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Tetrahedron Letters 47 (2006) 1213–1215
Tetrahedron Letters

Total synthesis of 6-epiprelactone-V via a *syn*-selective oxygen tethered intramolecular Michael reaction☆

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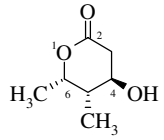
Received 12 September 2005; revised 24 November 2005; accepted 1 December 2005
Available online 20 December 2005

Abstract—The intramolecular protective group (benzylidene acetal) assisted *syn*-1,3-diol synthesis has been efficiently utilized in a short synthesis of 6-epiprelactone-V starting from (*S*)-malic acid.

Poly-substituted chiral δ-lactones have attracted considerable attention in recent years due to their importance as building blocks in natural product synthesis[1] and due to the fact that they form part of the structures of polyketide macrolides,[2] which have various biological profiles. These include bafilomycin A,[3] mevinolin and compactin.[4] Similarly, several substituted δ-lactones have been isolated from microorganisms. Prelactones are examples of such δ-lactones isolated from bafilomycin producing microorganisms and other polyketide macrolide producing organisms.[5] The structures of these compounds have been assigned on the basis of the proposed biosynthesis of macrolides.[6] Biologically, these lactones exhibit properties such as ATpase inhibitor and antibacterial, antifungal and immunosuppressive activities.[7]

Our group has been engaged in the development of practical synthetic approaches towards the substituted pyran scaffold in chiral form.[8] In this letter, we report a total synthesis of the non-natural enantiomer of prelactone, (−)-6-epiprelactone-V **1** (Fig. 1) employing a highly chemo-regio- and stereoselective tandem ester reduction, epoxide formation-reductive epoxide opening reaction protocol[9] and a base catalyzed oxygen tethered intramolecular Michael addition[10] as key steps. The highlight of the synthesis is the utilization of the chiral centre in commercially available (*S*)-malic acid **4** and creation of the *syn*-1,3-diol functionality through an intramolecular Michael addition of a benzyloxy tether.

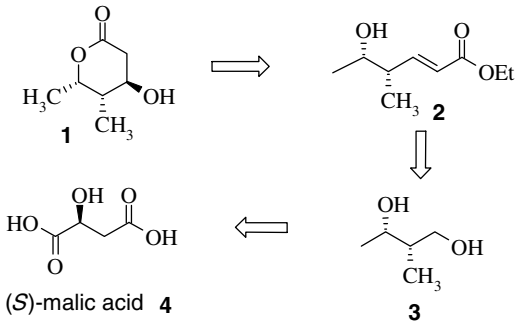


6-epiprelactone-V (1)

Figure 1.

Our approach to epiprelactone-V is depicted retrosynthetically in Scheme 1. The key to this approach was the synthesis of **3** and **11** starting from readily available (*S*)-malic acid **4**.

Commercially available (*S*)-malic acid **4** was subjected to esterification[11] using $BF_3{\cdot}OEt_2$ in methanol to give



Scheme 1.

Keywords: Keck allylation; Intramolecular oxy-Michael reaction; (−)-Centrolobine, 2,6-Disubstituted tetrahydropyran.
☆ IICT Communication No. 050615.
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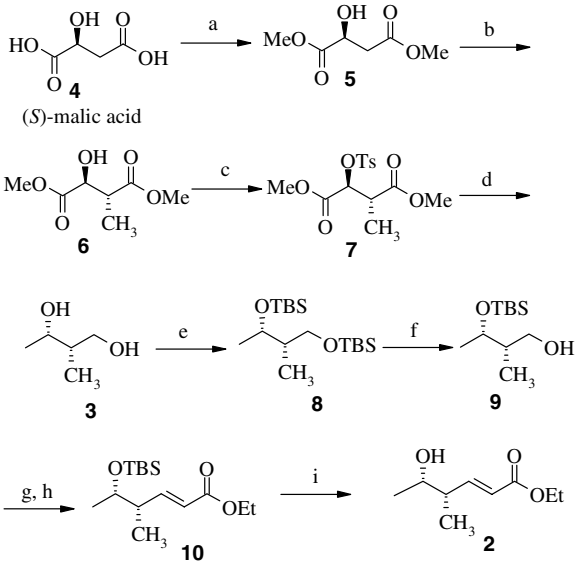
doi:10.1016/j.tetlet.2005.12.012



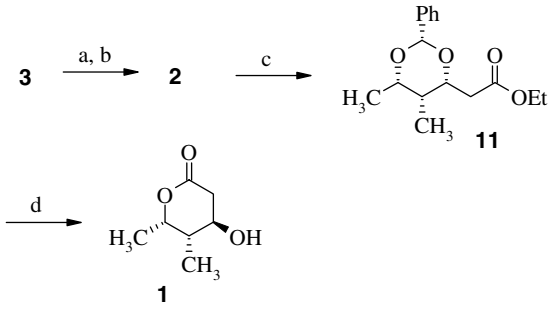
Scheme 2. Regents and conditions: (a) $BF_3{\cdot}OEt_2$, MeOH, 0 °C to rt, 98%; (b) LHMDS, CH_3I, THF, −78 °C, 5 h, 86%; (c) TsCl, py, CH_2Cl_2, rt, 30 h, 90%; (d) LAH, THF, 55 °C, 4 h, 79%; (e) TBDMSCI, immidazole, CH_2Cl_2, 0 °C to rt, 6 h, 95% ; (f) PTSA (cat), MeOH, 0 °C, 15–30 min, 75%; (g) IBX, THF, DMSO, rt, 1 h; (h) $Ph_3P{=}CHCO_2Et$, benzene, rt, 6 h, 87% (two steps); (i) PTSA (cat), MeOH, rt, 1 h, 92%.

dimethyl malate **5** in 98% yield. Diester **5** was treated with LHMDS and methyl iodide in THF at −78 °C to yield α-alkylated dimethyl malate **6** in good yield with high diasteroselectivity (12:1). However, the diastereomers could not be separated by chromatography. Tosylation of **6** gave a separable mixture of **7** and its *syn*-diastereoisomers in 90% yield. Treatment of the *anti*-isomer **7** with lithium aluminium hydride (6 M equiv) in THF afforded the desired diol **3** in 79% yield (Scheme 2).

1,3-Diol **3** was disilylated using TBDMSCl in dichloromethane and selective primary desilylation was achieved successfully using catalytic PTSA in methanol[12] at 0 °C to give primary alcohol **9** in 75% yield. To install the requisite α,β-unsaturated ester for the subsequent base catalyzed intramolecular oxygen tethered Michael reaction, the 1^0 alcohol group in **9** was oxidized[13] with IBX to the corresponding aldehyde, followed by two-carbon homologation using ethoxycarbonylmethylene triphenylphosphorane in benzene to furnish the (*E*)-α,β-unsaturated ester **10** in excellent yield. Deprotection of the hydroxy group in **10** was achieved using PTSA in methanol to provide the key synthon **2** in high yield (Scheme 3).

Alternatively, δ-hydroxy-α,β-unsaturated ester **2** was obtained by selective oxidation and Wittig olefination of **3**. Thus, diol **3** was selectively oxidized[14] with IBX, followed by two-carbon homologation with the stable Wittig ylide ethoxycarbonylmethylene triphenylphosphorane to furnish **2** in 64% yield.

The δ-hydroxy-α,β-unsaturated ester **2** was subjected to a base catalyzed intramolecular Michael addition using



Scheme 3. Regents and conditions: (a) IBX, THF, DMSO, rt, 1 h; (b) $Ph_3P{=}CHCO_2Et$, benzene, rt, 6 h, 64% (two steps); (c) PHCHO, K^tOBu, THF, 0 °C, 45 min, 76%; (d) concd H_2SO_4 (cat), THF, rt, 12 h, 95%.

1.1 equiv of benzaldehyde in the presence of 0.1 equiv of potassium *tert*-butoxide at 0 °C in THF to furnish benzylidene acetal **11** in good yield. The diastereoselectivity was greater than 95% favouring the more stable *syn*-isomer. Finally, hydrolysis of the benzylidene acetal and cyclization were successfully achieved in one pot[15] using catalytic concd H_2SO_4 in methanol to furnish the target molecule **1** in 95% yield.[16]

This letter describes a straightforward entry to tri-substituted δ-lactones in optically pure form. The simplicity of the approach should facilitate the total synthesis of complex lactone containing natural products.

Acknowledgements

Two of us (C.R. and S.J.P.) thank CSIR, New Delhi, for research fellowships.

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16. Spectral data for compound **1**: $[\alpha]_D^{25}$ −81.8 (*c* 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$); δ 4.94–4.85 (m, 1H), 4.05 (q, $J = 3.8$ Hz, 1H), 2.80 (dd, $J = 5.4$, 18.6 Hz, 1H), 2.54 (dd, $J = 3.3$, 18.6 Hz, 1H), 2.41–2.18 (m, 1H), 1.96–1.85 (m, 1H), 1.32 (d, $J = 6.7$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 75.4, 68.2, 37.8, 35.9, 18.0, 10.6; IR (KBr) cm^{-1} 3425, 2924, 1718, 1250, 1078; MS (LC): *m*/*z* 145.1 $(M+H)^+$, 167.0 $(M+Na)^+$, 127 $(M-17)^+$; HRMS: Calcd for $C_7H_{13}O_3$ $(M+H)^+$: 145.0864. Found: 145.0862.