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First stereoselective total synthesis of pectinolide C and total synthesis of pectinolide A

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ABSTRACT

The first stereoselective synthesis of pectinolide C and synthesis of pectinolide A, from easily accessible 1-hexyne and D-mannitol are reported in a convergent manner. The salient features include acetylenic addition to the chiral aldehyde and Still–Gennari olefination.

In recent times, naturally occurring 6-membered lactones have attracted significant interest among synthetic chemists and biologists due to their interesting biological activities. Pectinolides A–C (Fig. 1 and **1**–**3**)[1] are such examples, isolated from the Mexican shrub *Hyptis pectinata* (Lamiaceae), which was used as a remedy in the treatment of fevers, skin diseases, gastric disturbances,[2] rhinopharyngitis, and lung congestion.[3] In addition, pectinolides were found to exhibit significant cytotoxic activity (ED50 <4 μg/ml) against a variety of tumor cell lines as well as antibacterial activity against the Gram-positive bacteria. On the basis of spectral, chiroptical, and chemical evidence, the absolute stereochemistry of pectinolide A was established as 6*S*-[(3*S*-acetyloxy)-1*Z*-heptenyl]-5*S*-(acetyloxy)-5,6-dihydro-2*H*-pyran-2-one. Mosher ester derivatives were used with pectinolide B (**2**) for confirmation of the 3′-(*S*) absolute stereochemistry on the side chain chiral center of pectinolides A–C. The structures of pectinolides B (**2**) and C (**3**) were determined as the monodeacetylated forms of **1** by comparison of their spectral data and chemical correlation with the prototype compound. *Staphylococcus aureus* and *Bacillus subtilis* were sensitive to pectinolide A (**1**) in the concentration range of 6.25–12.5 μg/ml. Our continued interest on the synthesis of bio-active lactones,[4] prompted us to undertake the synthesis of these molecules. While our work on the synthesis of **1** and **3** was in progress, one synthesis of pectinlolide A has appeared,[5] whereas, there is no report on the synthesis of pectinolide C.

Herein, we report the first stereoselective total synthesis of pectinolide C and total synthesis of pectinolide A by a convergent strategy which relies on acetylenic addition onto a chiral aldehyde, and *cis*-Wittig olefination as the key steps.

Retrosynthetic analysis (Scheme 1) reveals that target pectinolides **3** and **1** can be obtained from *syn*, *anti*-isomer **4**, which was accessible from acetylenic compound **5** and aldehyde **6** by an addition reaction. Alkyne **5** and aldehyde **6** in turn could be obtained from readily available 1-hexyne **7** and D-mannitol, respectively.

The synthesis of MOM-protected propargylic alcohol **5** commenced from 1-hexyne **7** (Scheme 2) by converting it into propargylic alcohol **8**. Thus, we proceeded to couple the in situ metalated hexyne (obtained by treating **7** with ethyl magnesium bromide) with formaldehyde to afford **8** with 75% yield. Compound **8** was converted into chiral propargylic alcohol **9** in four steps as reported earlier.[4k] MOM protection of the resulting secondary alcohol in compound **9** afforded fragment **5** in 85% yield.[4l]

The aldehyde **6** is a known compound which was synthesized from the commercially available D-mannitol **10** according to the reported procedure in 85% yield.[6]

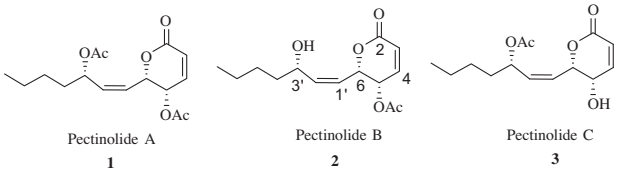

Figure 1. Structure of pectinolides A–C.

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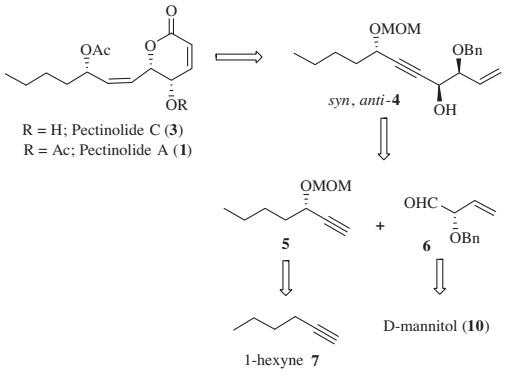
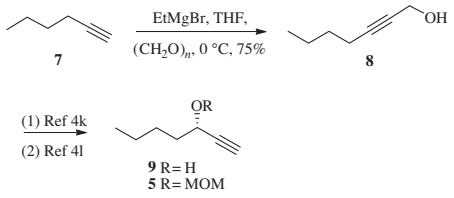


Scheme 1. Retrosynthesis of pectinolides C and A.

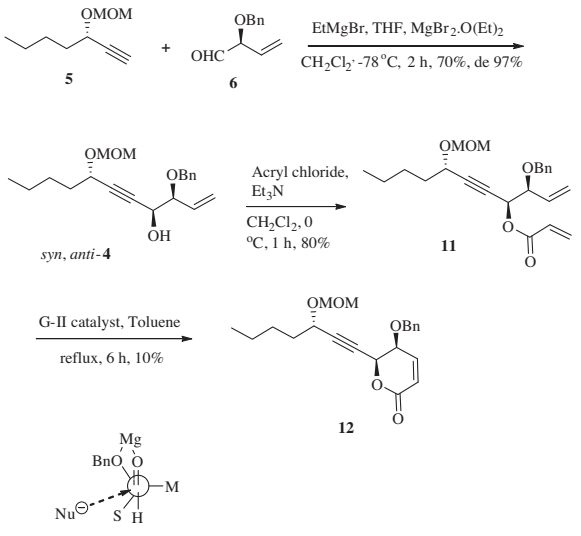


Scheme 2. Synthesis of MOM-protected propargylic alcohol **5**.

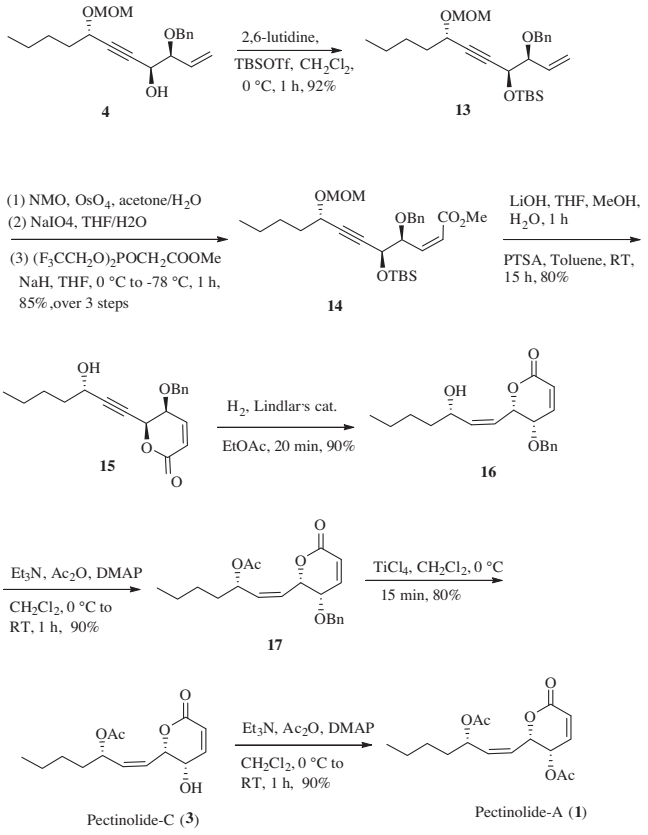
With the two intermediates **5** and **6** in hand, we proceeded to couple in situ metalated alkyne (obtained by treating **5** with ethyl magnesium bromide) with aldehyde **6** in the presence of $MgBr_2{\cdot}Et_2O$ at −78 °C to furnish the *syn, anti*-isomer **4** in 70% yield with high diastereomeric excess (de = >97%) analyzed by chiral HPLC.[7] Formation of major diastereomeric alcohol can be explained on the basis of chelation-controlled (Anti Felkin-Anh model) addition of Grignard nucleophile to the aldehyde leading to the single stereoisomer *syn*, *anti*-**4**.

Acylation of compound **4** with acryloyl chloride in the presence of NEt_3 in CH_2Cl_2 gave acrylate ester **11**. Unfortunately, several attempts for the ring-closing metathesis of diene **11** using Grubbs' second-generation ruthenium catalyst (Ru-II) were not successful, resulting in 10% yield of the required lactone **12** (Scheme 3).

Because of low yields in the RCM reaction, the terminal olefin in compound **4** needs to be cleaved and Still–Gennari reaction should be performed. The free hydroxyl group in **4** is thus protected as TBS ether using TBSOTf and 2,6-lutidine to provide **13**. The latter was



Scheme 3. Synthesis of lactone **12**.



Scheme 4. Synthesis of pectinolides C (**3**) and A (**1**).

then converted into the corresponding aldehyde by dihydroxylation of the terminal double bond, oxidative cleavage of the resulting 1,2-diol followed by modified Still–Gennari olefination with $(F_3CCH_2O)_2POCH_2COOMe$) in THF to afford *cis*-olefinic ester **14**. Since attempts to cyclize TBS-protected ester **14** to the lactone **15** failed under several conditions, we decided to hydrolyze the ester group. Ester **14** was thus converted into the corresponding acid by hydrolysis using 0.5 N aq LiOH in THF/MeOH (2:1), which without further purification, directly treated with PTSA in toluene at room temperature to form lactone **15** in a one-pot reaction via a *three*-step sequence (TBDMS deprotection, lactonization, and MOM deprotection) (85%, over two steps). Next, the triple bond was partially reduced to the *cis*-olefin **16** using Lindlar's catalyst and then free hydroxyl group was acetylated with acetic anhydride to furnish **17.**

Finally global debenzylation ($TiCl_4/CH_2Cl_2$/0 °C/15 min) gave the target pectinolide C (**3**) {$[\alpha]_D^{25}$ +72.4 (*c* = 0.5, MeOH), lit. $[\alpha]_D^{25}$ +80.99 (*c* = 0.76, MeOH)} (80%), whose spectroscopic data were identical to that of the natural product. Further, in a separate experiment, **3** was acetylated by using acetic anhydride/Et_3N to afford pectinolide A (**1**) {$[\alpha]_D^{25}$ +191.3 (*c* = 0.5, MeOH), lit. $[\alpha]_D^{25}$ +202.0 (*c* = 0.15, MeOH)} in 90% yield (Scheme 4). The physical and spectroscopic data of our synthetic sample **1** were identical to those of the reported natural and synthetic products.

We have accomplished the total synthesis of **3** and **1** starting from relatively cheap and commercially available D-mannitol and 1-hexyne by means of a versatile strategy utilizing acetylenic addition to the chiral aldehyde and Still–Gennari olefination.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.039.

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7. The diastereomeric excess of the product was determined using a Shimadzu high-performance liquid-chromatography (HPLC) system equipped with a chiral HPLC column (Chiralcel OD) and a UV detector at an absorbance of 225 nm. ATLANTIS DC18 150 × 4.6 mm, 5 μ (column) and a solvent system of acetonitrile and 0.1% formic acid at a flow rate of 1.0 ml/min were used. t_R: 15.9 and 17.2 min.
   Spectral data for selected compounds:
   (3S,4S,7S)-3-(benzyloxy)-7-(methoxymethoxy)undec-1-en-5-yn-4-ol (**4**): $[\alpha]_D^{25}$: −19.4 (*c* = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.29 (m, 5H), 5.97–5.75 (m, 1H), 5.46–5.35 (m, 2H), 4.92 (dd, *J* = 6.8, 4.5 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 2H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.39–4.32 (m, 1H), 3.96–3.83 (m, 1H), 3.36 (s, 3H), 1.82–1.62 (m, 2H), 1.48–1.27 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.0, 133.7, 128.4, 127.8, 127.7, 120.5, 94.0, 84.9, 83.2, 82.2, 70.8, 70.4, 65.1, 55.5, 35.2, 27.3, 22.3, 13.9; IR (neat) 3444, 2933, 2871, 1457, 1096, 1033, 738, 698 cm^{-1}; ESI HRMS *m/z* calcd for $C_{20}H_{28}O_4Na$ $[M+Na]^+$ 355.18798, found 355.18971.
   (*S,Z*)-1-((2*S*,3*S*)-3-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-1-en-3-yl acetate (**3**): $[\alpha]_D^{25}$ +72.4 (*c* = 0.5, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.01 (dd, *J* = 9.8, 5.3 Hz, 1H), 6.15 (d, *J* = 9.8 Hz, 1H), 5.78–5.64 (m, 2H), 5.51 (ddd, *J* = 9.8, 7.5, 6.0 Hz, 1H), 5.30 (dd, *J* = 6.0, 2.3 Hz, 1H), 4.15 (dd, *J* = 5.3, 2.3 Hz, 1H), 2.05 (s, 3H), 1.72–1.56 (m, 4H), 1.39–1.30 (m, 2H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 162.7, 144.2, 134.1, 125.5, 122.8, 77.8, 70.9, 63.1, 34.2, 27.1, 22.4, 21.1, 13.9; IR (neat) 3443, 2928, 1725, 1245, 1039 cm^{-1}; ESI HRMS *m/z* calcd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$ 291.12029, found 291.12109.
   (S,Z)-1-((2S,3S)-3-acetoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-1-en-3-yl acetate (**1**): $[\alpha]_D^{25}$ +191.3 (*c* = 0.5, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.96 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.24 (d, *J* = 9.8 Hz, 1H), 5.73 (dd, *J* = 11.1, 8.3 Hz, 1H), 5.62 (dd, *J* = 10.7, 8.3 Hz, 1H), 5.59 (dd, *J* = 7.9, 2.8 Hz, 1H), 5.35 (ddd, *J* = 13.5, 7.1, 6.6 Hz, 1H), 5.17 (dd, *J* = 5.7, 2.8 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.78-1.52 (m, 2H), 1.36–1.12 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 169.8, 162.0, 139.9, 133.1, 126.2, 125.1, 75.0, 69.4, 64.2, 34.0, 27.2, 22.4, 21.0, 20.4, 13.8; IR (neat) 2925, 2856, 1739, 1373, 1225, 1029, 771 cm^{-1}; ESI HRMS *m/z* calcd for $C_{16}H_{22}O_6Na$ $[M+Na]^+$ 333.13086, found 333.13196.