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First stereoselective total synthesis of pectinolide A

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ABSTRACT

The enantioselective synthesis of bio-active 5,6-dihydro-α-pyrone, pectinolide A, has been achieved in 10 steps in good overall yield. Of the three stereogenic centres, the C-5/C-6 *vic*-diol was obtained using diastereo- and enantioselective Brown hydroxyl crotylation, while the C-3′ stereocentre was created by Jacobsen hydrolytic kinetic resolution method.

Pectinolides A–C are a class of 5,6-dihydro-α-pyrones, isolated from *Hyptis pectinata* (Lamiaceae),[1] and possess an antimicrobial as well as cytotoxic activity (ED_{50} <4 μg/mL) against a variety of tumour cell lines (Fig. 1). *Staphylococcous aureus* and *Bacillus subtilis* were sensitive to pectinolide A (**1**) in the concentration range of 6.25–12.5 μg/mL. Based on spectral study and chemical evidence, the absolute stereochemistry of pectinolide A[2] (**1**) was established as 6*S*-[(3*S*-acetyloxy)-1*Z*-heptenyl]-5*S*-(acetyloxy)-5,6-dihydro-2*H*-pyran-2-one containing an α,β-unsaturated δ-lactone. As these natural products are available in scarce amounts, the synthesis of pectinolides is an attractive goal for further biological activity studies. To date there is no report on the synthesis of these natural products. Intrigued by the biological properties of this class of pyrones as well as, in continuation of our work on the synthesis of lactone containing natural products,[3] we have taken up the total synthesis of pectinolide A. Herein, we report the first stereoselective total synthesis of pectinolide A.

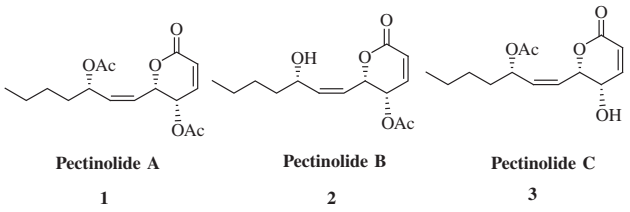
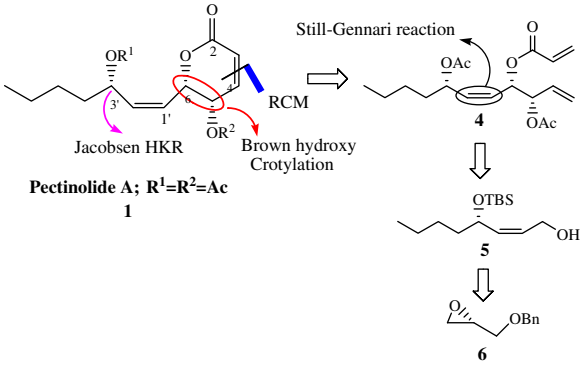


Figure 1. Structures of pectinolides.

Retrosynthetically, we envisioned that the target molecule pectinolide A can be obtained from the intermediate **4** by ring-closing metathesis. In turn the intermediate **4** could be envisioned from diastereo and enantioselective hydroxy crotylation of aldehyde obtained from TBS protected *Z* alkenol **5** followed by esterification with acrylol chloride. The compound **5** could be achieved from (*S*)-2-(benzyl oxymethyl) oxirane **6**. Thus, of the three stereogenic centres, the *vic*-diol is obtained from alkenol **5**, while the other chiral centre is introduced by Jacobsen hydrolytic kinetic resolution[4] of 2-(benzyl oxymethyl) oxirane (Scheme 1).



Scheme 1. Retrosynthetic analysis of pectinolide A.

Towards the synthesis of **1**, initially the chiral epoxide **6** was regioselectively opened with *n*-propylmagnesium bromide in THF, in the presence of CuI to afford secondary alcohol **7** (85%), which was protected as corresponding TBS ether **8** in 92% yield. Debenzylation of the benzyl ether **8** using 20% $Pd(OH)_2/C$ afforded the primary alcohol **9** in 89% yield. The primary alcohol **9** was oxidized under Swern oxidation conditions to afford the corresponding aldehyde **10** with 92% yield. Aldehyde **10** was subjected to a Still–Gennari reaction[5] in the presence of NaH in THF to provide the α,β-unsaturated ester compound **11** in 90% yield (Scheme 2).

The chemoselective reduction of α,β-unsaturated ester **11** with DIBAL-H was achieved at −20 °C to afford the allyl alcohol **5** in 95% yield. The allyl alcohol **5** was oxidized under Swern oxidation conditions to the corresponding aldehyde **12** with 90% yield. The treatment of aldehyde **12** with in situ generated [(*Z*)-γ-(methoxymethoxy)allyl]-diisopinocampheylborane, [prepared from methoxy-

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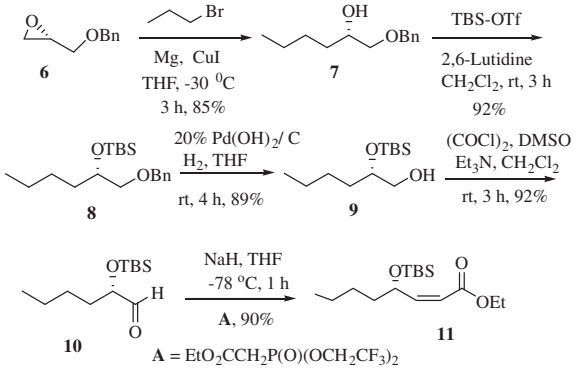
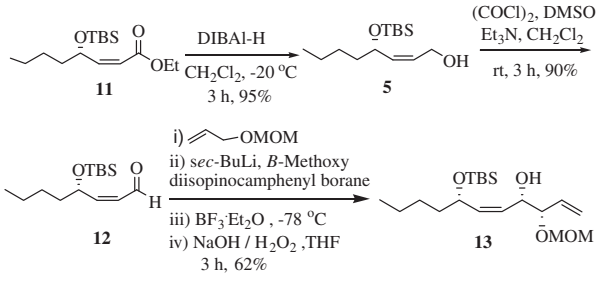


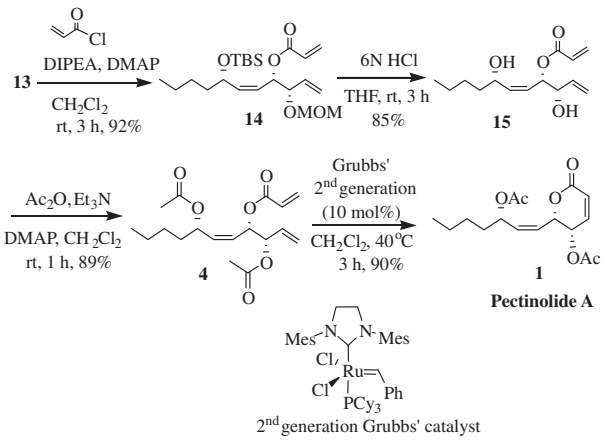
Scheme 2.



Scheme 3.

methyl allyl ether, *sec*-BuLi, IPC_2-BOMe (derived from (+)-α-pinene) and $BF_3{\cdot}OEt_2$] in THF at −78 to 25 °C in a regioselective and stereoselective manner to yield the corresponding *threo*-β-methoxymethylhomoallyl alcohol **13** in ⩾99% diastereoselectivity and >95% enantioselectivity (Scheme 3).[6]

The esterification of the secondary alcohol in **13** with acryloyl chloride was achieved in the presence of Hünig's base to afford compound **14** in 92% yield. Deprotection of TBS and MOM groups was achieved using 6 N HCl in THF at room temperature, to afford the diol compound **15** in 85% yield. Acetylation of the diol **15** was achieved with acetic anhydride and Et_3N to yield compound **4** (89%). Finally, ring-closing metathesis of the compound **4** was accomplished using Grubbs 2nd generation[7] catalyst for 3 h at 40 °C in CH_2Cl_2 to afford the required 5,6 dihydro-2*H* pyran-2-one **1** in 90% yield (Scheme 4). The ^1H NMR and ^{13}C NMR spectral data and optical rotation of our synthetic compound[8] were in good agreement with the data previously reported in literature.[2a]



Scheme 4.

In conclusion, a concise and efficient first total synthesis of pectinolide A has been achieved. Notable features include: (i) highly diastereo- and enantioselective hydroxy crotylation to control the configuration of the stereogenic centres. (ii) Still–Gennari reaction for the generation of *cis*-olefin.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.036.

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8. The ^1H and ^{13}C NMR spectral data and optical rotation, matched in comparison with the reported data for pectinolide A.[2a]
Spectroscopic data for representative compounds **1**: colourless oil, $[\alpha]_D^{29}$ +196.8 (*c* 0.5, MeOH), [lit. $[\alpha]_D$ +202.0 (*c* 0.15, MeOH)]. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, *J* = 6.8 Hz), 1.20–1.40 (m, 5H), 1.46–1.77 (m, 1H), 2.04 (s, 3H), 2.09 (s, 3H), 5.16 (dd, 1H, *J* = 3.02, 6.0 Hz), 5.33 (ddd, 1H, *J* = 6.0, 7.6, 9.8 Hz), 5.57 (dd, 1H, *J* = 3.0, 8.3 Hz), 5.61 (d, 1H, *J* = 9.8 Hz), 5.71 (dd, 1H, *J* = 8.3, 11.3 Hz), 6.23 (d, 1H, *J* = 9.8 Hz), 6.93 (dd, 1H, *J* = 6.0, 9.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 20.5, 21.1, 22.4, 27.2, 34.0, 64.2, 69.3, 75.0, 125.1, 126.2, 133.1, 139.9, 162.1, 169.8, 170.3; IR (neat): 2925, 2855, 1740, 1460, 1337, 1226, 1028, 823 cm^{-1}. Mass (ESI-MS): *m/z* 333 $(M+Na)^+$. HRMS (ESI) calcd for $C_{16}H_{22}O_6Na$ $(M+Na)^+$, 333.1314; found 333.1324.
Compound **11**: $[\alpha]_D^{31}$ +83.6 (*c* 1.5, $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.87 (s, 12H), 1.29 (t, 3H, *J* = 7.2 Hz), 1.22–1.59 (m, 6H), 4.16 (q, 2H, *J* = 7.2 Hz), 5.23–5.33(m, 1H), 5.66 (dd, 1H, *J* = 1.0, 11.7 Hz), 6.13 (dd, 1H, *J* = 8.3, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.6, 14.0, 14.2, 18.1, 22.6, 25.8, 27.3, 37.0, 60.0, 68.7, 117.4, 153.8, 165.9; IR (neat): 3473, 2934, 1722, 1661, 1371, 1174, 1036, 979 cm^{-1}. Mass (ESI-MS): *m/z* 323 $(M+Na)^+$.
Compound **13**: colourless syrup, $[\alpha]_D^{29}$ +56.6 (*c* 1.5, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 12H), 1.20–1.60 (m, 6H), 2.59 (bs, -OH), 3.39 (s, 3H), 3.84–3.94 (m, 1H), 4.16–4.30 (m, 1H), 4.35–4.51 (m, 1H), 4.57 (d, 1H, *J* = 6.6 Hz), 4.70 (d, 1H, *J* = 6.6 Hz), 5.22–5.37 (m, 3H), 5.45–5.75(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.3, 14.0, 17.6, 22.5, 25.8, 27.5, 37.7, 55.7, 68.7, 69.8, 80.9, 94.1, 119.6, 126.2, 134.2, 138.0; IR (neat): 3447, 2926, 2857, 1757, 1462, 1252, 1110, 1034, 931, 838, 775 cm^{-1}. Mass (ESI-MS): *m/z* 359 $(M+H)^+$;

HRMS (ESI) calcd for $C_{19}H_{38}NaO_4Si$ $(M+Na)^+$, 381.2437; found 381.2442. Compound **4**: $[\alpha]_D^{30}$ +68.7 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 6.6 Hz), 1.19–1.41 (m, 5H), 1.46–1.77 (m, 1H), 2.03 (s, 3H), 2.06 (s, 3H), 5.22–5.39 (m, 2H), 5.40–5.49 (m, 2H), 5.52–5.62 (m, 2H), 5.68–5.87 (m, 3H), 6.11 (dd, 1H, *J* = 10.4, 17.4 Hz), 6.41 (dd, 1H, *J* = 7.0, 17.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 20.9, 22.5, 27.1, 29.7, 34.3, 70.2, 74.5, 77.2, 119.3, 126.2, 128.1, 131.3, 131.8, 134.4, 164.6, 169.7, 170.1; IR (neat): 3445, 2926, 2856, 1720, 1496, 1499, 1374, 1243, 1167, 1060, 864, 794, 519 cm^{-1}. Mass (ESI-MS): *m/z* 361 $(M+Na)^+$; HRMS (ESI) calcd for $C_{18}H_{26}O_6Na$ $(M+Na)^+$, 361.1618; found 361.1614.