An Expedient Total Synthesis of (–)-Cladospolide A

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Abstract: A simple and efficient total synthesis of (–)-cladospolide A is described here, which involves either olefin cross metathesis or Julia–Kocienski olefination and Yamaguchi macrolactonization as key steps.

Key words: olefin cross metathesis, Julia–Kocienski olefination, macrolactonization, cladospolides, total synthesis

The twelve-membered macrolactone (–)-cladospolide A[1] (**1**) was first isolated from the culture filtrate of *Cladosporium fulvam* FI-113 along with its group member cladospolide B[2] (**2**) by Isogai and co-workers in 1985 (Figure 1). Later, **1** also has been isolated from the fungus *Cladosporium tenuissimum* as well as marine fungal species I962S215 together with other family members cladospolide C[3a] and isocladospolide B,[3b] respectively. The structure and absolute stereochemistry of **1** was determined as (4*R*,5*S*,11*R*,2*E*)-4,5-dihydroxy-2-decen-11-olide by means of Mosher's ester as well as X-ray crystallographic analysis.[1] While the plant growth regulator (–)-cladospolide A inhibits root growth of lettuce seedlings, cladospolide B promotes the growth. Another congener cladospolide C (**4**) has been reported to inhibit shoot elongation of rice seedlings.[2] The 4-oxo lactone, cladospolide D[4] (**5**), a newly isolated species from *Cladosporium sp*. FT-0012, shows antimicrobial activity against *Mucor racemosus* and *Pyricularia oryazae*.

Due to their impressive biological profiles, cladospolides have attracted the interest of synthetic chemists since their isolation and (–)-cladospolide A has been the subject of total synthesis[5] by the groups of Mori, Ichimoto, Solladié, and Banwell. In continuation of our interest in designing and synthesizing natural[6] and unnatural[7] products, we developed interest in the synthesis of (–)-cladospolide A and its congeners. Herein, we disclose a short and efficient synthesis of (–)-cladospolide A.

As per our retrosynthetic analysis (Scheme 1), the macrolide **1** could be easily obtained from the precursor **6**, which in turn could be synthesized from **7** through macrolactonization. The seco acid **7** could be traced back to compound **8** involving Horner–Wadsworth–Emmons reaction and compound **8** is expected to obtain from the intermediate **9**. Here, we envisioned that the key intermediate **9** could be constructed either by olefin cross-metathesis reaction between alkenes **10** and **12** or by Julia–Kocienski olefination between sulfone **13** and aldehyde **11**. Both the fragments **12** and **13** could be easily derived from a common intermediate **14** which could be synthesized from optically active D-ribose in few steps.

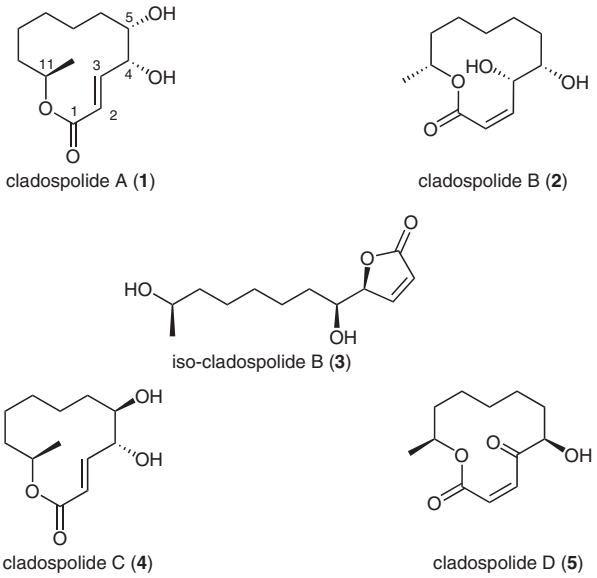

Figure 1 Cladospolide family

Our journey for the synthesis of (–)-cladospolide A began with the Wittig reaction on D-ribose monoacetonide **15**, using ethyl(triphenylphosphoranylidene)acetate in the presence of a catalytic amount of benzoic acid followed by protection of the resultant diol as di-TBS ether afforded the compound **16** in 80% yield. Saturation of the double bond provided ester **17** which upon careful reduction with LAH furnished the alcohol **18** in 82% yield. One carbon homologation to **19** was easily accomplished in 87% yield through oxidation of alcohol **18** with PCC to corresponding aldehyde followed by Wittig reaction with triphenyl phosphonium methylidene (Scheme 2).

Fragment **19** upon exposure to key olefin cross-metathesis reaction[8] conditions with the known alkene **20** in the presence of Grubbs II catalyst[9] **21** (5 mol%), underwent cross-coupling to the desired intermediate **22** as the major isomer, which was then hydrogenated with Pd-C to afford compound **23** in 42% yield over two steps (Scheme 3). The low yield in the olefin cross-metathesis step could be attributed to the formation of other self coupled products. However, the possible drawbacks of olefin cross-metathesis reaction have prompted us to identify an alternative way to synthesize the intermediate **22** and it readily

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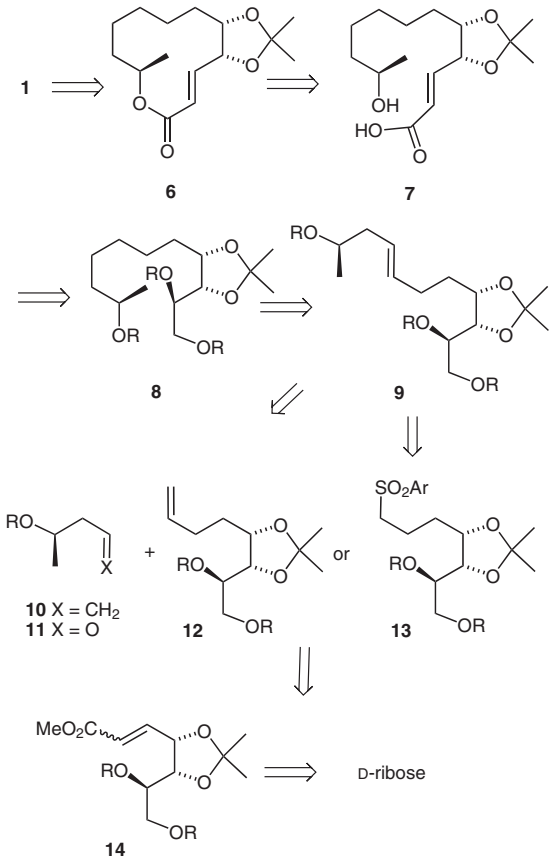
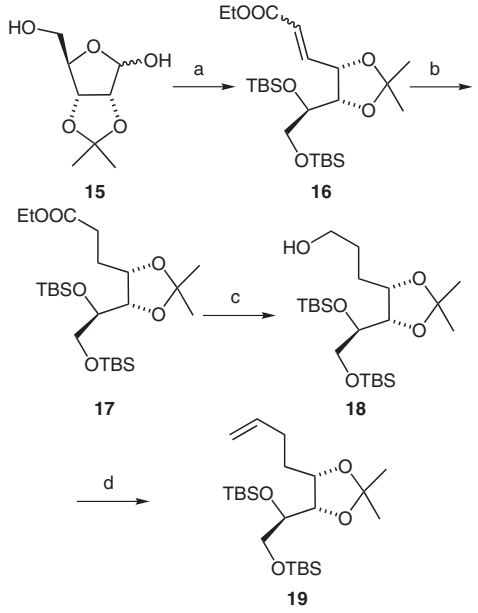
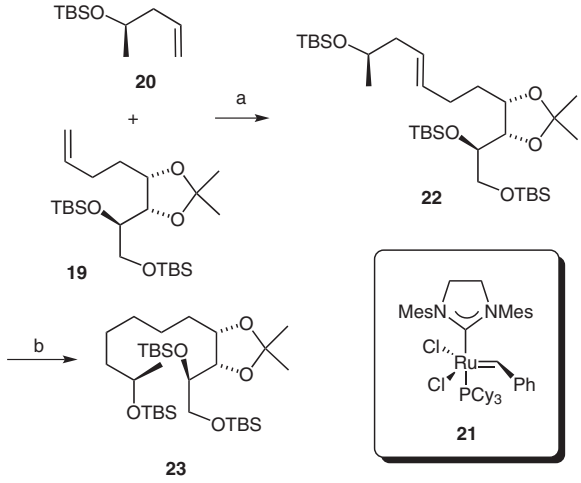


Scheme 1 Retrosynthetic analysis of (–)-cladospolide A



Scheme 2 *Reagents and conditions*: a) i) $Ph_3PCH{=}COOEt$, CH_2Cl_2, r.t.; ii) TBSCl, DMF, r.t., 2 h, 76% for two steps; b) 5% Pd-C/H_2, EtOH, r.t., 2 h, 90%; c) $LiAlH_4$, Et_2O, 0 °C, 15 min, 82%; d) (i) PCC, MeCOONa, 4 Å MS, CH_2Cl_2, 0 °C; ii) Ph_3PCH_2Br, KO*t*-Bu, THF, 0 °C, 78% for two steps.

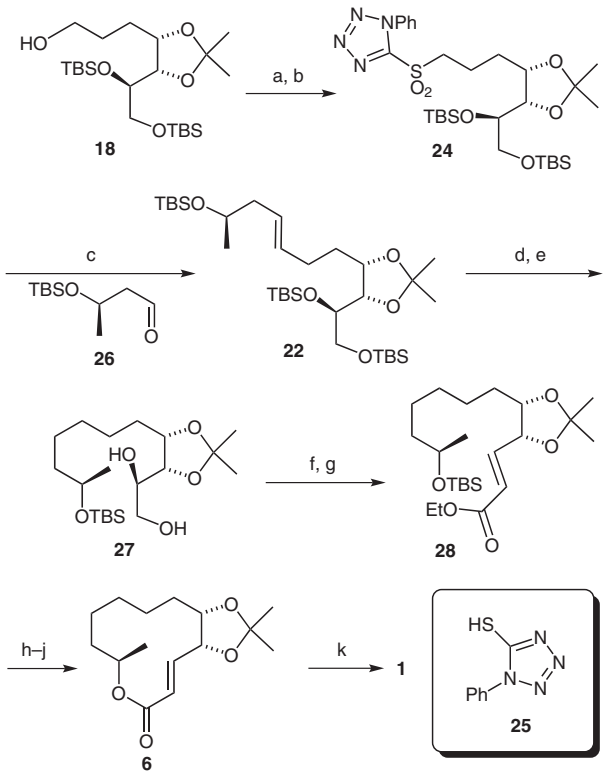
crossed our mind to utilize the Julia–Kocienski olefination[10] to construct the intermediate **22**.



Scheme 3 *Reagents and conditions*: a) **21** (5 mol%), toluene, 110 °C, 6 h; b) 5% Pd-C/H_2, EtOH, r.t., 2 h, 42% for two steps.

Thus, alcohol **18** was converted into the sulfone **24** in a couple of steps using Mitsunobu reaction with 1-phenyl-1*H*-tetrazol-5-thiol[11] **25**, followed by oxidation of the resultant sulfide (Scheme 4). Gratifyingly, Julia–Kocienski olefination between sulfone **24** and the aldehyde **26** in the presence of LHMDS proceeded smoothly to provide **22** in 83% yield. Having the intermediate **22** in hand in good quantity, we proceeded further to accomplish the total synthesis of **1**. Consequently, catalytic hydrogenation of **22** to its saturated counterpart **23**, followed by selective deprotection of vicinal TBS ethers with tetrabutylammonium fluoride at 0 °C afforded the diol **27** in good yield. Oxidative cleavage of diol **27** with silica gel supported $NaIO_4$[12] furnished the corresponding aldehyde which was immediately subjected to Horner–Wadsworth–Emmons reaction[13] to furnish *trans*-α,β-unsaturated ester **28** as the major isomer in 64% yield along with its *cis*-isomer in 14% yield. The saponification of the *trans*-ester **28** with LiOH followed by removal of the TBS ether and implementation of the key macrolactonization using Yamaguchi protocol[14] fruitfully underwent cyclization to give the macrolactone **6** in 71% yield. Finally, deprotection of the acetonide was accomplished with trifluoroaectic acid[15] to afford (–)-cladospolide A (**1**)[16] in 65% yield. The spectral data of synthetic **1** matches with that reported earlier,[5] thus confirming the accomplishment of a total synthesis of (–)-cladospolide A.

In summary, we have successfully accomplished the total synthesis of (–)-cladospolide A in 14 linear steps in 6% overall yield from D-ribose monoacetonide. This approach relies on four key reactions, explicitly, either olefin cross metathesis or Julia–Kocienski olefination for construction of the key intermediate **22**, Horner–Wadsworth–Emmons reaction to introduce exclusively the *trans*-α,β-unsaturated ester functionality and Yamaguchi macrolactonization to furnish the twelve-membered macrolide. This strategy is now being extended to synthesize its other congeners.



Scheme 4 *Reagents and conditions*: a) **25**, Ph_3P, DIAD, THF, –20 °C, 92%; b) $(NH_4)_6Mo_7O_{24}·4H_2O$, 30% H_2O_2, EtOH, r.t., 88%; c) LiHMDS, THF, –78 °C, **26**, 83%; d) 5% Pd-C/H_2, EtOH, r.t., 2 h, 84%; e) TBAF (1 M soln in THF), THF, 0 °C, 2 h, 80%. f) silica supp. $NaIO_4$, CH_2Cl_2, 0 °C, 1 h; g) $(OEt)_2P(O)CH_2COOEt$, LiCl, DIPEA, THF, 6 h, 64% for two steps; h) LiOH, THF–MeOH–H_2O, 4 h, 93%; i) TBAF (1 M soln in THF), THF, 55 °C, 81%; j) 2,4,6-trichlorobenzoyl chloride, Et_3N, 2 h, then DMAP, toluene, reflux, 8 h, 71%; k) TFA, MeCN–H_2O, 0 °C, 1 h, 65%.

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(16) **Spectral Data for Selected Compounds**
Compound **22**: R_f = 0.28 (2% EtOAc in hexane); $[\alpha]_D^{20}$ –27.6 (*c* 0.50, $CHCl_3$). IR (neat): 3020, 2931, 1657, 1216, 1045, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.45–5.42 (2 H, m), 4.09–4.05 (3 H, m), 3.80–3.74 (1 H, m), 3.66 (1 H, dd, *J* = 11.3, 4.8 Hz), 2.13–2.03 (4 H, m), 1.63–1.53 (2 H, m), 1.40 (3 H, s), 1.31 (3 H, s), 1.10 (3 H, d, *J* = 6.1 Hz), 0.90 (9 H, s), 0.88 (9 H, s), 0.86 (9 H, s), 0.11 (3 H, s), 0.08 (3 H, s), 0.06 (6 H, s), 0.04 (3 H, s), 0.03 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.0, 127.2, 107.8, 77.4, 76.4, 72.6, 68.8, 65.3, 43.0, 30.1, 29.1, 28.4, 26.0, 25.96, 25.90, 23.3, 18.4, 18.1, –3.5, –4.5, –4.6, –4.7, –5.3, –5.4.
Compound **23**: R_f = 0.26 (2% EtOAc in hexanes); $[\alpha]_D^{20}$ –29.7 (*c* 0.66, $CHCl_3$). IR (neat): 3021, 2930, 2858, 2640, 1380, 1216, 1044, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.08–4.04 (2 H, m), 3.79–3.73 (3 H, m), 3.68–3.64 (1 H, m), 1.65–1.24 (10 H, complex m), 1.39 (3 H, s), 1.30 (3 H,

s), 1.09 (3 H, d, *J* = 6.1 Hz), 0.90 (9 H, s), 0.87 (9 H, s), 0.85 (9 H, s), 0.10 (3 H, s), 0.07 (3 H, s), 0.05 (6 H, s), 0.037 (3 H, s), 0.033 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.7, 76.6, 72.6, 68.5, 65.3, 39.6, 30.0, 29.8, 28.4, 26.1, 26.0, 25.96, 25.90, 23.8, 18.4, 18.2, 18.1, –3.5, –4.4, –4.7, –4.8, –5.3, –5.4. HRMS (EI): *m/z* calcd for $[C_{32}H_{70}O_5Si_3 + Na]^+$: 641.4429; found: 641.4412.

Compound **6**: R_f = 0.34 (10% EtOAc in hexanes); $[\alpha]_D^{20}$ –12.7 (*c* 0.83, $CHCl_3$). IR (neat): 3020, 2937, 2401, 1712, 1382, 1216, 1023, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (1 H, dd, *J* = 15.7, 9.1 Hz), 6.05 (1 H, d, *J* = 15.8 Hz), 5.08–5.15 (1 H, m), 4.68 (1 H, dd, *J* = 8.8, 6.4 Hz), 4.10 (1 H, ddd, *J* = 7.9, 6.1, 1.8 Hz), 1.73–1.61 (2 H, m), 1.54–1.20 (7 H, m), 1.48 (3 H, s), 1.34 (3 H, s), 1.27 (3 H, d, *J* = 6.4 Hz), 0.98–0.92 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 145.1, 124.3, 109.4, 79.5, 76.4, 72.7, 33.3, 30.7, 28.1, 27.9, 25.4, 21.8, 20.0, 18.3.

(–)–Cladospolide A (**1**): R_f = 0.19 (50% EtOAc in hexanes); mp 90–92 °C; $[\alpha]_D^{20}$ –40.4 (*c* 0.50, $CHCl_3$). IR (KBr): 3437, 2927, 2870, 1713, 1651, 1462, 1377, 1269, 1165, 1021, 880 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (1 H, dd, *J* = 16.0, 5.5 Hz), 6.20 (1 H, dd, *J* = 16.0, 1.5 Hz), 5.15–5.08 (1 H, m), 4.55–4.53 (1 H, m), 3.65 (1 H, ddd, *J* = 9.1, 1.8, 1.2 Hz), 1.81–1.11 (9 H, complex m), 1.27 (3 H, d, *J* = 6.4 Hz), 0.90–0.84 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 145.5, 122.2, 74.6, 72.9, 72.8, 32.3, 30.6, 28.1, 25.0, 22.5, 18.9.