

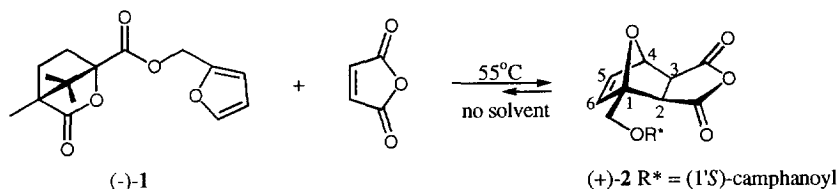
## Synthesis of Enantiomerically Pure 7-Oxabicyclo[2.2.1]hept-2-enes Precursors in the Preparation of Taxol Analogues.

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**Abstract:** (*S*)-Camphanate of furfuryl alcohol undergoes Diels-Alder addition in molten maleic anhydride giving one major crystalline adduct (+)-**2** ((1*S*,1*S'*,2*R*,3*S*,4*R*)-1-[(camphanoyloxy)methyl]-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboxylic anhydride), the absolute configuration of which was established through chemical correlation. Adduct (+)-**2** was converted into an enantiomerically pure intermediate as in Yadav's approach to the synthesis of taxol analogues. Copyright © 1996 Elsevier Science Ltd

Yadav et al.<sup>1</sup> have shown recently that the Diels-Alder adduct of furfuryl alcohol to maleic anhydride can be converted into racemic precursors of taxol analogues. The 7-oxanorbomane ring is proposed to become the C-ring, the 1-hydroxymethyl substituent the D-ring, and the carboxylic moieties at C(2) and C(3) can be used to attach an A-ring of taxoid precursors. In the preceding paper<sup>2</sup> we showed that homochiral furfural acetals can be equilibrated in molten maleic anhydride with one major Diels-Alder adduct that crystallizes, leading to a variety of enantiomerically pure 7-oxabicyclo[2.2.1]hept-2-ene derivatives in a very simple way.<sup>3</sup> We report here that (*S*)-camphanate of furfuryl alcohol also generates an enantiomerically pure Diels-Alder adduct with molten maleic anhydride, thus making Yadav's method amenable to enantiomerically pure taxoids.



Esterification of furfuryl alcohol with (-)-(*S*)-camphanoyl chloride (pyr., 20°C) afforded (-)-**1** in 80% yield. Heating (-)-**1** with an excess of molten maleic anhydride (55°C, 3 days) led to the Diels-Alder adduct (+)-**2** which was isolated pure in 68% yield after recrystallization. In order to establish its configuration we initially anticipated being able to rely on circular dichroism. The CD-spectrum of (+)-**2** (Figure 1) showed a negative Cotton Effect for its olefinic chromophore, suggesting a dipole/dipole coupling<sup>4</sup> with the ester chromophore of the camphanate leading to negative helicity for the two dipoles, as shown in Figure 2A. Alternatively, substitution of the bridgehead centre C(1) increases the polarisability of bond C(1)-C(2) which interacts with the olefinic  $\pi$  electrons, generating a possible axial allylic effect<sup>5</sup> which is also expected to contribute to the negative Cotton Effect observed for (+)-**2** (Figure 2B).

With the aim of confirming the above configurational assignment we converted (+)-**2** into a dichromophoric derivative which, hopefully, would show a chiron exciton coupled CD spectrum allowing a less

ambiguous determination of the absolute configuration. Adduct (+)-2 was hydrogenated ( $H_2/Pd-C$ ) to give (-)-3. Treatment of (-)-3 with aniline afforded the corresponding imide (-)-4.

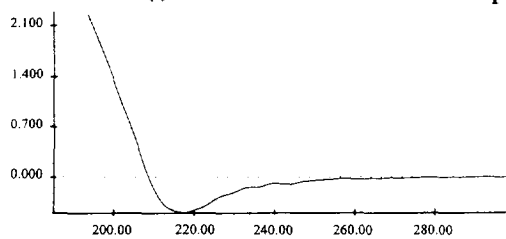


Figure 1. CD spectrum of (+)-2 in  $CH_3CN$

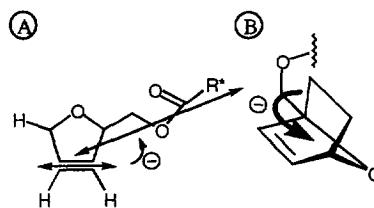


Figure 2. Possible interpretation of the negative CD effect of the olefinic chromophore of (+)-2

The CD spectrum of (-)-4 (Figure 3) displayed a double Cotton Effect, the one at the lowest energy transition ( $\lambda$ : 228 nm) being positive. Since molecular models did not allow one to decide whether the two main electric transition moments of the two aromatic chromophores constitute an exciton with right or left helicity, we decided to convert adduct (-)-2 into a derivative of known absolute configuration.

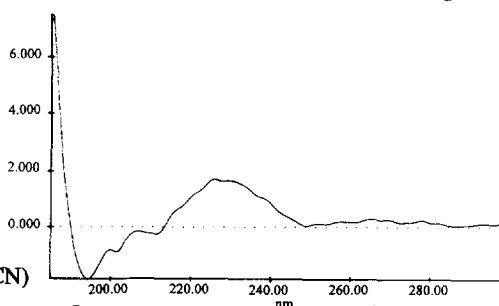
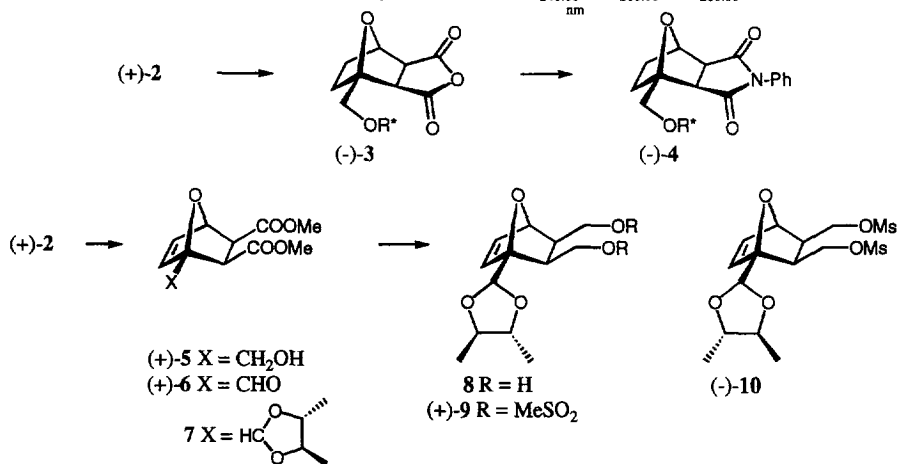
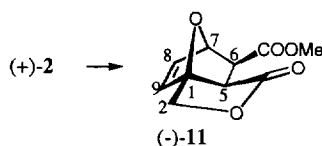


Figure 3. CD spectrum of (-)-4 ( $CH_3CN$ )



Saponification of (+)-2 ( $KOH/THF/H_2O$ ), followed by acidification and treatment with diazomethane provided the dimethyl ester (+)-5. The chiral auxiliary ((1*S*)-camphanic acid) was recovered at this stage. Oxidation of the alcoholic moiety of (+)-5 with Dess-Martin periodinane<sup>6</sup> afforded aldehyde (+)-6, the acetalization of which with (+)-(2*R*,3*R*)-butane-2,3-diol gave a mixture containing acetal 7 and products resulting from the transalcoholyses of the dimethyl diesters. Reduction of this mixture with  $LiAlH_4$  in THF furnished diol

**8** which was esterified<sup>5</sup> with  $\text{CH}_3\text{SO}_2\text{Cl}$ /pyridine to generate the crystalline dimesylate (+)-**9** ( $[\alpha]_{\text{D}}^{25} = +1.2$ ), a diastereomer (by 400 MHz  $^1\text{H-NMR}$ ) of the known<sup>2</sup> dimesylate (-)-**10** ( $[\alpha]_{\text{D}}^{25} = -20.2$ ). When the same reaction sequence was repeated with (-)-(2*S*,3*S*)-butane-2,3-diol, the dimesylate (-)-**10** was obtained,<sup>2</sup> thus establishing unambiguously the absolute configuration of (+)-**2** and of the derivatives described in this report.



A very simple and efficient method has been found to prepare enantiomerically pure 7-oxabicyclo[2.2.1]hept-2-ene derivatives through the Diels-Alder addition of maleic anhydride to homochiral furfuryl esters. Since the chiral auxiliaries (1*S*)- and (1*R*)-camphanic acid are both commercially available, the two enantiomeric forms of the 7-oxabicyclo[2.2.1]heptane systems can be obtained with the same ease. Saponification of (+)-**2** (KOH/THF/ $\text{H}_2\text{O}$ ) followed by treatment with 2 N HCl and with MeOH/DCC afforded the enantiomerically pure (e.e.  $\geq 98\%$ , diastereomeric purity of adduct (+)-**2** evaluated by 400 MHz  $^1\text{H-NMR}$  ( $^{13}\text{C}$  satellites)) lactone (-)-**11**, the intermediate used by Yadav and co-workers<sup>1</sup> in their synthesis of taxol analogues.

## Experimental Part

General remarks, see ref. 2.

(-)-Furfuryl (1*S*)-camphanate ((-)-**1**). (-)-Camphanoyl chloride (Fluka, e.e.  $>99\%$ , 2.35 g, 10.84 mmol) was dissolved in dry pyridine (25 ml); furfuryl alcohol was added (1.2 ml, 13.82 mmol). The mixture was stirred overnight at  $20^\circ\text{C}$  under Ar and was then poured into ether (400 ml), washed with 1N aq. HCl (200 ml, twice) and then with sat. aq.  $\text{NaHCO}_3$  (200 ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and the solvent was evaporated. Recrystallization from AcOEt/light petroleum yielded 2.43 g (80%), colourless crystals, m.p.  $68\text{--}69^\circ\text{C}$ .  $[\alpha]_{589}^{25} = -21$ ,  $[\alpha]_{577}^{25} = -22$ ,  $[\alpha]_{546}^{25} = -25$ ,  $[\alpha]_{435}^{25} = -45$ ,  $[\alpha]_{405}^{25} = -55$  ( $c = 1.1$ ,  $\text{CHCl}_3$ ). UV ( $\text{CH}_3\text{CN}$ ):  $\lambda_{\text{max}}$ : 224 nm ( $\epsilon = 3600$ ). IR (KBr)  $\nu$ : 2960, 2920, 1780, 1720, 1375, 1330, 1310, 1265, 1160, 1150, 1090, 1055, 1015, 920,  $750\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.43 (*dd*,  $^3J = 1.8$ ,  $^4J < 1$ , H-C(5)); 6.45 (*dd*,  $^3J = 3.0$ ,  $^4J < 1$ , H-C(3)); 6.36 (*dd*,  $^3J = 3.0$ ,  $1.8$ , H-C(4)); 5.26, 5.17 (*2d*, *AB*,  $^2J = 13.0$ ,  $\text{H}_2\text{C-C}(2)$ ); 2.43 (*ddd*,  $^2J = 13.5$ ,  $^3J = 10.5$ , 4.2), 2.03 (*ddd*,  $^2J = 13.5$ ,  $^3J = 9.1$ , 4.5), 1.93 (*ddd*,  $^2J = 13.0$ ,  $^3J = 10.5$ , 4.5), 1.67 (*ddd*,  $^2J = 13.0$ ,  $^3J = 9.1$ , 4.2),  $\text{H}_2\text{-C}(5')$ ,  $\text{H}_2\text{-C}(6')$ ; 1.10 (*s*,  $\text{CH}_3$ ); 1.00 (*s*,  $\text{CH}_3$ ); 0.88 (*s*, Me).  $^{13}\text{C-NMR}$  (100.61 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 177.9, 167.1 (2*s*); 148.6 (*s*, C(2)); 143.4 (*d*,  $^1J(\text{C,H}) = 202$ , C(5)); 111.3, 110.6 (2*d*,  $^1J(\text{C,H}) = 175$ , 176, C(3), C(4)); 90.9 (*s*, C(1')); 58.7 (*t*,  $^1J(\text{C,H}) = 150$ ,  $\text{H}_2\text{C-C}(2)$ ); 57.4, 54.7 (2*s*, C(4'), C(7')); 30.4, 28.9 (2*t*,  $^1J(\text{C,H}) = 138$ , 136, C(5'), C(6')); 16.6, 16.5, 9.6 (3*q*,  $^1J(\text{C,H}) = 127$ , 3 Me). CI-MS ( $\text{NH}_3$ ) *m/z*: 279 (5), 278 (25, *M*<sup>+</sup>), 183 (5), 182 (37), 165 (3), 164 (32), 137 (11), 136 (39), 111 (16), 109 (10), 83 (11), 81 (100). Anal. calc. for  $\text{C}_{15}\text{H}_{18}\text{O}_5$  (278.30): C 64.74, H 6.52; found: C 64.80, H 6.48.

(1*S*,1'*S*,2*R*,3*S*,4*R*)-1-[(Camphanoyloxy)methyl]-7-oxabicyclo[2.2.1]hept-5-ene-2-exo,3-exo-dicarboxylic anhydride ((+)-**2**). Ester (-)-**1** (1 g, 3.5 mmol) was mixed with maleic anhydride (1.06 g, 21.6 mmol) and heated to  $55^\circ\text{C}$ , under Ar, with shaking. After one day, more maleic anhydride was added (1.06 g, 21.6 mmol) and the mixture was allowed to react at  $55^\circ\text{C}$  for 3 more days. It was then poured into  $\text{CH}_2\text{Cl}_2$  (100 ml), filtered through activated charcoal, evaporated and recrystallized (AcOEt/light petroleum) yielding 921 mg (68%), colourless crystals, m.p.  $120.5\text{--}122^\circ\text{C}$ .  $[\alpha]_{589}^{25} = 14$ ,  $[\alpha]_{577}^{25} = 13$ ,  $[\alpha]_{546}^{25} = 15$ ,  $[\alpha]_{435}^{25} = 28$ ,  $[\alpha]_{405}^{25} = 34$  ( $c = 0.65$ ,  $\text{CHCl}_3$ ). CD ( $\text{CH}_3\text{CN}$ ):  $\Delta\epsilon_{217} = -1.5$ ;  $\Delta\epsilon_{209} = 0$  ( $c = 0.09\text{ mg/ml}$ ). IR (KBr)  $\nu$ : 2915, 1785, 1450, 1400, 1315, 1235, 1170, 1065, 1020, 925, 865, 740, 685, 650,  $580\text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ :

6.65 (*dd*,  $^3J = 5.8, 1.8$ , H-C(5)); 6.55 (*d*,  $^3J = 5.8$ , H-C(6)); 5.46 (*d*,  $^3J = 1.8$ , H-C(4)); 4.98, 4.70 (*2d*, *AB*,  $^2J = 12.5$ , H<sub>2</sub>C-C(1)); 3.38, 3.30 (*2d*,  $^3J = 6.9, 6.9$ , H-C(2), H-C(3)); 2.43 (*ddd*,  $^2J = 13.4$ ,  $^3J = 10.7, 4.5$ ), 2.08 (*ddd*,  $^2J = 13.4$ ,  $^3J = 9.2, 4.5$ ), 1.92 (*ddd*,  $^2J = 13.2$ ,  $^3J = 10.7, 4.5$ ), 1.69 (*ddd*,  $^2J = 13.2$ ,  $^3J = 9.2, 4.5$ ), H<sub>2</sub>-C(5'), H<sub>2</sub>-C(6'); 1.13, 1.08, 1.01 (*3s*, 3 Me). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 178.1, 169.2, 167.9, 166.8 (4*s*); 138.1, 137.3 (*2d*,  $^1J(\text{C,H}) = 180, 181$ , C(5), C(6)); 91.0, 90.1 (*2s*, C(1), C(1')); 82.3 (*d*,  $^1J(\text{C,H}) = 172$ , C(4)); 61.5 (*t*,  $^1J(\text{C,H}) = 151$ , CH<sub>2</sub>-C(1)); 54.9, 54.4 (*2s*, C(4'), C(7')); 51.2, 49.7 (*2d*,  $^1J(\text{C,H}) = 158, 158$ , C(2), C(3)); 30.7, 28.8 (*2t*,  $^1J(\text{C,H}) = 136, 137$ , C(5'), C(6')); 16.7, 16.6, 9.7 (*3q*,  $^1J(\text{C,H}) = 126, 3$  Me). CI-MS (NH<sub>3</sub>) *m/z*: 297 (22), 296 (73), 279 (8), 182 (6), 164 (4), 136 (8), 98 (17), 83 (8), 82 (7), 81 (100). Anal. calc. for C<sub>19</sub>H<sub>20</sub>O<sub>8</sub>(376.36): C 60.64, H 5.36; found: C 60.54, H 5.40.

(1*S*,1'*S*,2*R*,3*S*,4*R*)-1-[(Camphanoyloxy)methyl]-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dicarboxylic anhydride ((-)-3). Anhydride (+)-2 (2 g, 10.196 mmol) was dissolved in EtOAc (80 ml). After degassing, 5% palladium on activated charcoal (catalytic amount) was added. The mixture was stirred under an atmosphere of H<sub>2</sub>, at 20°C for 2.5 h. The solution was filtered through a *Celite* pad and the solvent was evaporated. Recrystallization from acetone/light petroleum yielded 1.6 g (80%), colourless crystals, m.p. 57-59°C. [α]<sub>589</sub><sup>25</sup> = -19, [α]<sub>577</sub><sup>25</sup> = -21, [α]<sub>546</sub><sup>25</sup> = -24, [α]<sub>435</sub><sup>25</sup> = -44, [α]<sub>405</sub><sup>25</sup> = -54 (*c* = 0.5, CHCl<sub>3</sub>). UV (CH<sub>3</sub>CN): final absorption: ε<sub>220</sub> = 1000. IR (KBr) *v*: 2965, 1845, 1770, 1475, 1445, 1400, 1325, 1310, 1275, 1235, 1175, 1095, 1065, 1020, 985, 940, 915 cm<sup>-1</sup>. <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 5.38 (*d*,  $^3J = 5.0$ , H-C(4)); 4.98, 4.84 (*2d*, *AB*,  $^2J = 12.0$ , H<sub>2</sub>C-C(1)); 3.20, 3.16 (*2d*,  $^3J = 7.2, 7.2$ , H-C(2), H-C(3)); 2.70 (*ddd*,  $^2J = 13.5$ ,  $^3J = 10.5, 4.2$ ), 2.36-1.88 (*m*), H<sub>2</sub>-C(5), H<sub>2</sub>-C(6), H<sub>2</sub>-C(5'), H<sub>2</sub>-C(6'); 1.35, 1.30, 1.22 (*s*, 3 Me). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 178.3, 170.9, 169.1, 166.8 (4*s*); 91.0, 86.7 (*2s*, C(1), C(1')); 80.4 (*d*,  $^1J(\text{C,H}) = 166$ , C(4)); 63.1 (*t*,  $^1J(\text{C,H}) = 150$ , H<sub>2</sub>C-C(1)); 54.8, 54.4 (*s*, C(4'), C(7')); 51.6, 51.5 (*2d*,  $^1J(\text{C,H}) = 146$ , C(2), C(3)); 31.3, 30.7, 29.3, 28.8 (4*t*,  $^1J(\text{C,H}) = 135, 136, 136, 136$ , C(5), C(6), C(5'), C(6')); 16.6, 16.5, 9.6 (*3q*, 3 Me). CI-MS (NH<sub>3</sub>) *m/z*: 259 (34), 258 (48), 217 (30), 216 (96), 173 (29), 150 (85), 120 (26), 115 (20), 104 (57), 101 (100), 92 (26), 76 (30). Anal. calc. for C<sub>19</sub>H<sub>22</sub>O<sub>8</sub> (378.38): C 60.30, H 5.86; found: C 60.22, H 5.83.

(1*S*,1'*S*,2*R*,3*S*,4*R*)-1-[(Camphanoyloxy)methyl]-*N*-phenyl-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dicarboximide ((-)-4). Anhydride (-)-3 (500 mg, 2.5 mmol) was dissolved in aniline (5 g, 54.8 mmol) and was stirred at 20°C for 1 h. The reaction mixture was poured into toluene (50 ml) and Et<sub>3</sub>N (300 μl) was added. The solution was heated under reflux for 1.5 h. (*Dean-Stark* apparatus). The solvent was evaporated and the residue purified by flash chromatography (light petroleum/AcOEt 2:1) yielding 590 mg (98%), colourless crystals m.p. 200-201°C. [α]<sub>589</sub><sup>25</sup> = -20, [α]<sub>577</sub><sup>25</sup> = -27, [α]<sub>546</sub><sup>25</sup> = -30, [α]<sub>435</sub><sup>25</sup> = -54, [α]<sub>405</sub><sup>25</sup> = -63 (*c* = 0.5, CHCl<sub>3</sub>). CD (CH<sub>3</sub>CN): Δε<sub>226</sub> = 0.5; Δε<sub>213</sub> = 0; Δε<sub>212</sub> = -0.1; Δε<sub>202</sub> = -0.3; Δε<sub>195</sub> = -0.6 (*c* = 0.08 mg/ml). UV (CH<sub>3</sub>CN): λ<sub>max</sub>: 203 nm (*ε* = 4500). IR (KBr) *v*: 2965, 1790, 1750, 1705, 1495, 1395, 1310, 1275, 1205, 1105, 1065, 980, 755, 695 cm<sup>-1</sup>. <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.51-7.36 (*m*); 7.29-7.25 (*m*); 5.03 (*d*,  $^3J = 5.0$ , H-C(4)); 4.77, 4.68 (*2d*, *AB*,  $^2J = 12.0$ , H<sub>2</sub>C-C(1)); 3.20, 3.16 (*2d*,  $^3J = 7.2, 7.2$ , H-C(2), H-C(3)); 2.45 (*ddd*,  $^2J = 13.3$ ,  $^3J = 10.5, 4.2$ ), 2.07-1.80 (*m*), 1.66 (*ddd*,  $^2J = 13.3$ ,  $^3J = 10.0, 4.0$ ), H<sub>2</sub>-C(5), H<sub>2</sub>-C(6), H<sub>2</sub>-C(5'), H<sub>2</sub>-C(6'); 1.11, 1.05, 1.01 (*3s*, 3 Me). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 178.2, 175.8, 174.0, 166.9, 131.5 (5*s*); 129.5 (*d*,  $^1J(\text{C,H}) = 161$ , C(arom)); 128.8 (*d*,  $^1J(\text{C,H}) = 162$ , C(arom)); 126.5 (*d*,  $^1J(\text{C,H}) = 163$ , C(arom)); 90.9, 85.9 (*s*, C(1), C(1')); 79.9 (*d*,  $^1J(\text{C,H}) = 164$ , C(4)); 63.6 (*t*,  $^1J(\text{C,H}) = 150$ , H<sub>2</sub>C-C(1)); 54.8, 54.3 (*2s*, C(4'), C(7')); 50.8 (*2d*,  $^1J(\text{C,H}) = 143$ , C(2), C(3)); 31.8, 30.7, 29.6, 28.8 (4*t*,  $^1J(\text{C,H}) = 135, 136, 134, 137$ , C(5), C(6), C(5'), C(6')); 16.6, 12.9, 9.7 (*3q*,  $^1J(\text{C,H}) = 126, 3$  Me). CI-MS (NH<sub>3</sub>) *m/z*: 454 (39, [M<sup>+</sup>+1]), 453 (100, M<sup>+</sup>),

445 (6), 410 (6), 406 (7), 323 (16), 322 (11), 274 (43), 264 (12), 256 (29), 255 (42), 237 (13), 207 (36), 136 (39), 119 (43), 109 (75), 108 (53), 95 (49), 83 (75), 77 (61). Anal. calc. for C<sub>25</sub>H<sub>27</sub>O<sub>7</sub>N (453.49): C 66.21, H 6.00; found: C 66.21, H 5.85.

*(1S,2R,3S,4R)*-Dimethyl 1-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-exo,3-exo-dicarboxylate ((+)-**5**). (+)-**2** (115 mg, 0.586 mmol) was dissolved in THF/H<sub>2</sub>O 2:1 (3 ml) and aq. KOH (3N, 1.5 ml) was added. The solution was stirred for 2 h. It was then acidified to pH 2 (aq. HCl, 1N) and the solvents were evaporated. The residue was taken up in anh. MeOH (20 ml) and CH<sub>2</sub>N<sub>2</sub> was added dropwise till the yellow colour persisted. AcOH (0.5 ml) was added and the solvent was evaporated. The residue was purified by chromatography (AcOEt/light petroleum 1:1) yielding 99 mg (77%), colourless oil. [ $\alpha$ ]<sub>589</sub><sup>25</sup> = 356, [ $\alpha$ ]<sub>577</sub><sup>25</sup> = 373, [ $\alpha$ ]<sub>546</sub><sup>25</sup> = 416, [ $\alpha$ ]<sub>435</sub><sup>25</sup> = 713, [ $\alpha$ ]<sub>405</sub><sup>25</sup> = 860 (*c* = 1.3, CHCl<sub>3</sub>). UV (CH<sub>3</sub>CN): final absorption  $\epsilon_{220}$  = 750. IR (KBr)  $\nu$ : 3495, 3000, 2950, 2850, 1740, 1730, 1435, 1360, 1260, 1220, 1200, 1165, 1035, 965, 735 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 6.50 (*dd*, <sup>3</sup>*J* = 5.7, 1.5, H-C(5)); 6.43 (*d*, <sup>3</sup>*J* = 5.7, H-C(6)); 5.42 (*d*, <sup>3</sup>*J* = 1.5, H-C(4)); 4.05, 4.03 (*2d*, *AB*, <sup>2</sup>*J* = 12.5, H<sub>2</sub>C-C(1)); 3.69, 3.69 (*2s*, 2 COOMe); 2.99, 2.85 (*2d*, <sup>3</sup>*J* = 8.9, 8.9, H-C(2), H-C(3)). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 171.6, 171.2 (*2s*); 137.4, 137.3 (*2d*, <sup>1</sup>*J*(C,H) = 176, 175, C(5), C(6)); 91.7 (*s*, C(1)); 79.6 (*d*, <sup>1</sup>*J*(C,H) = 169.1, C(4)); 60.6 (*t*, <sup>1</sup>*J*(C,H) = 144, H<sub>2</sub>C-C(1)); 52.1 (*q*, <sup>1</sup>*J*(C,H) = 147, Me); 49.5, 47.8 (*2d*, <sup>1</sup>*J*(C,H) = 134.1, 141.3, C(2), C(3)). CI-MS (NH<sub>3</sub>) *m/z*: 260 (1), 243 (1.0, [M<sup>+</sup>+1]), 192 (21), 165 (19), 146 (23), 145 (100), 121 (17), 113 (88), 98 (97), 97 (23), 81 (61).

*(1S,2R,3S,4R)*-Dimethyl 1-formyl-7-oxabicyclo[2.2.1]hept-5-ene-2-exo,3-exo-dicarboxylate ((+)-**6**). (-)-**5** (100 mg, 0.413 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4 ml) and Dess-Martin periodinane (1 g) was added. The solution was stirred overnight, was then filtered through *Celite* and was purified by chromatography on silica gel (AcOEt/light petroleum 1:1) yielding 90 mg (90%), colourless oil. [ $\alpha$ ]<sub>589</sub><sup>25</sup> = 17, [ $\alpha$ ]<sub>577</sub><sup>25</sup> = 23, [ $\alpha$ ]<sub>546</sub><sup>25</sup> = 6, [ $\alpha$ ]<sub>435</sub><sup>25</sup> = 10, [ $\alpha$ ]<sub>405</sub><sup>25</sup> = 6 (*c* = 0.52, CHCl<sub>3</sub>). UV (CH<sub>3</sub>CN): final absorption:  $\epsilon_{220}$  = 750. IR (KBr)  $\nu$ : 3470, 2955, 1730, 1435, 1335, 1220, 1035, 960, 815, 735. <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 10.12 (*s*, H-C=O); 6.57 (*dd*, <sup>3</sup>*J* = 5.9, 1.5, H-C(5)); 6.44 (*d*, <sup>3</sup>*J* = 5.9, H-C(6)); 4.76 (*d*, <sup>3</sup>*J* = 1.5, H-C(4)); 3.62, 3.69 (*2s*, COOMe); 3.23, 2.99 (*2d*, <sup>3</sup>*J* = 8.9, 8.9, H-C(2), H-C(3)). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 198.5 (*d*, <sup>1</sup>*J*(C,H) = 188.5, aldehyde); 171.0, 170.9 (*2s*); 137.2, 136.6 (*2d*, <sup>1</sup>*J*(C,H) = 179, 182, C(5), C(6)); 92.7 (*s*, C(1)); 81.0 (*d*, <sup>1</sup>*J*(C,H) = 179, C(4)); 52.6 (*q*, <sup>1</sup>*J*(C,H) = 148, Me); 49.7, 48.5 (*2d*, <sup>1</sup>*J*(C,H) = 141, 141, C(2), C(3)). CI-MS (NH<sub>3</sub>) *m/z*: 256 (0.1, [M<sup>+</sup>+NH<sub>3</sub>]), 210 (0.6), 166 (0.4), 134 (3), 124 (7), 114 (78), 113 (17), 97 (15), 81 (100).

*(1S,2R,3S,4R,4'S,5'S)*-1-(4',5'-Dimethyldioxolan-2'-yl)-7-oxabicyclo[2.2.1]hept-5-ene-2-exo,3-exo-dimethyl dimesylate ((-)-**10**). (+)-**6** (20 mg, 0.083 mmol) was dissolved in CHCl<sub>3</sub> (2 ml). After the addition of anh. MgSO<sub>4</sub> (50 mg), Dowex 50Wx8 resin (50-100 mg) and of (-)-(2*S*,3*S*)-butane-2,3-diol (38  $\mu$ l, 0.42 mmol), the mixture was heated under reflux for 2 h. After cooling to 20°C and filtration the solvent was evaporated and the residue taken up in THF (1 ml). This solution of acetal **7** was added dropwise to a stirred solution of LiAlH<sub>4</sub> (14 mg, 0.4 mmol) in anh. THF (1 ml) cooled to 0°C. After stirring at 0°C for 3 h, the mixture was stirred at 20°C for 14 h. After cooling to 0°C triethanolamine (20  $\mu$ l, 0.2 mmol) was added and the mixture was stirred at 0°C for 30 min. After filtration the solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (2 g, AcOEt), yielding 12 mg (60%) of diol **8**, which was dissolved in anh. pyridine (0.5 ml). After cooling to -15°C, CH<sub>3</sub>SO<sub>2</sub>Cl (0.1 ml) was added and the mixture was stirred at

0°C for 3 h. The mixture was poured into ice-cold H<sub>2</sub>O (20 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml, 4 times). The combined extracts were dried (MgSO<sub>4</sub>) and the solvent was evaporated. After recrystallization from MeOH, 10 mg (30%) of (-)-**10** was obtained, m.p. 103-105°C, [ $\alpha$ ]<sub>589</sub><sup>25</sup> = -20 (c = 0.2, MeOH).<sup>2</sup>

*Methyl (1S,5R,6S,7R)-4-oxo-3,10-dioxatricyclo[5.2.1.0<sup>1,5</sup>]dec-8-ene-6-exo-carboxylate* ((-)-**11**). (-)-**2** (200 mg, 1.02 mmol) was dissolved in THF/H<sub>2</sub>O 2:1 (5 ml) and aq. KOH (3N, 1 ml) was added. The mixture was stirred for 3 h. It was then acidified to pH 2 (aq. HCl 1N) and the solvent was evaporated. The residue was dissolved in anh. MeOH and DCC (231 mg, 1.122 mmol) was added. The solution was stirred overnight and then filtered through a *Celite* pad. The solvent was evaporated, the residue taken up in CHCl<sub>3</sub> (50 ml), washed with water (25 ml, 5 times) dried (MgSO<sub>4</sub>) and evaporated. The residue was purified by chromatography on silica gel (AcOEt/light petroleum 1:1) yielding 150 mg (70%), colourless crystals, m.p. 109-111°C. [ $\alpha$ ]<sub>589</sub><sup>25</sup> = -145, [ $\alpha$ ]<sub>577</sub><sup>25</sup> = -128, [ $\alpha$ ]<sub>546</sub><sup>25</sup> = -156, [ $\alpha$ ]<sub>435</sub><sup>25</sup> = -329, [ $\alpha$ ]<sub>405</sub><sup>25</sup> = -428 (c = 0.61, CHCl<sub>3</sub>). UV (CH<sub>3</sub>CN): final absorption:  $\epsilon_{220}$  = 800. IR (KBr)  $\nu$ : 3325, 2930, 1790, 1725, 1625, 1435, 1365, 1230, 1015, 965 cm<sup>-1</sup>. <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub>: 6.55 (d, <sup>3</sup>J = 5.5, H-C(9)); 6.49 (dd, <sup>3</sup>J = 5.5, 1.8, H-C(8)); 5.25 (d, <sup>3</sup>J = 1.8, H-C(7)); 4.77, 4.71 (2d, AB, <sup>2</sup>J = 11.1, H<sub>2</sub>-C(2)); 3.78 (s, COOMe); 2.91, 2.82 (2d, <sup>3</sup>J = 9.2, 9.2, H-C(5), H-C(6)). <sup>13</sup>C-NMR (100.61 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub>: 172.5, 171.3 (2s); 137.3, 133.9 (2d, <sup>1</sup>J(C,H) = 178, 179, C(8), C(9)); 92.0 (s, C(1)); 81.7 (d, <sup>1</sup>J(C,H) = 169, C(7)); 68.1 (dd, <sup>1</sup>J(C,H) = 156, 150, C(2)); 52.1 (q, <sup>1</sup>J(C,H) = 148, Me); 48.2, 45.9 (2d, <sup>1</sup>J(C,H) = 141, C(5), C(6)). CI-MS (NH<sub>3</sub>) m/z: 228 (13), 211 (12), 210 (1, M<sup>+</sup>), 151 (1), 134 (2), 124 (5), 114 (43), 113 (11), 98 (10), 97 (8), 82 (20), 81 (100). Anal. calc. for C<sub>10</sub>H<sub>10</sub>O<sub>5</sub> (210.18): C 57.14, H 4.80; found: C 57.25, H 4.85.

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## References and Notes

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