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

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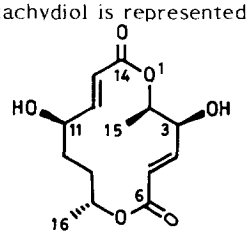
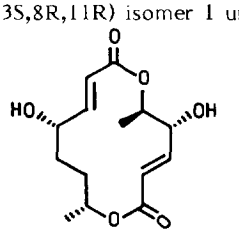
Abstract : The first total synthesis of clonostachydiol has been achieved from two appropriately protected hydroxy acids that are derived from (D)-xylose and 1,2-O-isopropylidene (D)-glyceraldehyde. This synthesis has proved the absolute configuration of four stereocenters in clonostachydiol as 2R,3S,8R,11R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

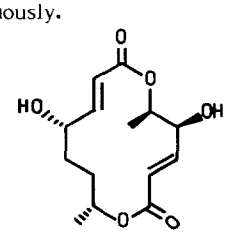
Clonostachydiol (**1**)[1] is a 14-membered fungal metabolite belonging to the macrodiolide class of compounds and related to colletodiol family[2]. From the analogy with colletodiol, the absolute configuration at C-2, C-8 and C-11 stereocenters of **1** was assumed to be 2R,8R and 11S, while the C-3 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.



1



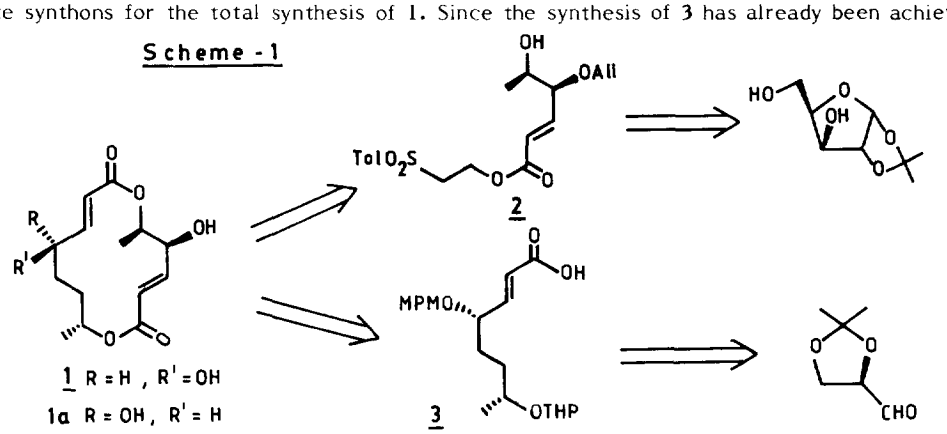
1a



1b

Based on the retrosynthetic reasoning (Scheme 1) **2** and **3** were thought to be the appropriate synthons for the total synthesis of **1**. Since the synthesis of **3** has already been achieved[3],

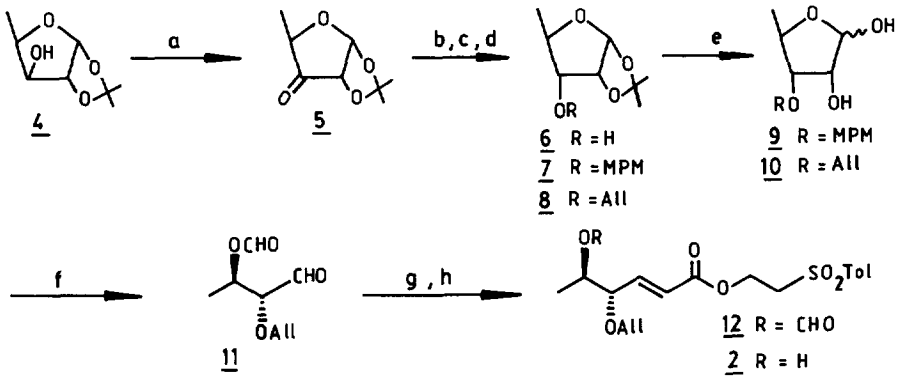
Scheme - 1



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**[4] (80%) $[\alpha]_D$ +40.5° (c 1, $CHCl_3$). 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

Scheme-2



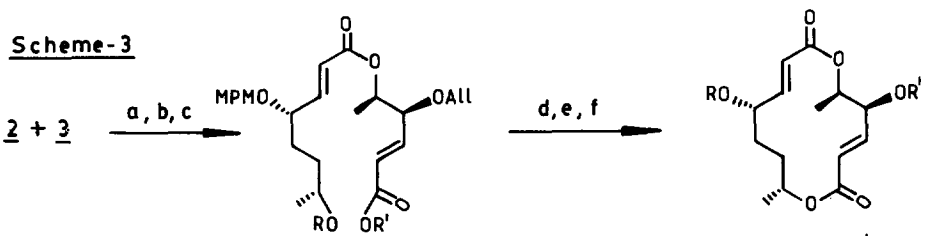
4 | 5 | 6 R = H, 7 R = MPM, 8 R = All | 9 R = MPM, 10 R = All | 11 | 12 R = CHO, 2 R = H

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) $Ph_3P{=}CHCO_2(CH_2)_2SO_2Tol$, 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, $CHCl_3$). Acidic (60% aq. AcOH, cat. H_2SO_4) hydrolysis of **8** was smoothly effected furnishing the lactol **10**, which on subsequent exposure to $NaIO_4$ followed by Wittig reaction on resultant aldehyde **11** with (p-toluenesulfonylethoxycarbonylmethylene)triphenylphosphorane[5] gave **12** (50%). Finally de-O-formylation with catalytic 2% HCl gave segment **2** in 92% yield, $[\alpha]_D$ +15° (c 1, $CHCl_3$).

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-

Scheme-3



13 R = THP, R' = SO_2Tol
14 R = H, R' = SO_2Tol
15 R = R' = H
16 R = MPM, R' = All
17 R = H, R' = All
1b R = R' = H

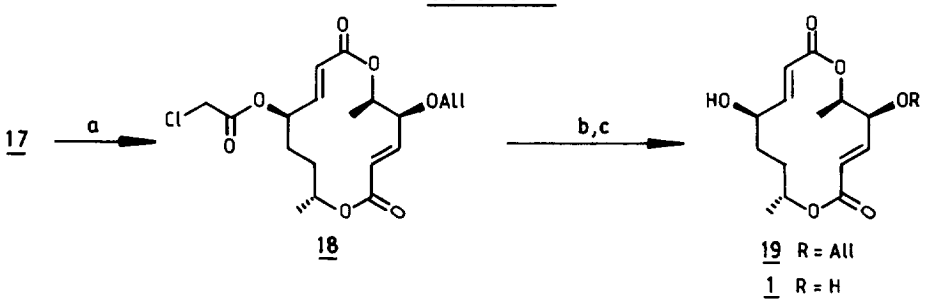
a) 2,4,6-Trichlorobenzoyl chloride, Et_3N. THF, then DMAP, $C_6H_5CH_3$, RT; b) Cat. conc. HCl, 1:1 MeOH-EtOAc; c) DBN, C_6H_6, RT; d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, $C_6H_6CH_3$, 95°C; e) DDQ, 18:1 CH_2Cl_2-H_2O; f) 10% Pd-C, PTSA, MeOH, 60°C.

bed earlier gave ester **13** (70%). Depyranylation of **13** with conc. HCl followed by saponification of **14** with DBN[5] resulted in the selective removal of PTSE group thus forming the seco-acid **15** (82%). Acid **15** through its mixed anhydride[6], 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, $CHCl_3$). Deprotections on **16** were effected by sequential treatment first with DDQ followed by Pd-C reaction of resultant **17** under acidic conditions[7] to furnish **1b** in 80% yield, whose TLC analysis (1:1 EtOAc-Pet.ether) indicated the same R_f 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 ^1H NMR spectrum of **1b** indicated the chemical shifts for H-3 and H-11 at δ 3.95 as a multiplet, while in natural isomer H-3 and H-11 resonated at δ 3.95 and 4.44 respectively while the olefinic protons pattern of **1b** was conspicuously different from natural isomer[8,9]. 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[10] inversion (scheme 4) using chloroacetic acid (DEAD, Ph_3P, THF) to afford the ester **18** (40%, H-11 δ, 5.62), which on

Scheme - 4



a) $ClCH_2CO_2H$, DEAD, Ph_3P, THF; b) thiourea, 1:1 MeOH-$CHCl_3$, RT; c) 10% Pd-C, PTSA, MeOH, 60°C.

subsequent deacetylation with thiourea[11] (MeOH-$CHCl_3$) furnished **19** (60%) with inverted C-11 stereocentre (H-11 δ, 4.58). Finally de-O-allylation of **19** with Pd/C-PTSA[7] gave **1** (70%), which was indistinguishable by TLC, IR and ^1H NMR from natural compound[8,9]. 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. ^{1}H NMR data (200 MHz, DMSO-d_6, δ in ppm): **1** - 1.13, 1.34 (2d, 6H, $J_{16,8}=J_{15,2}$ 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, $J_{12,13}$ 15.8 Hz, H-13), 5.9 (d, 1H, $J_{4,5}$ 16.0 Hz, H-5), 6.48 (dd, 1H, $J_{3,4}$ 8.9 Hz, H-4), 6.68 (dd, $J_{11,12}$ 4.2 Hz, H-12).
1a : 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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