New methods and strategies for the stereocontrolled synthesis of polypropionate-derived natural products

Ian Paterson
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract: By using the stereoregulated aldol reactions of chiral enol borinates with aldehydes, the synthesis of elaborate segments of polypropionate-derived natural products can be readily achieved. Stereocontrol may originate from the chiral influence of the boron reagent, the starting ketone (dependent on substitution pattern and enol borinate geometry), and the aldehyde, or from some combination of these (multiple asymmetric induction). Subsequent elaboration of the β-hydroxy ketone adducts can then be performed with a high level of overall diastereoselectivity. Examples of these reactions are given in the context of the synthesis of various polypropionate-derived natural products, including antibiotics (oleandomycin, rifamycin S), antitumour agents (swinholide A), enzyme inhibitors (ebelactone A), and marine polypropionates (denticulatin A and B).

INTRODUCTION
The polyketide family of natural products represent a diverse array of structurally complex compounds, having a wide range of biological activity (typically antibiotic, antitumour, antiparasitic, or immunomodulatory action). Many of these are referred to as polypropionates, reflecting their common biosynthesis from propionate and to a lesser extent acetate units.

Scheme 1

GENERAL ALDOL ANALYSIS FOR EXTENDED POLYPROPIONATES

As organic chemists strive to design and execute ever shorter and more efficient polypropionate syntheses, strategies using acyclic stereocontrol have become increasingly important [ref. 1]. Typically, this involves the aldol addition or allylation of an aldehyde by a suitable propionate equivalent. Excellent chiral propionate reagents have been developed by many research groups. However, their iterative application to polypropionate segments with many contiguous stereogenic centres, as occur in the secoacids of oleandomycin (1) or swinholide A (2), may not be ideal. In particular, such linear biomimetic approaches usually require several synthetic steps to give the new aldehyde for the next propionate addition.

The direct synthesis of extended polypropionate segments like 3 and 4 by aldol reactions of ethyl ketones 5–7 with aldehydes is outlined in Scheme 1. With unsaturated aldehydes, e.g. methacrolein, elaboration of the alkene groups in 4 allows further stereocentres to be introduced. Provided high levels of regio- and stereocontrol are possible, this strategy offers a simple and attractive alternative to conventional propionate extension on aldehydes. Both substrate- and reagent-based methods for achieving this control are discussed in this article.
THE BORON ALDOL REACTION FOR ETHYL KETONES

The aldol reaction of boron enolates [ref. 2] is especially useful in this context. The enol borinate is first generated from the ketone and a boron reagent, L₂BX (X = CI, OTf), then directly reacted with the required aldehyde as shown in Scheme 2. For sterically demanding L groups on boron, the relationship Z enolate → syn aldol and E enolate → anti aldol holds. This ensues from reaction through a chair transition structure with R² in the aldehyde equatorially arranged. Chiral substituents on the boron atom or the ketone give chiral Z and E enol borinates, leading to the diastereomeric chair transition structures (TS-I, II,...) shown. Using an aldol force field based on MM2, computer modelling of these competing transition structures reproduces experimental aldehyde re/si selectivities and isomer ratios (syn-I/II, anti-I/II) for a range of L, R¹ and R² [ref. 3].

Scheme 2

ALDOL TRANSITION STRUCTURES FOR R¹ AND/OR L CHIRAL

For general utility in polypropionate synthesis, the various stereo- and regiochemical criteria listed below must be satisfied. Ideally, the chiral boron reagents used should also be easily prepared without recourse to resolution.

- Enolisation regioselectivity with unsymmetrical ethyl ketones, R¹ ≠ Et?
- Enolisation E/Z stereoselectivity?
- Enol borinate re/si selectivity in aldol addition to aldehydes (achiral and chiral)?
- Extension to methyl ketones?

Three distinct types of ethyl ketone aldol reaction emerge from the general analysis in Scheme 1. These are considered in turn.

ALDOL-1: Enantioselective aldol reactions of ethyl ketones using chiral boron reagents (5→6 in Scheme 1)

For reagent control in the aldol reactions of ethyl and methyl ketones with aldehydes, we use the chiral boron reagents 9, 10, and 11, or their enantiomers. These are readily available in two steps from the appropriate enantiomer of α-pinene or menthone (i.e. no resolution step is required).

Syn aldol reactions. Ethyl ketone aldol reactions with reagent 9 and iPr₂NEt as the base proceed via the Z enol diisopinocampheylborinates 12, L = lpc (Scheme 3) [ref. 4]. With most unsymmetrical ketones, highly regioselective enolisation occurs towards the ethyl side. For this and other boron triflate reactions, Z enolates are presumably formed by the hindered amine selecting between the two available C=O·BL₂OTf complexes, leading to kinetic deprotonation trans to the boron group as shown [ref. 5]. These chiral enol borinates then add to aldehydes with high diastereoselectivity and useful levels of si/re discrimination (5:1-27:1 for syn-I/syn-II). For the (-)-lpc₂BOTf reaction, MM2 calculations [ref. 3] indicate that TS-I is preferred over TS-II, where the lpc ligands are conformationally locked (Fig. 1).
**Anti aldol reactions.** These require a hindered dialkylboron chloride reagent and Et$_3$N as the base for enolisation stereocontrol, e.g., reagent 10 gives predominantly the $E$ enol borinate 13, $L = \text{Ipc}$. Related results are known from Brown’s work using dicyclohexylboron chloride [ref. 6]. We believe that the unhindered amine selects between the two available C=O+BL$_2$Cl complexes, leading now to kinetic deprotonation cis to the boron group as shown. The conformational preferences and reactivity of these intermediate Lewis acid-ketone complexes are being probed by ab initio MO calculations [ref. 7]. Unfortunately, the Ipc ligands are ineffective for asymmetric anti aldol reactions. A collaboration with Cesare Gennari’s group at Milan has recently led to the computer-aided design of the new reagent 11 [ref. 8]. Molecular mechanics calculations (MM2) indicate that the aldol TS-IV is preferred over TS-II in Scheme 2, suggesting synthetically useful re/si selectivity. In fact, experiments show that reagent 11 gives anti aldols with good levels of enantioselectivity (4:1–16:1 for anti-II/anti-I). Improved reagents are now being designed and prepared using such rational transition state modelling.

\[ \text{Scheme 3} \quad \text{SYN ALDOL REACTION} \quad \text{ETHYL KETONES} \quad \text{ANTI ALDOL REACTION} \]

\[ \text{Fig. 1} \quad \text{steric repulsion} \quad \text{TS-I, si-face attack} \\
E = 0.0 \text{ kcal mol}^{-1} \quad \text{TS-II, re-face attack} \\
E = 1.4 \text{ kcal mol}^{-1} \]

**Methyl ketones.** The combination of chloride reagents 10 or 11 with Et$_3$N as base is particularly effective for enolising methyl ketones to give 14 (Scheme 4). Even methyl ethyl ketone only enolises towards the methyl side. Reagent 11 gives aldol adducts 15 with 54–76% ee, suggesting chair TS-IV in Scheme 2 is operating for both this and the $E$ enolate reaction [ref. 8]. The Ipc reagent 10 gives similar results [ref. 4], except that the hydroxyl configuration in 15 is reversed compared to 12 $\rightarrow$ syn-I. The aldehyde is now apparently reacting on its re-face with 14, $L = \text{Ipc}$, through a twist-boat transition structure. While the level of asymmetric induction is only modest, it may be useful for diastereoselective aldol additions using chiral methyl ketones and/or chiral aldehydes (double and triple asymmetric induction).

**ALDOL-2: Diastereoselective aldol reactions of $\alpha$-chiral ethyl ketones (7–8 in Scheme 1)**

We have introduced (R)- and (S)-16 as versatile dipropionate equivalents for the synthesis of polypropionate natural products (Scheme 5). These $\alpha$-chiral ethyl ketones are prepared in ≥97% ee in three steps from commercial (R)-(−) and (S)-(−)-methyl 2-methyl-3-hydroxypropionate, respectively [ref. 9]. Three out of four of the diastereomeric aldol adducts 17 can be obtained selectively for any aldehyde (Scheme 6). Using appropriate reagents, the subsequent ketone reduction gives either the syn or anti 1,3-diol 18, directly incorporating the six carbon atoms and stereogenic centre from 16. For $R = \text{isopropenyl}$ (i.e., methacrolein as the aldehyde), stereoregulated alkene hydration gives a general entry into stereopentads, 18 $\rightarrow$ 19 [ref. 10]. All thirty-two stereoisomers of 19 can be accessed in this way. Altogether, this provides a systematic approach to
specific stereopentad sequences for the synthesis of polypropionate-derived natural products of known structure, as well as assisting the assignment of stereochemistry in unknown structures and for the synthesis of unnatural analogues.

**Scheme 5**

**DIPROPIONATE EQUIVALENTS**

![Scheme 5](image)

**TRIPROPIONATE EQUIVALENTS**

**E-enolates.** Efficient substrate control is possible in the anti aldol reaction of (S)-16 via the E enol dicyclohexylborininate 20 to give the anti-anti adduct 21 in >95% ds by re-face attack on the aldehyde [ref. 9b]. This reaction is remarkable, as no chiral auxiliary or reagent is needed and the benzoxymethyl substituent appears to give optimum selectivity. We believe that the reaction proceeds preferentially through TS-V, which minimises A(1,3) allylic strain and has a contra-steric preference for the benzoxymethyl oxygen to be directed in towards the aldehyde. This effect must have an electronic origin, which is still to be defined.

**Z-enolates.** The analogous syn aldol reactions of (S)-16 via the Z enol borinate with achiral boron reagents, however, are non-selective [ref. 9a]. Here reagent control from the two enantiomeric lpc₂BOTf reagents can be used effectively, as in 22 → 23 (SA) and 24 → 25 (SS). For the syn-syn isomer, a substrate-controlled aldol reaction via Sn(II) enolate 26 is more convenient [ref. 11]. Internal chelation by the benzyl ether in the aldol TS-VI presumably leads to high levels of enolate π-face differentiation (not possible for boron).

**ALDOL-3:** Diastereoselective aldol reactions of α, β-chiral ethyl ketones (6→8 in Scheme 1)

We have also explored the stereocontrol resulting from a second aldol reaction using the syn and anti ethyl ketones formed in Scheme 3. In the case of (S,S)-27 and (S,R)-28 (or their enantiomers), prepared by aldol reactions of diethylketone with methacrolein and hydroxyl protection (P = SiMe₂Bu, SiPr₃ or PMB), these now function as tripropionate equivalents. The aldol products can be further elaborated, as shown in Scheme 5, by ketone reduction, 29 → 30, alkene hydroboration, 30 → 31, etc. Only about half the stereoisomers are readily accessible, making this strategy less general than that based on the α-chiral ethyl ketones (R)- and (S)-16.

**E-enolates.** Enolisation by dicyclohexylboron chloride and Et₃N gives the E enolates, 27 → 33 and 28 → 35, which now attack the si-face of an aldehyde like methacrolein to give mainly the anti-syn adducts 34 and 36 (Scheme 7) [ref. 12a,b]. Similar stereochemical results have been reported by Evans for related E enol borinates [ref. 12c]. We believe that the aldol addition is now proceeding preferentially through TS-VII, which minimises A(1,3) allylic strain with the E enol methyl group and directs the large RL group away from the pseudoaxial ligand on boron. Note that the enolate π-face selectivity has now reversed compared to that observed for 20, which lacks the alkyl β-substituent and gives only reaction on the aldehyde re-face. When RL is benzoxymethyl, re-face attack evidently wins out due to electronic effects, as in 20 → 21 (Scheme 6). However, the steric effect from a large RL group now overcomes any electronic preference from the ether oxygen orientation.

**Z-enolates.** Enolisation by 9-BBNOTf or °Bu₂BOTf and °Pr₂NEt gives the Z enolates, 27 → 37 and 28 → 39, which undergo aldol addition to the re-face of an aldehyde like methacrolein with high diastereoselectivity (Scheme 7)
The syn-syn adducts 38 and 40 are typically obtained with around 95% ds. The preferred transition structure is now TS-VIII, which is supported by our force-field analysis [ref. 3]. Note that high levels of substrate control in the Z enol borinates with a large \( R_L \) group can now be obtained, irrespective of its relative configuration, while it is greatly reduced when \( R_L \) is relatively small like benzyloxymethyl (cf. 16).

Scheme 6

![Scheme 6 diagram]

Scheme 7

![Scheme 7 diagram]
This process can be combined with a kinetic resolution (Scheme 8), by using the racemic ketone 27 with (+)-Lpc2BOTT (ent-9) enolisation to give a fast-reacting (matched) and slow-reacting (mismatched) Z enol borinate [ref. 13b]. Aldol reaction with 0.5 equivalent of methacrolein then gives the syn-syn aldol adduct 41 with high ds and ee, while the mismatched enolate is returned as enantiomerically enriched starting ketone. We have used 41 in an asymmetric synthesis of the ansa chain segment 42 of rifamycin S (via 29 → 30 → 32 in Scheme 5), illustrating the use of 27 as a tripropionate reagent.

Scheme 8

**KINETIC RESOLUTION**

\[ \text{ent-9} \stackrel{P_{2}NEt}{\longrightarrow} \text{syn - 8} \]

**TRIPROPIONATE**

This methodology has been extensively applied in our group to the total synthesis of a wide range of naturally-occurring polypropionates. Examples include:

- **ALDOL-1 /3 analysis:** oleandomycin [ref. 13a], ebelactone A [ref. 17], rifamycin S [ref. 13b].
- **ALDOL-2 analysis:** oleandomycin [ref. 14], denticulatin A and B [ref. 15a], muamvatrin [ref. 15b], swinholide A [ref. 16], tirandamycin A [ref. 9c], etheromycin [ref. 18], siphonarin B [ref. 19], scytophycin C [ref. 20].

A selection of these are briefly outlined here.

Scheme 9

**APPLICATIONS TO THE SYNTHESIS OF POLYPROPIONATE NATURAL PRODUCTS**

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Oleandolide

The boron-mediated aldol reactions of ethyl ketones with aldehydes were initially investigated in the context of a synthesis of the 14-membered macrolide, oleandolide (oleandomycin aglycone). Our first approach to its secoacid was based on the ALDOL-1 analysis of Scheme 1 [ref. 13a, 14b]. Here the synthesis of a suitable C8-C13 segment relied on sequential aldol reactions of diethylketone with acetaldehyde and crotonaldehyde (Scheme 9). This failed to deliver the desired syn-anti stereoisomer via the Z enol borinate from 43 (9-BBNOTf, Pr2NEt), giving instead 44 (see Scheme 7 for explanation). Use of the chiral reagent 9 reduces the stereoselectivity somewhat (SS : SA ca 3:1), but in this mismatched situation it cannot reverse the dominating substrate preference for the SS isomer [ref. 13a]. Changing the enolate stereochemistry from Z to E (Hex2BCl, Et3N) again failed to give the necessary anti relationship between the methyl groups at C10 and C12. Now the enolate reacted on its other face to give 45 (see Scheme 7 again)!

These stereochemical problems were finally solved by adopting the alternative ALDOL-2 analysis (Scheme 10). Using the more versatile dipropionate reagent (S)-16 and the aldol chemistry described in Scheme 6, syntheses of two different C8-C13 segments, 46 → 47 and 48 → 49, together with a C1-C7 segment, 50 → 51, were readily achieved. This has now evolved into two competing syntheses of oleandolide. The first is based on reagent-control in the aldol steps leading to the (9s)-macrolide [ref 14a], while the second is based on substrate-control giving the (9R)-macrolide 53 [ref. 14b].

Denticulatin A and B

The enantiomeric dipropionate reagent (R)-16 has been employed in the first stereocontrolled synthesis of (-)-denticulatin B [ref. 15a]. This is a member of an intriguing class of polypropionates isolated from Siphonariid pulmonate molluscs (false limpets) [ref. 21]. In our denticulatin synthesis (Scheme 11), the C3-C10 segment 54 was readily assembled with 96% ds by a substrate-controlled anti-anti boron aldol reaction and an in situ reduction of the aldolate by LiBH4. This was then elaborated at both ends to give the ethyl ketone 55, which was submitted to an Evans Ti(IV) syn-syn aldol reaction [ref. 22] (see similar reaction for boron in Scheme 7 via TS-VII) with a chiral aldehyde.
The major aldol adduct 56 was first oxidised to give 57 then deprotected to give exclusively (-)-denticulatin B, retaining the C10 configuration. Epimerisation of 57 at C10 occurs on silica gel, leading to (-)-denticulatin A. Related chemistry is being applied to the synthesis of other Siphonariid metabolites, including siphonarin B [ref. 23] and muamvatin (stereochemistry yet to be fully assigned) [ref. 24].

**Swinholide A**

Swinholide A, a novel cytotoxic macrolide from the marine sponge *Theonella swinhoei*, has an unusual 44-membered dilactone ring [ref. 25]. Boron aldol reactions, under both substrate and reagent control, feature in our planned synthesis of its secoacid 2 (Scheme 12) [ref. 18]. The dipropionate reagent (S)-16 was first combined, via its E dicyclohexylol borinate, with the aldehyde 58 to give the anti-anti adduct 59 with ≥97% ds. This was further elaborated by stereocontrolled ketone reduction and alkene hydroboration to give the C19-C32 segment 60. Reagent-controlled aldol coupling between the ethyl ketone 61, via the Z enol borinate 62, and the aldehyde 63 (triple asymmetric induction) should allow the stereocontrolled assembly of the secoacid precursor 64.

**Scheme 12**

**Scheme 13**

1. 9, Pr2NEt
2. TBSOTf
3. 9-BBNOTf, Et3N
4. Reagent control
5. Substrate control
Ebelactone A

The ALDOL-1/3 analysis in Scheme 1 was successfully applied to the first synthesis of the β-lactone enzyme inhibitor, ebelactone A [ref. 17, 26]. As shown in Scheme 13, diethylketone was sequentially aldol coupled with 2-ethylacrolein to give 65, then with methacrolein to give the syn-syn adduct 66. The ketone group at C9 can then be carried through the remainder of the synthesis without protection. An Ireland-Claisen rearrangement, 67 → 68, followed by a propionate aldol reaction to give 69, β-lactone formation, and hydrogenation at C12 gave ebelactone A.

As an extension of this work, the combination of sequential diethylketone aldol reactions and double Ireland-Claisen rearrangements was applied to two-directional polypropionate synthesis, as in 70 → 71 and 72 → 73 in Scheme 14 [ref. 12a]. Note again that the ketone carbonyl group can be successfully carried through these transformations without protection.

Scheme 14

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