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A convergent route to β-hydroxy δ-lactones through Prins cyclisation as the key step: synthesis of (+)-prelactones B, C and V☆

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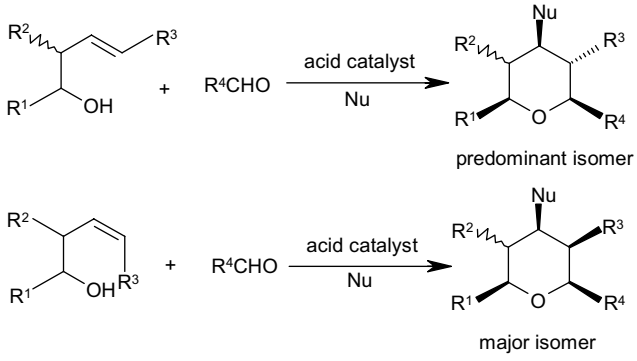
Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

Abstract—Reactions of homoallylic alcohols with aldehydes in the presence of acid catalysts gave multisubstituted tetrahydropyrans with the creation of one to three new stereogenic centres in a single-pot process. The utility of this approach is extended to the enantioselective syntheses of (+)-prelactones B, C and V.

A strategy that has been gaining importance for the stereoselective synthesis of tetrahydropyrans (THPs) is the acid-promoted Prins-type reaction involving cyclisation of an oxycarbenium ion generated in situ either from reaction of the parent homoallylic alcohol[1] with an aldehyde or from a homoallylic acetal[2] or α-acetoxy ester.[3] Such reactions have been widely used for the construction of tetrahydropyrans with different functionalities like hydroxyl,[1a,c,d] acetoxy,[2d,4] acylamino[5] or a halogen[1a,b,e,4a] at C-4 by judicious choice of reaction conditions. This strategy has the advantage of being very flexible; by correct choice of the appropriate aldehyde and the substitution pattern in the homoallylic alcohol, a range of functionalised side-chains with complex substitution patterns can be installed on the THP ring in a single-pot process (Scheme 1).[1a,b,6] This type of cyclisation has been successfully used in the synthesis of some natural products.[6,4b] In this report, we extend the use of this method for the synthesis of triketide δ-lactones.



Scheme 1.

δ-Lactones are of great importance, being structural components of a large number of organic natural products and serving as intermediates in the syntheses of several drugs and natural products. Prelactones **1**–**5** (Fig. 1) constitute an important group of highly functionalised chiral δ-lactones isolated from various polyketide macrolide producing microorganisms.[7] The discovery of these molecules supports the widely accepted hypothesis of step-by-step functionalisation of growing polyketide chains in the biosynthesis of macrolides.[8] They represent important structural moieties in a large number of bioactive natural products such as mevinolin and compactin, inhibitors of cholesterol biosynthesis,[9a] phomolactone[9b] and asperlin,[9c] antibiotics and massoialactone,[9d] tetrahydro 6-(1-hydroxyundecyl)-2*H*-pyran-2-one,[9e] attractant or defence substances for animals and insects. Hence, there has been increasing attention paid to the synthesis of δ-lactones.[10–12] The general strategy that we describe here for the synthesis of these prelactones, will allow the preparation of material for use as standards during mechanistic studies of

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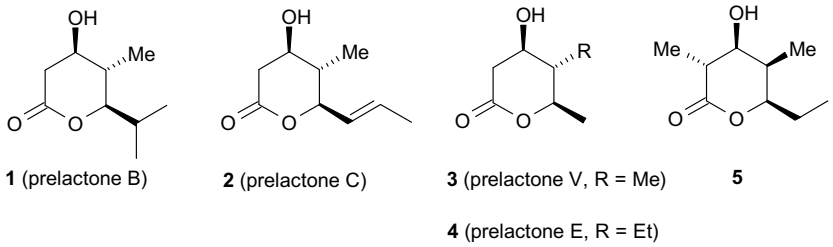
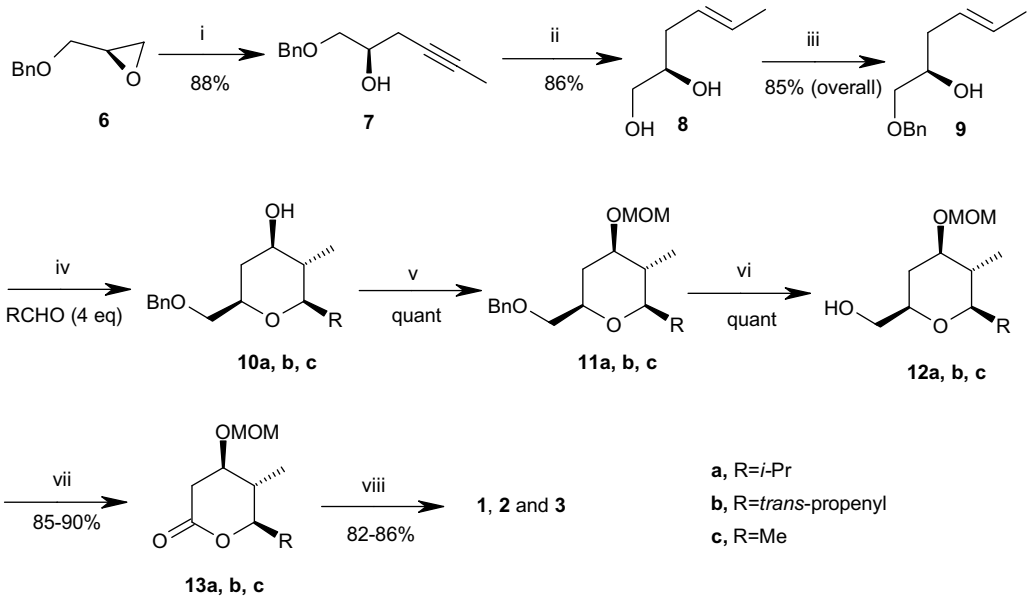


Figure 1.



Scheme 2. Reagents and conditions: (i) $CH_3C{\equiv}CLi$, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2 h; (ii) Na, NH_3 liq, THF, 5 h; (iii) BnBr, NaH, DMF, 0 °C–rt, 6 h; (iv) (a) amberlyst-15 (1 g for 5 mmol of **2**), DCM, reflux, 5–6 h, 48–55% or (b) TFA (30 equiv w.r.t. HAA to **9**), 0 °C, 3 h then K_2CO_3, MeOH, rt, 1 h, 60–68% or (c) $BF_3{\cdot}OEt_2$, AcOH, 0 °C, 2–3 h then K_2CO_3, MeOH, rt, 1 h, 52–60%; (v) $(^iPr)_2NEt$, MOMCl, DMAP, DCM, 0 °C–rt, 12 h (vi) Li, NH_3 liq, 2 min; (vii) PCC (4 equiv), benzene, reflux, 4–5 h; (viii) 1 N HCl, THF, 0 °C–rt, 6 h.

polyketide biosynthesis and will provide a flexible route for the synthesis of di-, tri- and tetra-substituted δ-lactones in a highly stereocontrolled manner.

In the synthesis (Scheme 2), the key intermediate, homoallylic alcohol **9**, was prepared from (+)-benzyl glycidyl ether **6**.[13] Opening of the epoxide in benzyl glycidyl ether **6** with propynyllithium in the presence of $BF_3{\cdot}OEt_2$ resulted in homopropargyl alcohol **7** in 88% yield. Birch reduction of **7** furnished dihydroxy *trans* olefin **8** in 86% yield. Selective protection of the primary hydroxyl group as a benzyl ether in the presence of NaH in DMF afforded **9** in 65% yield along with 20% of the di-*O*-benzyl protected material and 8% of starting material. The doubly protected compound could be converted back to diol **8** with lithium in liquid ammonia allowing repetition of the protection proceeded to give **9** was in 85% overall yield.

To carry out the crucial prins cyclisation reactions, a mixture of **9** and an aldehyde was treated with amberlyst-15[1c] in refluxing DCM for 5–6 h to produce the tetrasubstituted tetrahydropyrans **10a–c** in 48–55% yields along with 30–34% of recovered **9**. Whereas, the cyclisations with TFA[1a] or $BF_3{\cdot}OEt_2$ in AcOH[4b] afforded, after hydrolysis of the esters with potassium carbonate in MeOH, tetrahydropyrans **10a–c** in 60–68% and 52–60% yields, respectively, with the complete disappearance of **9**. The predominant isomers were isolated by flash column chromatography and were found to have all substituents in equatorial positions. The stereochemistry was assigned on the basis of ^1H NMR coupling constants [e.g., **10a** showed δ 3.30 (dt, $J = 11.8$, 4.8 Hz, 1H, 4-H), 2.82 (dd, $J = 12.0$, 6.1 Hz, 1H, 2-H), 1.96 (ddd, $J = 12.1$, 4.8, 1.6 Hz, 1H, 5-Heq)] and on the basis of previous studies.[1a,b,e,6] The stereochemical assignments were further confirmed after converting **10a–c** to the final lactones **1**, **2** and **3**, whose spectral data were identical in all respects with those reported.

The 6-pyranyl methanols **12a–c** were obtained quantitatively from **10a–c** after methoxymethyl protection of the 2° alcohol in the presence of diisopropylethylamine and deprotection of the resulting benzyl ether with Li in liquid ammonia. The alcohols **12a–c** on treatment with PCC in refluxing benzene afforded the lactones **13a–c** in 85–90% yields.[14] Deprotection of the methoxymethyl ether with 1 N HCl in THF furnished the prelactones **1**,

2 and **3** in 82–86% yields. The spectroscopic (^{1}H NMR, ^{13}C NMR, IR, mass) and physical data[15] (specific rotations and melting points) of all the lactones were in good agreement with those reported.[11,12]

In conclusion, a flexible and efficient approach to the asymmetric synthesis of triketide δ-lactones such as (+)-prelactones B, C and V has been described involving Prins cyclisation as the key step. A variety of functionalised chains can be installed at C-3, C-5 and C-6 of the lactones. Further applications of the methodology in the synthesis of several complicated chiral intermediates for polyketide synthesis are in progress and the results will be published in due course.

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15. Selected physical data for compound **1**. $R_f = 0.45$ (silica, 60% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +36.8 (*c* 0.72, MeOH); mp 97–98 °C; IR (KBr): ν_{max} 3475, 2969, 2925, 1718, 1465, 1274, 1004 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.72 (m, 2H), 2.89 (dd, $J = 17.6$, 5.9 Hz, 1H), 2.52 (br s, OH, 1H), 2.48 (dd, $J = 17.8$, 8.0 Hz, 1H), 1.98 (m, 1H), 1.76 (ddq, $J = 10.0$, 7.0, 6.1 Hz, 1H), 1.12 (d, $J = 6.0$ Hz, 3H), 1.08 (d, $J = 6.0$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.33, 86.38, 69.65, 38.96, 38.89, 28.89, 19.94, 14.04, 13.60; EIMS: *m/z* (%) 129 ($M^+ - C_3H_7$, 25), 111 (23), 87 (28), 58 (55), 43 (100). Anal. Calcd for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36%. Found: C, 62.84; H, 9.41%. Compound **2**. $R_f = 0.5$ (silica, 70% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +54.4 (*c* 0.76, MeOH); IR (neat): ν_{max} 3400, 2925, 1730, 1225 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.79 (ddq, $J = 15.2$, 6.6, 1.0 Hz, 1H), 5.43 (ddq, $J = 15.2$, 8.2, 2.0 Hz, 1H), 4.17 (dd, $J = 10.4$, 8.2 Hz, 1H), 3.74 (ddd, $J = 8.0$, 7.0, 5.8 Hz, 1h), 3.07 (br s, OH, 1H), 2.87 (dd, $J = 17.0$, 5.8 Hz, 1H), 2.46 (dd, $J = 17.0$, 8.0 Hz, 1H), 1.77 (dd, $J = 6.6$, 2.0 Hz, 3H), 1.64 (ddq, $J = 10.4$, 7.0, 6.8 Hz, 1H), 1.02 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.34, 132.41, 127.61, 84.11, 69.53, 41.49, 39.08, 17.62, 13.66; EIMS: *m/z* (%) 152 ($M^+ - H_2O$, 14), 109 (10), 82 (40), 71 (100), 58 (31), 43 (53). Anal. Calcd for $C_9H_{14}O_3$ (170.20): C, 63.51; H, 8.29%. Found: C, 63.46; H, 8.31%. Compound **3**. $R_f = 0.4$ (silica, 60% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +32.8 (*c* 0.98, MeOH); mp 46 °C; IR (KBr): ν_{max} 3435, 2980, 2932, 1730, 1383, 1267, 1095, 1046, 979 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.93 (dt,

J = 5.7, 7.2 Hz, 1H), 3.75 (dq, J = 6.2, 10.1 Hz, 1H), 2.9 (dd, J = 5.6, 16.6 Hz, 1H), 2.42 (dd, J = 7.2, 16.6 Hz, 1h), 1.98 (br s, OH, 1H), 1.58 (ddq, J = 10.2, 7.2, 6.8 Hz, 1H), 1.38 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.53, 79.04, 69.67, 43.32, 39.07, 19.55, 13.71; EIMS: m/z (%) 144 (M^+, 50), 102 (100), 71 (75), 41 (95). Anal. Calcd for $C_7H_{12}O_3$ (144.16): C, 58.32; H, 8.39%. Found: C, 58.26; H, 8.44%.