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Total synthesis of Patulolide A *via* ring closing metathesis

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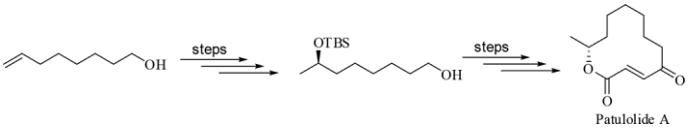
Full experimental details, spectral data of the products, ^{1}H NMR and ^{13}C NMR of all the new compounds can be found via the Supplementary Content section of this article's Web page.

ABSTRACT

A simple and efficient total synthesis of Patulolide A from readily available 7-Octen-1-ol is reported by asymmetric synthetic approach. The key reactions involved are asymmetric dihydroxylation using AD-mix-β and Grubbs' RCM reaction for the synthesis macrocyclic ring system".

GRAPHICAL ABSTRACT



KEYWORDS: 1,3 dithiane, AD-mix, Patulolide A, ring closing metathesis

Introduction

Patulolide A is naturally occurring antimicrobial twelve membered α,β- unsaturated γ-keto macrolide isolated from culture broth of the *Penicillium urticae* mutant S11R59 by Yamada and co-workers.[1] Interestingly, Patulolide A exhibited antibacterial, antifungal, and anti-inflammatory activities.[2,3] Current reports postulates that the R-antipode of Patulolide A inhibits IgE induced release of histamine for human leucocytes better than the degranulation inhibitor, theophylin.[4]

The first total synthesis of Patulolide A was reported by Mori and Co-Workers in 1987 beginning from ethyl (*R*)-3-hydroxybutanoate.[5] To date several approaches for the synthesis of Patulolide A have been described and attracted attention from synthetic chemists due to its interesting biological activities.[6–10] Nevertheless, the reported synthetic routes to Patulolide A mainly associated with the long reaction sequences, lower yields, inaccessible materials and

dependence on the chiral pool resources are some of the disadvantages in the earlier reported methods. To overcome the problems associated with the earlier approaches, here in, we report a concise and facile synthesis of Patulolide A using enantioselective dihydroxylation and RCM approach as key steps from commercially available inexpensive starting materials.

Results and Discussion

Ring closing metathesis widely used practice of olefin metathesis in organic chemistry for the synthesis of unsaturated rings using intra molecular metathesis of two terminal alkenes. We envisioned that olefinic double bond in Patulolide A can plausibly accessed *via* ring closing metathesis by using suitable bis-olefin.

As shown in Scheme 1, the retrosynthetic analysis of macrolide **1** revealed that bis-olefin **2** could be the late stage intermediate, which on RCM protocol would generate the macrolide ring structure. We intended to obtain patulolide A by suitable bis-olefin assembling together. Bis-olefin **2**in turn, could be prepared from alcohol **3**, while, the alcohol **3** could be readily accessible and synthesized from commercially available 7-Octen-1-ol **4**.

The synthesis of **1** commenced with readily available 7-Octen-1-ol **4**, accordingly, which on treatment with PMB-Br in presence of NaH in THF as solvent at RT for 8h afforded PMB protected ether **5**in 79% yield. Terminal olefin in PMB ether **5** was subjected to Asymmetric dihydroxylation with AD-mix-β to afford Diol **6**in 76% yield. (dr 9:1).[11] Diol **6** on further mono tosylation in the presence of TsCl and Et_3N in CH_2Cl_2 followed by the deoxygenation using $LiAlH_4$in dry THF furnished **7**in 73% yield. Next Hydroxyl group in **7** was masked with TBSCl in the presence of imidazole at 0°C to afford silyl ether **8**in 81% yield. As expected selective cleavage of PMB group was achieved from **8**in the presence of DDQ in aq. CH_2Cl_2 to give the

alcohol **3**in 88% yield. Alcohol **3** was converted into bromide **3a** by using with CBr_4 in the presence of Ph_3P in CH_2Cl_2, which on alkylation with 2-vinyl-1,3-dithiane in dry THF gave compound **9**in 77% yield. Subsequent desilylation of **9** with TBAF in dry THF afforded alcohol **10**in 88% yield, which on esterification with acryloyl chloride and DIPEA in CH_2Cl_2 furnished bis-olefin **2**in 71% yield. Bis-olefin **2** was then subjected to the RCM reaction using 10mol % of Grubb's-II[12] generation catalyst in dry CH_2Cl_2 at reflux temperature yielded macrolide **11**in 69% yield. Finally, deprotection of 1, 3 dithaine group in compound **11** with $CaCO_3$ and I_2, in THF: H_2O (4:1) for 5h afforded the Patulolide A **1**in 71% yield. The analytical data of our synthetic compound are in full agreement with the reported data.[4] Thus we accomplished the total synthesis of Patulolide A in an enantioselective way *via* RCM approach.

Experimental Section

(R, E)-11-Methyl-10-oxa-1, 5-dithiaspiro [5.11] heptadec-7-en-9-one (11):

To a solution of **2 (**0.26g, 0.29 mmol) in CH_2Cl_2 (250mL), 10mol % Grubbs catalyst II (54mg, 0.06 mmol) was added and stirred for 12h at reflux under N_2 atmosphere. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2h under air bubbling in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to furnish **11** (0.16g, 69%) as a syrup; $[\alpha]^{25}_D$ = + 6.4 (*c* 0.74, EtOH); IR (neat): 3080, 3052 2955, 2880, 1705, 1470, 1370, 1260, 910, 730, 698cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400MHz): δ 6.98 (d, 1H, *J* = 16.1Hz, olefinic), 6.26 (d, 1H, *J* = 16.1Hz, olefinic), 5.09-5.09 (m, 1H, -OCH), 2.94-2.62 (m, 4H, 2 x -SCH_2), 2.07-1.99 (m, 2H, -CH_2), 1.93-1.61 (m, 5H, 5 x -CH), 1.62-1.37 (m, 7H, 7 x -CH), 1.31 (d, 3H, *J* = 6.2Hz, –CH_3); ^{13}C NMR (100MHz,

$CDCl_3$): δ 168.0, 152.1, 125.1, 89.8, 73.2, 42.4, 33.3, 28.2, 27.6, 27.3, 25.4, 22.4, 21.6, 19.7; HRMS (ESI): *m/z* calculated for $C_{15}H_{24}O_2S_2Na$ $[M + Na]^+$ 323.1218, found 323.1222.

Patulolide A (1)

To a solution of compound **11** (110mg, 0.36 mmol) and $CaCO_3$ (360mg, 3.66 mmol) in THF/H_2O (v/v, 4:1, 10mL) was added I_2 (270mg, 1.02 mmol) at 0 °C. The resulting mixture was stirred at 0°C for 20min . The reaction was quenched by adding saturated aqueous $Na_2S_2O_3$, filtered through a pad of celite, and then extracted with EtOAc (3 × 20mL), water, brine, dried over Na_2SO_4 and concentrated *in vacuo* . Purification by flash chromatography on silica gel (60-120 Silica gel, 15% EtOAc in pet. ether) gave compound **1** (54mg, 71% yield; M.P. 82–84 °C; (lit.:[1] 83–85 °C); $[\alpha]^{25}_D$ = + 33.4 (*c* 0.39, EtOH); (lit.:[1] + 30.1 (c 0.95, EtOH); IR (neat): 3400, 3325, 3070, 3025, 2935, 2855, 1700, 1680, 1620, 1460, 1340, 1260, 1200, 980, 776, 698cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.23 (d, 1H, *J* = 15.9Hz, olefinic), 6.81 (d, 1H, *J* = 15.9Hz, olefinic), 4.91-4.86 (m, 1H, –OCH), 2.81-2.72 (m, 1H, –CH), 2.50-2.42 (m, 1H, –CH), 1.93-1.83 (m, 2H, $–CH_2$), 1.79-1.64 (m, 4H, 2 x $–CH_2$), 1.57-1.44 (m, 4H, 2 x $–CH_2$), 1.37 (d, 3H, *J* = 7.1Hz, $-CH_3$); ^{13}C NMR (100MHz, $CDCl_3$): δ 202.4, 166.5, 141.3, 130.1, 74.7, 38.6, 34.9, 25.6, 25.3, 24.5, 22.3, 20.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1256, found 233.1259.

Conclusion

In conclusion, total synthesis of Patulolide A (**1**) has been accomplished in a divergent way starting from commercially available inexpensive materials. In this approach asymmetric dihydroxylation and ring-closing metathesis reactions (RCM) used as a key reactions. Efforts to

explore this methodology for the synthesis of other natural products will be published in due course.

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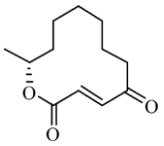
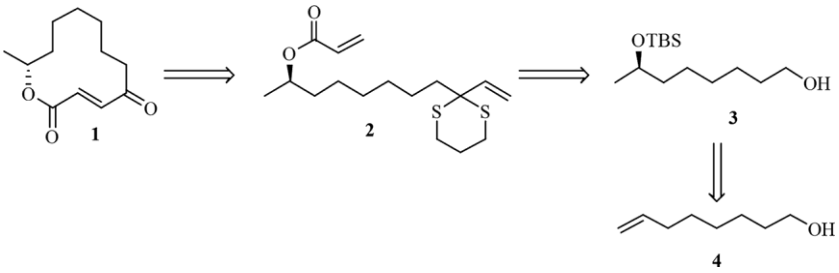
References

[1] (a) Sekiguchi, J.; Kuruda, H.; Yamada, Y.; Okada, H. *Tetrahedron Lett.* **1985**, *26*, 2341. (b) Rodpha, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiotics* **1986**, *39*, 629.
[2] Rodphya, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiotics* **1986**, *39*, 629.
[3] Makita, A.; Yamada, Y.; Okada, H. *J. Antibiotics* **1986**, *39*, 1259.
[4] Sharma, A.; Sankaranarayan, S.; Chattopadhyaya, S. *J. Org. Chem.* **1996**, *61*, 1814.
[5] Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, *25*, 13.
[6] Bestmann, H. J.; Kellermann, W.; Pecher, B. *Synthesis* **1993**, *1*, 149.
[7] Kamezawa, M.; Kitamura, M.; Nagaoka, H.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *Liebigs Ann.* **1996**, *2*, 167.
[8] Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron* **1999**, *55*, 5177.
[9] Doyle, M. P.; Hu, W.; Phillips, I.; Wee, A. G. H. *Org. Lett.* **2000**, *2*, 1777.
[10] Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 1878.
[11] Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
[12] (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 1013.

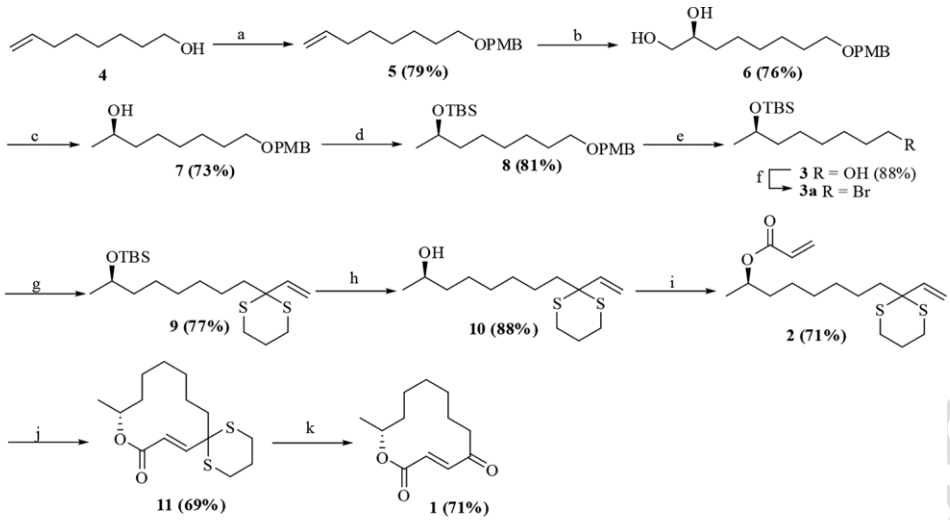
Figure 1. Structure of Patulolide A (1).



Scheme 1. Retro-analysis of Patulolide A (1).



Scheme 2. Synthesis of Patulolide A (1).



Reagents and conditions: (a) PMB-Br, NaH, THF, 0 ºC to 25 ºC, 8 h; (b) AD-mix-β, t-BuOH/H_2O, 0 ºC to rt, 32 h (c) (i) TsCl, Et_3N, dibutyltin oxide (cat), dry CH_2Cl_2, 0 ºC to rt, 12 h; (ii) $LiAlH_4$, THF, reflux, 3 h, (d) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (e) DDQ, CH_2Cl_2:H_2O (19:1), rt, 3 h; (f) CBr_4, Ph_3P, CH_2Cl_2, 0 ºC to rt, 3 h; (g) 2-vinyl-1,3-dithiane, *n*-BuLi, dry THF, -78 ºC, 3 h; (h) TBAF, THF, 0 ºC to rt, 3 h; (i) acryloyl chloride, DIPEA, CH_2Cl_2, rt, 3 h; (j) Grubb's second generation catalyst, CH_2Cl_2, reflux, 6 h; (k) $CaCO_3$, I_2, THF:H_2O (4:1), 0 ºC.