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A general synthetic approach for the synthesis of β-hydroxy-δ-lactones: asymmetric total synthesis of prelactones and *epi*-prelactones V and E☆

Gowravaram Sabitha,* P. Padmaja, K. Bhaskar Reddy and J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A general synthetic approach for the synthesis of prelactones and *epi*-prelactones V and E has been reported using an Evans' aldol reaction as the key step.

β-Hydroxy-δ-lactones represent an important structural motif present in a large number of organic natural products[1] such as mevinolin and compactin,[2a] phomolactone[2b] and massoialactone.[2c] Prelactones **1**–**7** isolated from bafilomycin-producing microorganisms and various polyketide macrolide producing microorganisms belong to this class of compounds.[3] These lactones exhibit properties such as ATPase inhibition and antibacterial, antifungal and immunosuppressive activities.[2a,b,4] The discovery of these molecules supports the widely accepted hypothesis of step-by-step functionalization of a growing polyketide chain in the biosynthesis of macrolides.[5] Furthermore, highly functionalized chiral δ-lactones have attracted considerable attention in recent years due to their importance as building blocks in natural product synthesis.[6] Although there are many methods reported for the synthesis of prelactones, very few are known for *epi*-prelactones.[7] Therefore, an efficient and flexible approach for the enantioselective synthesis of prelactones and *epi*-prelactones is essential. Herein, we report a general route for the synthesis of prelactones and *epi*-prelactones V and E, **3**–**6**. The approach described here also gives access to the other prelactones as well as to additional derivatives with potential relevance in biological studies (Fig. 1).

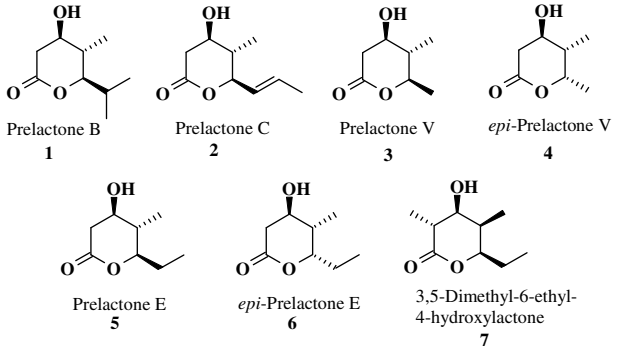

Figure 1.

The Evans' asymmetric aldol reaction[8] was chosen as the key step for the synthesis of these molecules. Thus, aldol reaction of aldehyde **9** with (4*R*)-*N*-propionyl-4-benzyloxazolidinone **8** using dibutylboron triflate and triethylamine in DCM at −78 °C for 30 min provided the *syn* aldol product **10** in 82% yield as a single diastereomer. The chiral auxiliary was removed by transamidation to afford Weinreb amide **11**. Amide **11** was subjected to a Grignard reaction with MeMgI to afford keto compound **12**, which on stereoselective reduction with tetramethylammonium triacetoxyborohydride[9] provided the 1,3-*anti* diol **13** (98:2 dr). The diol **13** was protected as acetonide **14** and its structure confirmed by ^{13}C NMR spectral studies.

After reductive debenzylation of compound **14**, the alcohol was oxidized to the corresponding acid via a two

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* Corresponding author. Tel./fax: +91 40 27160512; e-mail: sabitha@iictnet.org

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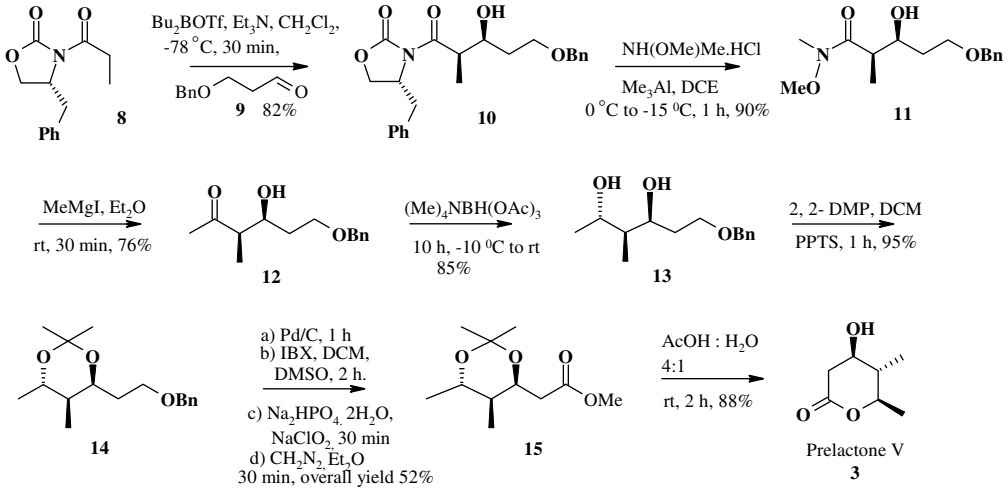
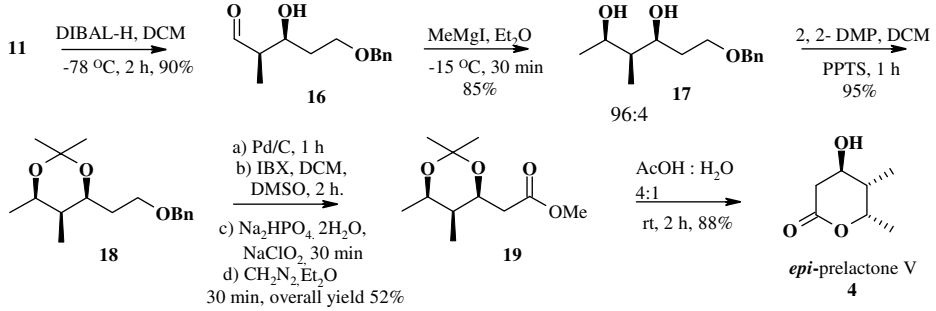
step process; firstly to an aldehyde using IBX in DMSO and then by perchlorite oxidation to the acid, which was converted into methyl ester **15** on treatment with diazomethane in ether (52% over four steps). Exposure of compound **15** to AcOH/H_2O (4:1) at room temperature for 2 h resulted in acetonide cleavage and subsequent cyclization furnished the target prelactone V, **3** (Scheme 1).

For the synthesis of *epi*-prelactone V, Weinreb amide **11** was treated with DIBAL-H to afford the aldehyde **16**. Grignard reaction of **16** with excess MeMgI in ether at −15 °C for 30 min afforded the 1,3-*syn* diol **17** in 85% yield. The *syn* stereochemical relationship of diol **17** was verified by analysis of the ^{13}C NMR spectrum of the corresponding acetonide **18**. The chemical shifts of the acetonide were observed at 98.7 and 19.7 ppm, in agreement with values commonly observed for a *syn* diol.[10] Debenzylation, IBX oxidation, conversion into the acid and treatment with diazomethane as described in Scheme 1 afforded ester **19**. Treatment of compound **19** with AcOH/H_2O (4:1) at rt afforded *epi*-prelactone V, **4** in 88% yield (Scheme 2).

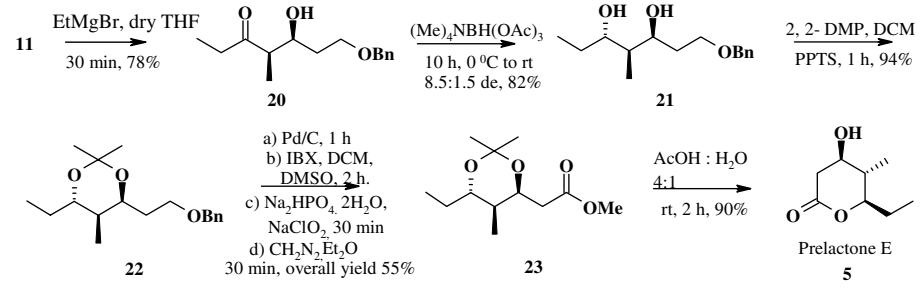
For the synthesis of prelactone E, the Weinreb amide **11** was treated with ethyl magnesium bromide to afford ketone **20** in 78% yield. Stereoselective reduction of the keto group using tetramethylammonium triacetoxyborohidride[9] afforded 1,3-*anti* diol **21** (98:2 dr) in 82% yield. After acetonide protection, the same



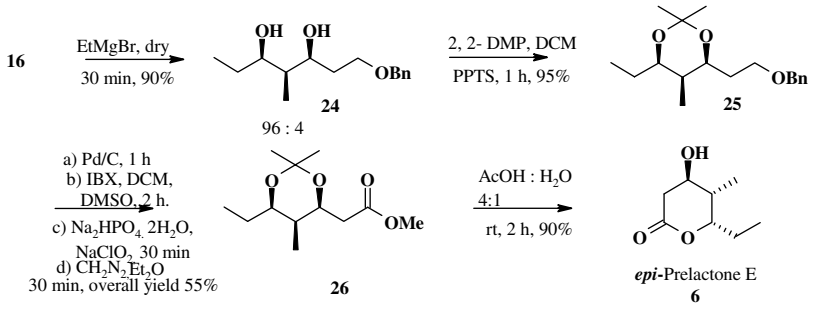
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

sequence of reactions as described in Scheme 1, afforded ester **23**. Exposure of **23** to AcOH/H_2O (4:1) at rt furnished prelactone E, **5** in 90% yield (Scheme 3).

The synthesis of *epi*-prelactone E began with the intermediate aldehyde **16**. Accordingly, Grignard reaction of **16** with excess EtMgBr in dry THF at −15 °C for 30 min afforded the 1,3-*syn* diol **24** in 90% yield. The *syn* stereochemical relationship of diol **24** was verified by analysis of the ^{13}C NMR spectrum of the corresponding acetonide **25**. The chemical shifts of the acetonide were observed at 98.7 and 19.6 ppm, in agreement with values commonly observed for a *syn* diol.[10] Debenzylation, IBX oxidation, conversion into the acid, and treatment with diazomethane as before afforded ester **26**. Reaction of **26** with AcOH/H_2O (4:1) at rt afforded *epi*-prelactone E, **6** (Scheme 4).

In conclusion, we have accomplished the stereoselective synthesis of prelactones V, E and *epi*-prelactones V, E using an Evans' aldol reaction as the key step. The methodology presented here is general and should allow access to novel analogues of the prelactones.

References and notes

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(*c* 8 mg/ml in Et_2O), [Reported[7p] value: +41.9 (*c* 8 mg/ml in Et_2O)]; *epi-prelactone E* (**6**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (tt, $J = 3.0$, 5.2 Hz, 1H), 4.01 (m, 1H), 2.76 (dd, $J = 5.2$, 18.1 Hz, 1H), 2.49 (dd, $J = 2.2$, 18.1 Hz, 1H), 1.93 (m, 1H), 1.78 (m, 1H), 1.42–1.67 (m, 1H), 1.04 (t, $J = 7.5$ Hz, 3H), 0.94 (d, $J = 7.5$ Hz, 3H), 1.25 (br, 1H, OH); ^{13}C NMR($CDCl_3$, 75 MHz): 170.1, 79.2, 68.8, 48.2, 37.1, 25.0, 10.2, 10.1; LCMS: 181.0 [M+Na]; IR: 3426, 2926, 1728, 1461, 1379, 1252, 1099, 950 cm^{-1}; $[\alpha]_D^{25}$ +4.3 [*c* 0.5, $CHCl_3$]; *prelactone V acetonide* (**14**): ^{1}H NMR ($CDCl_3$, 200 MHz): 7.14–7.42 (m, 5H), 4.46 (s, 2H), 3.98–4.14 (m, 2H), 3.44–3.58 (m, 2H), 1.48–1.85 (m, 3H), 1.4 (s, 3H), 1.34 (s, 3H), 1.24 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 137.6, 128.6, 127.4, 127.2, 100.2, 71.6, 68.4, 68.1, 66.2, 35.2, 33.4, 25.6, 24.3, 18.3, 4.2; LCMS: 301 [M+Na]; IR (neat): 3412, 2984, 2842, 1634, 1462, 1370, 1265, 1112, 930, 828 cm^{-1}; *epi-prelactone V acetonide* (**18**): ^{1}H NMR ($CDCl_3$, 200 MHz): 7.19–7.44 (m, 5H), 4.50 (s, 2H), 4.0–4.17 (m, 2H), 3.46–3.61 (m, 2H), 1.50–1.92 (m, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.12 (d, $J = 6.2$ Hz, 3H), 0.87 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.5, 128.3, 127.6, 127.5, 98.7, 73.0, 69.9, 68.9, 66.7, 36.1, 33.3, 30.0, 19.7, 18.8, 4.4; LCMS: 301 (M+Na); IR (neat): 3420, 2976, 2868, 1622, 1455, 1177, 1263, 1105, 909, 739 cm^{-1}; $[\alpha]_D^{25}$ −17.8 (*c* 1, $CHCl_3$); *Prelactone E acetonide* (**22**): ^{1}H NMR ($CDCl_3$, MHz): 7.21–7.33 (m, 5H), 4.46 (s, 2H), 3.95–4.04 (m, 1H), 3.47–3.53 (t, $J = 6.0$ Hz, 2H), 3.05–3.14 (m, 1H), 1.40–1.68 (m, 5H), 1.37 (s, 6H), 0.89–0.97 (t, $J = 6.8$ Hz, 3H), 0.79–0.85 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.3, 128.9, 128.3, 128.1, 100.6, 77.4, 73.6, 67.8, 65.8, 40.1, 31.6, 27.4, 24.2, 25.1, 12.4, 10.9; LCMS: 315 [M+Na]; IR (neat): 3429, 2928, 1641, 1457, 1380, 1271, 1109, 1072, 969, 884 cm^{-1}; $[\alpha]_D^{25}$ −21 (*c* 1, $CHCl_3$); *epi-Prelactone E acetonide* (**25**): ^{1}H NMR ($CDCl_3$, 200 MHz): 7.23–7.36 (m, 5H), 4.49 (AB quartet, $J = 12.5$ Hz, 2H), 4.0–4.12 (m, 1H), 3.67–3.80 (m, 1H), 3.41–3.59 (m, 2H), 1.43–1.89 (m, 5H), 1.39 (s, 3H), 1.35 (s, 3H), 0.76–0.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): 138.5, 128.3, 127.6, 127.4, 98.7, 74.8, 73.0, 70.0, 66.7, 34.3, 33.4, 29.9, 25.5, 19.6, 9.6, 4.5; LCMS: 315 [M+Na]; IR (neat): 3443, 2965, 2858, 1624, 1456, 1380, 1260, 1106, 1037, 970, 737 cm^{-1}; $[\alpha]_D^{25}$ −16 (*c* 1, $CHCl_3$).

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