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Enantioselective synthesis of (+)-patulolide C via proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination

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ABSTRACT

The enantioselective total synthesis of (+)-patulolide C isolated from *Penicillium urticae* has been achieved from commercially available 9-decen-1-ol. Jacobsen's kinetic resolution and sequential α-aminooxylation and Horner–Wadsworth–Emmons (HWE) olefination followed by Yamaguchi lactonization are used as the key reaction steps.

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1. Introduction

Patulolides A **1**, B **2**, and C **3** (Fig. 1) were isolated from the culture broth of the *Penicillium urticae* S11R59 and characterized by Yamada and co-workers.[1] These macrolides were found to show antifungal, antimicrobial, and anti-inflammatory activities. The reported pharmacological properties and structural features of patulolides make them highly attractive target molecules for the synthesis. Although several racemic[2] and enantioselective[3] approaches have been reported for the synthesis, most of them are rather lengthy, suffer from poor enantiocontrol, and use of inaccessible materials.

Within our recently initiated program on the synthesis of macrolides,[4] herein, we report an efficient synthesis of (+)-patulolide C **3** from the readily available 9-decen-1-ol utilizing Jacobsen's hydrolytic kinetic resolution and the MacMillan α-hydroxylation for the creation of two stereogenic centers. Finally, Yamaguchi's protocol was used for the construction of macrolide.

The retrosynthetic approach is outlined in Scheme 1. Patulolide C **3** could be envisioned to be obtained by Yamaguchi lactonization of enone **4**, which in turn could be made by a D-proline-catalyzed Macmillan α-hydroxylation and tandem olefination of aldehyde **5**, which could be obtained from commercially available 9-decen-1-ol **6**.

2. Results and discussion

The synthesis commences with 9-decen-1-ol **6**, protected as its benzyl ether **7** (Scheme 2). Epoxidation of alkene **7** with *m*-chloroperbenzoic acid (MCPBA) gave the racemic epoxide, which was subjected to Jacobsen's hydrolytic kinetic resolution[5] using (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) to give chiral epoxide **8**, 46%, (98% ee). Epoxide **8** on treatment with LAH in THF at 0 °C to rt for 2 h afforded secondary alcohol **9** in 87% yield, which was protected as its TBS ether **10** with TBSCl and imidazole in dry CH_2Cl_2. The subsequent removal of benzyl group using Li in liquid NH_3 in dry THF gave the primary alcohol, which was oxidized using IBX in dry CH_2Cl_2/DMSO to give the key aldehyde **5** in 82% yield.

The sequential α-aminooxylation-olefination[6] on aldehyde **5** catalyzed by 40 mol % D-proline using nitrosobenzene in DMSO at room temperature followed by in situ Horner–Wadsworth–Emmons (HWE) olefination with triethyl phosphonoacetate and

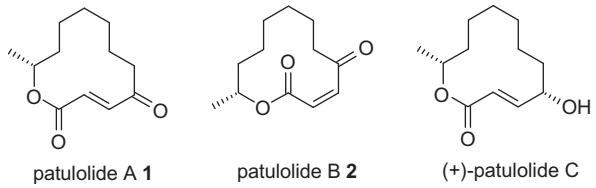

Figure 1. Twelve-membered natural macrolides.

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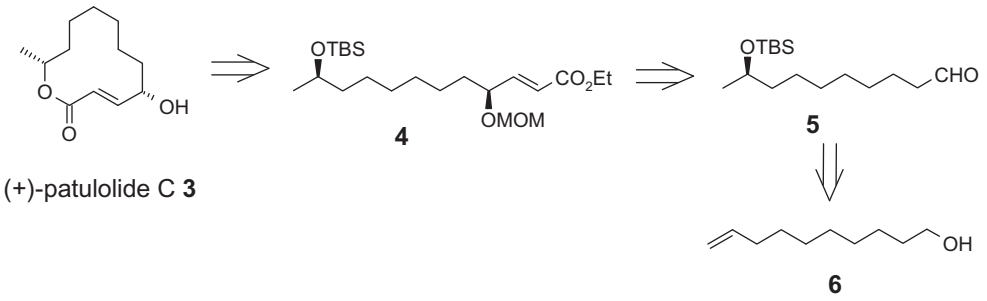
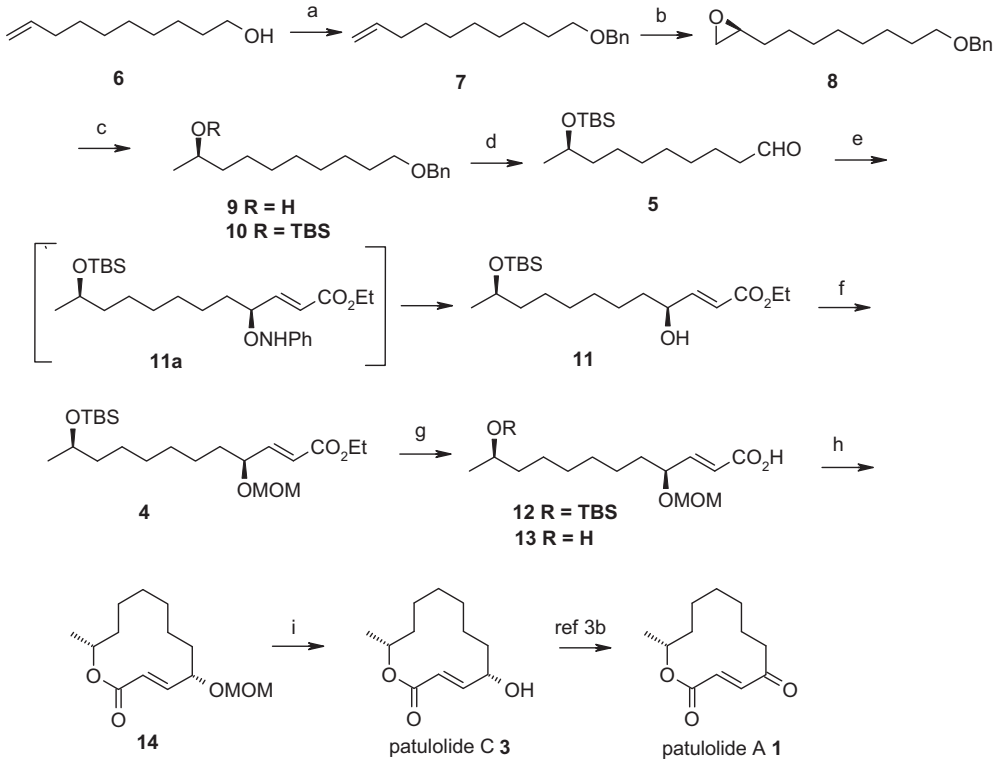


Scheme 1. Retrosynthesis.



Scheme 2. Reagents and conditions. (a) BnBr, NaH, dry THF, 0 °C to rt, 4 h, 95%; (b) (i) *m*-CPBA, $NaHCO_3$, dry DCM, 0 °C to rt, 4 h, 87%; (ii) (*S*,*S*)-Salen-Co(III-)-(OAc), (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C to rt, 19 h, 46% (98% ee); (c) (i) LAH, dry THF, 0 °C to rt, 2 h, 87%; (ii) TBSCl, imidazole, dry DCM, 0 °C 1 h, 92%; (d) (i) Li, liq NH_3, dry THF, 10 min, rt, 95%; (ii) IBX, dry DCM/DMSO, 0 °C, 4 h, 82%; (e) (i) PhNO, D-proline (40 mol %), triethyl phosphonoacetate, cesium carbonate, dry DMSO, rt, 1 h, 57%; (ii) $Cu(OAc)_2$, EtOH, rt, 12 h, 85%, (98% de); (f) MOMCl, *N*,*N*-diisopropylethyl amine, dry DCM, 0 °C, 5 h, 83%; (g) (i) LiOH, MeOH/H_2O, (4:1), 0 °C to rt, 14 h, 92%; (ii) PPTS, THF/H_2O, (1:1), rt, 18 h, 68%; (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 16 h, 70%; (i) $CeCl_3{\cdot}7H_2O$, CH_3CN/MeOH (2:1), 48 h, reflux, 60%.

Cs_2CO_3 as a base resulted in the formation of aminooxy olefinic ester **11a** in 57% yield, which followed by cleavage of the O–N bond using $Cu(OAc)_2$ in EtOH at rt gave the γ-hydroxy α,β-unsaturated ester **11** (98% de), a key intermediate in 85% yield. The hydroxy group was protected as its MOM ether **4** which followed by hydrolysis of ethyl ester using LiOH in aq MeOH gave the corresponding carboxylic acid **12** in 92% yield. Removal of the TBS group became problematic and could not be cleaved using TBAF and *p*-TsOH in MeOH (unidentified material with disappearance of double bond protons in ^1H NMR spectroscopy), but finally in the presence of PPTS in THF/H_2O (1:1) we were successful in removal affording the corresponding hydroxyacid **13** in 68% yield. The hydroxyacid **13** was subjected to macrolactonization by using the Yamaguchi procedure[7] (2,4,6-trichlorobenzoyl chloride and triethyl amine in THF followed by treatment with DMAP) to provide patulolide C MOM ether **14** in 70% yield. Removal of MOM group failed under the conditions using PTSA/MeOH, where the decomposition of material was observed. Finally, removal of the MOM group in **14** under neutral conditions using $CeCl_3{\cdot}7H_2O$ in CH_3CN/MeOH (2:1)[8] furnished the target patulolide C **3**. The spectroscopic properties and optical rotation of synthetic **3** were identical with those reported for the natural product.[1a]

In conclusion, a short synthesis of (+)-patulolide C has been achieved featuring Jacobsen's kinetic resolution, MacMillan aminooxylation, and HWE followed by Yamaguchi lactonization as the key reaction steps. Since patulolide C can be converted to patulolide A[3b] by simple oxidation reaction it becomes the formal synthesis of **1**.

3. Selected spectral data

3.1. (2*S*)-2-[8-(Benzyloxy)octyl]oxirane (8)

$[\alpha]_D^{25}$: −5.7 (*c* 1, $CHCl_3$); ^1H NMR: ($CDCl_3$, 300 MHz): δ 7.31–7.27 (m, 5H), 4.46 (s, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.86–2.81 (m, 1H), 2.68 (t, *J* = 4.15 Hz, 1H), 2.4 (dd, *J* = 2.64, 5.1 Hz, 1H), 1.64–1.23 (m,

14H); ^{13}C NMR; 132.7, 129.4, 128.2, 127.5, 127.3, 72.7, 70.4, 65.1, 52.3, 47.1, 32.4, 29.6, 29.3, 29.2, 29.1, 29, 28.6, 26.1, 26, 25.9, 25.8; IR (Neat): 1718, 1455. 1274, 1104 cm^{-1}; LC–MS *m*/*z*: 285, [M+Na]$^+$.

3.2. (2*R*)-10-(Benzyloxy)decan-2-ol (9)

$[\alpha]_D^{25}$: −4.8 (*c* 1, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 7.33–7.27 (m, 5H), 4.46 (s, 2H), 3.79–3.69 (m, 1H), 3.42 (t, *J* = 6.1 Hz, 2H), 1.63–1.53 (m, 2H), 1.42–1.26 (m, 13H), 1.16 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR: 138.5, 128.2, 127.5, 127.3, 126.7, 72.7, 70.3, 69.9, 39.2, 29.6, 29.4, 29.2, (2C), 26, 25.6, 23.3; IR (Neat): 3387, 2928, 2854, 1455, 1103 cm^{-1}; LC–MS *m*/*z*: 287 [M+Na]$^+$.

3.3. Ethyl (*E*,4*S*,11*R*)-11-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4-hydroxy-2-dodecenoate (11)

$[\alpha]_D^{25}$: +1.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (dd, *J* = 4.8, 15.6 Hz, 1H), 5.98 (d, *J* = 15.6 Hz, 1H), 4.29–4.24 (m, 1H), 4.18 (q, *J* = 7.8, 14.6 Hz, 2H), 3.77–3.71 (m, 1H), 1.60–1.53 (m, 2H), 1.49–1.28 (m, 11H), 1.30 (t, 3H, *J* = 6.8 Hz), 1.1 (d, 3H, *J* = 5.8 Hz), 0.87 (s, 9H), 0.02 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): 166.7, 150.1, 120.2, 71.1, 68.5, 60.4, 39.6, 36.5, 29.5, 29.4, 25.8, 25.6, 25.1, 23.8, 14.2, 14.1; IR (Neat): 3447, 2930, 1719, 1655, 1463, 1254, 1042 cm^{-1}; mass: 395 [M+Na]$^+$.

3.4. Ethyl (*E*,4*S*,11*R*)-11-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4-(methoxymethoxy)-2-dodecenoate (4)

$[\alpha]_D^{25}$: −4.4 (*c* 1, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 6.75 (dd, *J* = 6.4, 15.6 Hz, 1H), 5.92 (d, *J* = 15.6 Hz, 1H), 4.56 (dd, *J* = 6.7, 20.1 Hz, 2H), 4.18 (q, *J* = 7.1, 14.3 Hz, 2H), 4.16–4.12 (m, 1H), 3.78–3.70 (m, 1H), 3.35 (s, 3H), 1.63–1.17 (m, 15H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.02 (d, *J* = 1.5 Hz, 6H). ^{13}CNMR ($CDCl_3$, 75 MHz): 167.6, 149.8, 121.3, 94.5 72.2, 69.5, 61.4, 52.3 39.5, 35.5, 29.6, 29.5, 25.7, 25.6, 24.9, 23.8, 14.2, 14.1.IR (Neat): 2934, 1722, 1635, 1452, 1254, 1120, 1050 cm^{-1}; mass: 439 [M+Na]$^+$. HRMS: *m*/*z* calcd for $C_{22}H_{44}O_5Si$ + Na [M+Na]$^+$: 439.1212; found: 439.1216.

3.5. (*E*,4*S*,11*R*)-11-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4-(methoxymethoxy)-2-dodecenoic acid (12)

$[\alpha]_D^{25}$: −24 (*c* 1, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 6.89 (dd, *J* = 6.1, 15.1 Hz, 1H), 5.96 (d, *J* = 15.8 Hz, 1H), 4.58 (dd, *J* = 6.7, 14.3 Hz, 2H), 4.23–4.15 (m, 1H), 3.78–3.69 (m, 1H) 3.36 (s, 3H) 1.64–1.24 (m, 13H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 2.2 Hz, 6H). ^{13}CNMR ($CDCl_3$, 75 MHz): 170.8, 150.8, 121, 94.7 75.2, 68.6, 55.6, 39.6, 34.7, 29.6, 29.6, 29.5, 29.4, 25.9, 25.6, 25, 23.8, −4.4, −4.7. IR (Neat): 3432, 2930, 1698, 1653, 1459, 1034 cm^{-1}; MASS: 411 [M+Na]$^+$. HRMS: *m*/*z* calcd for $C_{20}H_{40}O_5Si$ + Na [M+Na]$^+$: 411.1315; found: 411.1324.

3.6. (*E*,4*S*,11*R*)-11-Hydroxy-4-(methoxymethoxy)-2-dodecenoic acid (13)

$[\alpha]_D^{25}$: −70.2 (*c* 1, $CHCl_3$), ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 6.89 (dd, *J* = 5.3, 15.1 Hz, 1H), 5.96 (d, *J* = 15.9 Hz, 1H), 4.58 (dd, *J* = 7.1, 17.6 Hz, 2H), 4.23–4.16 (m, 1H), 3.81–3.71 (m, 1H) 3.36 (s, 3H) 1.65–1.25 (m, 13H), 1.18 (d, *J* = 6.1 Hz, 3H), ^{13}CNMR ($CDCl_3$, 75 MHz): 170.3, 150.9, 120.9, 94.7 75.1, 68.1, 55.6, 39.2, 34.7, 29.6, 29.6, 29.4, 25.6, 24.9, 23.4. IR (Neat): 3446, 2927, 2855, 1703, 1657, 1270, 1100, 1034 cm^{-1}; mass: 297 [M+Na]$^+$. HRMS: *m*/*z* calcd for $C_{14}H_{26}O_5$ + Na [M+Na]$^+$: 297.1276; found: 297.1284.

3.7. (5*S*,12*S*)-5-(Methoxymethoxy)-12-methyl-1-oxa-3-cyclododecen-2-one (14)

$[\alpha]_D^{25}$: −24.4 (*c* 1, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 6.77 (dd, *J* = 7.5, 15.8 Hz, 1H), 6.01 (d, *J* = 16.6 Hz, 1H), 5.08–4.98 (m, 1H), 4.57 (dd, *J* = 6.7, 15.1 Hz, 2H), 4.34–4.27 (m, 1H), 3.33 (s, 3H), 1.86–1.14 (m, 12H), 1.29 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.4, 148.4, 122.8, 75, 73.2, 55.3, 33.8, 33, 29.6, 28.1, 27.6, 22.5, 21.2, 19.5. IR (Neat): 2923, 1722, 1649, 1461 cm^{-1}; mass: 279 [M+Na]$^+$. HRMS: *m*/*z* calcd for $C_{14}H_{24}O_4$ + Na [M+Na]$^+$: 279.1572; found: 279.1581.

3.8. (5*S*,12*S*)-5-Hydroxy-12-methyl-1-oxa-3-cyclododecen-2-one (3)

$[\alpha]_D^{25}$: +5.7 (*c* 1, MeOH); ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 6.84 (dd, *J* = 6.4, 15.8 Hz, 1H), 6.08 (dd, *J* = 1.5, 15.8 Hz, 1H,), 5.06 (m, 1H), 4.49 (m, 1H), 1.81–1.13 (m, 12H), 1.29 (d, *J* = 6.79 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): 19.8, 23.7, 24.1, 27.9, 28.5, 34.2, 36.3, 69.1, 71.5, 120.1, 150.1, 166.3. IR (Neat): 3448, 2924, 2854, 1731, 1642 cm^{-1}; mass: 234 [M+Na]$^+$.

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