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AN EFFICIENT SYNTHESIS AND RESOLUTION OF (±)-*cis*,*cis*-SPIRO[4.4]NONANE-1,6-DIOL

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Abstract: A four step highly stereoselective synthesis of (±)-*cis*,*cis*-spiro[4.4]nonane-1,6-diol (**4**) in 55% overall yield is described in detail beginning with ethyl 2-oxocyclopentanecarboxylate. A new resolution of diol (±)-**4** using (1*R*)-(+)-camphor is also reported.

In 1993 we communicated a new synthesis and resolution of (±)-*cis*,*cis*-spiro[4.4]nonane-1,6-diol (**4**).[1,2,3] The absolute configuration of (+)- and (-)-**4** was confirmed[4] in 1995 using a combination of an X-ray crystal structure, vibrational circular dichroism and 6-31G*(0.3) *ab initio* level calculations.[5] Since then, the diol **4** has been used successfully as 1) a substrate bound chiral auxiliary for an intermolecular Diels-Alder reaction,[6] 2) as a bisphosphinite ligand for rhodium catalyzed hydrogenation of 2-acetamidoacrylic acid derivatives,[7] and 3) as a chiral auxiliary for $LiAlH_4$ reductions of ketones.[8] As

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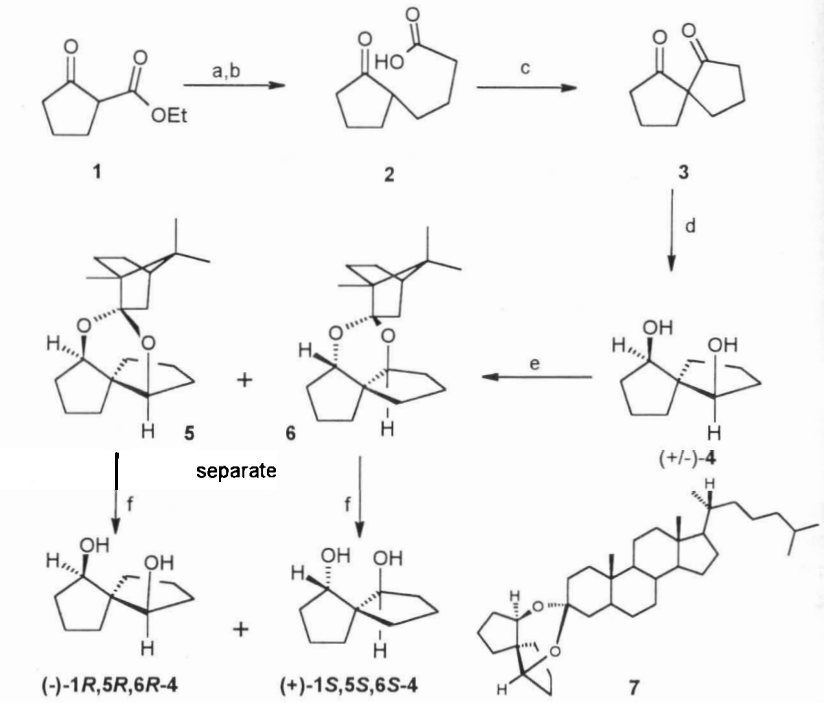
Scheme 1



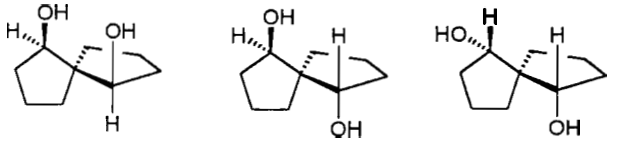
Reagents: a) KH, THF, then $Br(CH_2)_3CO_2Et$ (97%); b) 10% HCl, reflux (86%); c) TsOH, toluene (72%); d) Li *t*-Bu(iBu)$_2$AlH, THF, -78 °C (91%); e) 1*R*-(+)-camphor, TsOH, C_6H_6 (90%); f) TsOH, CH_2Cl_2:H_2O (40:1), (90%).

the interest in using diol **4** in various chiral transformations has been steadily increasing, we report herein a full account of our synthesis and resolution of diol (±)-**4**.[9]

The synthesis and resolution of **4** is shown in Scheme 1. Treatment of keto-ester **1** with KH followed by ethyl 4-bromobutanoate gave a keto-diester that was immediately heated with 10% HCl to give keto-acid **2** (83% over two steps). Cyclization to spiroketone **3** (72%) was effected by heating **2** with

Table 1

Ratio of Diasteromeric Diols Obtained by Reduction of Spirodione 3 With Various Reducing Agents



cis,cis-**4** cis,trans-**4** trans,trans-**4**

Reducing Agent	Conditions	cis,cis : cis,trans : trans:trans[a]	Yield
$LiAlH_4$	Et_2O	22:59:19	82
DIBAL-H	THF -78°C	27:57:16	96[b]
Red-Al	THF -78°C	4:82:14	78
$LiEt_3BH$	THF -78°C	91:9:0	96[b]
Li *t*-Bu(iBu)$_2$AlH	THF -78°C	100:0:0	91

a) ratio determined by ^{1}H NMR spectroscopy. b) crude yield

TsOH in toluene with azeotropic removal of water. With dione **2** in hand, attention was turned towards developing a stereoselective reduction to hopefully form only *cis,cis*-diol **4**.

The dione was treated with a variety of reducing agents (Table 1) and only lithium *t*-butyldiisobutylaluminium hydride at -78 °C in THF gave exclusively (±)-*cis,cis*-diol **4** (91%). This result was extremely useful as separation of the three diastereomeric diols by column chromatography was a very tedious task and usually the fractions were still contaminated by minute amounts of the other diols.

The resolution of (±)-*cis,cis*-diol **4** was performed by refluxing **4** with 1*R*-(+)-camphor in the presence of a catalytic amount of TsOH in benzene with azeotropic removal of water (Scheme 1). Two diastereomers **5** and **6** were formed that could be easily separated on a silica gel column using hexanes

(R_f=0.36 and 0.19 respectively). The camphor ketal was removed by heating **5** or **6** in a CH_2Cl_2:water mixture (40:1) with a catalytic amount of TsOH providing (-)-1*R*,5*R*,6*R*-**4** and (+)-1*S*,5*S*,6*S*-**4**[10] respectively in 90% yield. As mentioned above, the absolute and relative stereochemistry was confirmed by obtaining an X-ray crystal structure of **7** (Scheme 1).[1,4]

In summary, we have developed a short, efficient synthesis and resolution of (±)-*cis*,*cis*-spiro[4.4]nonane-1,6-diol (**4**).

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ACE-200 (^{1}H 200 MHz, ^{13}C 50 MHz) spectrometer. All samples were obtained in $CDCl_3$ and the chemical shifts (ppm) are relative to the $C\underline{H}Cl_3$ peak as an internal reference (7.27 ppm for ^{1}H and 77.00 for ^{13}C). Infrared (IR) spectra were recorded on a Mattson Model 4030 FT-IR spectrometer. Mass spectra (MS) were run on either a Varian CH5 or a VG 7070 instrument. High resolution mass spectrometry (HRMS) were recorded on a Kratos MS80. Microanalyses were performed by Ms. D. Fox, Dept. of Chemistry, University of Calgary. All melting and boiling points are uncorrected. Anhydrous THF was distilled from sodium benzophenone ketyl. Anhydrous benzene and CH_2Cl_2 were obtained from distillation from CaH_2. All reactions were performed in oven-dried glassware under an N_2 atmosphere.

4-(2-Oxocyclopentyl)butanoic Acid ((±)-2)

Potassium hydride (0.86 g of 35% dispersion, 7.5 mmol of KH) was placed in a 100 mL three-necked round bottom flask under nitrogen. The mineral oil was

removed by washing three times with 10 mL aliquots of anhydrous THF. To the dried KH was added 35 mL of dry THF, and after cooling to -78°C, freshly distilled ethyl 2-oxocyclopentanecarboxylate (**1**) (1.06 g, 6.79 mmol) was washed into the reaction vessel with THF (5 mL). The reaction mixture was warmed to room temperature and when all the precipitate had dissolved (in some cases additional THF was needed to solvate all the precipitate), freshly distilled ethyl 4-bromobutanoate (1.07 mL, 7.47 mmol) was added. The reaction was refluxed for 30 h, after which the THF was removed *in vacuo*. Water was added and the resulting solution was extracted with chloroform and ether. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvents removed *in vacuo*. Purification by distillation yielded 1.78 g (6.60 mmol) of ethyl 4-(1-ethoxycarbonyl-2-oxocyclopentyl)butanoate in 97% yield. bp 80-85 °C (air heat)/ 0.04 Torr (lit.[11,2a] 140-145 °C at 0.4 mm Hg), IR 1739, 1728 cm^{-1}; ^{1}H-NMR 4.08 (q, 2H, J=7.2 Hz), 4.04 (q, 2H, J=7.2 Hz), 2.46-2.18 (m, 5H), 1.95-1.83 (m, 4H), 1.56-1.48 (m, 3H), 1.17 (t, 6H, J=7.2 Hz); ^{13}C-NMR 214.3,172.6, 170.4, 61.2, 60.1, 60.0, 37.6, 34.1, 32.9, 32.5, 20.1, 19.4, 14.0, 13.9; Mass spectrum 280, 242, 224, 156.

Ethyl 4-(1-ethoxycarbonyl-2-oxocyclopentyl)butanoate (0.27 g, 1.0 mmol) was placed in a 50 mL round bottomed flask with 10% HCl (8 mL) and refluxed for 12 h (disappearance of starting material was monitored by GC). Upon completion, the reaction mixture was extracted with ether. The combined ether layers were combined and extracted with saturated $NaHCO_3$. The combined

saturated $NaHCO_3$ layer was acidified (to pH≤2) and extracted with ether. The combined ether layers were dried over anhydrous Na_2SO_4, filtered and the ether was removed *in vacuo*. Distillation produced 0.147 g (0.864 mmol) of a colourless liquid (**2**) in 86% yield. bp 110-115°C (air heat)/ 0.05 Torr (lit.[11] 153-156°C / 0.2 mm Hg), ^{1}H-NMR 2.41 (t, 2H, J=6.5 Hz), 2.31-1.93 (m, 4H), 1.92-1.25 (m, 7H); ^{13}C-NMR 221.4, 179.2, 47.9, 37.9, 33.9, 29.4, 28.9, 22.6, 20.6; Mass spectrum 170, 152, 84.

(±)-Spiro[4.4]nonane-1,6-dione ((±)-3)

Keto acid **2** (4.35 g, 25.6 mmol) was placed in a 250 mL round bottomed flask and toluene (200 mL) and TsOH (2.43 g, 12.8 mmol) were added. The solution was refluxed, with azeotropic removal of water, and the disappearance of starting material was monitored (by GC or TLC (*n*-butanol:AcOH:H_2O 4:1:5)). Saturated $NaHCO_3$ was added and the two phases were vigorously stirred for 15 min. The aqueous layer was extracted with ether. The ether and toluene layers were combined, dried over anhydrous Na_2SO_4, filtered and the solvents removed *in vacuo*. Unreacted starting material could be re-isolated by: acidification of the aqueous layer, extraction with ether, drying of the organic layer, and removal of the ether *in vacuo*. Spiro[4.4]nonane-1,6-dione (**3**) was purified by distillation which yielded a white solid (2.80 g, 18.4 mmol (72%)). mp 37-38 °C (lit.[2a,e,f] mp 38-40°C) bp 99-104 °C (air heat)/ aspirator (lit.[2e] 91 - 92°C/9 Torr); IR 1746, 1723 cm^{-1}; ^{1}H-NMR 2.45 - 2.00 (m, 8H), 1.95-1.72 (m, 4H); ^{13}C-NMR 217.3, 65.0, 39.1, 34.9, 20.4; Mass spectrum 152, 97; Exact mass

calc'd for $C_9H_{12}O_2$: 152.0837. Found: 152.0831. Analysis calc'd for $C_9H_{12}O_2$: C, 71.03%; H, 7.95%. Found: C, 69.65%; H, 7.76%.

Spiro[4.4]nonane-1,6-diol (4)

Method A: Compound (±)-4 From Dione 3.

DIBAL-H (86.1 mL, 1.0 M in THF) was placed in a 250 mL three-necked round bottom flask and cooled to -78°C. *t*-Butyllithium (50.6 mL, 1.7 M in pentane) was added slowly turning the solution an orange colour. The solution was allowed to warm to room temperature, where it changed to a light yellow colour, and then was cooled down to -78°C. To this reaction vessel was slowly added, *via* an addition funnel, a solution of freshly distilled (±)-dione **4** (4.37 g, 28.7 mmol) in THF (50 mL). The reaction mixture was warmed to room temperature overnight. The resulting solution was poured into a mixture of 0.5 M $KHSO_4$ (404 mL) and $CHCl_3$ (148 mL) and stirred vigorously. The aluminium salts were removed by filtering through Celite.® The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ and ether. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. Flash column chromatography (1:2) provided a colourless oil (±)-**4** (4.10 g, 26.2 mmol) in 91% yield. bp 68-76°C (air heat)/ 0.052 Torr (lit.[2b] bp 160-165 °C (aspirator)); IR 3366 cm^{-1}; ^{1}H-NMR 4.17-4.13 (m, 2H), 2.77 (br. s, 2H), 1.93-1.84 (m, 4H), 1.79-1.58 (m, 6H), 1.38-1.25 (m, 2H); ^{13}C-NMR 79.4, 58.1, 34.0, 33.5, 21.0; Mass spectrum 138, 120, 94; Analysis calc'd for $C_9H_{16}O_2$: C, 69.19%; H, 10.32%. Found: C, 69.15%; H, 10.12%.

Method B: Compound (1*R*,5*R*,6*R*)-(-)-4 From Ketal 5.

Ketal **4** (0.170 g, 0.585 mmol) was placed in a round bottom flask and CH_2Cl_2 (20 mL), TsOH (0.040 g, 0.21 mmol) and H_2O (0.5 mL) were added. The solution was refluxed until no starting ketal was observed by GC. More H_2O was added and the solution was extracted with CH_2Cl_2 and EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (1:2) produced a white solid, (-)-**4** (0.0869 g, 0.556 mmol), in 90% yield. mp 30.5-31 °C; IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrum were identical with those obtained for (±)-**4**. Comparison of the optical rotation ($[\alpha]_D^{22.5}$ -101 (c 11.06, 0.1 dm, abs. EtOH)) to the predicted value by Kabuto *et al.*[12] ($[\alpha]_D^{20}$ -99 (α_D^{20} -25.9 (c 1.21, EtOH), of a mixture with a 26% ee)) indicated that (-)-4 was almost enantiomerically pure.

Method C: Compound (1*S*,5*S*,6*S*)-(+)-4 From Ketal 6.

Ketal **6** (0.1784 g, 0.614 mmol) was placed in a round bottomed flask and CH_2Cl_2 (20 mL), TsOH (0.040 g, 0.21 mmol) and H_2O (0.5 mL) were added. The solution was refluxed until no starting ketal was observed by GC. More H_2O was added and the solution was extracted with CH_2Cl_2 and EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo* to provide crude product. Purification by flash column chromatography (1:2) produced a white solid, (+)-**4** (0.0811 g, 0.519 mmol), in 90% yield. mp 29-29.5 °C; IR, ^{1}H-NMR, ^{13}C-NMR and mass

spectrum were identical with those obtained for (±)-**4**. Comparison of the optical rotation ($[\alpha]_D^{23}$ +97.1 (c 8.70, 0.1 dm, abs. EtOH)) to the predicted value by Kabuto *et al.*[12] ($[\alpha]_D^{20}$ -99 (α_D^{20} -25.9 (c 1.21, EtOH) of a mixture with a 26% ee)) indicated that (+)-**4** was almost enantiomerically pure (98% ee).

(1*R*,5*R*,6*R*)-Spiro[4.4]nonane-1,6-diol (1′*R*)-(+)-Camphor Ketal ((-)-5) and (1*S*,5*S*,6*S*)-Spiro[4.4]nonane-1,6-diol (1′*R*)-(+)-Camphor Ketal ((+)-6)

Freshly distilled (±)-diol **4** (4.10 g, 26.2 mmol), (+)-1*R*-camphor (14.0 g, 91.7 mmol), benzene (350 mL) and TsOH (0.045 g, 0.24 mmol) were placed in a 500 mL round bottom flask. The solution was refluxed with azeotropic removal of H_2O until (±)-diol **4** was no longer observed by TLC. Anhydrous K_2CO_3 was added and the solution was stirred for 15 minutes. The mixture was filtered and washed with hexanes and ether. The organic phases were combined, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. The diastereomers were separated by flash column chromatography (hexanes) which provided two compounds **5** (3.40 g, 11.7 mmol, R_f=0.36) and **6** (3.42 g, 11.8 mmol, R_f=0.19) in 89% and 90% yield respectively.

Compound **5** was a colourless oil that solidified on standing producing a clear colourless solid. mp 34-36 °C; bp 84-90°C (air heat)/ 0.06 Torr; IR 2951, 2940, 2930 cm^{-1}; ^{1}H-NMR 3.85 (dd, 1H, J=1.3 and 3.4 Hz), 3.75 (dd, 1H, J=1.8 and 5.6 Hz), 2.03-1.47 (m, 15H), 1.40-1.06 (m, 4H), 1.01 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); ^{13}C-NMR 107.6, 79.8, 79.7, 55.9, 54.0, 46.1, 44.8, 43.5, 37.5, 36.8, 33.3, 31.5, 26.5, 27.0, 24.5, 23.7, 20.8, 20.7, 10.7; Mass

spectrum 290, 219, 121; Analysis calc'd for $C_{19}H_{30}O_2$: C, 78.57%; H, 10.41%. Found: C, 78.74%; H, 10.45%. Optical rotation obtained was $[\alpha]_D^{21.5}$ +4.30 (c 18.4, 0.1 dm, CH_2Cl_2).

Compound **6** was a colourless oil. bp 81-88 °C (air heat)/ 0.057 Torr, IR 2953, 2917, 2874 cm^{-1}; ^{1}H-NMR 3.84 (d, 1H, J=5.4 Hz), 3.80 (d, 1H, J=3.8 Hz), 2.16 (dt, 1H, J=3), 2.03-1.43 (m, 12H), 1.38-1.10 (m, 6H), 0.97 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H); ^{13}C-NMR 107.3, 80.5, 78.2, 56.9, 53.7, 48.7, 44.9, 43.8, 37.2, 36.7, 32.8, 31.9, 29.2, 27.2, 24.6, 23.9, 20.9, 20.8, 11.6; Mass spectrum 290, 219, 121; Analysis calc'd for $C_{19}H_{30}O_2$: C, 78.57%; H, 10.41%. Found: C, 78.73%; H, 10.54%. Optical rotation obtained was $[\alpha]_D^{21}$ -18.10 (c 17.1, 0.1 dm, CH_2Cl_2).

Reference and Notes

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9. In the past year, nine different research groups around the globe have written or emailed us regarding the details on the synthesis and resolution of diol **4**.

10. For the assignment of absolute stereochemistry to the spiro carbon atom, it is treated as a centre of chirality (formally a (ab)C(ba) system), not as an axis of chirality. For more information, see: Cahn, R.S.; Ingol, C.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385.

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