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First synthesis and determination of the absolute stereochemistry of *iso*-cladospolide-B and cladospolides-B and C☆

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Abstract—The syntheses of *iso*-cladospolide-B, cladospolide-B and cladospolide-C are reported with 4*S*,5*S*,11*S*-configuration. Of the three stereogenic centres, the C-4/C-5 *vic*-diol was created by Evans aldol condensation, while the C-11 stereocentre was created by Jacobsen's method. The synthesis of cladospolides **1**–**3** defined the absolute stereochemistry of these natural products.

1. Introduction

Cladospolide-B (**1**) and cladospolide-C (**2**) were isolated[1] from *Cladosporium tenuissimum*, while *iso*-cladospolide-B (**3**) was isolated[2] from marine fungal species. Based on the earlier proposals,[2,3] we have synthesised (4*S*,5*S*,11*R*)-**1A**, (4*R*,5*R*,11*R*)-**2A** and (4*S*,5*S*,11*R*)-**3A**, besides the C-11 epimer (4*R*,5*R*,11*S*)-**2B**, whose spectral data and optical rotation values, however, did not match the reported data. From the preceding study[4] on the synthesis of **2B**, it was observed that epimerisation at C-11 significantly modified the optical rotation from a negative value ($[\alpha]_D$ −40.99 (*c* 0.3, $CHCl_3$)) in (4*R*,5*R*,11*R*)-**2A** to a positive value $[\alpha]_D$ +29.4 (*c* 0.3, $CHCl_3$) in (4*R*,5*R*,11*S*)-**2B**, while the reported value for cladospolide-C was $[\alpha]_D$ +59.7 (*c* 0.4, MeOH).[2] Based on this observation, it was proposed to synthesise **1**–**3** with 4*S*,5*S*,11*S*-configurations. During the course of our synthetic studies, Carmeli and co-workers[5] reported the isolation of *iso*-cladospolide-B (**3**) from a different *Cladosporium* sps. and determined the absolute stereochemistry of **3** as 4*S*,5*S*,11*S* by Riguera's method and circular dichroism. Further, they proposed the same stereochemical configuration for **1**. Herein, we report the first syntheses of **1**–**3** and the determination of their absolute stereochemistry (Fig. 1).

Retrosynthetic analysis (Scheme 1) of **1** and **3** revealed that both compounds could be envisioned from the seco-acid **4**, while **4** could be prepared through **5** and **6** from 5-carbon acetylenic alcohol **7**. A similar consideration on **2** revealed that the corresponding *trans*-acid **8** is the late stage intermediate, which could also be realised from **7**. Thus, in the present study, the salient features are that the *vic*-diol will be generated by an Evans aldol condensation, while the C-11 stereocentre would be obtained by Jacobsen kinetic resolution.

Accordingly, **7** (Scheme 2) on reaction with NaH–BnBr followed by coupling of **9** with allyl bromide gave **10** (77%), which on further treatment with *m*-CPBA furnished racemic epoxide **11** (80%). Kinetic resolution of racemic epoxide **11** with *R*,*R*-Jacobsen's catalyst[6] afforded chiral epoxide **12** (43%) and diol **13** (40%). Reduction of epoxide **12** with LAH followed by silylation of carbinol **14** with TBDPSCl gave TBDPS ether **15** (97%).

Catalytic hydrogenation of **15** in one-pot effected reduction of the triple bond along with debenzylation to afford saturated alcohol **6** in 92% yield. Oxidation of alcohol **6** with IBX and aldol condensation[7] of aldehyde **16** with *R*-chiral auxiliary (**I**) furnished **17** in 65% yield. Removal of the *p*-methoxybenzyl group in **17** followed by acetonation of diol **18** afforded **19** (85%), which on reduction with $LiBH_4$ gave alcohol **5** (79%). Oxidation of **5** with IBX, followed by Wittig olefination in MeOH, furnished *cis*-product **21** in 80% yield. Base catalysed hydrolysis of methyl ester **21** followed by desilylation of **22** with HF–pyridine afforded seco-acid **4** (75%). Macrolactonisation of **4** under Yamaguchi reaction

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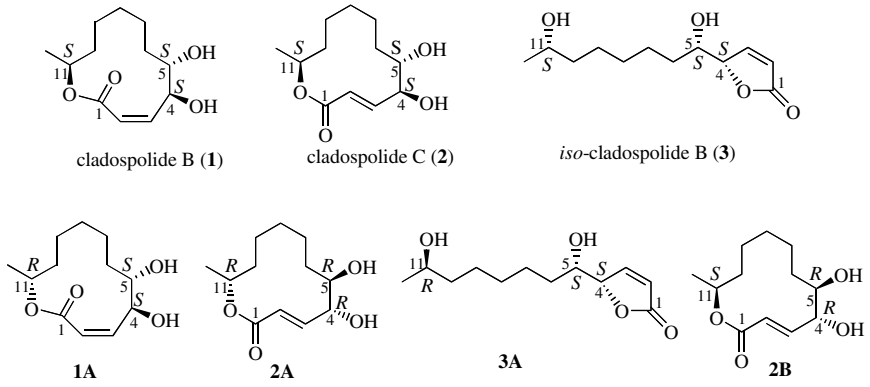
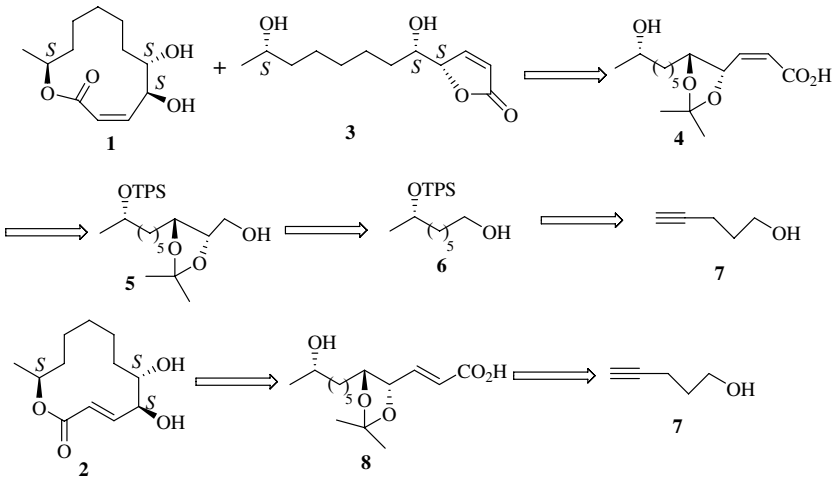


Figure 1.



Scheme 1.

conditions[8] gave macrolide **23** in 66% yield, which on acetonide hydrolysis with $TiCl_4$ furnished cladospolide-B **1** as the exclusive product in 85% yield, while exposure of **23** to aq AcOH (60%) gave cladospolide-B **1** and *iso*-cladospolide **3** in 52% and 20% yields, respectively.

The comparable optical rotation value of synthetic (4*S*,5*S*,11*S*)-**3**, $[\alpha]_D$ −59.6 (*c* 0.3, $CHCl_3$), with that of the reported[5] value of $[\alpha]_D$ −61.0 (*c* 16.6, MeOH) thus establishes the absolute configuration of butenolide **3** as 4*S*,5*S*,11*S*. Similarly, the optical rotation value of synthetic (4*S*,5*S*,11*S*)-**1** $[\alpha]_D$ +24.8 (*c* 0.4, $CHCl_3$), which is comparable with the reported[9] value of $[\alpha]_D$ +26.9 (*c* 0.4, MeOH), confirms the absolute configuration of **1** as 4*S*,5*S*,11*S*.

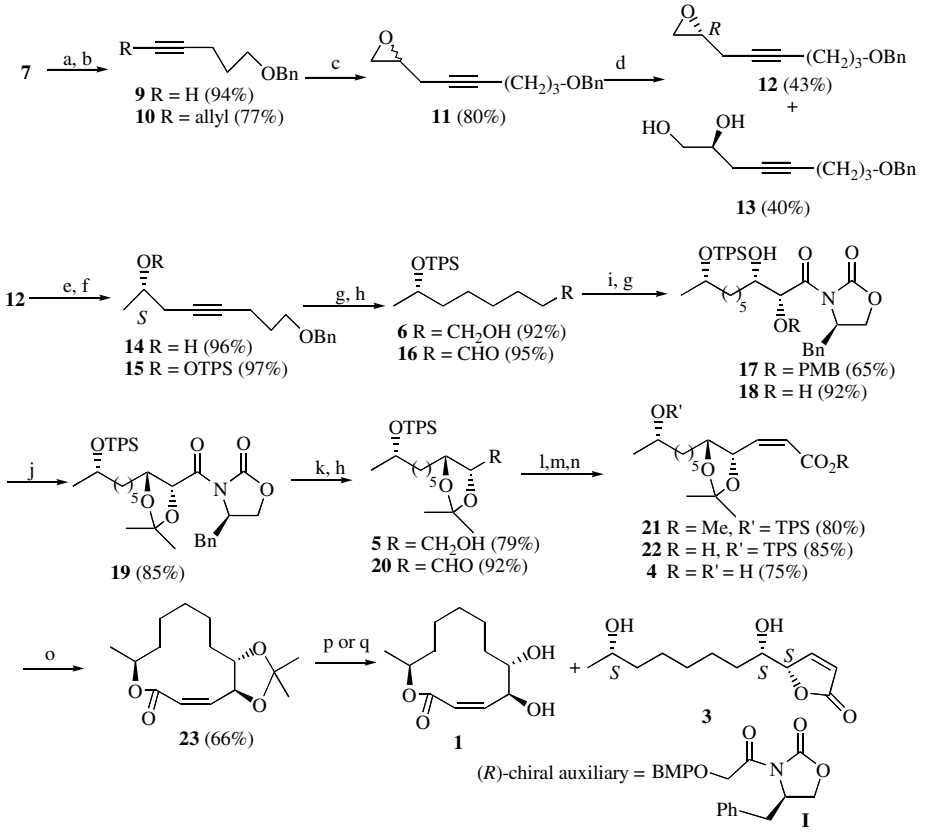
In a further study on the synthesis of cladospolide-C **2**, aldehyde **20** (Scheme 3) was converted into *trans*-ester **24** (85%). Hydrolysis of ester **24** with 4 N NaOH followed by treatment of **25** with HF–pyridine gave seco-acid **8**. Reaction of **8** with 2,4,6-trichlorobenzoyl chloride under Yamaguchi conditions furnished macrolide **26**, which on exposure to $TiCl_4$ underwent facile deprotection to afford cladospolide-C **2** in 85% yield. The optical rotation value of synthetic (4*S*,5*S*,11*S*)-**2**, $[\alpha]_D$ +45.9 (*c* 0.4, $CHCl_3$), was comparable with the reported[1] optical rotation $[\alpha]_D$ +59.7 (*c* 0.4, MeOH). Similarly, the optical rotation $[\alpha]_D$ −40.9 (*c* 0.3, $CHCl_3$) observed for synthetic (4*R*,5*R*,11*R*)-**2A** and (4*S*,5*S*,11*S*)-**2** differs in the sign of rotation. The spectroscopic analysis and optical rotation value were in accordance with the reported data.

Thus, in conclusion, taking clues from the synthesis of the (4*R*,5*R*,11*S*)-isomer **2B** of cladospolide C, the syntheses of **1**, **2** and **3** were achieved with (4*S*,5*S*,11*S*)-configuration. This study accomplished the first synthesis of **1**–**3** and the determination of their absolute stereochemistry. A further study on the synthesis of related molecules to determine their absolute stereochemistry is in progress.

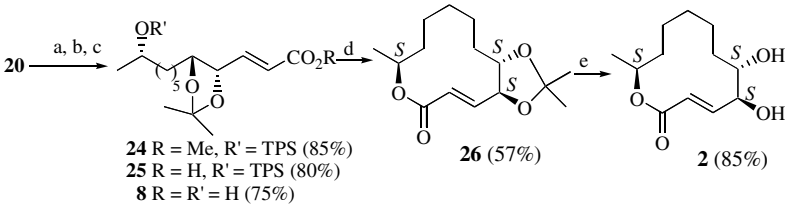
2. Spectral data for selected compounds

2.1. Cladospolide-B (1)

Colourless solid, mp 100–102 °C (lit.[9] mp 98–102 °C); $[\alpha]_D$ +24.8 (*c* 0.4, $CHCl_3$); (lit.[9]) $[\alpha]_D$ +26.9 (*c* 0.4, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, $J = 6.6$ Hz, H-12), 1.17–2.05 (m, 10H, 5 × $-CH_2$), 3.84–3.94 (m, 1H, H-5), 4.96–5.03 (m, 1H, H-11), 5.06–5.16 (m, 1H, H-4), 5.85 (dd, 1H, $J = 11.9$, 1.1 Hz, H-2), 6.13 (dd, 1H, $J = 12.0$, 8.5 Hz, H-3); ^{13}C NMR



Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C–rt, 5 h; (b) allyl bromide, CuI, K_2CO_3 and TBAI, DMF, rt, 12 h; (c) *m*-CPBA, CH_2Cl_2, rt, 10 h; (d) *R,R*-Jacobsen's catalyst, H_2O, rt, 12 h; (e) LAH, THF, 0 °C–rt, 5 h; (f) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt, 3 h; (g) 10% Pd/C, MeOH, H_2, 12 h; (h) IBX, DMSO, 0 °C–rt, 5 h; (i) (*R*)-chiral auxiliary (**I**), Bu_2BOTf, DIPEA, CH_2Cl_2, 0–78 °C, 4 h; (j) 2,2-DMP, CSA, 0 °C–rt, 30 min; (k) $LiBH_4$, THF–H_2O (2:1), 0 °C–rt, 3 h; (l) $Ph_3P{=}CHCOOMe$, MeOH, 0 °C–rt, 2 h; (m) 4 N NaoH, MeOH, 0 °C–rt, 4 h; (n) HF–pyridine, THF, 0 °C–rt, 12 h; (o) 2,4,6-trichlorobenzoyl chloride, THF, Et_3N, 0 °C–rt, 8 h, DMAP, toluene, reflux, 20 h; (p) $TiCl_4$, CH_2Cl_2, 0 °C–rt, 2 h, 85% exclusive **1**; (q) 80% AcOH, rt, 12 h, **3**, in 20% and **1** in 52%.



Scheme 3. Reagents and conditions: (a) $Ph_3P{=}CHCOOMe$, toluene, reflux, 4 h; (b) 4 N NaOH, MeOH, 0 °C–rt, 4 h; (c) HF–pyridine, THF, 0 °C–rt, 12 h; (d) 2,4,6-trichlorobenzoyl chloride, THF, Et_3N, 0 °C–rt, 8 h, DMAP, toluene, reflux, 20 h; (e) $TiCl_4$, CH_2Cl_2, 0 °C–rt, 2 h.

(75 MHz, $CDCl_3$): δ 19.6, 21.5, 24.6, 25.8, 30.5, 32.3, 68.1, 73.8, 74.5, 121.5, 149.0, 166.8; IR (KBr): 1075, 1282, 1350, 1635, 1715, 2940, 3320 cm^{-1}; ESIMS: (*m/z*, %): 229 (M^++1, 35), 167 (58), 149 (24), 109 (100); HRMS (ESI): *m/z* calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1436.

2.2. Cladospolide-C (2)

Colourless solid, mp 90–92 °C; (lit.[1] mp 90–91 °C); $[\alpha]_D$ +45.9 (*c* 0.4, $CHCl_3$); lit.[1] $[\alpha]_D$ +59.7 (*c* 0.4, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J = 6.0$ Hz, H-12), 1.15–1.90 (m, 10H, 5 × CH_2), 3.45–3.57 (m, 1H, H-5), 4.15–4.22 (m, 1H, H-4), 5.15–5.25 (m, 1H, H-11), 6.12 (d, 1H, $J = 14.9$ Hz, H-2), 7.08 (dd, 1H, $J = 14.9$, 3.0 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 24.2, 24.5, 27.4, 32.1, 34.4, 74.3, 76.6, 77.8, 124.2, 145.6, 166.2; IR (KBr): 850, 1170, 1265, 1635, 1710, 2925, 3518 cm^{-1}; FABMS: (*m/z*, %): 251 (M^++23, 12), 187 (94), 151 (26), 127 (100), 55 (44); HRMS (FABMS): *m/z* calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1432.

2.3. *iso*-Cladospolide-B (3)

Colourless syrup, $[\alpha]_D$ −59.6 (*c* 0.3, $CHCl_3$); (lit.[5] $[\alpha]_D$ −61.0 (*c* 16.6, MeOH)); ^1H NMR (500 MHz, $CDCl_3$): δ 1.19 (d, 3H, $J = 5.8$ Hz, H-12), 1.22–1.61 (m, 10H, 5 × –CH_2), 3.70 (m, 1H, H-11), 3.77 (m, 1H, H-5), 4.97 (q, 1H, $J = 1.8$ Hz, H-4), 6.18 (dd, 1H, $J = 5.8$,

1.5 Hz, H-2), 7.54 (dd, 1H, $J = 5.8$, 1.3 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 26.8, 26.5, 30.4, 34.8, 40.3, 68.6, 71.9, 88.0, 122.3, 157.4, 175.8; IR (KBr): 1175, 1262, 1638, 1715, 3520 cm^{-1}; FABMS: (m/z, %): 251 (M^++23, 42), 167 (17), 149 (18), 109 (100); HRMS (FABMS): m/z calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1439, found 229.1435.

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