In this case, nOe effects were observed between protons H(3a)–H(5), H(5)–H(7) and H(3a)–H(7) (Scheme 4).

Acetal **4** is an acetal of type **I,** which has a chair conformation with one axial and one equatorial substituent (Scheme 5). Acetals of type **I** have been cleaved diastereoselectively by using a variety of nucleophiles, in the presence of Lewis acids.[6] Chelation of these acetals with Lewis acids gives a single complex.[7] This is quite understandable, if we consider complexes **II** and **III**. In complex **II**, the Lewis acid (LA) chelates to O(1), next to the axial methyl group, and therefore the C(2)–O(1) bond is lengthened, and the C(2)–O(3) bond is shortened by the anomeric effect. This is quite favorable since the elongation of the C(2)–O(1) bond increases the distance between the hydrogen atom in position 2 and the methyl group in position 6, and releases ring strain (1,3-diaxial interaction). On the other hand, in complex **III**, the C(2)–O(3) bond is elongated and, by the anomeric effect, the C(2)–O(1) bond is shortened. This situation increases the 1,3-diaxial interaction between the hydrogen atom in position 2 and the methyl group



Scheme 1

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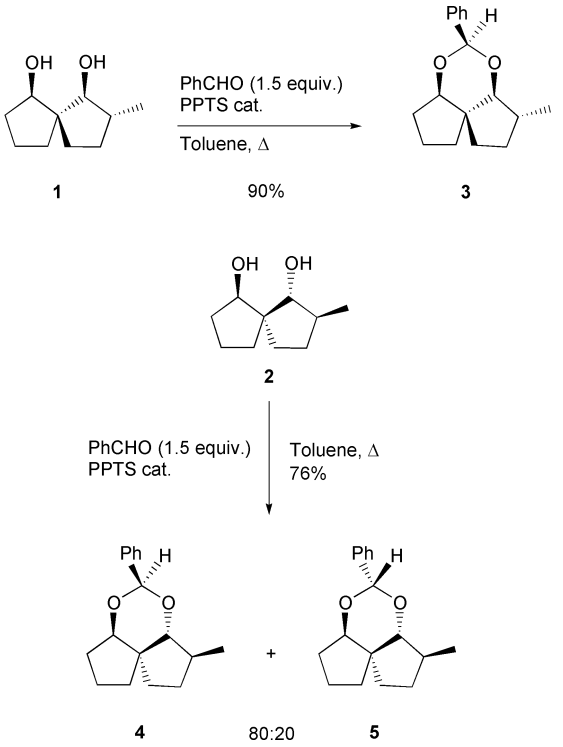
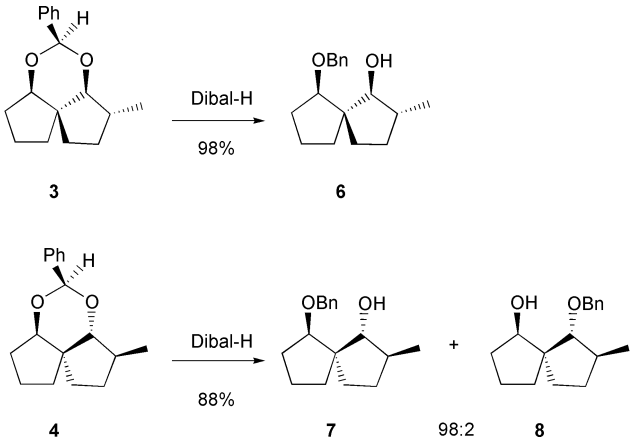
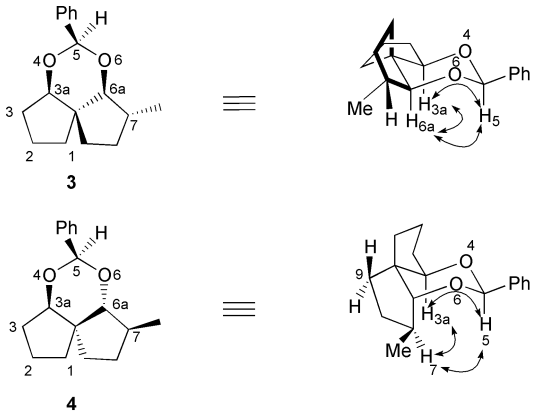


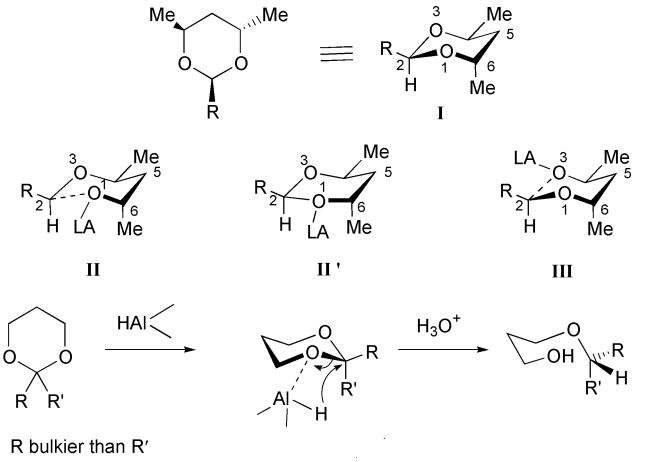
Scheme 2 Acetalization of spiro diols **1** and **2** with benzaldehyde.



Scheme 3 Reductive opening of acetals **3** and **4**.



Scheme 4 Conformation of **3** and **4**.



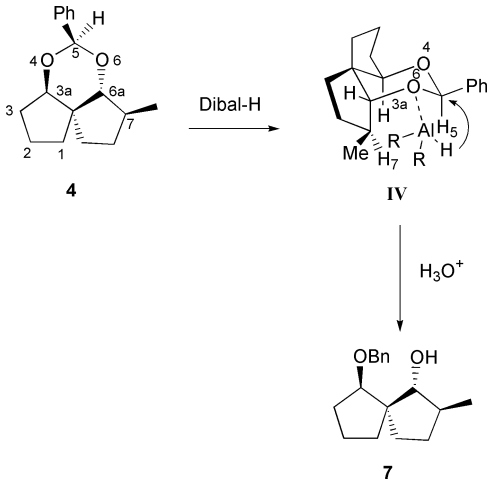
Scheme 5 Acetal ring opening by DIBAL-H.

in position 6, making the formation of such a complex less likely. According to recent stereochemical and NMR investigations on these acetals, it may be assumed that, upon coordination with the Lewis acid, the oxygen atom rehybridizes toward sp^2, giving a planar or weakly pyramidal complex (complex **II′**).[7,8] In this trigonal-like configuration, the Lewis acid is more sterically hindered by a vicinal equatorial group than by an axial one. Thus, the preferential formation of complex **II′** is easily understood (Scheme 5).

Once the chelate is formed, the nucleophile is then able to attack the acetal carbon, leading to cleavage of the weakened C–O bond. Depending on the substrate and on the reactants, Lewis acid mediated nucleophilic substitution of acetals can occur by direct displacement (S_N2) or by oxocarbenium ion (S_N1) mechanisms.[9] Results were reported that can only be explained by a delicate balance between a direct displacement mechanism and an oxocarbenium ion.[10] For this reason, in past years, a general view has emerged that involves a reaction mechanism continuum with these two processes as extrema.[11] In the particular case of reductive cleavage of acetals by aluminium hydrides (such as DIBAL-H), it has been clearly demonstrated that coordination of the organoaluminium reagent to one of the acetal oxygens is followed by hydride attack *syn* to the cleaved carbon–oxygen bond (Scheme 5).[12]

The regioselective reductive ring opening of acetal **4** by DIBAL-H is in accordance with the results reported in the literature. In compound **4**, DIBAL-H should complex O(6), leading to **IV**, and an intramolecular delivery of hydride will take place, implying the cleavage of the C(5)–O(6) bond and the formation of the observed monoprotected spiro diol **7** (Scheme 6).

In compound **3**, the acetal has two equatorial alkyl groups α to O(4) and O(6). In this compound, O(4) and O(6) are in comparable environments and complexation by the Lewis acid would be difficult at either position. Thus, low reactivity and regioselectivity should be observed for the reductive ring opening of **3** by DIBAL-H. On the contrary, the reduction product **6** is formed in high yield and the regioselectivity is excellent. One explanation could be that when O(6) or O(4) is coordinated with the Lewis acid, the complexes **V** and **VI** are formed. Due to the complexation of the oxygens a release of the steric interactions between the methyl and the cyclopentane ring (*syn*-pentane interaction) can take place. A boat conformer can be formed to produce complexes **VII** or **VIII** in which the acetal has one equatorial group α to O(4) and one axial group α to O(6). The 1,3-diaxial interaction with the phenyl group that appears in these boat conformations is smaller for **VII** than for **VIII**, since the C(5)–O(6) bond



4 **IV** **7**

Scheme 6

is lengthened by chelation of O(6) by DIBAL-H, and is shortened by chelation of O(4). Consequently, the formation of **VII** should be easier, leading to the monoprotected spiro diol **6** by intramolecular hydride delivery (Scheme 7).

The reduction of acetals **3** and **4** by DIBAL-H is a highly regioselective reaction that leads to the monoprotection of spiro diols in excellent yield. To our knowledge, the reduction of acetal **3** would be the first example of a reductive ring opening by DIBAL-H occuring *via* a boat conformation. The transformation of the monoprotected spiro diols **6** and **7** into substituted spiroketals is under investigation and will be reported in due course.

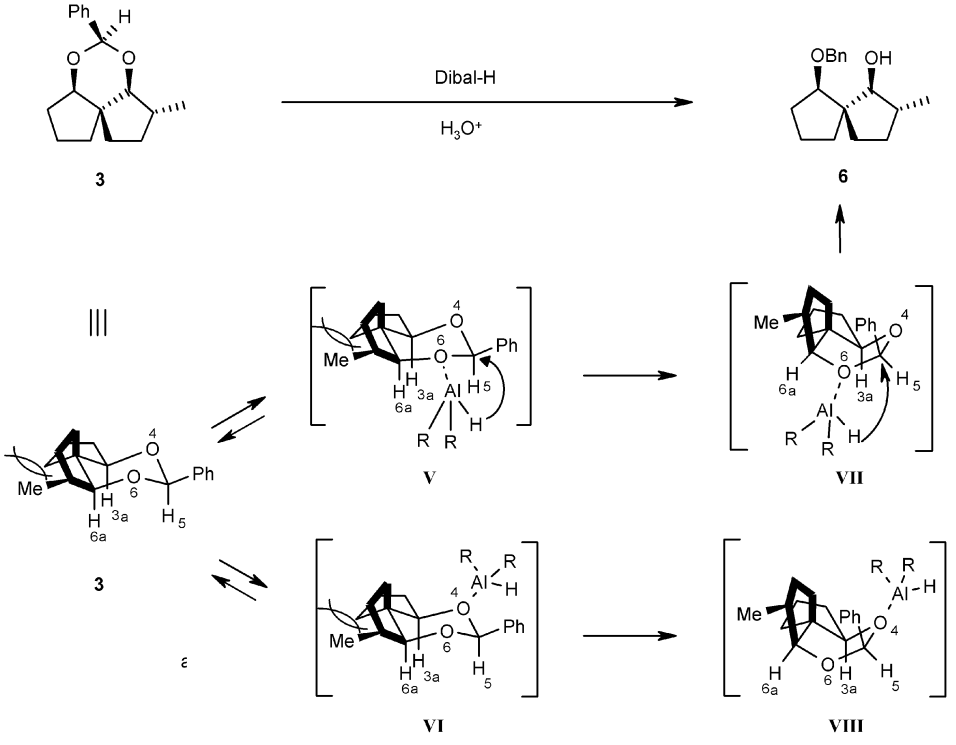
Experimental

General procedures

All experiments were run under an argon atmosphere. Dry toluene and dichloromethane were obtained by distillation from CaH_2. Flash chromatographies were carried out on Kieselgel 60 (230–400 mesh) with petroleum ether and ethyl acetate. Analytical thin layer chromatography (TLC) was run on Merck silica Kieselgel 60 GF_{254}. Mass spectra were obtained by GC/MS with electron impact ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. ^{1}H and ^{13}C NMR spectra were respectively recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz. Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) are expressed in ppm relative to residual $CHCl_3$ at $\delta = 7.27$ for ^{1}H and to $CDCl_3$ at $\delta = 77.1$ for ^{13}C. ^{1}H NMR J values are given in Hz. IR spectra were recorded as neat films (NaCl cell) on a Perkin–Elmer 298.

Syntheses

(±)-(3a*RS*,5*RS*,6a*SR*,7*RS*,9a*SR*)-7-Methyl-5-phenylocta-hydrodicyclopenta[*d*,*e*][1,3]dioxine, 3. A solution of spiro diol **1**[1] (2.55 g, 15.0 mmol, 1.0 equiv.), benzaldehyde (1.91 g, 18.0 mmol, 1.2 equiv.) and PPTS (0.05 g, 0.30 mmol, 0.02 equiv.) in dry toluene (40 mL) was heated under reflux for 3 h in a Dean–Stark apparatus. After being cooled to room temperature, the solution was neutralized with a saturated aqueous solution of $NaHCO_3$ (2×10 mL), diluted with Et_2O (20 mL) and washed with brine (3×10 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether 10 : 90) to provide acetal **3** as a colorless oil. Yield: 3.5 g (90%). $R_f = 0.78$ (silica gel, ethyl acetate–petroleum ether 10 : 60). IR (neat, cm^{-1}): 1450, 1370, 1350, 1150, 1120. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.54 (m, 2H), 7.45–7.35 (m, 3H), 5.53 (s, 1H), 3.77 (dd, 1H, $J = 12.1$ and $J = 7.3$ Hz), 3.74 (s, 1H), 2.34–2.13 (m, 3H), 2.06–1.95 (m, 1H), 1.88–1.52 (m, 4H), 1.47–1.28 (m, 3H), 1.05 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7 (s), 128.7 (d), 128.2 (2d), 126.4 (2d), 101.5 (d), 93.2 (d), 81.2 (d), 49.4 (s), 39.0 (d), 30.5 (t), 29.3 (t), 27.1 (t), 26.1 (t), 20.0 (q), 17.6 (t). EI MS: m/z (relative intensity): 258 ($M^{\bullet+}$, 7), 187 (6), 152 (31), 151 (48), 135 (100), 136 (97), 119 (31), 108 (56), 107 (62), 94 (58), 93 (58), 81 (77),



3 **6** **V** **VII** **3** **VI** **VIII**

Scheme 7 Complexation of **3** by DIBAL-H: intermediates **V**–**VIII**.

79 (61). HRMS calcd for $C_{17}H_{22}O_2$: 258.161978, found 258.161976.

Compounds 4 and 5. Acetalization of spiro diol **2**[1] (2.55 g, 15.0 mmol) with benzaldehyde was performed by using a similar procedure as for the preparation of **3**. Purification of the crude residue on silica gel (ethyl acetate–petroleum ether 10 : 90) afforded the two diastereomers **4** (2.35 g, 9.10 mmol) and **5** (0.59 g, 2.3 mmol) as colorless oils in an 80 : 20 ratio and a 76% overall yield.

(±)-(3a*RS*,5*RS*,6a*RS*,7*SR*,9a*RS*)-7-Methyl-5-phenyloctahydrodicyclopenta[*d*,*e*][1,3]dioxine, 4. $R_f = 0.87$ (silica gel, ethyl acetate–petroleum ether 10 : 60). IR (neat, cm^{-1}): 1450, 1370, 1350, 1150, 1120. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62–7.50 (m, 2H), 7.45–7.34 (m, 3H), 5.72 (s, 1H), 3.97 (br d, 1H, $J = 5.2$ Hz), 3.74 (d, 1H, $J = 9.6$ Hz), 2.50 (m, 1H), 2.32 (m 1H) 2.10–1.77 (m, 4H), 1.74–1.40 (m, 3H), 1.39–1.20 (m, 2H), 1.14 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.1 (s), 128.5 (d), 128.2 (2d), 126.2 (2d), 94.0 (d), 86.6 (d), 83.7 (d), 47.7 (s), 35.1 (t), 34.1 (d), 33.2, (t), 30.9 (t), 29.0 (t), 21.5 (t), 18.0 (q). EI MS: m/z (relative intensity): 258 ($M^{\cdot+}$, 7), 257 (9), 152 (31), 135 (48), 134 (100), 107 (51), 94 (89), 81 (66), 79 (61), 67 (39).

(±)-(3a*RS*,5*SR*,6a*RS*,7*SR*,9a*RS*)-7-Methyl-5-phenyloctahydrodicyclopenta[*d*,*e*][1,3]dioxine, 5. $R_f = 0.83$ (silica gel, ethyl acetate–petroleum ether 10 : 60). IR (neat, cm^{-1}): 1450, 1370, 1350, 1150, 1120. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.50 (m, 2H), 7.45–7.30 (m, 3H), 5.28 (s, 1H), 4.16 (dd, 1H, $J = 5.9$ and $J = 5.5$ Hz), 3.62 (d, 1H, $J = 1.8$ Hz), 2.42–1.21 (m, 11H), 1.18 (d, 3H, $J = 7.3$ Hz). EI MS: m/z (relative intensity): 258 ($M^{\cdot+}$, 7), 257 (6), 152 (23), 135 (34), 134 (71), 119 (14), 105 (49), 94 (100), 81 (56), 79 (66), 67 (39).

(±)-(1*SR*,2*RS*,5*RS*,6*RS*)-6-(Benzyloxy)-2-methylspiro[4.4]nonan-1-ol, 6. A solution of DIBAL-H in hexane (30 mL, 30 mmol, 6 equiv) was added dropwise to a solution of acetal **3** (1.3 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and poured into a cold (0 °C) aqueous 10% HCl solution (20 mL). The organic layer was separated, washed with a saturated aqueous $NaHCO_3$ solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether 10 : 90) to provide **6** a colorless oil. Yield: 1.26 g (98%). $R_f = 0.59$ (silica gel, ethyl acetate–petroleum ether 10 : 60). IR (neat, cm^{-1}): 3480, 1450, 1065. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H), 4.63 (d, 1H, $J = 12.0$ Hz), 4.47 (d, 1H, $J = 12.0$ Hz), 3.98 (dd, 1H, $J = 7.7$ and $J = 7.4$ Hz), 3.33 (br d, 1H, $J = 5.9$ Hz), 2.24 (br s, 1H, OH), 2.22–1.99 (m, 2H), 1.94–1.49 (m, 7H), 1.36 (ddd, 1H, $J = 12.9$, $J = 8.1$ and $J = 2.4$ Hz), 1.24–1.08 (m, 1H), 1.06 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8 (s), 128.2 (2d), 127.3 (d), 127.2 (2d), 86.4 (d), 81.4 (d), 71.1 (t), 54.7 (s), 42.9 (d), 35.4 (t), 29.6 (t), 29.2 (t), 28.7 (t), 19.6 (t), 18.6 (q). EI MS: m/z (relative intensity): 260 ($M^{\cdot+}$, 1), 242 ($M - H_2O$, 1), 169 ($M - Bn$, 2), 151 (17), 134 (40), 133 (32), 107 (28), 91 (Bn, 100), 81 (31). HRMS calcd for $C_{17}H_{22}O$: ($M - H_2O$): 242.16706, found 242.16717.

Compounds 7 and 8. The treatment of acetal **4** (1.3 g, 5.0 mmol, 1.0 equiv.) with DIBAL-H by the same procedure as for acetal **3** afforded an inseparable mixture of the two diastereomers **7** and **8** in a 98 : 2 ratio in favor of **7**, as a colorless oil. Yield 1.14 g (88%). $R_f = 0.70$ (silica gel, ethyl acetate–petroleum ether 10 : 60). IR (neat, cm^{-1}): 3480, 1450, 1065.

(±)-(1*RS*,2*SR*,5*SR*,6*RS*)-6-(Benzyloxy)-2-methylspiro[4.4]nonan-1-ol, 7. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.25 (m, 5H), 4.61 (d, 1H, $J = 11.8$ Hz), 4.34 (d, 1H, $J = 11.8$ Hz), 4.08 (m, 1H, OH), 3.91 (dd, 1H, $J = 4.6$ and $J = 1.6$ Hz), 3.51 (d, 1H, $J = 6.3$ Hz), 2.04–1.10 (m, 11H), 1.08 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.7 (s), 128.4 (2d), 127.7 (d), 127.6 (2d), 87.9 (d), 86.2 (d), 70.3 (t), 56.2 (s), 41.2 (d), 35.0 (t), 34.4 (t), 29.3 (t), 29.0 (t), 21.3 (t), 19.0 (q). EI MS: m/z (relative intensity): 242 ($M - H_2O$, 1), 169 ($M - Bn$, 1), 152 (12), 134 (72), 133 (20), 107 (22), 91 (Bn, 100), 81 (28), 79 (33), 67 (20).

(±)-(1*RS*,5*RS*,6*RS*,7*SR*)-6-(Benzyloxy)-7-methylspiro[4.4]nonan-1-ol, 8. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.27 (m, 5H), 4.72 (d, 1H, $J = 11.2$ Hz), 4.48 (d, 1H, $J = 11.2$ Hz), 4.09 (dd, 1H, $J = 4.8$ and $J = 1.8$ Hz), 3.83 (br s, 1H, OH), 3.55 (d, 1H, $J = 4.8$ Hz), 2.24 (m, 1H), 2.06–1.28 (m, 10H), 1.25 (d, 3H, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.8 (s), 128.4 (2d), 127.8 (d), 127.7 (2d), 94.3 (d), 79.3 (d), 72.0 (t), 57.5 (s), 39.6 (d), 34.4 (t), 34.3 (t), 32.0 (t), 30.6 (t), 20.1 (t), 19.1 (q). EI MS: m/z (relative intensity): 242 ($M - H_2O$, 1), 169 ($M - Bn$, 1), 152 (16), 134 (44), 121 (12), 119 (12), 108 (26), 91 (Bn, 100), 81 (44), 67 (15).

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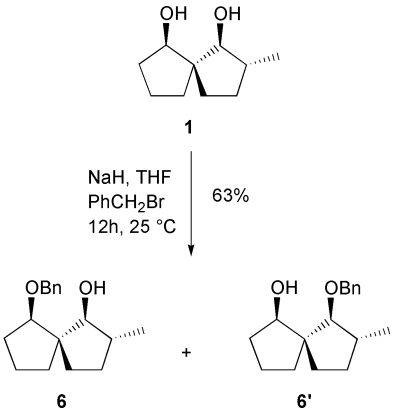
3 By treatment of diol **1** with NaH (1 equiv) in THF and benzyl bromide (1.1 equiv), two regioisomeric monobenzyl ethers **6** and **6′** were formed as a 45 : 55 mixture in 63% yield.



4 When acetal **3** was treated with $BH_3{\cdot}Me_2S$ in THF, the ring opening of the acetal was not regioselective as **6** and its regioisomer **6′** were isolated in 88% yield as a 57 : 43 mixture.

5 Optimized molecular structures were generated using the combination of CS-Chemdraw Pro 5.0 (1998) and CS-Chem3D Pro 5.0 (1999), Cambridge Soft, Cambridge, MA.

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