Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 9087-9090, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01940-1

Manipulation of the Aldol Adducts from Lactate-Derived Ketones. A Versatile Chiral Auxiliary for the Asymmetric Synthesis of β-Hydroxy Carbonyl Compounds.

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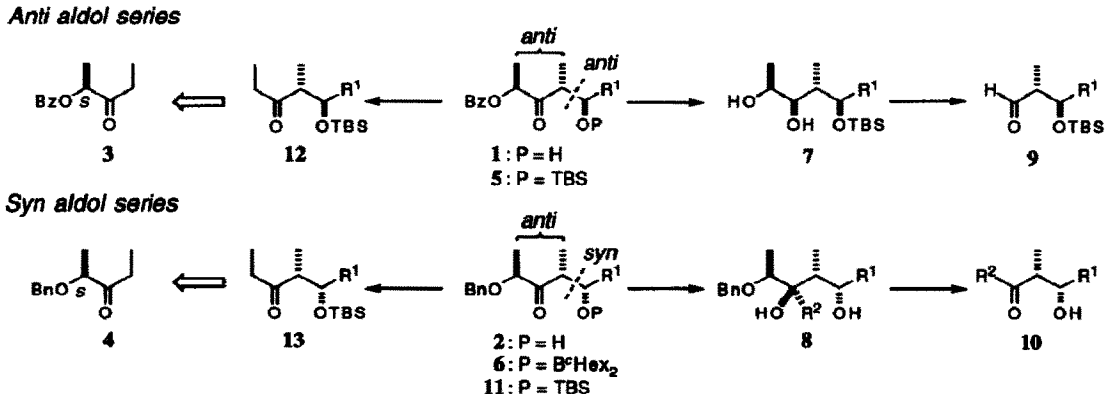
Abstract: The ketones **1** and **2** can be transformed into a wide range of enantiomerically-pure *anti* and *syn* α-methyl-β-hydroxy ketones and aldehydes. The α'-methyl group in **5** and **11** may be retained, demonstrating the use of the lactate-derived group as an optional chiral auxiliary.

In recent years, the aldol reaction using chiral enolates has proved to be a powerful tool for acyclic stereocontrol and the assembly of polypropionate natural products.[1] The use of a temporary chiral auxiliary attached to a stereodefined enolate is a popular tactic, with removal of the auxiliary after the aldol step. In the preceding paper,[2] we have described the use of a new lactate-derived auxiliary for the asymmetric synthesis of *anti* and *syn* aldols such as **1** and **2** (**Scheme 1**). Using boron enolate chemistry, the stereochemical outcome of the aldol reaction is determined by the hydroxyl protecting group (Bn *vs* Bz) in the respective ketone precursors **3** and **4**. Notably, the *anti* aldol reactions of **3** are found to be especially selective (up to 200 : 1 ds), enabling reagent-control in additions to chiral aldehydes.

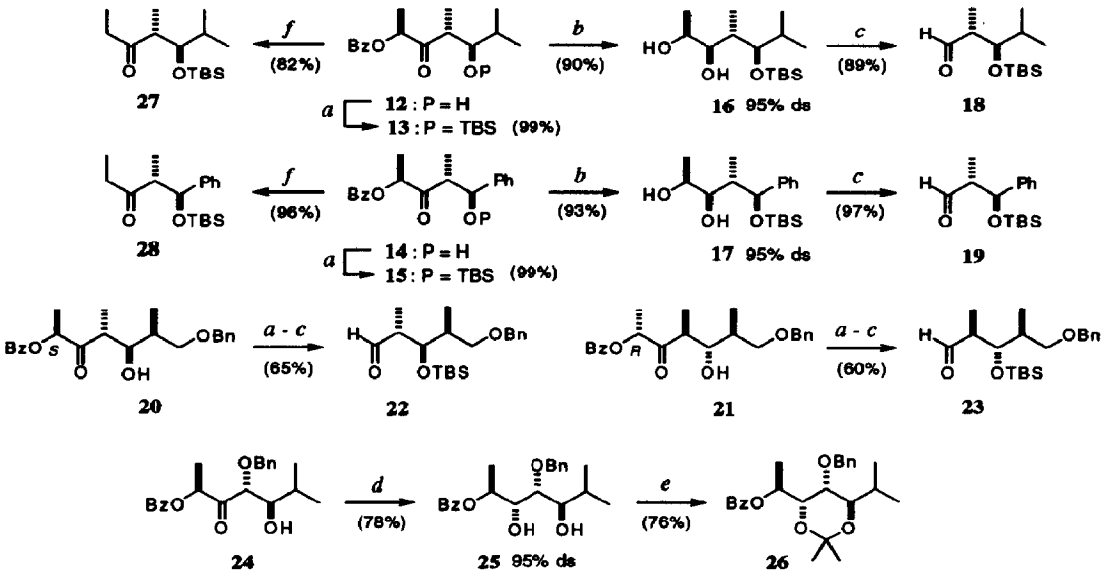


Scheme 1

In this paper, we demonstrate the manipulation of these aldol adducts to provide a wide range of enantiomerically-pure, β-hydroxy carbonyl compounds and derivatives. All of these compounds are useful intermediates in the synthesis of polypropionate natural products. For example, addition of a metal hydride and carbon nucleophile (R^2MgX or R^2Li) to the ketone carbonyl group in **5** and **6**, respectively, leads to monoprotected triols, such as **7** and **8**. In contrast to more conventional auxiliaries, these stereotetrads may be further elaborated, retaining the lactate-derived residue, into appropriate target structures. Glycol cleavage provides the corresponding aldehyde, as in **7** → **9**, or ketone, as in **8** → **10**. Alternatively, the α'-methyl group in **5** and **11** may be retained, since reductive removal of the α'-oxygen substituent using SmI_2 leads overall to **12** and **13**, which correspond to the silyl-protected *anti* and *syn* aldol adducts of diethylketone respectively.

Anti aldol series As shown in **Scheme 2**, the *anti* aldol adducts obtained[2] from the α'-benzoyloxy ketones (*R*)- and (*S*)-**3** can be transformed in various ways. The β-hydroxy group in **12** was first converted into its TBS ether **13** using *tert*-butyldimethylsilyl triflate.[3] Similarly, **14** was converted into the silyl ether **15**. Reduction of the ketone group by $LiBH_4$ at 20 °C was accompanied by removal of the α'-benzoate, giving the corresponding 1,2-diols, **13** → **16** and **15** → **17**, with high diastereoselectivity (95% ds).[4,5] Such mono-protected 1,2,4-triols, having four contiguous stereocentres, can thus be prepared in only three steps from ethyl ketone **3**. For the general synthesis of protected propionaldehyde *anti* aldols, periodate glycol cleavage proceeded smoothly, as in **16** → **18** and **17** → **19**.[6] A similar sequence of reactions performed on ketones **20** and **21** gave the corresponding aldehydes **22** (65%) and **23** (60%),[7] thus enabling the iterative aldol construction of elaborate polypropionate systems.

This new aldol / reduction sequence can be extended to the stereocontrolled construction of contiguous polyols. Reduction of the lactate-derived ketone **24**[2] by $LiBH_4$ at –78 °C gave the diprotected tetrol **25**, which was converted into acetonide **26** permitting a secure stereochemical determination by NMR analysis.

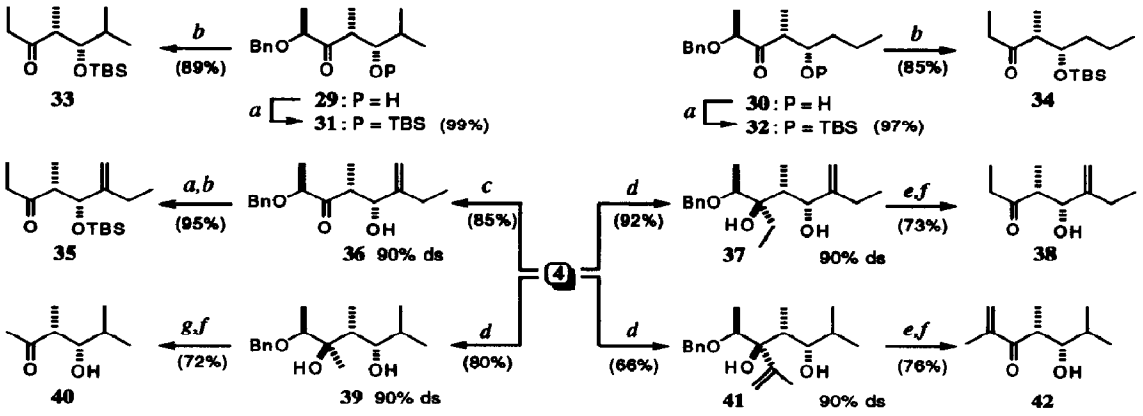


Scheme 2 (a) ^{t}BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (b) $LiBH_4$, THF, 20 °C, 16 h; (c) $NaIO_4$, aq. MeOH, 20 °C, 15-60 min; (d) $LiBH_4$, THF, –78 °C, 2 h; (e) $(MeO)_2CMe_2$, CH_2Cl_2, PPTS, 20 °C, 16 h; (f) SmI_2, THF, MeOH, –78 °C, 15 min.

As an alternative to cleavage of the auxiliary group, the α'-methyl group in the aldol adduct may be retained. Reductive removal[8] of the α'-benzoate substituent in the TBS-protected ketones **13** and **15** by SmI_2 gave the corresponding ethyl ketones **27** (82%) and **28** (89%) in enantiomerically-pure form. Notably, this asymmetric synthesis of diethylketone aldols complements previous routes using chiral boron reagents.[9] By using a second aldol reaction on the ethyl side, such ketones permit the highly stereocontrolled synthesis of elaborate polypropionate systems.

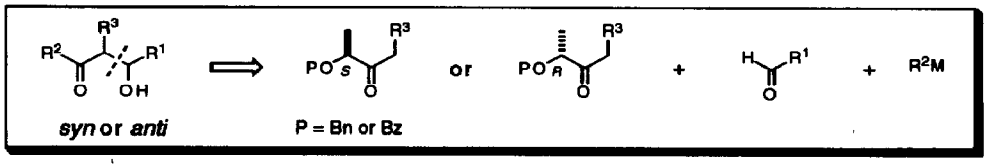
Syn aldol series As shown in **Scheme 3**, the *syn* aldol adducts **29**[10] and **30**, obtained from the α'-benzyloxy ketone **4**,[2] can be transformed in a related fashion. Here, treatment[8] of the TBS-protected ketones **31** and **32** with SmI_2 gave the corresponding ethyl ketones **33** (89%) and **34** (85%) in enantiomerically-pure form. Such an aldol / reduction sequence was also applied to the preparation of ketone **35** (from **36**). This is a key intermediate in the asymmetric synthesis of ebelactone A and B.[11,12]

We have previously shown that *in situ* reduction of dicyclohexylboron aldolate intermediates, as generated by boron aldol addition reactions, provides a rapid entry into 1,3-diols with a high level of stereocontrol.[4b,13] This can now be extended to the use of carbon nucleophiles. Using the aldol reactions of lactate-derived ketone **4**, combined with *in situ* addition of Grignard reagents (or organolithium reagents), provides the corresponding tertiary alcohols. For example, aldol addition of **4** to 2-ethylacrolein using $^{c}Hex_2BCl$ / Et_3N in Et_2O gave the intermediate boron aldolate, which was directly reacted with excess EtMgBr, leading to isolation of the 1,3-diol **37** (92%) with 90% ds. In this one-pot sequence, three new stereocentres are controlled. Following reductive debenzylation, glycol cleavage then gave the *syn* aldol adduct **38** (*cf.* **35**).[9a]



Scheme 3 (a) $^{t}BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (b) SmI_2, THF, MeOH, –78 °C, 15 min; (c) $^{c}Hex_2BCl$, Et_3N, Et_2O, –78 °C, 1 h; $H_2C{=}C(Et)CHO$, –78 → –20 °C, 16 h; (d) as (c) then EtMgBr (for **37**), MeMgBr (for **39**), or $H_2C{=}C(Me)MgBr$ (for **41**), 0 °C, 2 h; (e) Li, di-*tert*-butylbiphenyl, THF, 20 °C, 1 h; (f) $NaIO_4$, aq. MeOH, 20 °C, 15–60 min; (g) H_2, 10% Pd/C, EtOH, 16 h.

The above procedure is particularly useful for the asymmetric synthesis of stereochemically defined triols and aldol adducts from unsymmetrical ketones. A simple example is provided by the addition of MeMgBr to the boron aldolate formed from **4** and isobutyraldehyde, which gave the *anti* 1,3-diol **39** in 80% yield with 90% ds.[14] This result (as well as **4** → **37**) presumably arises by chelation from the adjacent benzyl ether in the Grignard addition step.[15] A similar reaction with MeLi gave an 88% yield of a 2.5 : 1 mixture of **39** and its epimeric tertiary alcohol.[14] Debenzylation and oxidative cleavage then gave the methyl ketone **40**, which corresponds to the *syn* aldol adduct of butanone.[16] Related transformations can also be performed on the *anti* boron aldolates derived from ketone **3**.[17] A further example is provided by the addition of a vinylic Grignard reagent to give the allylic alcohol **41**, which was similarly transformed into the *syn* aldol adduct **42**.



Scheme 4

In summary, the boron-mediated aldol chemistry of **3** and **4** (and their enantiomers) enables the practical asymmetric synthesis of *syn* and *anti* β-hydroxy carbonyl compounds and their derivatives in enantiopure form. By varying R^1, R^2 and R^3, as shown in **Scheme 4**, the aldol reactions of these lactate-

derived ketones should allow access to a wide variety of ketone aldols with complete regio- and stereochemical control. This approach is most useful for the enantiocontrolled synthesis of ketone aldols, which otherwise are not easily accessible. We are now applying these new methods to the synthesis of various polypropionate-derived natural products.

Acknowledgement: We thank the EPSRC (GR/J63019), BP Chemicals (CASE studentship to DJW), and EC (HCM Network CHRXCT930141) for support, Dr D. Hall (BP Chemicals, Hull) for helpful discussions and Silvia Velázquez for some preliminary experiments.

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1. Reviews: (a) Franklin, A. S.; Paterson, I. *Contemporary Organic Synthesis* **1994**, *1*, 000. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Vol 3, p 111, Morrison J. D., Ed.; Academic Press; New York (1983); (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*, Vol.13, p 1, Wiley-Interscience; New York, (1982). (d) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*, Vol. 2, Trost, B. M.; Fleming, I., Eds., Pergamon Press; Oxford (1991).
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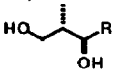
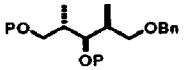
3. All new compounds gave spectroscopic data in agreement with the assigned structures.
4. The stereoselectivity of the ketone reduction in **13** and **15** appears to arise by Felkin-Anh control from the bulky TBS-containing residue. For related examples, see: (a) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021. (b) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797.
5. The 1,2-diol stereochemistry in **16** and **17** was determined by appropriate NOE analysis of the derived *cis* acetonides.
6. The stereochemistry of **18** and **19** was confirmed by conversion into the known 1,3-diols **i** and **ii** of defined absolute configuration. Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

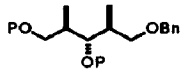


i : R = ^{i}Pr
ii : R = Ph

7. The stereochemistry of **22** and **23** were confirmed by conversion into **iii** / **iv** and **v** / **vi** of defined absolute configuration. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.



iii : P = H
iv : P = Bn



v : P = H
vi : P = Bn

8. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
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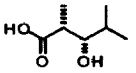
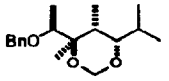
10. The stereochemistry in **29** was confirmed by conversion into the known acid **vii** by (*i*) H_2, 10% Pd/C, THF; (*ii*) $NaIO_4$, aq. MeOH. Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.

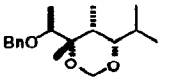


vii

11. Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821.
12. Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513.
13. (a) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801. (b) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790.
14. The stereochemistry of **39** and its epimeric tertiary alcohol were determined by NOE studies on the derived methylidene acetals **viii** and **ix**.



viii



ix

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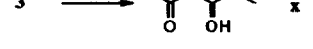
16. Note that direct enolisation of butanone by boron triflate reagents gives only moderate regioselectivity. Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.
17. As with **4** → **40**, the epimeric aldol **x** was obtained by a similar sequence performed on the *anti* boron aldolate from **3** and isobutyraldehyde using methyl lithium followed by periodate cleavage.



x

(*Received in UK* 1 *September* 1994; *accepted* 30 *September* 1994)