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Stereoselective synthesis of polyketide precursors containing an *anti*-1,3-diol system via a Prins cyclisation and reductive cleavage sequence

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Abstract—A new approach for the stereoselective synthesis of polyketide precursors containing *anti*-1,3-diol units flanked by a variety of alkyl branches and functional groups through a Prins cyclisation and reductive cleavage sequence is described.

Natural products of polyketide biosynthetic origin represent an important class of synthetic targets that display a range of potent and diverse biological activities.[1,2] These activities range from antibacterial and antifungal to cytotoxic and immunosuppressive. Members of this class have long served to stimulate the development of methods designed to access their highly functionalised acyclic architectures. As such, a variety of methods have been developed for the synthesis of 1,3-polyol units,[3] one of the widespread and challenging structural motifs. Specifically, the *anti*-1,3-diol system is a key unit of several biologically active molecules such as (+)-strictifolione **1**, (−)-pironetin **2**, (−)-salicylihalamide A **3** and crocacin C **4** and is also a key intermediate of several complex molecules.[4] Synthetic access to such subunits is still in great demand (Fig. 1).

In this letter, we describe a new strategy for the synthesis of acyclic *anti*-1,3-diol units flanked by a variety of alkyl chains and functional groups, from multi-substituted

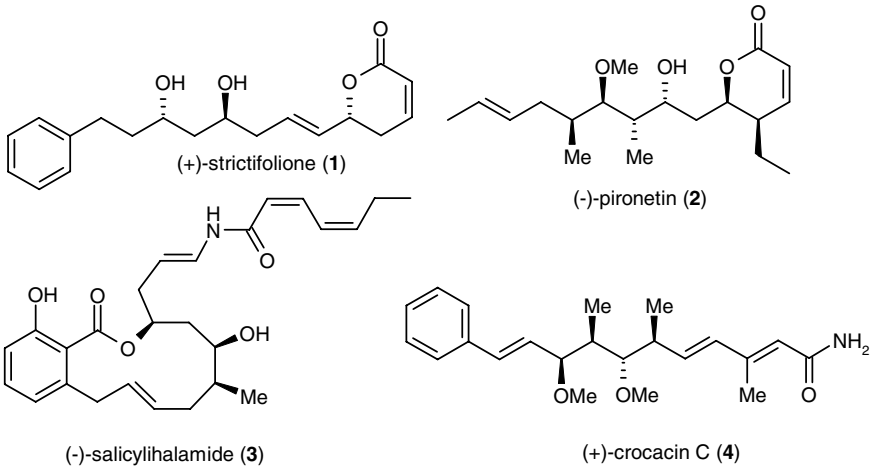

Figure 1.

Keywords: Prins cyclisation; Tetrahydropyrans; Polyketide; 1,3-Diol.
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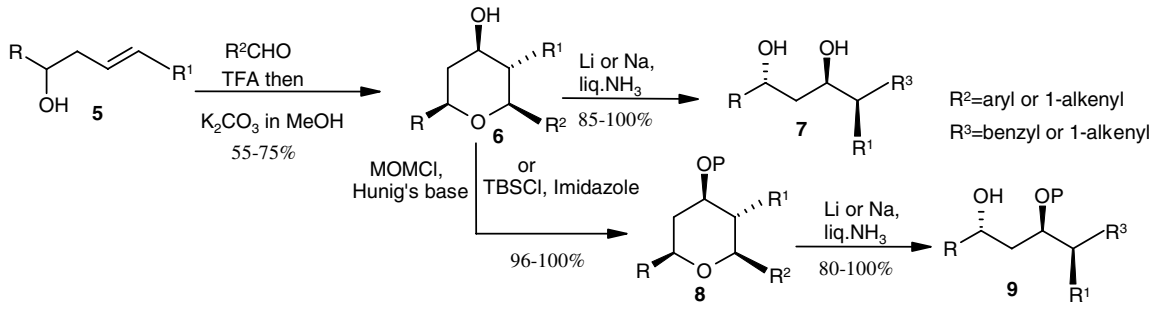


Scheme 1.

Table 1. Synthesis of polyketide precursors containing *anti*-1,3-diol units

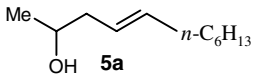
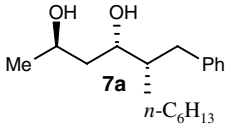
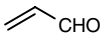
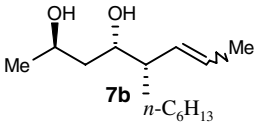
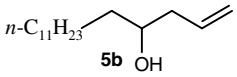
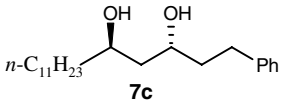
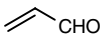
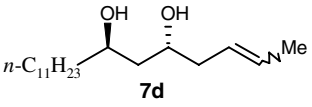
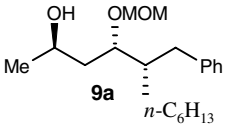
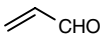
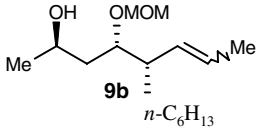
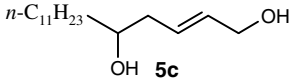
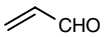
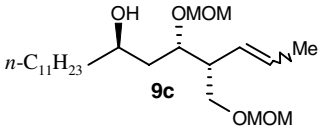
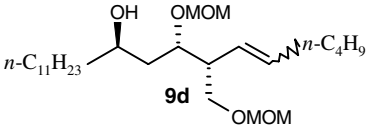
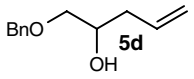
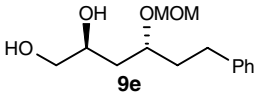
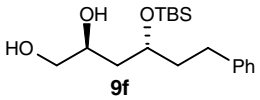
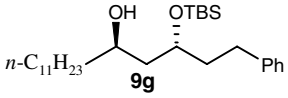
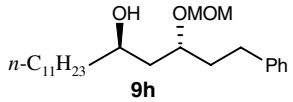
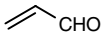
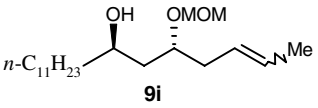
Homoallylic alcohol	Aldehyde	Product	Overall yield (%)
 **5a**	PhCHO	 **7a**	75
5a		 **7b**	60
 **5b**	PhCHO	 **7c**	62
5b		 **7d**	54
5a	PhCHO	 **9a**	72
5a		 **9b**	58
 **5c**		 **9c**	42
5c	*trans*-2-Hexenal	 **9d**	44

Table 1 (*continued*)

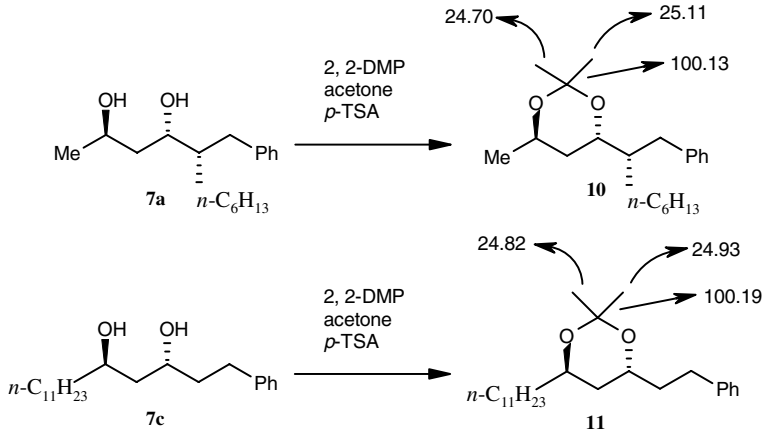
Homoallylic alcohol	Aldehyde	Product	Overall yield (%)
 **5d**	PhCHO	 **9e**	51
5d	PhCHO	 **9f**	48
5b	PhCHO	 **9g**	55
5b	PhCHO	 **9h**	57
5b		 **9i**	50

tetrahydropyrans (THPs) which in turn were constructed through a highly stereoselective Prins cyclisation from simple aldehydes and homoallylic alcohols.

The Prins cyclisation has become a powerful tool for synthetic chemists as it is useful in the stereoselective synthesis of tetrahydropyrans (THPs) involving cyclisation of an oxycarbonium ion generated in situ either from reaction of the parent homoallylic alcohol[5] with an aldehyde or from a homoallylic acetal[6] or α-acetoxy ether.[7] It has been widely used in the construction of THPs with complex substitution patterns and has been successfully utilised in the synthesis of natural products.[8] We recently developed a general route to β-hydroxy δ-lactones via a Prins cyclisation[8a] and started to explore the potential of this reaction in the synthesis of acyclic frameworks which are useful in polyketide synthesis. Herein, we further expand the scope of the Prins cyclisation to the synthesis of a variety of polyketide precursors containing *anti*-1,3-diol units.

Scheme 1 outlines our method in detail. Initially, we constructed the pyrans **6** through the Prins cyclisation of a homoallylic alcohol **5** and aromatic or α,β-unsaturated aldehydes in the presence of trifluoroacetic acid in DCM followed by hydrolysis of the trifluoroacetate with K_2CO_3 in MeOH. The predominant isomers were isolated by flash column chromatography and were found to have all substituents in equatorial positions.[5a,8a] ^{1}H NMR of the crude products showed 2–5% of other diastereomers.

The pyran **6**, with the requisite aryl or 1-alkenyl groups at C-1 or C-6 and without protection of the hydroxy



Scheme 2.

group at C-4, was subjected to Li or Na in liquid NH_3 mediated benzylic or allylic cleavage to deliver the open chain unprotected *anti*-1,3-diol system **7**. The results are outlined in Table 1.[9–14]

Next, we developed a route for the partially protected *anti*-1,3-diol system **9**. The 2° alcohol of THP **6** was protected, either as its MOM ether in the presence of MOM chloride, DMAP and DIPEA as base in DCM, or as its TBS ether in the presence of TBS chloride, DMAP and imidazole as base in DCM, to yield **8** which in turn was subjected to Li or Na in liquid NH_3 mediated benzylic or allylic cleavage to afford the open chain alcohol system **9**. The results are described in Table 1.[9–14] Benzylic cleavage was very quick (1–2 min) and led to quantitative yields whereas allylic cleavages were slower (30–50 min) and led to 80–90% conversion along with the recovered starting material. Products obtained in allylic cleavages were 1:1 *cis*- and *trans*-olefins with respect to the migrated olefin bond (as was clearly evident from ^1H and ^{13}C NMR spectroscopy).

Though the stereochemistry of the resultant pyrans in Prins cyclisation is well established,[5a,8a] we further demonstrated that the 1,3-diols synthesised in this report were *anti*. We took two examples, **7a** and **7c**, and converted them in to their acetonides **10** and **11** using 2,2-DMP and *p*-TSA in acetone. ^{13}C analysis of the acetonides clearly revealed that the alcohols at C-1 and C-3 were *anti* related (Scheme 2).[15]

Thus, we have reported simple two- and three-step sequences for the synthesis of polyketide precursors containing *anti*-1,3-diol units with a variety of alkyl branches and functional groups. The method successfully utilises the stereochemical control in Prins cyclisation. Applications of the method to the synthesis of several polyketide intermediates and biologically active molecules like strictifolione, attenol A, crocacin C, etc., are in progress and the results will be published in due course.

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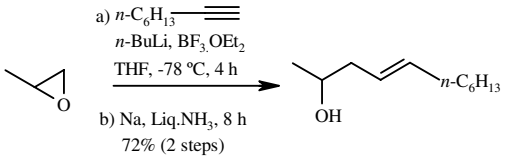
9. Selected physical data for compound **7a**. IR (KBr): ν_{max} 3379, 2927, 2857, 1454, 1376, 1068, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.24–7.10 (m, 5H), 4.08–3.96 (m, 1H), 3.92–3.86 (m, 1H), 3.20 (br s, 2H), 2.76 (dd, 1H, $J = 13.6$, 6.04 Hz), 2.43 (dd, 1H, $J = 13.6$, 8.3 Hz), 1.72–1.60 (m, 2H), 1.40–1.12 (m, 14H), 0.82 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.1, 128.2, 125.7, 69.4,

65.5, 45.9, 40.8, 36.4, 31.7, 29.5, 29.0, 27.3, 23.2, 22.5, 14.0. ESIMS: 279 (M^++H). HRMS *m/z* calcd for $C_{18}H_{31}O_2$ $[M+H]^+$ 279.2324. Found 279.2309. Compound **9a**. IR (KBr): ν_{max} 3441, 2927, 2856, 1457, 1149, 1036, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.03–7.06 (m, 5H), 4.68 (d, 1H, $J = 6.7$ Hz), 4.61 (d, 1H, $J = 6.7$ Hz), 4.06–3.92 (m, 1H), 3.90–3.78 (m, 1H), 3.44 (s, 3H), 2.90 (dd, 1H, $J = 13.5$, 4.2 Hz), 2.41 (br s, 1H), 2.24 (dd, 1H, $J = 13.5$, 10.1 Hz), 1.96–1.8 (m, 1H), 1.68–1.08 (m, 15H), 0.84 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.0, 128.1, 125.6, 96.6, 76.9, 64.1, 55.9, 43.8, 39.0, 35.8, 31.6, 29.7, 29.4, 27.3, 23.4, 22.5, 13.9. ESIMS: 345 (M^++Na). HRMS *m/z* calcd for $C_{20}H_{34}O_3Na$ $[M+Na]^+$ 345.2405. Found 345.2390. Compound **9h**. IR (KBr): ν_{max} 3445, 2925, 2853, 1458, 1098, 1036, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.28–7.08 (m, 5H), 4.65 (s, 2H), 3.88–3.76 (m, 2H), 3.41 (s, 3H), 2.76–2.59 (m, 3H), 2.00–1.74 (m, 2H), 1.59 (t, 2H, $J = 5.9$ Hz), 1.46–1.22 (m, 20H), 0.89 (t, 3H, $J = 6.7$ Hz); ESIMS: 401 (M^++Na). HRMS *m/z* calcd for $C_{24}H_{42}O_3Na$ $[M+Na]^+$ 401.3031. Found 401.3050.

10. For the synthesis of starting materials **5a**, **5b**, **5c** and **5d**, see Refs. 11, 12, 13 and 14, respectively.

11.



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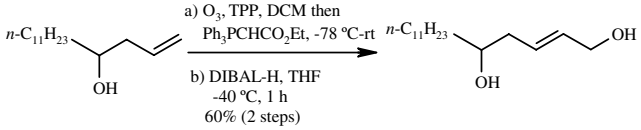
13.



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