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## The first synthesis and determination of absolute stereochemistry of clonostachydiol - Part II

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**Abstract :** The first total synthesis of clonostachydiol has been achieved from two appropriately protected hydroxy acids that are derived from (D)-xylose and 1,2-O-isopropylidene (D)-glyceraldehyde. This synthesis has proved the absolute configuration of four stereocenters in clonostachydiol as 2R,3S,8R,11R unambiguously.

Clonostachydiol  $(1)^1$  is a 14-membered fungal metabolite belonging to the macrodiolide class of compounds and related to colletodiol family<sup>2</sup>. From the analogy with colletodiol, the absolute configuration at C-2, C-8 and C-11 stereocenters of 1 was assumed to be 2R,8R and 11S, while the C-3 could either be R or S. However, the synthetic 3R isomer 1a (preceding communication) was distinguishably different from the natural counterpart, hence a synthesis of 3S isomer 1b was desired to prove the absolute stereochemistry. In this paper we report the first total synthesis of clonostachydiol (1) and its 11S isomer 1b and demonstrate that clonostachydiol is represented as (2R,3S,8R,11R) isomer 1 unambiguously.



Based on the retrosynthetic reasoning (Scheme 1) 2 and 3 were thought to be the appropriate synthesis of 1. Since the synthesis of 3 has already been achieved<sup>3</sup>,



as described in the preceding paper, a synthesis of 2 routed from (D)-xylose was planned, where the inversion at C-3 position was effected efficiently to prepare the 3S isomer.

Thus, the known compound 4 (Scheme 2), prepared from D-xylose (preceding communication), on PDC oxidation followed by  $NaBH_4$  reduction of resulting 5 gave 6<sup>4</sup> (80%) [ $\alpha$ ]<sub>D</sub> +40.5° (c 1, CHCl<sub>3</sub>). Treatment of 6 with MPMBr gave 7, which on exposure to acid resulted 9 along with MPM deprotected product albiet in poor yields. Hence, a different protecting group was



a) PDC,  $Ac_2O$ ,  $CH_2Cl_2$ , 40°C; b)  $NaBH_4$ , EtOH; c) NaH, MPMBr, THF; d) NaH, allyl bromide, THF; e) Conc.  $H_2SO_4$ , 60% aq. AcOH, 40°C; f)  $NaIO_4$ , MeOH; g)  $Ph_3P=CHCO_2(CH_2)_2SO_2ToI$ ,  $C_6H_6$ , 80°C; h) 2% HCl, 1:1 dioxane-water.

chosen in the present study. Accordingly, compound 6 on reaction with allyl bromide (NaH, THF) afforded 8 (75%)  $[\alpha]_D$  +98.1 (c 2, CHCl<sub>3</sub>). Acidic (60% aq. AcOH, cat. H<sub>2</sub>SO<sub>4</sub>) hydrolysis of 8 was smoothly effected furnishing the lactol 10, which on subsequent exposure to NaIO<sub>4</sub> followed by Wittig reaction on resultant aldehyde 11 with (p-toluenesulfonylethoxycarbonylme-thylene)triphenylphosphorane<sup>5</sup> gave 12 (50%). Finally de-O-formylation with catalytic 2% HCl gave segment 2 in 92% yield,  $[\alpha]_D$  +15° (c 1, CHCl<sub>3</sub>).

The total synthesis of 1 was efficiently completed from the enantiopure segments 2 and 3. Accordingly, esterification of 2 and 3 (Scheme 3) through the mixed anhydride as descri-



a) 2,4,6-Trichlorobenzoyl chloride, Et<sub>3</sub>N, ThF, then DMAP,  $C_6H_5CH_3$ , RT; b) Cat. conc. HCl, 1:1 MeOH-EtOAc; c) DBN,  $C_6H_6$ , RT; d) 2,4,6-trichlorobenzoyl chloride, Et<sub>3</sub>N, THF, then DMAP,  $C_6H_6CH_3$ , 95°C; e) DDQ, 18:1  $CH_2Cl_2-H_2O$ ; f) 10% Pd-C, PTSA, MeOH, 60°C. bed earlier gave ester 13 (70%). Depyranylation of 13 with conc. HCl followed by saponification of 14 with DBN<sup>5</sup> resulted in the selective removal of PTSE group thus forming the seco-acid 15 (82%). Acid 15 through its mixed anhydride<sup>6</sup>, prepared on reaction with 2,4,6-trichlorobenzoyl chloride underwent smooth macrolactonisation (DMAP, Toluene) under high dilution conditions to afford 16 (70%),  $[\alpha]_D$  -27.8° (c 1, CHCl<sub>3</sub>). Deprotections on 16 were effected by sequential treatment first with DDQ followed by Pd-C reaction of resultant 17 under acidic conditions<sup>7</sup> to furnish 1b in 80% yield, whose TLC analysis (1:1 EtOAc-Pet.ether) indicated the same R<sub>f</sub> value (0.30) for both the synthetic and natural isomers. However, other physical characteristics of 1b were not identical with that of natural one. The <sup>1</sup>H NMR spectrum of 1b indicated the chemical shifts for H-3 and H-11 at  $\delta$ 3.95 as a multiplet, while in natural isomer H-3 and H-11 resonated at  $\delta$  3.95 and 4.44 respectively while the olefinic protons pattern of 1b was conspicuously different from natural isomer<sup>8,9</sup>. Further, optical rotation  $[\alpha]_D$  -32° (c 0.15, MeOH) of 1b was quite different from that of natural isomer  $[\alpha]_D$  +103° (c 1.0 MeOH). Thus, to our dismay the 2R,3S,8R,11S isomer 1b was also found to have non-identical spectral analysis with natural isomer.

Having met with failure in the preparation of natural isomer 1, inspite of inversion at the C-3 centre, it was next planned to effect the inversion at C-11 stereocentre to get the target molecule.

Accordingly, compound 17 was subjected to Mitsunobu<sup>10</sup> inversion (scheme 4) using chloroacetic acid (DEAD,  $Ph_3P$ , THF) to afford the ester 18 (40%, H-11  $\delta$ , 5.62), which on



## a) CICH<sub>2</sub>CO<sub>2</sub>H, DEAD, Ph<sub>3</sub>P, THF; b) thiourea, 1:1 MeOH-CHCl<sub>3</sub>, RT; c) 10% Pd-C, PTSA, MeOH, 60°C.

subsequent deacetylation with thiourea<sup>11</sup> (MeOH-CHCl<sub>3</sub>) furnished **19** (60%) with inverted C-11 stereocentre (H-11  $\delta$ , 4.58). Finally de-O-allylation of **19** with Pd/C-PTSA<sup>7</sup> gave **1** (70%), which was indistinguishable by TLC, IR and <sup>1</sup>H NMR from natural compound<sup>8,9</sup>. The specific optical rotation value of +102° (c 0.1, MeOH) was in excellent agreement with the reported value +103° (c 1, MeOH) and substantiated the absolute stereochemistry of **1**, which can be depicted as 2R,3S,8R,11R.

In summary, we have demonstrated the absolute stereochemistry of 1 to be 2R,3S,8R,11R from the first total synthesis by a convergent and enantioselective approach starting from (D)-xylose and 1,2-O-isopropylidene (D)-glyceraldehyde.

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- 9. <sup>1</sup>H NMR data (200 MHz, DMSO-d<sub>6</sub>,  $\delta$  in ppm): 1 1.13, 1.34 (2d, 6H, J<sub>16,8</sub>=J<sub>15,2</sub> 6.5 Hz, H-15,16), 1.44 (m, 2H, H-9), 1.54, 1.80 (m, 2H, H-10), 3.95 (m, 1H, H-3), 4.45 (m, 1H, H-11), 4.7 (m, 1H, H-2), 5.02 (m, 2H, H-8, OH), 5.68 (d, 1H, OH), 5.78 (dd, 1H, J<sub>12,13</sub> 15.8 Hz, H-13), 5.9 (d, 1H, J<sub>4,5</sub> 16.0 Hz, H-5), 6.48 (dd, 1H, J<sub>3,4</sub> 8.9 Hz, H-4), 6.68 (dd, J<sub>11-12</sub> 4.2 Hz, H-12).

la : 1.13, 1.27 (2d, 6H,  $J_{16,8}=J_{15,2}$  6.5 Hz, H-15,16), 1.4 (m, 2H, H-9), 1.52, 1.78 (m, 2H, H-10), 3.92 (m, 1H, H-11), 4.32 (m, 1H, H-3), 4.98 (m, 1H, H-2), 5.17 (pseudoquintet, 1H, H-8), 5.78 (d, 1H,  $J_{13,12}$  15.3 Hz, H-13), 6.01 (d, 1H,  $J_{5,4}$  15.0 Hz, H-5), 6.58 (dd, 1H,  $J_{3,4}$  6.5 Hz, H-4), 6.65 (dd, 1H,  $J_{11,12}$  3.2 Hz, H-12).

**1b**: 1.13, 1.34 (2d, 6H,  $J_{16,8}$  6.6 Hz,  $J_{15,2}$  6.4 Hz, H-15,16), 1.5 (m, 2H, H-9), 1.78 (m, 2H, H-10), 3.95 (m, 2H, H-3,11), 4.72 (m, 1H, H-2), 4.95 (psuedoquintet, 1H, H-8), 5.69 (d, 1H, OH), 5.87 (2d, 2H,  $J_{12,13}$  15.2 Hz,  $J_{4,5}$  15.7 Hz, H-5,13), 6.45 (dd, 1H,  $J_{3,4}$  6.0 Hz, H-4), 6.45 (dd, 1H,  $J_{11,12}$  8.5 Hz, H-12).

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