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Stereoselective synthesis of (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone

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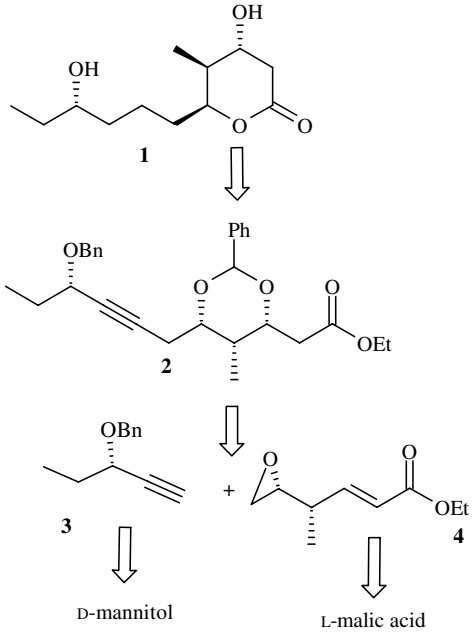
Abstract—A stereoselective synthesis of the pentaketide lactone (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone has been achieved.

The biosynthesis of macrolides occurs via step-by-step functionalization of a polyketide chain, which is synthesized in biological systems by enzymes. In the biosynthesis of spinosyn, an agriculturally important polyketide macrolide,[1] a truncated version of the gene of the polyketide synthon was identified and expressed in a heterologous host *Saccharopolyspora erythracea*, which resulted in the formation of a novel pentaketide lactone identified as (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone **1**.[2] This experiment demonstrated that the spinosyn polyketide synthase genes can be expressed heterologously in *S. erythracea* and can be used as the part of a functional hybrid polyketide synthase.[3] Thus, by utilizing biosynthetic engineering, one can access analogues of natural products in the search for novel and active molecular architectures. Biosynthetic engineering also helps in understanding the biosynthetic pathways to natural products.

An elegant synthetic approach to this class of lactone would augment the process of understanding their biosynthesis, and the mechanisms of the enzyme systems involved in polyketide synthesis. Herein, we describe the total synthesis of lactone **1** following a convergent strategy (see Scheme 1).

The retrosynthetic analysis reveals two fragments, **3** and **4**, the C1–C6 and C7–C11 skeletons, respectively. It was envisaged that fragment **4** could be obtained following a chiron approach from L-malic acid, while fragment **3** could be synthesized from a protected chiral glyceraldehyde (see Scheme 2).



Scheme 1. Retrosynthetic analysis.

The synthesis began with derivatization of L-malic acid in dry MeOH and $BF_3{\cdot}OEt_2$ to afford the corresponding dimethyl ester. Subjecting this ester to stereoselective alkylation following Seebach's protocol afforded **5** in an excellent yield with good stereocontrol. The free

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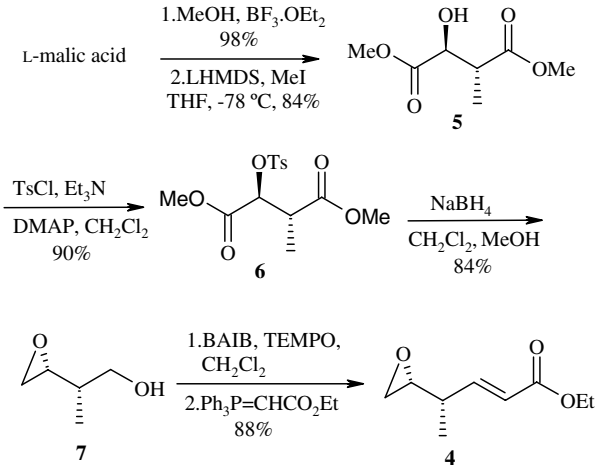
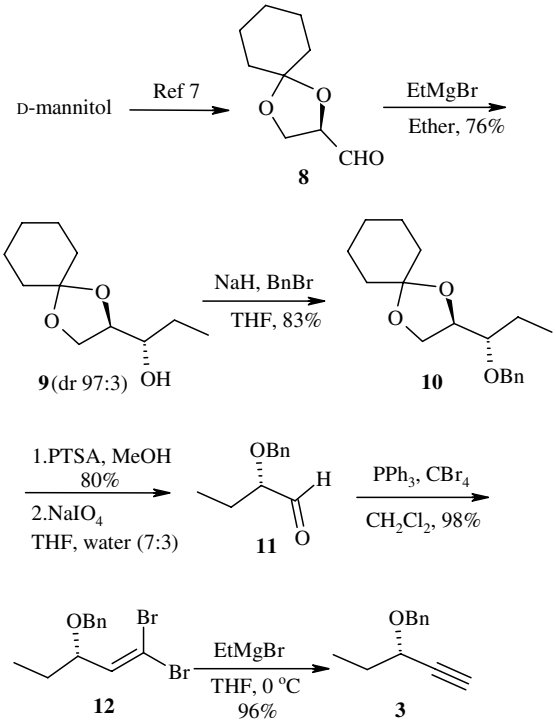
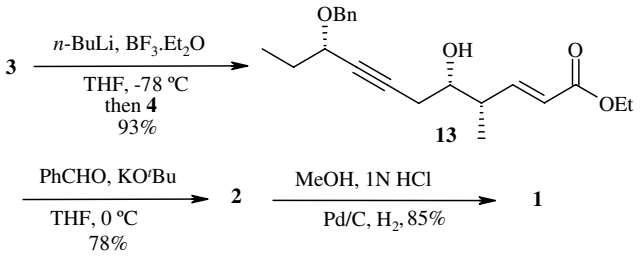


Scheme 2. Stereoselective synthesis of **4**.

hydroxyl group of **5** was converted into the corresponding tosylate **6**.[4] The next objective was the reduction of the diester followed by base induced epoxidation.[5] Surprisingly, reduction of ester **6** with $NaBH_4$ in dichloromethane/methanol (1:1) resulted in epoxy alcohol **7** as the sole product. The primary hydroxyl of compound **7** was subjected to one-pot oxidation/olefination following Vatale's protocol[6] to form α,β-unsaturated ester **4**. Thus, the primary hydroxyl was oxidized with bisacetoxyiodobenzene/iodobenzenediacetate (BAIB) and catalytic TEMPO to afford the aldehyde, which was subsequently subjected to a two-carbon homologation using ethoxycarbonylmethylene triphenylphosphorane in dichloromethane to furnish (*E*)-α,β-unsaturated ester **4** in an excellent yield.



Scheme 3. Synthesis of fragment **3**.



Scheme 4. Coupling of fragments **3** and **4**.

The construction of fragment **3**, started from a chiral glyceraldehyde, which could be prepared easily from D-mannitol in multigram scale.[7] The cyclohexylidene protected glyceraldehyde **8** was treated with ethylmagnesium bromide in ether at 0 °C to yield *anti* addition product[8] **9** (97:3). The hydroxyl group was protected as its benzyl ether **10** and then the cyclohexylidene group was removed using a catalytic amount of *p*-TSA in methanol to afford the corresponding diol, which was cleaved to give aldehyde **11** via $NaIO_4$. Dibromoolefination of the aldehyde using the Corey–Fuchs protocol[9] using PPh_3 and CBr_4 furnished *gem*-dibromoolefin **12**, which upon treatment with ethylmagnesium bromide afforded alkyne **3** in a 96% yield.[10]

With both fragments **3** and **4** in hand, the stage was set for assembling[11] those fragments. Accordingly, alkyne **3** was treated with *n*-BuLi to generate the corresponding lithium-acetylide, to which was added a catalytic amount of $BF_3{\cdot}OEt_2$ and subsequently a solution of **4** in THF to furnish the coupled product **13** in a 93% yield (see Scheme 3).

Formation of the new C–O bond with a concomitant new stereocentre was achieved via an oxy-anion assisted Michael addition[12] using KO^{t}Bu and benzaldehyde in THF at 0 °C. A *syn* 1,3-diol in the form of a benzaldehyde acetal (**2**) was obtained in a 78% yield (see Scheme 4).

Deprotection of the benzylidene acetal led to formation of a six-membered lactone and saturation of the triple bond and debenzylation were successfully achieved in one-pot using Pd/C in acidic methanol to furnish the target molecule **1** in an 85% yield.[13]

Acknowledgement

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13. Physical and analytical data matched with the reported data. (a) See Ref. 1. (b) Chakraborty, T. K.; Rajib, K. G.: *Tetrahedron Lett*. **2004**, *45*, 7637. Spectral data for compound **3**: $[\alpha]_D^{25}$ −98.4 (*c* 2.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 4.75 (d, 1H, $J = 11.3$ Hz), 4.44 (d, 1H, $J = 11.3$ Hz), 3.96 (t, 1H, $J = 6.0$ Hz), 2.38 (s, 1H) 1.76 (m, 2H), 1.02 (t, 3H, $J = 6.7$ Hz); MS (ESI) *m*/*z* 197 $(M+Na)^+$. Compound **4**: $[\alpha]_D^{25}$ −13.2 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (dd, 1H, $J = 6.7$, 9.0 Hz), 5.84 (dd, 1H, $J = 1.5$, 14.3 Hz), 4.16 (q, 2H, $J = 7.5$ Hz), 2.81–2.72 (m, 2H), 2.52–2.50 (m, 1H), 2.23–2.14 (m, 1H), 1.32–1.22 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 148.0, 121.8, 60.3, 54.8, 45.9, 38.8, 15.7, 14.1; IR: 2924, 1720, 1268, 1183, 1036 cm^{-1}; MS (ESI) *m*/*z* 193 $(M+Na)^+$. Compound **13**: $[\alpha]^{25}$ −4.02 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 6.85 (dd, 1H, $J = 8.5$, 15.6 Hz), 5.83 (dd, 1H, $J = 1.5$, 15.6 Hz), 4.73 (d, 1H, $J = 11.7$ Hz), 4.45 (d, 1H, $J = 12.5$ Hz) 4.16 (q, 2H, $J = 7.0$ Hz), 3.98 (tt, 1H, $J = 1.5$, 6.2 Hz), 3.63 (q, 1H, $J = 6.2$ Hz), 2.58–2.30 (m, 3H), 2.23 (br s, 1H), 1.81–1.67 (m, 2H), 1.30 (t, 3H, $J = 7.0$ Hz), 1.16 (d, 3H, $J = 7.0$ Hz), 1.00 (t, 3H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 138.1, 133.6, 130.1, 128.4, 128.3, 127.8, 127.5, 82.3, 72.3, 70.4, 70.2, 60.3, 41.2 29.0, 25.4, 14.3, 14.2, 9.7; MS (ESI) *m*/*z* 345 $(M+H)^+$; IR: 3424, 3030, 2925, 1718, 1276, 1019 cm^{-1}. Compound **1**: Liquid $[\alpha]_D^{25}$ −33.8 (*c* 0.24, $CHCl_3$); IR 3445, 2924, 1728, 1459, 1104 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 4.71 (ddd, 1H, $J = 2.5$, 4.7, 8.1 Hz), 4.06 (ddd, 1H, $J = 3.2$, 3.4, 5.6 Hz), 3.55 (m, 1H), 2.81 (dd, 1H, $J = 5.5$, 18.5 Hz), 2.53 (ddd, 1H, $J = 0.9$, 3.2, 18.1 Hz), 1.95 (m, 1H), 1.74 (m, 1H), 1.65 (m, 2H), 1.50 (m, 3H), 1.42 (m, 2H), 0.95 (d, 3H, $J = 7.2$ Hz), 0.94 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 78.0, 73.0, 68.6, 37.3, 36.4, 35.8, 31.7, 30.3, 21.6, 10.2, 9.8; MS (ESI) *m*/*z* 231 $(M+H)^+$, 253 $(M+Na)^+$.