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## Cyclic Chiral Diols with C<sub>2</sub> Symmetry: Synthesis of (2R, 3R)-dihydroxy-1,2,3,4-Tetrahydronaphthalene

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**Abstract** - (2R, 3R)-dihydroxy-tetrahydronaphthalene **4** has been prepared via an efficient three-step synthesis from *cis*-(1R, 2S)-dihydroxy-1,2-dihydronaphthalene **1**. The latter was obtained by bioconversion of naphthalene by a modified strain of *Pseudomonas fluorescens*. The diol **4** has been successfully tested in a conjugate asymmetric addition of lithium dibutyl cuprate to the monocrotonate **7**. Copyright © 1996 Elsevier Science Ltd

Among chiral auxiliaries for asymmetric synthesis, optically active compounds with C<sub>2</sub> symmetry elements provide higher levels of absolute stereochemical control as compared to those lacking any symmetry<sup>1</sup>. In several cases the chiral source has been acyclic diols with C<sub>2</sub> symmetry and, more recently, cyclic diols as cyclohexane-, cyclopentane- and cycloheptane-1,2-diol<sup>2</sup>, prepared by enzymatic resolution of the corresponding racemic acetates<sup>3</sup>.

In this paper an efficient three-step synthesis of the diol **4**, with a C<sub>2</sub> symmetry axis, from *cis*-(1R, 2S)-dihydroxy-1,2-dihydronaphthalene **1**, is described<sup>4</sup>. With respect to the above mentioned chiral diols, the presence of the aromatic ring was expected to give derivatives more easily to be crystallized. Furthermore the aromatic ring could also influence the stereoselectivity.

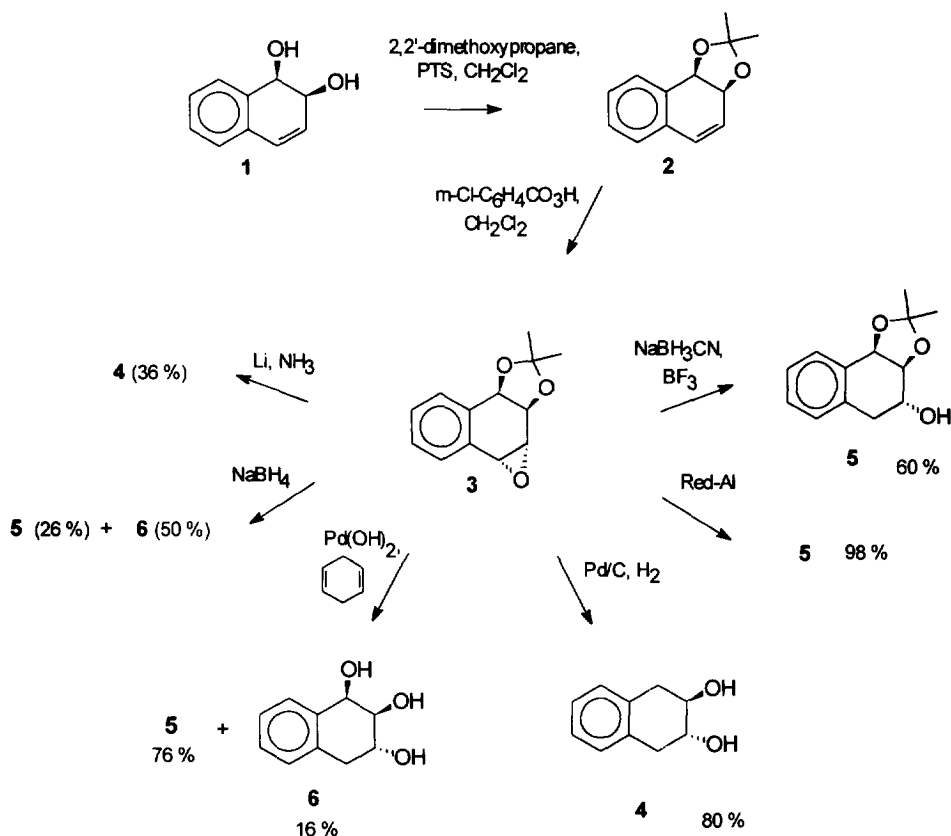
The chiral diol **1** was easily produced by bioconversion of naphthalene by a modified strain of *Pseudomonas fluorescens*<sup>5</sup>.

In the first step of the synthetic pathway, the two hydroxyl groups present in the diol **1** were protected as ketal to give the compound **2**. Protection was strictly required to obtain the correct relative stereochemistry of the 2- and 3- hydroxyl groups in the final diol **4** (see below). The choice of the experimental conditions had to be carefully selected as in acid media aromatization of **1** to naphthol by easy elimination of water may occur. The best results (97% yield) have been obtained by reaction with 2,2'-dimethoxypropane in methylene chloride at 0°C in the presence of a catalytic amount of *p*-toluenesulphonic acid.

By treatment of ketal **2** with *m*-chloroperbenzoic acid in methylene chloride, epoxidation of the stilbenic double bond occurred with excellent yield (97.5%) and on the opposite site with respect to the ketal ring<sup>6</sup>. Direct epoxidation of the *cis*-diol **1** led to the epoxidation from the same site of the hydroxyl groups.

Since, to be useful, a chiral auxiliary must be easily available in large amounts, the conversion of the epoxide **3** to the diol **4** has been investigated under a variety of conditions to select the best in terms of yields, convenience, reproducibility and applicability to large scale. Compound **3** can be directly converted to the diol **4** by two different routes; a) reduction with lithium-ammonia, and b) catalytic reduction with palladium on charcoal in the presence of an acid. The latter method afforded the diol **4** in 75.7 % overall yield from **1** (80 % yield in the reduction step). The former produced a lower yield of **4** (36 %).

Scheme 1



The other procedures were less straightforward. Reduction with diisobutylaluminum hydride (DIBAH)<sup>7</sup> or with sodium bis-(2-methoxyethoxy)aluminum dihydride (Red-Al)<sup>8</sup> afforded in excellent yields the hydroxy ketal **5** which was further reduced with palladium on charcoal to **4**. Compound **5** was also obtained by reduction of **3** with NaBH<sub>3</sub>CN-BF<sub>3</sub><sup>9</sup> albeit with lower yields (60%). The reduction of **3** with NaBH<sub>4</sub> gave a mixture of the hydroxy ketal **5** and the triol **6**. Compounds **5** and **6** were also obtained by reduction with palladium hydroxide in the presence of cyclohexadiene, albeit in a different ratio<sup>10</sup>.

As a test of the effectiveness of **4** in asymmetric synthesis the conjugate addition<sup>11</sup> of lithium dibutyl cuprate to the monochrotonate **7** was considered. The reaction proceeded in 92 % yield and afforded the two expected diastereoisomers **8** in a 93/7 diastereoisomeric ratio<sup>12</sup>.

Work is in progress to broaden the applications of the diol **4** to asymmetric synthesis.



## Experimental

### Starting Materials and Procedures.

Reagents grade tetrahydrofuran, 1,2-dimethoxyethane and pyridine were refluxed over  $\text{LiAlH}_4$  and distilled. Reagent grade dichloromethane was refluxed over  $\text{P}_2\text{O}_5$  and distilled. Reagent grade dimethylformamide was distilled at low pressure under nitrogen and kept over 4Å molecular sieves. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were obtained with Varian L-200 and Bruker AC-300 instruments. I.R. spectra were recorded with a Perkin-Elmer 681 spectrophotometer and mass spectra with a VG 7070 E 9 spectrometer. Melting points were obtained by using a Buchi 535 apparatus, the  $[\alpha]_D$  were obtained with a Perkin-Elmer 241 Polarimeter and the microanalyses for the new compounds were determined on a Perkin-Elmer 240 Elemental Analyzer. Flash-column chromatography was performed on silica gel Merck Kieselgel 60 (230-400 mesh ASTM). Thin-layer chromatography was carried out on silica gel plates (60 F254, Merk): zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol/ $\text{H}_2\text{SO}_4$  9:1, followed by heating at 100° C.

All reactions were carried out at 25° C in a dry nitrogen atmosphere, using glassware dried by flaming in a stream of dry nitrogen (if not otherwise stated).

### Synthesis of the ketal **2**.

2,2'-Dimethoxy propane (3.7 mmol, 0.45 ml) and *p*-toluenesulphonic acid monohydrate (0.003 g) were added to a suspension of the diol **1** (0.3 g, 1.85 mmol) in dry methylene chloride (6 ml). The reaction was monitored by thin-layer chromatography (silica gel, *n*-hexane/ethyl acetate 8/2). After 30 min at room temperature, IRA 900 ( $\text{OH}^-$  form) resins were added until neutral pH. The resins were filtered, washed with methylene chloride and the combined organic extracts were eluted over a column of IRA 900 resins (4.5 g). The solvent was evaporated under reduced pressure and afforded **2** (0.364 g, 1.8 mmol, 97.3 % yields).

**2**: colorless syrup;  $[\alpha]_D = +129.26$  ( $c = 0.3$ ; MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.4 (s, 3H), 1.5 (s, 3H), 4.9 (dd, 1H,  $J = 7.5$ ,  $J = 3.0$  Hz), 5.05 (d, 1H,  $J = 7.5$  Hz), 5.9 (dd, 1H,  $J = 10.5$ ,  $J = 3.0$  Hz), 6.45 (d, 1H,  $J = 10.5$  Hz), 7.10 (dd, 1H,  $J = 7.5$ ,  $J = 2.3$  Hz), 7.25 (ddd, 1H,  $J = 7.5$ ,  $J = 7.5$ ,  $J = 1.5$  Hz), 7.30 (ddd, 1H,

$J = 7.5$ ,  $J = 7.5$ ,  $J = 2.3$  Hz), 7.43 (dd, 1 H,  $J = 7.5$ ,  $J = 1.5$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 26.2 (q) 27.5 (q), 73.1 (d), 73.8 (d), 107.2 (s), 126.99 (d), 127.0 (d), 127.21 (d), 127.69 (s), 128.10 (d), 129.30 (d), 130.03 (d), 131.55 (s); MS,  $m/z$ : 202 ( $\text{M}^+$ ), 187 ( $\text{M}^+ - \text{CH}_3$ ), 145 ( $\text{M}^+ - \text{CH}_2\text{COCH}_3$ ), 144 ( $\text{M}^+ - \text{CH}_3\text{COCH}_3$ ).  
 Anal. Calcd. for  $\text{C}_{13}\text{H}_{14}\text{O}_2$ : C, 77.23 %; H, 6.93 %. Found: C, 77.26 %; H, 6.65 %.

### Synthesis of the epoxide 3.

m-Chloroperbenzoic acid (0.175 g, 1.17 mmol) was added to a solution of **2** (0.200 g, 1.12 mmol) in dry methylene chloride at  $0^\circ\text{C}$  (1.5 ml). The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 8/2). The reaction mixture was stirred at  $0^\circ\text{C}$  for 24 hr, diluted with methylene chloride (10 ml), washed with 10% sodium hydroxide, then water. The organic solvent was dried ( $\text{Na}_2\text{SO}_4$ ) and removed under reduced pressure to give the epoxide **3** (0.238 g, 1.093 mmol, 97.5 % yields).

Colorless syrup;  $[\alpha]_{\text{D}} = +143.05$  ( $c = 0.75$ ; MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ , 1.18 (s, 3H), 1.47 (s, 3H), 3.78 (dd, 1H,  $J = 4.3$ ,  $J = 2.3$  Hz), 3.95 (d, 1H,  $J = 4.3$  Hz), 4.85 (dd, 1H,  $J = 6.5$ ,  $J = 2.3$  Hz), 5.0 (d, 1H,  $J = 6.5$  Hz), 7.3-7.5 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 26.45 (q), 27.90 (q), 51.51 (d), 52.70 (d), 72.10 (d), 73.05 (d), 110.37 (s), 127.97 (d), 129.07 (d), 129.51 (d), 129.78 (d), 130.75 (s) 134.72 (s); MS,  $m/z$ : 218 ( $\text{M}^+$ ), 203 ( $\text{M}^+ - \text{CH}_3$ ), 161 ( $\text{M}^+ - \text{CH}_2\text{COCH}_3$ ).

Anal. Calcd. for  $\text{C}_{13}\text{H}_{14}\text{O}_3$ : C, 71.56 %; H, 6.42 %. Found: C, 71.92 %; H, 6.67 %.

### Reduction reactions of the epoxide 3.

*With sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al)* - To a solution of **3** (0.3 g, 1.38 mmol) in dry tetrahydrofuran (10 ml) was added dropwise a solution of Red-Al in toluene (3.5 M, 1.4 ml, 4.92 mmol). The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1) and stirred overnight. Diluted (1:1) HCl was slowly added till neutral pH, and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure to afford **5** as a chromatographically homogeneous solid (0.30 g, 1.364 mmol, 98.8 %).

**5**: Colorless needles (n-hexane/ethyl acetate); mp =  $90 - 92^\circ\text{C}$ ;  $[\alpha]_{\text{D}} = +50.23$  ( $c = 0.1$ , MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.48 (s, 3H), 1.50 (s, 3H), 2.2 (bs, 1H, disappears with  $\text{D}_2\text{O}$ ), 2.75 (dd, 1H,  $J = 15.6$ ,  $J = 9.5$  Hz), 3.05 (dd, 1H,  $J = 15.6$ ,  $J = 5.2$  Hz), 4.05 (ddd, 1H,  $J = 9.5$ ,  $J = 7.5$ ,  $J = 5.2$  Hz), 4.25 (dd, 1H,  $J = 7.5$ ,  $J = 7.5$  Hz), 5.25 (d, 1H,  $J = 7.5$  Hz), 7.10 (dd, 1H,  $J = 7.5$ ,  $J = 2.3$  Hz), 7.25 (ddd, 1H,  $J = 7.5$ ,  $J = 7.5$ ,  $J = 1.5$  Hz), 7.30 (ddd, 1H,  $J = 7.5$ ,  $J = 7.5$ ,  $J = 2.3$  Hz), 7.43 (dd, 1 H,  $J = 7.5$ ,  $J = 1.5$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 25.34 (q), 27.67 (q), 34.27 (t), 69.69 (d), 74.98 (d), 79.53 (d), 109.13 (s), 127.10 (d), 128.69 (d), 129.17 (d), 129.72 (d), 132.66 (s), 134.40 (s); MS,  $m/z$ : 220 ( $\text{M}^+$ ), 205 ( $\text{M}^+ - \text{CH}_3$ ), 163 (205-  $\text{CH}_2\text{CO}$ ), 145 (163-  $\text{H}_2\text{O}$ ); IR: 3620, 1520, 1470, 1420  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}\text{O}_3$ : C, 70.91 %; H, 7.27 %. Found: C, 70.85 %; H, 7.08 %.

*With diisobutyl aluminum hydride (DIBAH)* - To a solution of **3** (0.112 g, 0.51 mmol) in dry tetrahydrofuran (5.6 ml) was added dropwise at  $0^\circ\text{C}$  a solution of DIBAH (1.6 M, 1.12 ml, 2 mmol) in

tetrahydrofuran. The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). The reaction was diluted with ethyl acetate (10 ml), acidified with 3 N HCl (cautiously added dropwise until neutral pH), and extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure to afford **5** as a chromatographically homogeneous solid (0.094 g, 0.427 mmol, 83.7 % yield).

*With sodium cyanoborohydride* - To a stirred solution of **3** (0.198 g, 0.91 mmol) in dry tetrahydrofuran (4 ml) at 0°C were added few crystals of bromocresol green indicator, followed by sodium cyanoborohydride (0.170 g, 2.7 mmol). A solution of boron trifluoride etherate (0.5 ml) in dry tetrahydrofuran (2ml) was added dropwise until the blue color turned to yellow. The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). The reaction mixture was diluted with ethyl acetate (5 ml), and washed with brine. The aqueous phase was extracted three times with ethyl acetate (3 x 10 ml). The combined organic extracts were washed, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 8/2) to afford starting epoxide **3** (0.052 g, 0.24 mmol, 26.2 %) and compound **5** (0.121 g, 0.55 mmol, 60.4 % yield).

*With sodium borohydride* - Sodium borohydride (0.167 g, 4.42 mmol) was added to a solution of **3** (0.1 g, 0.5 mmol) in ethanol (1 ml) and water (1 ml). The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1:1). The reaction was diluted with ethyl acetate (10 ml), acidified with 1N HCl, and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure. The crude material was chromatographed (silica gel, n-hexane/ethyl acetate 1/1 followed by chloroform/methanol 9/1) to afford compound **5** (0.028 g, 0.13 mmol, 26%) and **6** (0.045 g, 0.25 mmol, 50 %).

**6**: colorless solid (n-hexane/ethyl acetate); mp = 88.2- 90.6°C;  $[\alpha]_{\text{D}} = -187.15$  (c = 0.3 ; MeOH);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ ):  $\delta$  . 3.10 (dd, 1H, J = 17.5, J = 8.8 Hz), 3.55 (dd, 1H, J = 17.5, J = 6.3 Hz), 4.38 (dd, 1H, J = 7.8, J = 3.8 Hz), 4.82 (ddd, 1H, J = 8.8, J = 7.8, J = 6.3 Hz), 5.38 (d, 1H, J = 3.8 Hz), 6.00 (bs, 3H, disappears with  $\text{D}_2\text{O}$ ), 7.15 ( dd, 1H, J = 8.0, J =2.0 Hz), 7.25 ( m, 2H), 7.8 (dd, 1H, J = 8.0, J = 1.5 Hz);  $^{13}\text{C}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ ): 37.5 (t), 68.33 (d), 70.86 (d), 75.10 (d), 126.68 (d), 128.09 (d), 129.33 (d), 130.27(d), 135.8 (s), 136.2 (s); MS, m/z: 180 ( $\text{M}^+$ ), 162 ( $\text{M}^+ - \text{H}_2\text{O}$ ), 144 ( $\text{M}^+ - 2\text{H}_2\text{O}$ ), 119 (162-  $\text{CH}_2\text{COH}$ ); IR ( $\text{CHCl}_3$ ): 3600  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_3$ : C, 66.67 %; H, 6.67 %. Found: C, 66.66 %; H, 6.73 %.

*With palladium on charcoal* - A solution of **3** (0.320 g, 1.46 mmol) in ethanol (20 ml) containing five drops of acetic acid was hydrogenated on 5 % Pd/C (0.300 g) at room temperature and atmospheric pressure. After the theoretical amount of hydrogen was consumed, the reaction mixture was filtered over a celite pad, which was washed several times with ethanol, and the solvent was removed under reduced pressure. The crude residue was flash-chromatographed (silica gel, chloroform/methanol 9/1) to give **4** (0.192 g, 1.17 mmol, 80%) and **5** (0.04 g, 0.18 mmol, 12.3 %).

**4**: Colorless solid n-hexane/ethyl acetate); mp = 158 -160 °C;  $[\alpha]_{\text{D}} = -98.86$  (c = 0.25; EtOH) [ lit.<sup>4a</sup>:  $[\alpha]_{\text{D}} = -99$ ; c=0.77; EtOH ];  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ ):  $\delta$ , 3.1 (ddd, 2H, J = 14.4, J = 8.6, J = 1.3 Hz), 3.5 (dd, 2H, J =

14.4,  $J = 5.7$  Hz), 4.3 (m, 2H), 6.7 (s, 2H, disappears with  $D_2O$ ), 7.15 (m, 4H);  $^{13}C$  NMR ( $C_5D_5N$ ): 2 x 37.32 (t), 2 x 72.62 (d), 2 x 127.36 (d), 2 x 130.05 (d), 2 x 135.55 (s); MS,  $m/z$ : 164 ( $M^+$ ), 146 ( $M^+ - H_2O$ ), 128 (146-  $H_2O$ ), 117 (146- CHO); IR ( $CHCl_3$ ): 3600, 3500-3350,  $cm^{-1}$ .  
 Anal. Calcd. for  $C_{10}H_{12}O_2$ : C, 73.17; H, 7.32. Found: C, 73.32; H, 7.57.

*With palladium hydroxide* - To a stirred solution of **3** (0.149 g, 0.68 mmol) in ethanol (3.6 ml) were added 1,4-cyclohexadiene (3 ml, 0.046 mmol) and 20 % palladium hydroxide (0.100 g). The reaction was refluxed for 24 hr, filtered over a celite pad and the solvent removed under reduced pressure. The crude material was chromatographed (silica gel, n-hexane/ethyl acetate 1/1, followed by chloroform/methanol 9/1) to afford **5** (0.114 g, 0.52 mmol, 76%) and **6** (0.020 g, 0.11 mmol, 16.33 %).

*With lithium/liquid ammonia* - A solution of the epoxide **3** (0.430 g, 1.97 mmol) in dry tetrahydrofuran (2 ml) was added to the deep blue solution of lithium (0.144 g, 20.6 mmol) in dry liquid ammonia (30 ml) at  $-40^\circ C$ . The reaction mixture was stirred at  $-40^\circ C$  for 15 min, then tert-butanol was added (1 ml). Stirring was continued for 2 hr, then the reaction was allowed to warm to room temperature. The mixture was cautiously treated with methanol to consume the excess of metal. Water was added (10 ml) and the aqueous phase was extracted three times with ethyl acetate (3 x 15 ml). The combined organic phases were dried ( $Na_2SO_4$ ), and the solvent removed under reduced pressure. The crude residue was flash-chromatographed (silica gel, n-hexane/ethyl acetate) to afford **4** (36 %).

#### *Catalytic Reduction of compound 5*

A solution of **5** (0.2 g, 0.91 mmol) in ethanol (15 ml) containing five drops of acetic acid was hydrogenated on 5 % Pd/C (0.180 g) as described above for compound **3**. The crude residue was flash-chromatographed to give **4** (0.114 g, 0.69 mmol, 77%) and **5** (0.026 g, 0.12 mmol, 13.3 %).

#### *Synthesis of the monocrotonate 7.*

To a solution of the diol **4** (0.330 g, 2.01 mmol) in dry methylene chloride (5.1 ml) and dry pyridine (0.5 ml) was added dropwise a solution of crotonic anhydride (0.39 ml, 2.67 mmol) and 4-dimethylamino pyridine (0.024 g) in dry methylene chloride. The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). The reaction was stirred at room temperature for 5 hr, diluted with ethyl acetate (10 ml) and washed with brine. The aqueous phase was extracted three times with ethyl acetate (3 x 10 ml). The combined organic phases were washed with water, dried ( $Na_2SO_4$ ), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 1/1) to afford monocrotonate **7** (0.360 g, 1.55 mmol, 77.1 %) and dicrotonate (0.063 g, 0.21 mmol, 10.4 %).

**7**: colorless amorphous solid;  $[\alpha]_D^{25}$ : -85.34 ( $c = 0.21$ ; MeOH);  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$ , 1.9 (dd, 1H,  $J = 7.9$ ,  $J = 1.0$  Hz), 2.5 (s, 1H, disappears with  $D_2O$ ), 3.22 (dd, 1H,  $J = 16.5$ ,  $J = 6.0$  Hz), 3.32 (dd, 1H,  $J = 16.5$ ,  $J = 6.0$  Hz), 2.85 (dd, 1H,  $J = 16.5$ ,  $J = 9.0$  Hz), 2.88 (dd, 1H,  $J = 16.5$ ,  $J = 9.0$  Hz), 4.1 (ddd, 1H,  $J = 9.0$ ,  $J = 9.0$ ,  $J = 6.0$ ), 5.07 (ddd, 1H,  $J = 9.0$ ,  $J = 9.0$ ,  $J = 6.0$  Hz), 5.9 (dd, 1H,  $J = 15.8$ ,  $J = 2.6$  Hz), 6.98 (dq, 1H,  $J = 15.8$ ,  $J = 7.9$ ,  $J = 7.9$ ,  $J = 7.9$  Hz), 7.7 (m, 4H);  $^{13}C$  NMR ( $CDCl_3$ ): 18.52 (q), 33.79 (t), 36.51 (t), 69.75

(d), 74.88 (d), 123.14 (d), 126.97 (d), 127.0 (d), 129.21 (d), 129.39(d), 133.69 (s), 134.06 (s), 146.12 (d), 167.20 (s). MS, m/z : 232 ( $M^+$ ), 215 ( $M^+ - OH$ ); IR ( $CHCl_3$ ) : 3620, 1720, 1660  $cm^{-1}$ .

Anal. Calcd. for  $C_{14}H_{16}O_3$ : C, 72.41 %; H, 6.90 %. Found: C, 72.76 %; H, 6.92 %.

**Dicrotonate:** colorless amorphous solid;  $[\alpha]_D = -70.58$  ( $c = 0.2$ , MeOH);  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$ , 1.83 (dd, 6H,  $J = 2.6$ ,  $J = 7.9$  Hz), 2.95 (m, 2H), 3.2 (dd, 2H,  $J = 18.4$ ,  $J = 5.4$  Hz), 5.33 (dd, 2H,  $J = 5.4$ , 2.8 Hz), 5.83 (dd, 2H,  $J = 2.6$ ,  $J = 15.8$  Hz), 6.95 (dq, 2H,  $J = 15.8$ ,  $J = 7.9$ ,  $J = 7.9$ ,  $J = 7.9$  Hz), 7.0 - 7.2 (m, 4H); MS, m/z : 300 ( $M^+$ ), 231 ( $M^+ - COCHCHCH_3$ ); IR ( $CHCl_3$ ): 1720, 1660  $cm^{-1}$ .

Anal. Calcd. for  $C_{18}H_{20}O_4$ : C, 72.00 %; H, 6.67 %. Found: C, 71.91 %; H, 6.83 %.

#### Conjugate addition of $Bu_2CuLi$ to the monocrotonate 7.

To a suspension of  $CuBr \cdot x(CH_3)_2S$  (0.177 g, 0.86 mmol) in dry ethyl ether (1 ml) was added, at  $0^\circ C$ , dimethyl sulfide (1 ml). To the obtained yellow solution, butyllithium in n-hexane (1.6 M in n-hexane, 1.12 ml, 1.8 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. The monocrotonate 7 (0.100 g, 0.43 mmol) in ethyl ether (1 ml) was added at  $-30^\circ C$  and the reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). After being stirred for 3 hr, the reaction mixture was diluted with ethyl acetate (5 ml), and washed with a saturated  $NH_4Cl$  solution. When all the solid dissolved and the aqueous layer turned deep blue, the two phases were separated and the aqueous phase was extracted three times with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine, dried ( $Na_2SO_4$ ), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 7/3) to give the 1,4-adduct 8 as a 93/7 mixture of diastereoisomers (0.108 g, 0.37 mmol, 92%).

**8:** colorless oil;  $^1H$ -NMR (major diastereoisomer) :  $\delta$ , 0.9 (t, 3H,  $J = 6.8$ ,  $J = 6.8$ ,  $J = 6.8$  Hz), 0.95 (d, 3H,  $J = 7.9$  Hz), 1.35 (m, 6H), 1.97 (ddq, 1H,  $J = 7.9$ ,  $J = 7.9$ ,  $J = 7.9$ ,  $J = 7.5$ ,  $J = 6.0$  Hz), 2.18 and 2.38 (ABX system, 2H,  $J_{AB} = 15.0$ ,  $J_{AX} = 7.5$ ,  $J_{BX} = 6.0$  Hz), 2.15 (s, 1H, disappears with  $D_2O$ ), 2.82 (dd, 1H,  $J = 16.5$ ,  $J = 7.5$  Hz), 2.85 (dd, 1H,  $J = 16.5$ ,  $J = 9.0$  Hz), 3.20 (dd, 1H,  $J = 16.5$ ,  $J = 6.0$  Hz), 3.28 (dd, 1H,  $J = 16.5$ ,  $J = 6.0$  Hz), 4.05 (ddd, 1H,  $J = 9.0$ ,  $J = 6.0$ ,  $J = 6.0$  Hz), 5.20 (ddd, 1H,  $J = 7.5$ ,  $J = 6.0$ ,  $J = 6.0$  Hz), 7.1 (m, 4H);  $^{13}C$  NMR : 14.61 (q), 20.34 (q), 23.41 (t), 29.74 (t), 31.11 (d), 33.99 (t), 36.79 (t), 37.05 (t), 42.69 (t), 70.21 (d), 75.19 (d), 129.28 (d), 129.32 (d), 129.35 (d), 129.48 (d), 133.76 (s), 134.10 (s), 174.13 (s); MS, m/z : 290 ( $M^+$ ), 273 ( $M^+ - H_2O$ ); IR ( $CHCl_3$ ) : 3600, 1730, 1520  $cm^{-1}$ .

Anal. calcd. for  $C_{18}H_{26}O_3$ : C, 74.48 %; H, 8.96 %. Found: C, 74.24 %; H, 8.58 %.

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