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An efficient total synthesis of (+)-Cladospolide C

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ABSTRACT

The asymmetric synthesis of (+)-Cladospolide C has been achieved in 11 steps with 26% overall yield. Key steps in the sequence involve KAPA-promoted alkyne Zipper reaction, TPP-promoted enyne ester (ynoate) to diene ester (dienoate) isomerization, Sharpless asymmetric dihydroxylation and Yamaguchi macrolactonization.

Cladospolide C (**1**), a 12-membered macrolide was isolated in 1995 by Fukuda and co-workers from a culture filtrate of the fungus, *Cladosporium tenuissimum*[1] along with the already known Cladospolide A (**2**) and Cladospolide B (**3**, Fig. 1). These 12-membered macrolides are plant growth regulators and have been shown to inhibit shoot elongation in rice seedlings.[2–5] The biological properties of Cladospolide C suggest the inhibition of gibberellin synthesis.[1] The biological activity and structure of these macrolides have attracted the interest of organic chemists and various research groups have reported total synthesis of Cladospolide A and B.[6,7] However, there are only four reports on the total synthesis of Cladospolide C.[8–11] Herein, we report an efficient asymmetric synthesis of (+)-Cladospolide C in high yield compared to the earlier reported methods.

The synthesis commenced with the (*R*)-propylene oxide **4**, which was treated with the lithiated 1-octyne to afford alkynol **5** in 89% yield. The alkynol **5** was subjected to potassium 3-aminopropylamide (KAPA)-mediated alkyne zipper reaction,[12] in which alkyne functionality moves from the centre to the terminus of a chain to give the alkyne **6** in 80% yield. The hydroxyl group of compound **6** was then protected as *tert*-butyl dimethylsilyl ether **7** (TBDMSCl, imidazole, 95% yield). In the next step, the carboxylation of terminal alkyne was carried out using *n*-butyl lithium and ethyl chloroformate to obtain alkyne ester **8** in 98% yield. With the alkyne ester **8** in hand, the stage was set for the formation of the diene ester under the Rychnovsky modified condition of the Trost isomerization.[13] Thus, the ynoate **8**, exposed to Ph_3P/PhOH in benzene at room temperature for 12 h led to the clean formation of diene ester **9** in 93% yield. The dienoate **9** was treated under enantio- and regio-selective Sharpless asymmetric dihydroxylation[14] conditions using AD-mix-β to give a diol **10** in 82% yield, which was treated with 2,2-dimethoxypropane in presence of catalytic amount of camphor sulfonic acid to afford **11** in 87% yield. To set the stage for Yamaguchi macrolactonization, the compound **11** was subjected to ester hydrolysis (LiOH, THF/H_2O, 96% yield) followed by desilylation (TBAF, THF, 85% yield) reaction to provide the hydroxyl acid **13**. Macrolactonization of **13** using Yamaguchi conditions gave the lactone **14** in 86% yield[15] which on exposure to titanium tetrachloride for the cleavage of acetonide furnished the Cladospolide C **1** in 85% yield (Scheme 1).[16] The physical

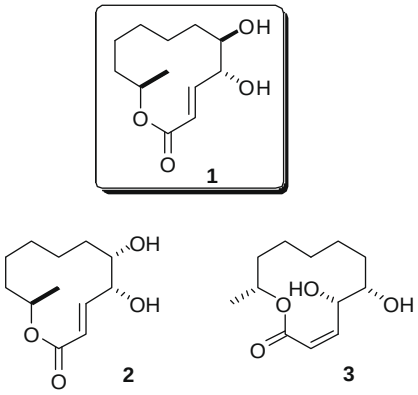

Figure 1.

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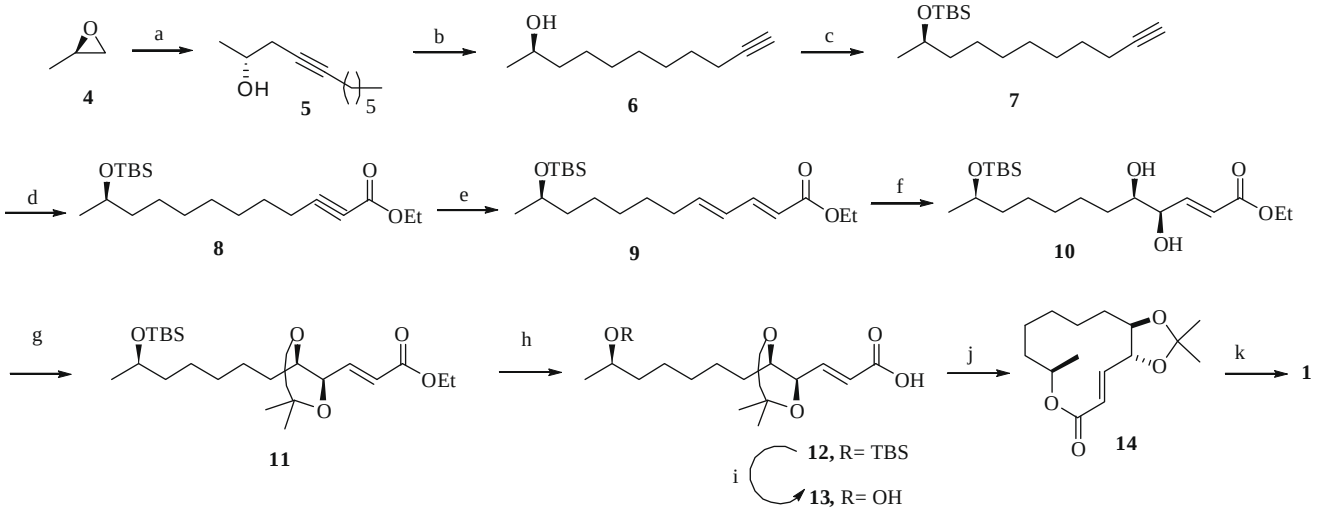

Scheme 1. Reagents and conditions: (a) 1-octyne, *n*-BuLi, THF, HMPA, −40 °C to 0 °C to −20 °C, 16 h, 89%; (b) KH, 1,3-diaminopropane, rt, 3 h, 80%; (c) TBDMSCl, imidazole, DMF, 0 °C to rt, 2 h, 95%; (d) ethyl chloroformate, *n*-BuLi, −78 °C, 1 h, 98%; (e) PPh_3, PhOH, benzene, 12 h, 93%; (f) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 24 h, 82%; (g) 2,2-DMP, CSA (cat.), CH_2Cl_2, 1 h, 87%; (h) LiOH, THF/H_2O, rt, 12 h, 96%; (i) TBAF, THF, rt, 24 h, 85%; (j) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, DMAP, benzene, reflux, 10 h, 85%; (k) $TiCl_4$, CH_2Cl_2, 0 °C, 1 h, 86%.

(mp, specific rotation) and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR and MS) of the obtained target molecule were in full agreement with the reported natural product data. The specific rotation of the synthetic Cladospolide C, (+58.0, *c* 0.45, MeOH), was comparable with the natural product (+59.7, *c* 0.4, MeOH).[1]

In conclusion, an efficient synthesis of 12-membered macrolide (+)-Cladospolide C has been achieved using alkyne zipper reaction, ynoate to dienoate isomerization, Sharpless asymmetric dihydroxylation and Yamaguchi macrolactonization as the key steps. The chemistry described here offers a high yielding strategy (26% overall yield), which has potential for application to the synthesis of other stereoisomers and analogues of Cladospolide C.

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16. *Spectral data of new compounds*: *(R)-undec-3-yn-2-ol* **(5)**: $[\alpha]_D^{27}$ −11.6 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3508, 2923, 2855, 1465, 901 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (sextet, *J* = 6.5 Hz, 1H), 2.36–2.19 (m, 2H), 2.15 (tt, *J* = 7.3, 2.2 Hz, 2H), 1.80 (br s, OH), 1.53–1.29 (m, 8H), 1.21 (d, *J* = 5.8 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 83.0, 76.0, 66.4, 31.2, 29.2, 28.8, 28.4, 22.4, 22.0, 18.6, 13.9; MS (ESI): *m*/*z* 169.0 $(M+H)^+$.*(R)-Undec-10-yn-2-ol* **(6)**: $[\alpha]_D^{27}$ −6 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3737, 3416, 2926, 2858, 2354, 1630, 1088, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80–3.70 (m, 1H), 2.16 (td, *J* = 7.0, 2.6 Hz, 2H), 1.84 (t, *J* = 2.6 Hz, 1H), 1.57–1.23 (m, 12H), 1.17 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 84.6, 68.1, 68.0, 39.2, 29.4, 29.0, 28.6, 28.4, 25.6, 23.4, 18.0.
(R)-tert-Butyldimethyl(undec-10yn-2-yloxy)silane **(7)**: $[\alpha]_D^{27}$ −8 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3508, 3312, 2932, 2858, 2219, 1462, 1251, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80–3.70 (m, 1H), 2.16 (td, *J* = 6.8, 2.6 Hz, 2H), 1.81 (t, *J* = 2.6 Hz, 1H), 1.58–1.25 (m,12H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 84.6, 68.6, 68.0, 39.7, 29.5, 29.1, 28.7, 28.5, 25.9, 25.7, 23.8, 18.4, −4.4, −4.7; HRMS: calcd for $C_{18}H_{33}OSi$ $(M-H)^+$: 281.2480, found: 281.2486.
(R)-Ethyl-11-(tert-butyldimethylsilyloxy)dodec-2-ynoate **(8)**: $[\alpha]_D^{28}$ −5 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2929, 2856, 2235, 1712, 1464, 1252, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.2 (q, *J* = 7.2 Hz, 2H), 3.80–3.68 (m, 1H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.65–1.53 (m, 2H), 1.46–1.22 (m, 13H), 1.11 (d, *J* = 6.0, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.8, 89.3, 73.1, 68.5, 61.7, 39.6, 29.4, 29.0, 28.7, 27.5, 25.8, 25.6, 23.8, 18.6, 18.0, 14.0, −4.4, −4.7; MS (ESI): *m*/*z* 355.1 $(M+H)^+$.
(R,2E,4E)-Ethyl-11-(tert-butyldimethylsilyloxy)dodecan-2,4-dienoate) **(9)**: $[\alpha]_D^{28}$ −4.7 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2931, 2858, 1774, 1717, 1642, 1463, 1257, 1173, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 (dd, *J* = 15.4, 10.3 Hz, 1H), 6.19–6.04 (m, 2H), 5.73 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.80–3.70 (m, 1H), 2.17 (q, *J* = 6.6 Hz, 2H), 1.49–1.21 (m, 11H), 1.1 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 145.0, 144.5, 128.3, 119.1, 68.5, 60.0, 39.5, 32.9, 29.2, 28.6, 25.8, 25.6, 25.4, 23.7, 14.2, −4.4, −4.7; HRMS: calcd for $C_{20}H_{39}O_3Si$ $(M+H)^+$: 355.2668, found: 355.2663.
(4R,5R,11R,E)-Ethyl-11-(tert-butyldimethylsilyloxy)4,5-dihydroxydodec-2-enoate) **(10)**: $[\alpha]_D^{25}$ +12 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3395, 2931, 2858, 1709, 1656, 1270, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (dd, *J* = 15.6, 4.9 Hz, 1H), 6.09 (dd, *J* = 15.6, 1.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.13–4.03 (m, 1H), 3.80–3.69 (m, 1H), 3.56–3.46 (m, 1H),2.59 (br s, 1H), 2.27 (br s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.64–1.22 (m, 10H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 147.3, 122.1, 74.0, 73.9, 68.5, 60.5, 39.5, 32.9, 29.6, 25.8, 25.7, 25.6, 23.7, 18.0, 14.1, −4.4, −4.7; HRMS: calcd for $C_{20}H_{41}O_5Si$ $(M+H)^+$: 389.2726, found: 389.2718.
(E)-Ethyl-3-((4R,5R)-5-((R)-6-(tert-butyldimethylsily-loxy)heptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate **(11)**: $[\alpha]_D^{27}$ +4.5 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3432, 2931, 2858, 1720, 1658, 1372, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (dd, *J* = 15.6, 5.7 Hz, 1H), 6.06 (dd, *J* = 15.6, 1.3 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.12–4.05 (m, 1H), 3.80–3.63 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.62–1.24 (m, 16H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.9, 144.1, 122.6, 109.2, 80.5, 80.2, 68.5, 60.5, 39.5, 32.0, 29.7,

27.2, 26.6, 25.8, 25.6, 23.8, 18.14, 14.2, −4.4, −4.7; HRMS: calcd for $C_{23}H_{44}NaO_5Si$ $(M+Na)^+$: 451.2862, found: 451.2850.*(E)-3-((4R,5R)-5-((R)-6-(tert-Butyldimethylsilyloxy) heptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid* **(12)**: $[\alpha]_D^{26}$ +3.5 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3438, 2931, 2858, 1702, 1658, 1374, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.94 (dd, *J* = 15.4, 5.2 Hz, 1H), 6.10 (d, *J* = 15.4, 1H), 4.15–4.10 (m, 1H), 3.81–3.73 (m, 1H), 3.72–3.66 (m, 1H), 1.63–1.24 (m, 16H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 146.8, 121.7, 109.5, 80.5, 80.1, 65.6, 39.6, 32.1, 29.7, 29.2, 26.6, 25.9, 25.6, 23.8, 18.1, −4.4, −4.7; MS (ESI): *m*/*z* 399.1 $(M+H)^+$.

(E)-3-((4R,5R)-5-((R)-6-Hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid **(13)**: $[\alpha]_D^{27}$ +8 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3446, 2922, 2852, 1706, 1643, 1461, 1260, 1168, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.94 (dd, *J* = 15.4, 5.3 Hz, 1H), 6.10 (dd, *J* = 15.4, 1.1 Hz, 1H), 4.18–4.10 (m, 1H), 3.84–3.66 (m, 2H), 1.64–1.24 (m, 16H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3, 145.6, 122.3, 109.3, 80.4, 79.9, 68.0, 38.7, 31.8, 29.3, 27.0, 26.4, 25.7, 25.3, 22.9; HRMS: calcd for $C_{15}H_{25}O_5$ $(M-H)^+$: 285.1701, found: 285.1710.

(3aR,8R,13aR,E)-2,2,8-Trimethyl-9,10,11,12,13,13a-hexahydro-3aH-[1,3]dioxolo-[4,5-e][1]oxacyclododecin-6(8H)-one **(14)**:[8] $[\alpha]_D^{26}$ +10.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.78 (dd, *J* = 15.8, 9.5 Hz, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 5.05–4.93 (m, 1H), 4.04 (dd, *J* = 9.3, 8.5 Hz, 1H), 3.90 (ddd, *J* = 11.0, 8.3, 4.2 Hz, 1H), 2.10–1.90 (m, 1H), 1.70–1.50 (m, 3H), 1.48–1.35 (m, 8H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.26–1.15 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 143.8, 125.9, 109.2, 80.3, 80.0, 75.3, 35.3, 29.7, 27.8, 27.2, 26.8, 25.1, 24.9, 20.6; MS (ESI): *m*/*z* 269.1 $(M+H)^+$.