TOTAL SYNTHESIS OF (-)- AND (+)-SANADAOL: THE ABSOLUTE CONFIGURATION OF SANADAOL AND DICTYODIAL

Hiroto Nagaoka, Kaoru Kobayashi and Yasuji Yamada\* Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Summary: Both (-)- and (+)-sanadaol were synthesized stereoselectively from D-mannitol <u>via</u> chiral bicyclo[2.2.2]octane derivative  $\underline{4}$ . This accomplishment determined the absolute configuration of sanadaol and that of dictyodial as shown by 1 and 3, respectively.

Sanadaol<sup>1,2</sup> and dictyodial<sup>3</sup> are structurally unique marine diterpenes isolated from the brown algae <u>Pachydictyon coriaceum</u> and <u>Dictyota crenulata</u>. Dictyodial, the major diterpene of these algae, is chemically correlated to sanadaol. Absolute structures, however, remain to be determined. We previously reported the synthesis of racemic sanadaol,<sup>4</sup> and an effective synthetic method for chiral bicyclo[2.2.2]octane derivatives, (-)-4 and (+)-4, from Dmannitol using asymmetric sequential Michael reaction toward the synthesis of optically active sanadaol.<sup>5</sup> Herein, we wish to report the enantioselective total synthesis of (-)-sanadaol (2) and (+)-sanadaol (1) from (-)-4 and (+)-4, respectively. This defines the absolute configuration of sanadaol as well as dictyodial.



The bicyclo[2.2.2]octane derivative, (-)-4,<sup>5</sup> was converted into  $(E)-\alpha,\beta$ unsaturated ester  $\underline{6}^{6}$  ( $[\alpha]_{D}$  -24.7°, c=0.15, CHCl<sub>3</sub>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  3.35 ppm (3H, s), 3.71 (3H, s), 5.84 (1H, d, J=15.5 Hz), 6.91 (1H, ddd, J=15.5, 8.9, 6.2 Hz)) <u>via</u> hemiacetal <u>5</u> by eleven step sequence (Scheme I). The ratio of (E)- and (Z)- $\alpha,\beta$ -unsaturated ester was 16:1 in Wittig reaction of <u>5</u> with Ph<sub>3</sub>P=CHCO<sub>2</sub>Me. Intramolecular Michael reaction of <u>6</u> with 0.12 equiv of potassium t-butoxide in THF at -78°C gave tricyclic keto ester <u>7</u> ( $[\alpha]_{D}$  +15.2°, c=2.32, CHCl<sub>3</sub>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  2.63 ppm (1H, dd, J=15.5, 7.0 Hz), 2.68 (1H, dd, J=15.5, 8.5 Hz), 3.35 (3H, s), 3.66 (3H, s)) as a single isomer in quantitative yield. After conversion of <u>7</u> into keto lactone <u>8</u> ( $[\alpha]_{D}$  +22.7°, c=0.35, CHCl<sub>3</sub>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  2.64 ppm (1H, dd, J=18.8, 2.3 Hz), 2.70 (1H, dd, J=18.8, 4.3 Hz), 3.50 (1H, dd, J=9.4, 7.2 Hz), 3.55 (1H, t, J=9.4 Hz)), the carbonyl group at C-18 in <u>8</u> was reduced with



Reagents: a)  $Zn(BH_4)_2/THF/-78^{\circ}C/98\%$ , b)  $PhCH_2Br/NaH/53\%$ , c) L-selectride/THF/-78^{\circ}C/95\%, d) DHP/dl-CSA/98\%, e) LiAlH\_4/THF/RT/99\%, f) Swern oxd./91\%, g)  $Ph_3P=CHOMe/THF/0^{\circ}C/65\%$ , h) AcOH- $H_2O(4:1)/40^{\circ}C/67\%$ , i)  $Ph_3P=CHCO_2Me/PhH/50^{\circ}C/77\%$ , j) PCC/4A molecular sieves/79\%, k) MeOCH\_2C1 /i- $Pr_2NEt/CH_2C1CH_2C1/55^{\circ}C/91\%$ , l) t-BuOK/THF/-78°C/99\%, m) c.HCl-MeOH(1:10)/RT then dl-CSA/ PhH/50°C/70\%, n) L-selectride/THF/-78°C/98\%, o) MeOCH\_2C1/i- $Pr_2NEt/98\%$ , p) LDA/THF then MeI/ 88\%, q) Dibal-H/THF/-78°C/98\%, r)  $Ph_3P=CHCO_2Me/CH_2C1CH_2C1/50^{\circ}C/80\%$ , s)  $H_2/10\%$  Pd-C/MeOH/91\%.

L-selectride, the resulting hydroxyl group was protected and then  $\alpha$ -position of the lactone carbonyl group was methylated stereoselectively to give 9 ([ $\alpha$ ]<sub>D</sub> +46.1°, c=0.75, CHCl<sub>3</sub>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.30 ppm (3H, d, J=7.4 Hz), 3.36 (3H, s)). Lactone 9 was subjected to reduction with Dibal-H, Wittig reaction with  $Ph_3P=CHCO_2Me$  and catalytic hydrogenation to afford diol <u>10</u> ([ $\alpha$ ]<sub>D</sub> -14.0°, c=1.03, CHCl<sub>3</sub>), whose NMR and IR spectra were identical to those of racemic 10 previously prepared.<sup>4</sup> From 10, compound 2 was synthesized via enone <u>11</u> ( $[\alpha]_{\rm D}$  -3.77°, c=0.42, CHCl<sub>3</sub>) by applying the procedure of our previous synthesis.<sup>4</sup> The optical rotation of  $2^7$  thus obtained was, however, observed as  $[\alpha]_D$  -64.6° (c= 0.52, CHCl<sub>3</sub>) contrary to that of natural sanadaol ( $[\alpha]_{D}$  +74.8°, c=1.33, CHCl<sub>3</sub>).<sup>1</sup> Synthesis of the antipodal (-)-sanadaol ( $\underline{2}$ ) revealed the absolute configuration of the natural sanadaol as shown in 1 (2S, 3S, 7S, 10R, 18R), and also disclosed the absolute configuration of dictyodial as shown in 3 (2S, 3S, 10R).<sup>8</sup> The absolute structures were further confirmed by synthesis of (+)-sanadaol  $(\underline{1})^7$ starting from (+)-4 in similar manner. The optical rotation of synthetic 1 was observed as  $[\alpha]_D$  +74.0° (c=0.19, CHCl<sub>3</sub>) coinciding with that of natural sanadao1.

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## **REFERENCES AND NOTES**

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- 6) All new compounds have been fully characterized by IR, NMR (400 MHz) and high resolution mass spectroscopy and/or combustion analysis.
- 7) NMR and IR spectra of this compound were identical with those of natural sanadaol.
- 8) Treatment of dictyodial with silica gel or BF3.0Et2 gives sanadaol (ref. 1 and ref. 2).

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