



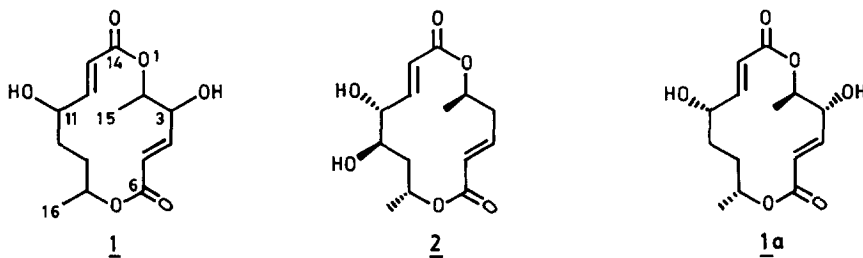
Studies directed towards the synthesis of clonostachydiol - Part I

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Abstract : A strategy was developed for the first total synthesis of clonostachydiol which in turn would assign the absolute configuration, based on the chiron approach, using carbohydrate derived chiral synthons. This study however culminated in the synthesis of (2R,3R,8R,11S) isomer of clonostachydiol.

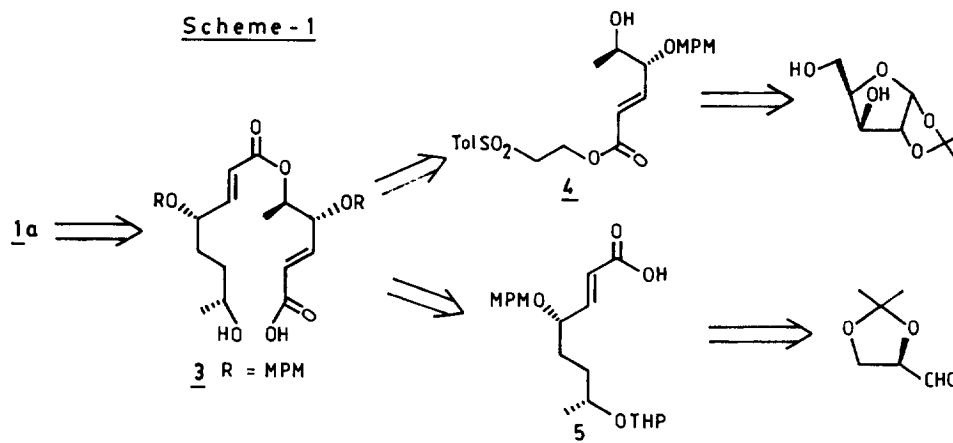
Clonostachydiol (**1**), a 14-membered non-symmetric macrocyclic bis(lactone), belongs to a group of structurally related fungal metabolites such as colletodiol (**2**)¹. Compound **1** was isolated² from the strain FH-A 6607 classified as *Clonostachys cylindrospora*³. It has shown a weak cytostatic effect and *in vivo* antihelminthic activity. Its gross structure as **1** was fully characterised from the spectral studies without defining the absolute stereochemistry at 2,3,8 and 11 carbon centres. Based on the assumption that **1** is closely related to members like **2**, except for the placement of hydroxy groups, herein, we summarise our results directed towards the first synthesis of **1**, which resulted in the synthesis of **1a**, using carbohydrate derived chiral synthons as building blocks.



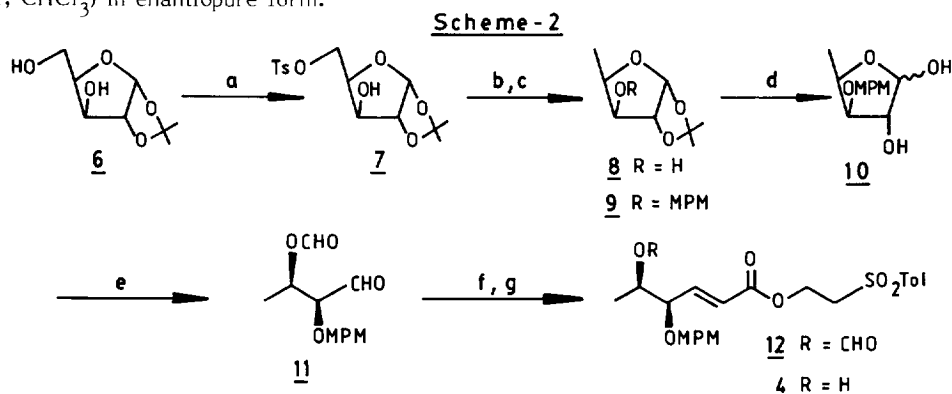
By analogy with colletodiol (**2**) the absolute stereochemistry of **1** at C-2, C-8 and C-11 was assumed to be 2R, 8R and 11S, while the new stereocentre at C-3 could be either R or S. At the first instance a protocol was developed to synthesise the 3R isomer i.e. (2R, 3R, 8R, 11S) **1a** by a convergent approach.

The basic design for the synthesis of **1a** was arrived at from the disconnection approach (Scheme 1), where delactonisation and further dissection of seco acid **3** would give two hydroxy acid segments viz. a) O-1 to C-6 unit **4** and b) O-7 to C-14 fragment **5**. Thus, the synthetic strategy lies in the preparation of the appropriately protected enantiopure segments **4** and **5** starting from (D)-xylose and 1,2-O-isopropylidene (D)-glyceraldehyde respectively.

Segment **4** was made starting from (D)-xylose derivative **6** where a) the C-3, C-4 hydroxy groups are retained, b) C-5 is converted into methyl group and c) the aldehyde obtained from C-1, C-2 is used for the carbon chain extension.



Thus, 1,2-O-isopropylidene- α -D-xylose (**6**) was tosylated (Pyr, CH_2Cl_2) selectively (Scheme 2) to give **7**⁴ (80%), which on subsequent LAH reduction furnished **8** (80%), $[\alpha]_{\text{D}} -15.6^\circ$ (c 2, CHCl_3). Reaction of **8** with MPMBR (NaH, THF) resulted **9** which on exposure to acid (Cat. H_2SO_4 in 60% aq. AcOH) afforded **10**. Oxidative cleavage of **10** (NaIO_4) and subsequent olefination of unstable aldehyde **11** with (p-toluenesulfonylethoxycarbonylmethylene)triphenylphosphorane⁵ gave **12** (55%). Finally, de-O-formylation of **12** with 2% HCl afforded **4** (92%), $[\alpha]_{\text{D}} -11^\circ$ (c 1, CHCl_3) in enantiopure form.



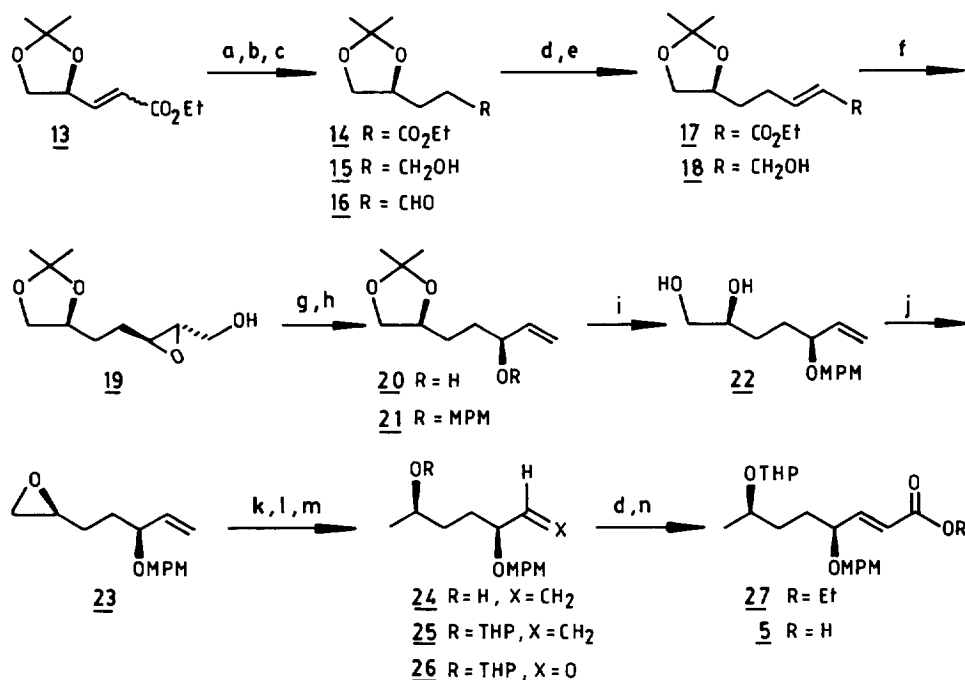
a) TsCl , Pyr, CH_2Cl_2 ; b) LAH, THF; c) NaH, MPMBR, THF; d) Cat. H_2SO_4 , 60% aq. AcOH; e) NaIO_4 , MeOH; f) $\text{Ph}_3\text{P}=\text{CHCO}_2(\text{CH}_2)_2\text{SO}_2\text{Tol}$, C_6H_6 , 80°C ; g) 2% HCl, 1:1 dioxane-water.

Synthesis of O-7 to C-14 segment **5** was achieved from 1,2-O-isopropylidene-(D)-glyceraldehyde, where the requisite number of carbons were incorporated through sequential Wittig reactions, while the C-11 hydroxy of **1** was added through the Sharpless asymmetric epoxidation reaction.

Accordingly, the known⁶ ester **13** (scheme 3) on catalytic hydrogenation (Pd-C , H_2) followed by LAH reduction of **14** gave **15** (80%), $[\alpha]_{\text{D}} +13.4^\circ$ (c 1, CHCl_3). PDC oxidation of **15** and subsequent reaction of **16** with (ethoxycarbonylmethylene)triphenylphosphorane gave the ester **17** (63%). DIBAL-H reduction of **17** furnished **18** (80%) $[\alpha]_{\text{D}} + 18.5^\circ$ (c 1, CHCl_3),

which on subsequent asymmetric epoxidation under standard Sharpless reaction conditions⁷ (TBHP, TIP, (+)DIPT, CH_2Cl_2) gave the oxirane **19** (80%) $[\alpha]_{\text{D}} -15.8^\circ$ (c 1, CHCl_3). Titanocene⁸ mediated (Zn , ZnCl_2 , THF) regioselective ring opening of **19** furnished the allylic carbinol **20** (65%), which on exposure to MPMBBr afforded **21** $[\alpha]_{\text{D}} -12.6^\circ$ (c 1, CHCl_3). Compound **21** was exposed to PTSA to result the diol **22**, which on treatment with TsCl (NaH , THF) furnished **23** (79%). Oxirane in **23** was regioselectively opened with LAH to furnish **24** (80%) $[\alpha]_{\text{D}} -37.8^\circ$ (c 1, CHCl_3), which on further reaction with dihydropyran (PTSA, CH_2Cl_2) gave **25** (95%).

Scheme - 3

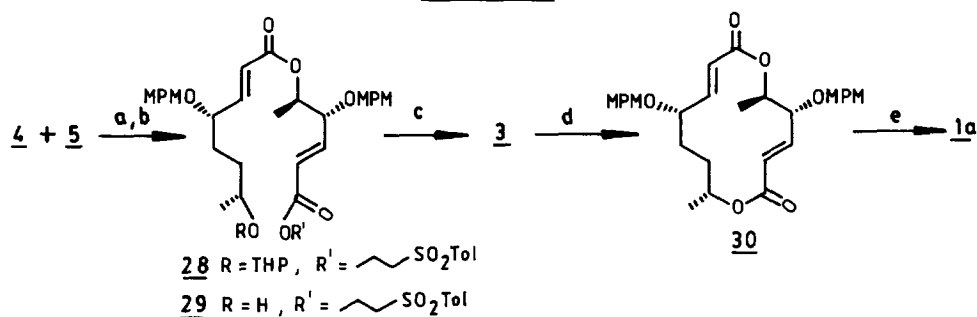


a) H_2 , Pd-C, EtOAc; b) LAH, THF, 0°C ; c) PDC, CH_2Cl_2 , 40°C ; d) $\text{Ph}_3\text{P=CHCO}_2\text{Et}$, C_6H_6 , 80°C ; e) DIBAL-H, CH_2Cl_2 ; f) TBHP, (+)DIPT, TIP, CH_2Cl_2 , -20°C ; g) CP_2TiCl_2 , Zn , ZnCl_2 , THF; h) NaH , MPMBBr, THF; i) Cat. PTSA, MeOH; j) NaH , TsCl , THF, 0°C ; k) LAH, ether; l) Dihydropyran, PTSA, CH_2Cl_2 ; m) O_3 , CH_2Cl_2 , -78°C then Ph_3P ; n) LiOH , aq. THF.

Finally acid **5** was made in three steps from **25**. Thus, ozonolysis of **25** followed by reaction of resulting **26** with $\text{Ph}_3\text{P=CHCO}_2\text{Et}$ afforded the ester **27**. Saponification (LiOH , aq. THF) of **27** furnished the O-7 to C-14 segment **5** in quantitative yield.

Having successfully made both the fragments **4** and **5** they were then subjected to esterification (Scheme 4). Accordingly, the mixed anhydride prepared on reaction of **5** with 2,4,6-trichlorobenzoylchloride (Et_3N , THF) followed by reaction with **4** in presence of DMAP afforded the ester **28** (60%), which on depyranylation with conc. HCl gave **29** (80%) $[\alpha]_{\text{D}} -16.3^\circ$ (c 1, CHCl_3). Further, selective hydrolysis of PTSE ester in **29** was effected with DBN^5 (C_6H_6 , RT) to furnish **3** (82%). The crucial macrolactonisation reaction on **3** was carried out essentially under Yamaguchi conditions¹⁰, through the corresponding mixed anhydride, made on reaction

Scheme-4



a) i. 2,4,6-Trichlorobenzoyl chloride, Et_3N , THF; ii. DMAP, $\text{C}_6\text{H}_5\text{CH}_3$, RT; b) Cat. conc. HCl, 1:1 MeOH-EtOAc; c) DBN, C_6H_6 ; d) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, then DMAP, $\text{C}_6\text{H}_5\text{CH}_3$, 95°C ; e) DDQ, 18:1 $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$.

with 2,4,6-trichlorobenzoyl chloride, under high dilution conditions in toluene to afford **30** (60%) $[\alpha]_D -65^\circ$ (c 1, CHCl_3). Finally exposure of **30** to DDQ (aq. CH_2Cl_2) gave a compound (50%) which was later identified as (2R,3R,8R,11S) isomer **1a** from spectral data. The TLC analysis (1:1 ethyl acetate, pet. ether indicated R_f values 0.20 and 0.30 for synthetic and natural isomers respectively. The synthetic **1a** was fully characterised from its ^1H NMR spectrum, where H-2, H-3 and H-11 signals resonating at δ 5.17 (pseudoquintet), 4.32 (m) and 3.92 (m) respectively were not concurrent to the observed values for the natural isomer¹¹ at δ 4.70, 3.95 and 4.45. Besides the diagnostic chemical shifts as well as the splitting pattern for the olefinic protons was distinguishably different. Moreover, the inconsistent optical rotation values of $[\alpha]_D +20^\circ$ (c 1, MeOH) and $+103^\circ$ (c 1, MeOH) for the synthetic and natural compounds respectively, is further evidence that both are not the same.

Thus, from the foregoing discussion it is obvious that the synthetic 2R,3R,8R,11S compound is not the right isomer. Assuming that **1** is closely related to colletodiol (**2**), where the absolute stereochemistry is known, the synthesis of 3S isomer of **1a** is warranted for arriving at the absolute stereochemistry of **1** unambiguously.

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