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Studies in Polypropionate Synthesis: A General Approach to the Synthesis of Stereopentads.

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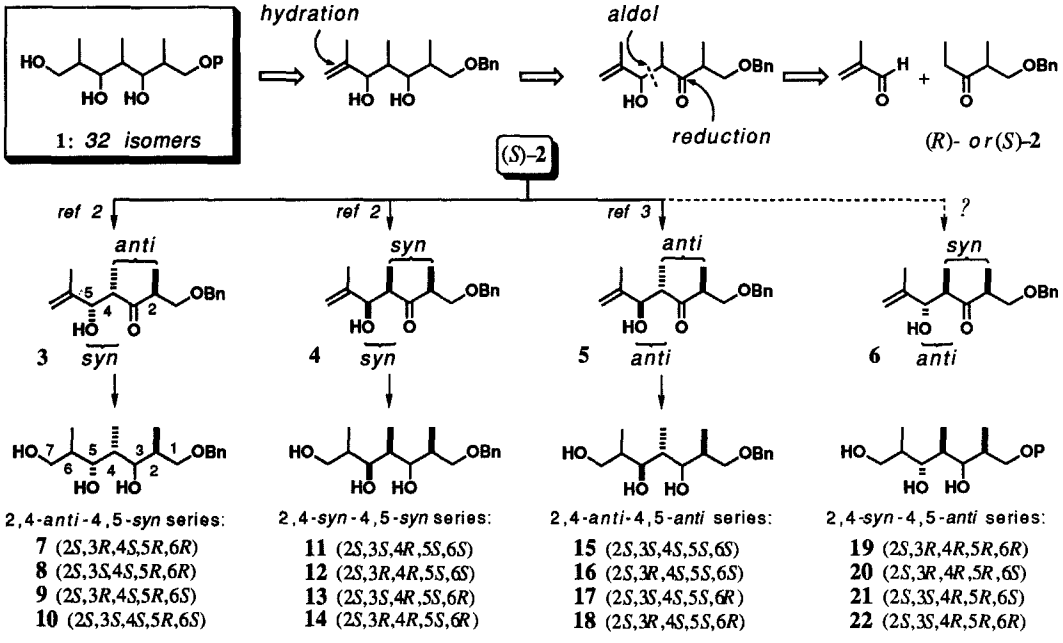
Abstract: A general protocol for the synthesis of specific isomers of the stereopentad **1** from the α-chiral ethyl ketones (*R*)- and (*S*)-**2** has been developed. From (*S*)-**2**, this involves stepwise elaboration of each of the three aldol adducts **3**, **4** and **5** by stereoselective ketone reduction and alkene hydration. Selective access to any of the 32 stereopentad isomers is possible.

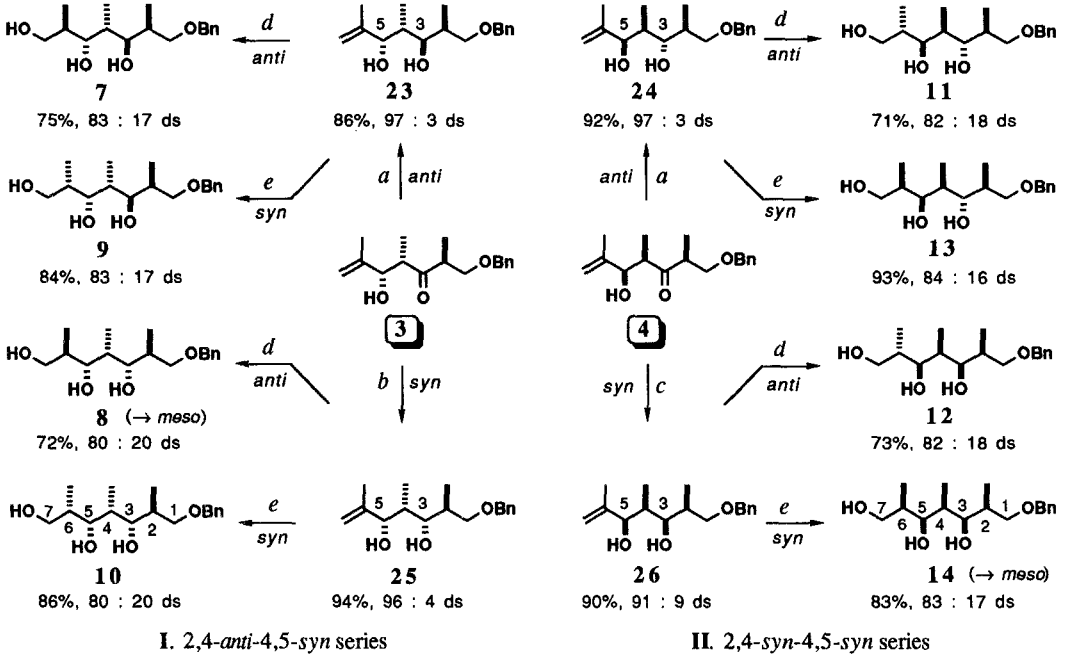
As part of our studies on the development of new methods and strategies for the synthesis of polypropionate-derived natural products, we have focused on finding simple, efficient routes to acyclic segments with extended sequences of alternating methyl and hydroxyl groups. For stereopentad systems **1** (*i.e.* having five contiguous chiral centres),[1] we now report a general, systematic approach to the synthesis of all thirty-two possible stereoisomers using acyclic stereocontrol (**Scheme 1**). This relies on some novel stereoselective reactions, including a *syn*-selective hydroboration of allylic 1,3-diols with BH_3•THF and a boron-mediated aldol/reduction sequence.



Scheme 1

By starting with the ethyl ketones (*R*)- or (*S*)-**2**, an efficient, stereocontrolled synthesis of the majority of these isomers (for P = Bn in **1**) can be realised in only three steps: (*i*) aldol addition to methacrolein *via* their *E* or *Z* enol borinates,[2,3] (*ii*) ketone reduction, and (*iii*) alkene hydration. This is illustrated in **Scheme 1** for the single enantiomer (*S*)-**2**, where the twelve triols **7**–**18** are obtained. A further group of three triols **19**–**21** (P = TBDPS) can be easily obtained by switching terminal hydroxyl protecting groups.

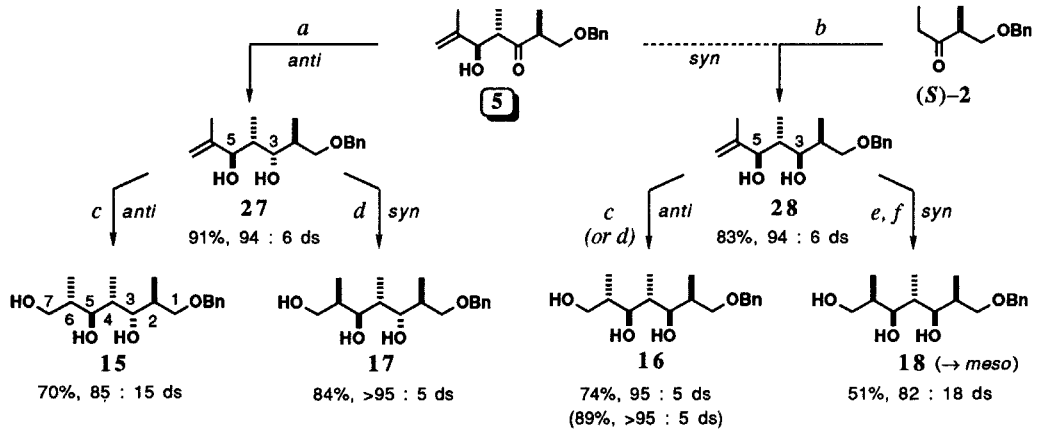
Our previous work on the boron enolate aldol reactions of the α-chiral ethyl ketones (*R*)- and (*S*)-**2**[2-4] allows the enantio- and stereocontrolled synthesis of six out of the eight possible isomeric adducts with methacrolein. Starting with (*S*)-**2**, these correspond to the two *syn* aldol isomers **3** and **4** in **Scheme 1**, which are formed selectively using the appropriate *Z* enol diisopinocampheyl borinate derivative (reagent control),[2] and the *anti* aldol **5** formed *via* the *E* enol dicyclohexyl borinate (substrate control).[3] However, the remaining *anti* aldol isomer **6** is presently inaccessible. Elaboration of these three γ,δ-unsaturated-β-hydroxy ketones, in turn, to specific stereopentad isomers requires control of the ketone reduction[5] and alkene hydration in all four possible stereochemical senses. This has been achieved by a suitable choice of reagents (**Schemes 2** and **3**).



Scheme 2 (*a*) $Me_4NBH(OAc)_3$, 1:1 MeCN-AcOH, -40 → -20 °C, 16 h; (*b*) *n*-Bu_2BOMe, 5:1 THF-MeOH, $LiBH_4$, -78 °C, 1 h; H_2O_2, pH7 buffer, 20 °C, 1 h; (*c*) DIBAL, Et_2O, -78 °C, 20 min; 10% aq. HCl; (*d*) $(+)\text{-}(Ipc)_2BH$, 3 equiv, THF, 20 °C, 1 h; NaOOH; (*e*) BH_3•THF, 3 equiv, THF, 20 °C, 1 h; NaOOH.

The preparation of the eight stereopentad isomers **7**–**14** (the 2,4-*anti*-4,5-*syn* and 2,4-*syn*-4,5-*syn* series) from the appropriate *syn* aldol adducts **3** and **4** is shown in **Scheme 2**. The 3,5-*anti* diols **23** and **24** were readily obtained with 97% ds by hydroxyl-directed reduction using $Me_4NBH(OAc)_3$.[6,7] The 3,5-*syn* diol **25** was prepared from **3** with 96% ds *via* the di-*n*-butylboron chelate by a modified[3] Narasaka reduction[8] using *n*-Bu_2BOMe and $LiBH_4$. However, this method proved much less selective with **4**. Here the required 3,5-*syn* diol **26** could be obtained with 91% ds by DIBAL reduction.[9] In each case, the diol isomers were separable by silica gel chromatography (8% Et_2O/CH_2Cl_2 eluant).

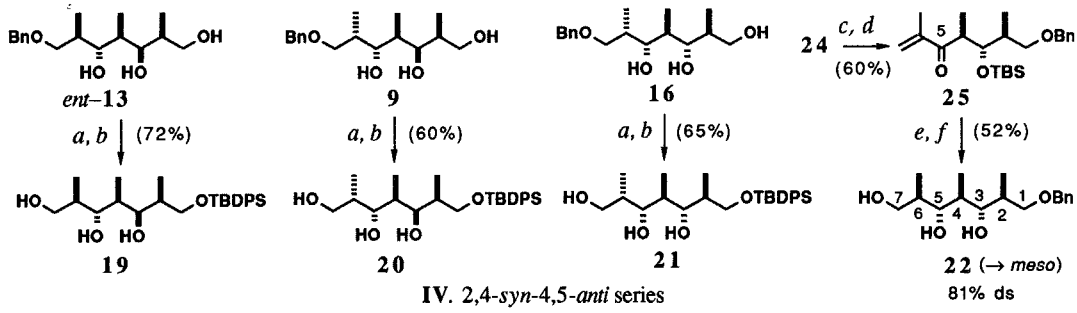
Hydroboration of the terminal alkene in these four diols could then be achieved in both the *syn* and *anti* sense with ≥80% ds. Use of $(+)\text{-}(Ipc)_2BH$[10,11] (or 9-BBN[12]) led to selective formation of the 5,6-*anti* isomers in all cases, providing the four stereopentads **7**, **8**, **11** and **12**.[7] Selective formation of the corresponding 5,6-*syn* isomers,[7] **23** → **9**, **25** → **10**, **24** → **13** and **26** → **14**, was possible by simply using BH_3•THF. This is an unexpected result, since simple allyl alcohols usually undergo hydroboration with clear *anti* selectivity using 9-BBN — whereas BH_3•THF gives little or no stereoselectivity.[12] With the more complex allylic 1,3-diols **23**–**26**, other conformational factors may come into play leading to preferred *syn* addition with the sterically undemanding BH_3•THF.[13]



III. 2,4-*anti*-4,5-*anti* series

Scheme 3 (*a*) $Me_4NBH(OAc)_3$, 1:1 MeCN-AcOH, -40 → -20 °C, 16 h; (*b*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; $H_2C{=}C(Me)CHO$, 2 h; $LiBH_4$, -78 °C, 1 h; NaOOH, MeOH, 20 °C, 1 h; (*c*) (+)-$(Ipc)_2BH$, 3 equiv., THF, 20 °C, 1 h; NaOOH; (*d*) BH_3•THF, 3 equiv, THF, 20 °C, 1 h; NaOOH; (*e*) $(Me_2SiH)_2NH$, CH_2Cl_2, 20 °C, 2 h; (*f*) $(Ph_3P)_3RhCl$, THF, 20 °C, 12 h; H_2O_2, $NaHCO_3$, MeOH, 70 °C, 3 h.

The preparation of the four stereopentads **15–18** (the 2,4-*anti*-4,5-*anti* series) from the *anti* aldol adduct **5**[3] is shown in **Scheme 3**. Reduction with $Me_4NBH(OAc)_3$ gave the 3,5-*anti* diol **27** with 94% ds. The corresponding *syn* reduction was less straightforward, *e.g.* use of *n*-Bu_2BOMe and $LiBH_4$ gave a 2:1 ratio of **27** and **28**. This problem was overcome by employing a novel, boron-mediated aldol/reduction sequence.[14] When the intermediate dicyclohexylboron aldolate[3] formed from (*S*)-**2** and methacrolein in ether was reduced *in situ* by $LiBH_4$, this provided the required 3,5-*syn* diol **28** with 94% overall ds in 83% yield. As before, *anti*-selective hydroboration of the alkene was achieved using (+)-$(Ipc)_2BH$, *i.e.* **27** → **15** and **28** → **16**.[7] *Syn*-selective hydroboration with BH_3•THF was again possible for **27** → **17**[7] (90% ds). However, the corresponding reaction of BH_3•THF with **28** now favoured formation of the 5,6-*anti* isomer **16** (>95% ds). The configuration at C_3 appears to control the outcome of this hydroboration in this system, *cf.* **27** → **17**. To obtain the 5,6-*syn* isomer **18**[7] selectively (82% ds), we turned to intramolecular Rh(I)-catalysed hydrosilation[15] on the *bis*-dimethylsilyl ether of **28**.



IV. 2,4-*syn*-4,5-*anti* series

Scheme 4 (*a*) *t*-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 20 °C, 12 h; (*b*) H_2, 10% Pd-C, EtOH, 20 °C, 12 h; (*c*) MnO_2, CH_2Cl_2, 20 °C, 72 h; (*d*) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 2 h; (*e*) $LiAlH_4$, Et_2O, -78 °C, 10 min; 10% aq. HCl, 20 °C, 5 min; (*f*) (+)-$(Ipc)_2BH$, 3 equiv, THF, 20 °C, 1 h; NaOOH.

Whilst direct access to the four remaining stereopentads in the 2,4-*syn*-4,5-*anti* series cannot be achieved due to the unavailability of the remaining *anti* aldol isomer **6** (**Scheme 1**), we can still reach three of these simply by switching over the terminal hydroxyl protecting group as required. We have used this trick

(**Scheme 4**) to make the mono-TBDPS protected stereopentads, *i.e. ent*-**13** (from (*R*)-**2**[4]) → **19**, **9** → **20** and **16** → **21**.[7] Finally, the one remaining stereopentad **22** was prepared from the enone **25** (obtained from **24** by selective oxidation at C_5 by MnO_2 and TBS-protection) by reduction[16] with $LiAlH_4$ (97% ds) and hydroboration with (+)-$(Ipc)_2BH$ (84% ds). *Thus by starting with the appropriate enantiomer of* **2**, *it should be possible to gain access to any of the thirty-two isomers of the stereopentad* **1**.

Confirmation of the assigned 3,5-*syn* or *anti* stereochemistry of all the intermediate diols **23–28** was achieved by ^{13}C NMR analysis of the corresponding acetonide derivatives ($Me_2C(OMe)_2$, cat. PPTS, CH_2Cl_2).[17] The stereochemical assignments made for certain pairs of stereopentads, **8** *vs* **10**, **12** *vs* **14** and **16** *vs* **18**, were confirmed by debenzylation (H_2, 10% Pd/C, EtOH). With **8**, **14**, **18** and **22**, this produced *meso* tetraol systems having relatively simple ^1H and 6-line, ^{13}C NMR spectra with no measurable value of $[\alpha]_D^{20}$. All the other isomers gave unsymmetrical, optically-active tetraols. In addition, all of the sixteen stereopentads **7–22**[7] were fully characterised as their triacetate derivatives (Ac_2O, Et_3N, cat DMAP, CH_2Cl_2).

In summary, these methods allow an efficient, general synthesis of the stereopentads **1** by starting from the appropriate enantiomer of the ethyl ketone **2**. As well as providing the first systematic approach[1] to specific stereopentad sequences for the synthesis of polypropionate-derived natural products of known structure,[14] they should also be valuable for the determination of stereochemistry in unassigned structures and for the synthesis of unnatural analogues.

Acknowledgement: We thank the SERC for support (Studentship to JAC; Grant GR/F 73458). IP thanks the Royal Society of Chemistry for a Hickinbottom Research Fellowship.

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