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Attempts directed towards the synthesis and determination of the absolute stereochemistry of *iso*-cladospolide-B and cladospolides-B and C☆

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Abstract—Attempts to synthesise *iso*-cladospolide-B, cladospolide-B and cladospolide-C resulted in macrolides **1**, **2** and **4** along with butenolide **3**. Of the three stereogenic centres, the C-4/C-5 *vic*-diol was obtained from tartaric acid and D-glucose, while the C-11 stereocentre was created by Jacobsen's method.

1. Introduction

Cladospolide-B (**1**) was isolated[1] from *Cladosporium cladosporioides* F1-113 and was found to be a plant growth promoter. It was also isolated[2] along with cladospolide-C (**2**) from *Cladosporium tenuissimum*. Macrolide **1** was found to inhibit shoot elongation of rice seedlings (*Oryza sativa* L.), while **2** damages the plants and causes necrosis. Based on the absolute configuration of cladospolide-A[3] (4*R*,5*S*,11*R*), the relative configurations for **1** and **2** were proposed[2] as (4*S*,5*S*,11*R*)- and (4*R*,5*R*,11*R*)-, respectively. *iso*-Cladospolide-B (**3**)[4] was isolated along with **1** from the fermentation broth of the fungal isolate I96S215 obtained from a tissue sample of a marine sponge, and its structure was defined from spectroscopic studies. The synthesis by Figadere and co-workers[5] has established the absolute stereochemistry of **3**[6] as (4*S*,5*S*,11*R*)-, analogous to macrolide **1**.[6] Herein, we report the synthesis and attempts to determine the absolute stereochemistry of **1**, **2**, **3** and **4**, which is the C-11 epimer of **2** (Fig. 1).

An antithetic analysis of **1** and **3** (Scheme 1) suggested that seco-acid **5** is an appropriate late stage intermediate which could be realised from **6**, which in turn could be accessed from **7** and **8**. Thus, of the three stereogenic centres, the *vic*-diol is obtained from **7**, while the other chiral centre is introduced by the Jacobsen hydrolytic kinetic resolution method.[7]

Accordingly, diol **8** (Scheme 2) on reaction with TBDPSCl gave TBDPS ether **9** (76%), which on treatment with Ph_3P and I_2, followed by reaction of the resulting iodide **10** with Ph_3P (toluene, reflux), afforded

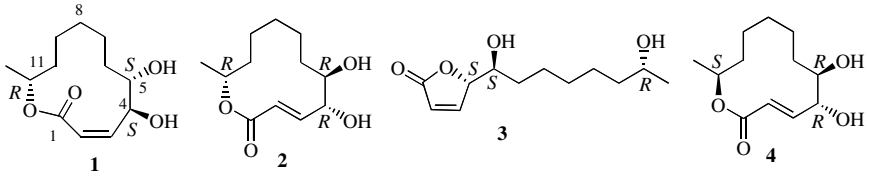

Figure 1.

Keywords: *Cladosporium* sps.; *vic*-Diol; Jacobsen's method; Seco-acid; Mcrolactonisation.
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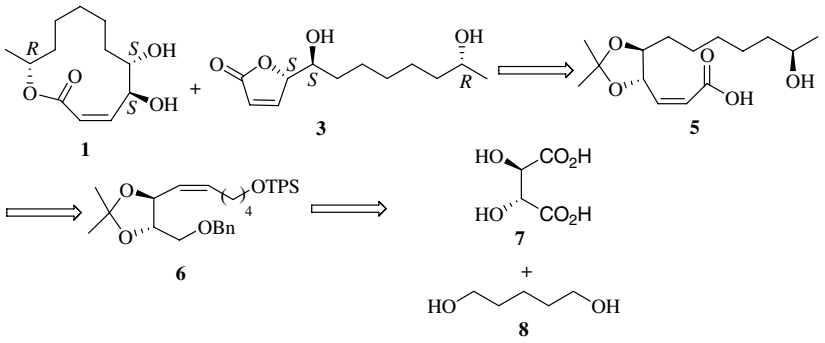
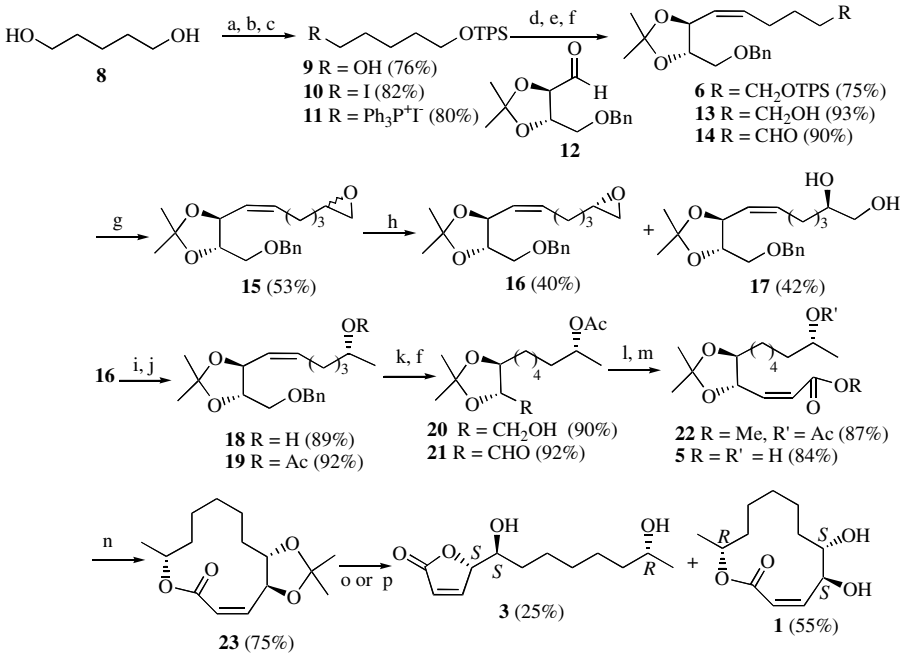


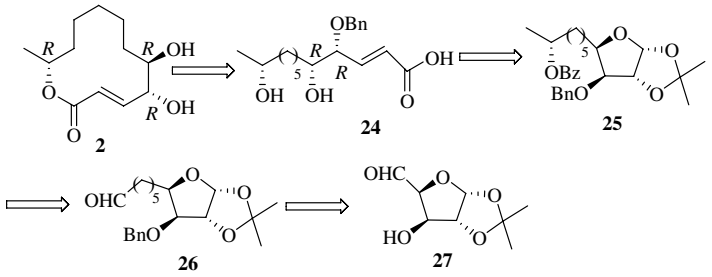
Scheme 1.



Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 12 h; (b) I_2, Ph_3P, imidazole, toluene, rt, 30 min; (c) Ph_3P, toluene, reflux, 24 h; (d) *n*-BuLi, dry THF, 0 °C, 2 h; (e) TBAF, dry CH_2Cl_2, 12 h; (f) $(COCl)_2$ dry DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (g) TMSOI, *t*-BuOK, dry DMSO, 0 °C, 1 h; (h) *S*,*S*-Jacobsen catalyst, H_2O, rt, 12 h; (i) LAH, dry THF, 0 °C, 1 h; (j) AcCL, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (k) H_2, Pd/C, EtOAc, rt, 12 h; (l) $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C, 2 h; (m) 4 N NaOH, MeOH, rt, 4 h; (n) 2,4,6-trichlorobenzoyl chloride, Et_3N, CH_2Cl_2, DMAP, toluene, reflux, 24 h; (o) 80% aq AcOH, 70 °C, 1 h and (p) $TiCl_4$, dry CH_2Cl_2, 0 °C, 2 h.

phosphonium salt **11** (80%). Wittig olefination of the known aldehyde **12**,[8] (prepared from diol **7**) with phosphonium salt **11** afforded olefin **6** (75%). Desilylation (TBAF, CH_2Cl_2) of **6**, followed by Swern oxidation of alcohol **13**, furnished aldehyde **14** (90%). One carbon extension on **14** with trimethylsulfoxonium iodide (TMSOI) (*t*-BuOK, DMSO) afforded the diastereoisomeric epoxides **15** (53%). Kinetic resolution of epoxide **15** under Jacobsen reaction conditions[7] using the (*S*,*S*)-catalyst gave epoxide **16** (40%) and diol **17** (42%). Reductive opening of epoxide **16** with LAH afforded **18** (89%), which on acetylation followed by catalytic hydrogenation of acetate **19** furnished saturated alcohol **20** (90%). Oxidation of alcohol **20** and Wittig reaction of aldehyde **21** with $Ph_3P{=}CHCO_2Me$ in MeOH afforded α,β-unsaturated ester **22** (87%) with cis-geometry as observed from the ^1H NMR spectrum. Base catalysed deprotection of both the ester functionalities in **22** gave seco-acid **5** (84%), which on macrolactonisation under Yamaguchi reaction conditions[9] gave macrolide **23** (75%). Finally, attempted deprotection of acetonide in **23**, with aq AcOH (80%) for 1 h gave (4*S*,5*S*,11*R*)-butenolide **3** (25%) and (4*S*,5*S*,11*R*)-macrolide **1** (55%) as a separable mixture of isomers. However, **23** on reaction with $TiCl_4$ gave **1** (73%) as the exclusive product. Besides the ^1H NMR data, the optical rotation values for **1**: $[\alpha]_D$ −95.0 (*c* 0.3, $CHCl_3$) [(lit.[1] $[\alpha]_D$ +26.9 (*c* 0.4, MeOH); lit.[2] $[\alpha]_D$ +45.0 (*c* 0.4, MeOH))] and for **3**: $[\alpha]_D$ −40.2 (*c* 0.3, $CHCl_3$) [lit.[4] $[\alpha]_D$ −90.0 (*c* 0.23, MeOH), lit.[5] $[\alpha]_D$ −47.0 (*c* 0.75, MeOH)], respectively, did not match with each other.

Similarly, an antithetic analysis of (4*R*,5*R*,11*R*)-**2** (Scheme 3) revealed that macrolactonisation of acid **24** would give **2**, while **24** in turn could be envisioned from the C-5 extended D-xylose derivative **25**. Aldehyde **26**

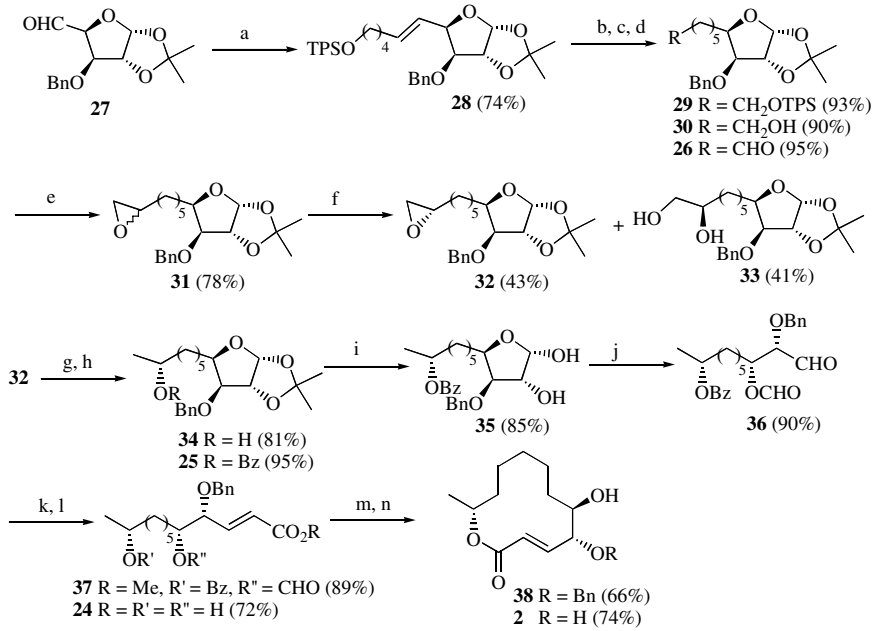


Scheme 3.

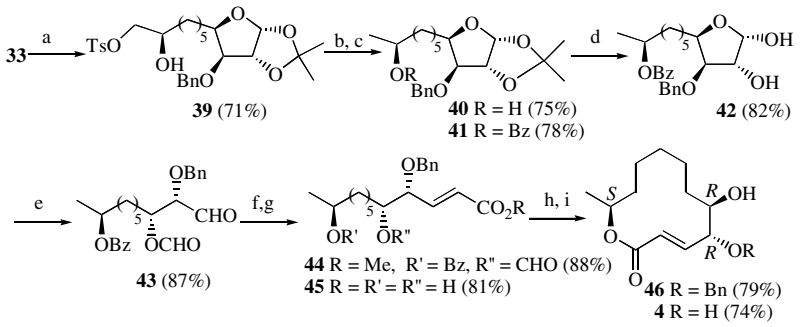
could be prepared from the known aldehyde **27**,[10] a product of D-glucose. Thus, the main strategy would be to use the C-2/C-3 hydroxy groups as the *R*,*R*-*vic*-diol system of **2**, while the other stereocentre is introduced by the Jacobsen method.[7]

Accordingly, Wittig olefination of aldehyde **27** (Scheme 4) with phosphonium salt **11** and subsequent hydrogenation of olefin **28** afforded **29** (93%). Desilylation (TBAF) of TPS ether **29** followed by oxidation of alcohol **30** gave aldehyde **26** (95%). Reaction of aldehyde **26** with trimethylsulfoxonium iodide/KOBu-*t* gave diastereoisomeric epoxides **31** (78%), which on Jacobsen kinetic resolution (*S*,*S*-catalyst) furnished epoxide **32** (43%) and diol **33** (41%). Reductive (LAH) opening of **32** gave alcohol **34** (81%), which on benzoylation (BzCl, Et_3N) furnished benzoate **25** (95%). Acid (60% aq AcOH) catalysed hydrolysis of the isopropylidene group in **25** followed by oxidative cleavage of the diol in **35** with H_5IO_6 afforded aldehyde **36** in 90% yield. Wittig olefination of **36** in toluene at reflux gave the α,β-unsaturated ester **37** with trans-geometry ($J_{2,3} = 13.0$, $J_{3,4} = 5.6$ Hz) in 89% yield. Exposure of ester **37** to 4 N NaOH cleaved the benzoyl, formyl and methyl ester groups to furnish seco-acid **24** (72%), which on Yamaguchi macrolactonisation using 2,4,6-trichlorobenzoyl chloride afforded **38** (66%). Finally, **38** on reaction with $TiCl_4$ underwent facile debenzylation to furnish (4*R*,5*R*,11*R*)-macrolide **2** (74%), whose spectral data as well as optical rotation value $[\alpha]_D$ −40.9 (*c* 0.3, $CHCl_3$) [lit.[2] $[\alpha]_D$ +59.7 (*c* 0.4, MeOH)] did not match the reported data.

Assuming that the stereochemical assignment of macrolide **2** was not correct, (4*R*,5*R*,11*S*)-macrolide **4**, the C-11 epimer of **2**, was synthesised from **33**. Thus, selective tosylation of diol **33** (Scheme 5) was followed by reduction of monotosylate **39** with LAH to give alcohol **40** (75%). Benzoylation of **40** was followed by hydrolysis (60% aq AcOH) of **41** to afford diol **42** (82%). Oxidative cleavage of diol **42** and subsequent Wittig reaction of aldehyde **43** furnished *trans*-product **44** (88%).



Scheme 4. Reagents and conditions: (a) **11**, *n*-BuLi, dry THF, −78 °C, 2 h; (b) H_2, PtO_2, EtOAc, rt, 12 h; (c) TBAF, dry CH_2Cl_2, rt,12 h; (d) $(COCl)_2$, dry DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (e) TMSOI, *t*-BuOK, dry DMSO, 0 °C, 1 h; (f) *S*,*S*-Jacobsen catalyst, H_2O, rt, 12 h; (g) LAH, dry THF, 0 °C, 1 h; (h) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (i) 60% aq AcOH, 70 °C, 12 h; (j) H_5IO_6, EtOAc–H_2O (1:1), 0 °C, 1 h; (k) $Ph_3P{=}CHCO_2Me$, toluene, reflux, 2 h; (l) 4 N NaOH, CH_3OH, rt, 2 h; (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, reflux, 24 h and (n) $TiCl_4$, dry CH_2Cl_2, 0 °C, 2 h.



Scheme 5. Reagents and conditions: (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 12 h; (b) LAH, dry THF, 0 °C, 1 h; (c) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (d) 60% aq AcOH, 70 °C, 12 h; (e) H_5IO_6, EtOAc:H_2O (1:1), 0 °C, 1 h; (f) $Ph_3P{=}CHCO_2Me$, toluene, reflux, 2 h; (g) 4 N NaOH, CH_3OH, rt, 2 h; (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, reflux, 24 h and (i) $TiCl_4$, dry CH_2Cl_2, 0 °C, 2 h.

One-pot base (NaOH) catalysed deprotection of all the ester groups in **44** gave seco-acid **45**, which under Yamaguchi reaction conditions underwent smooth macrolactonisation to afford **46** (79%). Exposure of **46** to $TiCl_4$ furnished macrolide **4** (74%), whose spectral data also did not match with the reported data for cladospolide-C; however, the optical rotation value $[\alpha]_D$ +29.7 (*c* 0.3, $CHCl_3$) [lit.[2] $[\alpha]_D$ +59.7 (*c* 0.4, MeOH)] was observed with a positive sign.

Thus, even though the syntheses of **1**, **2** and **3** along with **4** were achieved from two chiral synthons with *vic*-diols from tartaric acid and D-glucose, the absolute stereochemistry of the target natural products could not be determined. From the observed change in the sign of rotation in **4**, it was proposed to attempt the synthesis of **1**, **2** and **3** with the 4*S*,5*S*,11*S*-configuration.[11]

2. Spectral data for selected compounds

Macrolide **1**: Colourless solid, mp 105–110 °C (lit.[2] mp 109–110 °C); $[\alpha]_D$ −95.0 (*c* 0.5, $CHCl_3$); lit.[2] $[\alpha]_D$ +45.0 (*c* 0.4, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (d, 3H, $J = 6.0$ Hz, H-12), 1.17–2.05 (m, 10H, 5 × –CH_2), 3.82 (dd, 1H, $J = 9.0$, 5.2 Hz, H-5), 4.89 (dq, 1H, $J = 10.5$, 1.5, 6.0 Hz, H-11), 5.24 (t, 1H, $J = 8.3$ Hz, H-4), 5.80 (d, 1H, $J = 12.0$ Hz, H-2), 6.12 (dd, 1H, $J = 9.0$, 8.3 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.7, 21.2, 24.1, 25.7, 30.6, 32.0, 67.4, 73.8, 74.4, 121.6, 148.7, 165.9; IR (KBr): 1075, 1282, 1350, 1635, 1715, 2940, 3320 cm^{-1}; FABMS: (*m*/*z*, %): 251 (M^++23, 22), 167 (28), 149 (12), 109 (100); HRMS (ESI): *m*/*z* calculated for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1429.

Macrolide **2**: Colourless solid, mp 80–85 °C (lit.[2] mp 90–91 °C); $[\alpha]_D$ −40.9 (*c* 0.3, $CHCl_3$); lit.[2] $[\alpha]_D$ +59.7 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (d, 3H, $J = 6.0$ Hz, H-12), 1.15–1.90 (m, 10H, 5 × CH_2), 3.99–4.04 (m, 1H, H-5), 4.40–4.30 (m, 1H, H-4), 5.10–5.20 (m, 1H, H-11), 6.08 (d, 1H, $J = 8.0$ Hz, H-2), 6.98 (dd, 1H, $J = 8.0$, 2.8 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 22.4, 25.5, 31.4, 31.8, 38.2, 39.3, 64.9, 72.5, 124.8, 144.0, 174.3; IR (KBr): 850, 1170, 1265, 1710, 2925, 3518 cm^{-1}; FABMS: (*m*/*z*, %): 251 (M^++23, 12), 187 (94), 151 (26), 127 (100), 55 (44); HRMS (ESI): *m*/*z* calculated for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1430.

Lactone **3**: Colourless syrup, $[\alpha]_D$ −40.2 (*c* 0.3, $CHCl_3$); lit.[4] $[\alpha]_D$ −90.0 (*c* 0.23, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, 3H, $J = 6.2$ Hz, H-12), 1.22–1.61 (m, 10H, 5 × –CH_2), 3.70 (m, 1H, H-11), 3.77 (m, 1H, H-5), 5.07 (q, 1H, $J = 1.8$ Hz, H-4), 6.16 (dd, 1H, $J = 5.8$, 2.0 Hz, H-2), 7.63 (dd, 1H, $J = 5.8$, 1.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.2, 26.1, 26.7, 30.6, 34.0, 40.2, 68.4, 71.8, 88.4, 122.6, 157.1, 175.9; IR (KBr): 1175, 1262, 1715, 3520 cm^{-1}; FABMS: (*m*/*z*, %): 251 (M^++23, 42), 167 (17), 149 (18), 109 (100); HRMS (ESI): *m*/*z* calculated for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1433.

Macrolide **4**: Colourless solid, mp 80–82 °C; $[\alpha]_D$ +29.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, 3H, $J = 6.5$ Hz, H-12), 1.20–1.82 (m, 10H, 5 × CH_2), 3.34–3.41 (m, 1H, H-5), 3.98–4.05 (m, 1H, H-4), 4.70–4.92 (m, 1H, H-11), 6.08 (d, 1H, $J = 9.3$ Hz, H-2), 6.98 (dd, 1H, $J = 9.3$, 5.3 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.8, 26.2, 26.6, 30.8, 35.0, 41.2, 68.5, 72.2, 88.5, 122.6, 155.8, 174.3; IR (KBr): 1170, 1265, 1710, 3518 cm^{-1}; FABMS: (*m*/*z*, %): 251 (M^++23, 32), 187 (94), 151 (26), 127 (100), 55 (44); HRMS (ESI): *m*/*z* calculated for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1431.

Acknowledgements

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