Tetrahedron Letters, Vol. 34, No. 27, pp. 4393-4396, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

1,3–Asymmetric Induction in the Aldol Reactions of α-Methylene-β-Alkoxy Aldehydes.

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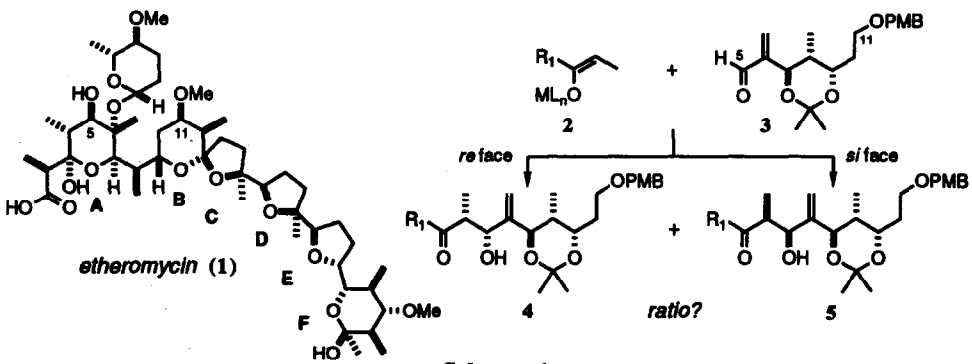
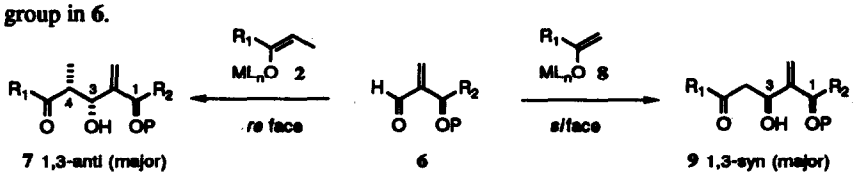
Abstract: The aldol reactions of the α-methylene-β-alkoxy aldehydes **3** and **6** were examined for a range of Ti(IV), Sn(II), and B enolates. The sense and level of 1,3-asymmetric induction (up to 95% ds) varies with the enolate structure and the β-hydroxyl protecting group in the aldehyde.

The aldol reaction of metal enolates with aldehydes is of fundamental importance in the control of acyclic stereochemistry, largely due to the usually secure relationship between the enolate geometry and product stereostructure.[1] The sense and degree of π-face selectivity found in the aldol reactions of complex chiral aldehydes, however, are less predictable.[1,2] For example, in studies directed towards the synthesis of a C_1–C_{11} subunit of the polyether etheromycin (**1** in **Scheme 1**),[3] we required the enolate **2** to favour *re*-face attack on the aldehyde **3** leading to **4**. Whilst this problem was solved by relying on the high π-face selectivity of a chiral enolate, we were curious as to the induction arising from such α-methylene-β-alkoxy aldehydes.



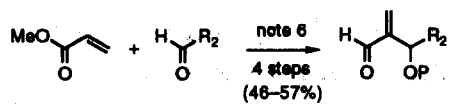
Scheme 1

We now report the first systematic analysis of 1,3-asymmetric induction in simple ethyl and methyl ketone aldol reactions with α-methylene-β-alkoxy aldehydes of general structural type **6** (**Scheme 2**), together with further results for aldol additions to **3**. The stereoselectivity arising from the β-stereocentre in **6** was found to vary with the structure of both the enolate and the aldehyde components: (*i*) Ti(IV), Sn(II), and B enolates **2** give 1,3-anti-3,4-syn adducts preferentially, **6** → **7** (*re*-face attack); (*ii*) unsubstituted enolates **8** favour the 1,3-anti adduct, **6** → **9** (*si*-face attack); (*iii*) the degree of stereocontrol (up to 95% ds) increases with the size of the protecting group in **6**.



Scheme 2

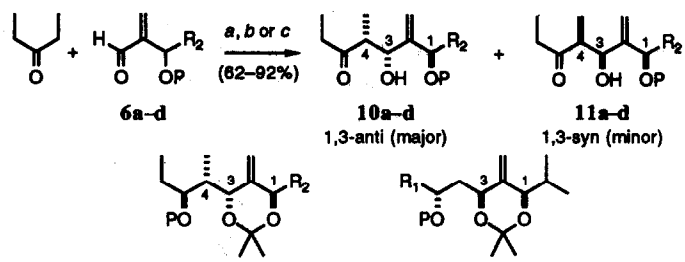
By starting with a Baylis-Hillman reaction[4] between methyl acrylate and isobutyraldehyde or butyraldehyde, the *racemic* α-methylene-β-alkoxy aldehydes **6a–d** were readily prepared in four steps.[5,6] Hydroxyl protecting groups of increasing steric demands were used: **6a**, P = benzyl (Bn); **6b**, P = *tert*-butyldimethylsilyl (TBS); **6c** and **6d**, P = *tert*-butyldiphenylsilyl (TBDPS).



6a R_2 = ^{i}Pr; P = Bn
6b R_2 = ^{i}Pr; P = TBS
6c R_2 = ^{i}Pr; P = TBDPS
6d R_2 = ^{n}Pr; P = TBDPS

To ensure high levels of simple diastereoselectivity, the syn aldol reactions of diethyl ketone with the aldehydes **6a–d** were performed using its titanium,[7a,b] tin(II),[7c] or boron[7d,e] *Z* enolates (**Scheme 3**). This gave the 1,3-anti-3,4-syn adduct **10** as the major product, together with varying amounts of the 1,3-syn-3,4-syn isomer **11**.[8] The 1,3-anti stereochemistry was established by ^{1}H NMR NOE experiments and analysis of the ^{13}C NMR chemical shift data[9] on the derived acetonides **12a** and **12b**.[10] The highest stereoselectivity was obtained using the titanium enolate, with **6c** → **10c** (84%) and **6d** → **10d** (85%) proceeding in 95% and 90% ds. Lower levels of induction were generally obtained for the Sn(II)- and B-mediated reactions.

SYN ALDOL REACTIONS WITH ETHYL KETONES



6a–d **10a–d** 1,3-anti (major) **11a–d** 1,3-syn (minor)

12a R_2 = ^{i}Pr, P = TBDPS
12b R_2 = ^{n}Pr, P = TBS

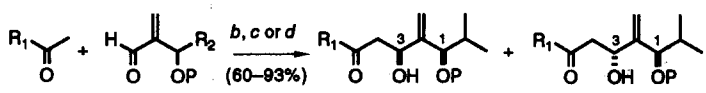
15a R_1 = ^{i}Pr, P = H
15b R_1 = Et, P = TBDPS

Isomer ratios for **10**:**11**.

	Bu_2BOTf [a]	$Sn(OTf)_2$ [b]	$TiCl_4$ [c]
6a	69 : 31	71 : 29	76 : 24
6b	75 : 25	74 : 26	88 : 12
6c	93 : 7[§]	89 : 11	95 : 5
6d	–	–	90 : 10

§ Yield = 26%; all other yields in the range 62–92%.

ALDOL REACTIONS WITH METHYL KETONES



6b, c **13a** R_1 = ^{i}Pr, P = TBDPS **14a** R_1 = ^{i}Pr, P = TBDPS
13b R_1 = Et, P = TBS **14b** R_1 = Et, P = TBS
1,3-syn (major) 1,3-anti (minor)

Isomer ratios for **13**:**14**.

	c-Hex_2BCl [d]	$Sn(OTf)_2$ [b]	$TiCl_4$ [c]
6c[§]	89 : 11	78 : 22	62 : 38
6b[†]	76 : 24	–	–

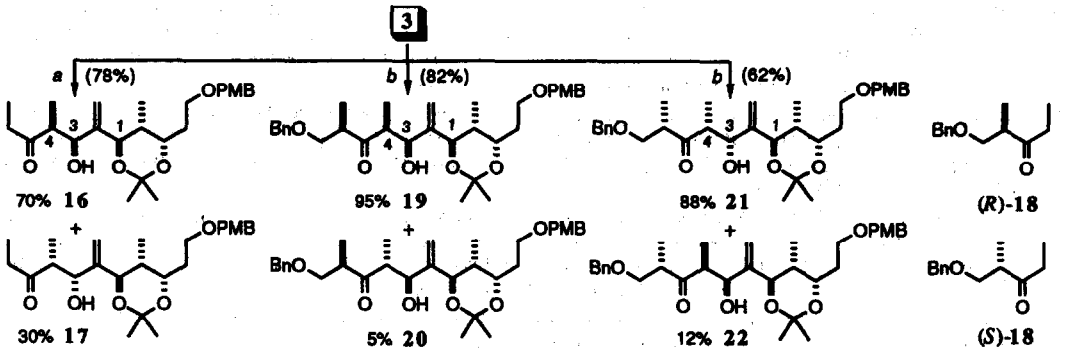
§ R_1 = ^{i}Pr † R_1 = Et

Scheme 3 Aldol conditions: (*a*) Et_2CO, ^{n}Bu_2BOTf, ^{i}Pr_2NEt, CH_2Cl_2, –78 °C, 2 h; **6**, –78 → –25 °C, 16 h; H_2O_2, MeOH–pH7 buffer; (*b*) Et_2CO or ^{i}PrCOMe, $Sn(OTf)_2$, Et_3N, CH_2Cl_2, –78 °C, 2 h; **6**, –78 → –25 °C, 3 h; (*c*) Et_2CO or ^{i}PrCOMe, $TiCl_4$, CH_2Cl_2, –78 °C, 30 min; ^{i}Pr_2NEt, 1 h; **6**, 1 h; (*d*) ^{i}PrCOMe or EtCOMe, (*c*-C_6H_{11})$_2$BCl, Et_3N, Et_2O, 0 °C, 2 h; **6**, –78 → –25 °C, 16 h; H_2O_2, MeOH–pH7 buffer.

In contrast, methyl ketone aldol reactions gave the 1,3-syn adduct as the major product, as in **6c** → **13a**. A high level of induction (89% ds) was achieved using the dicyclohexylboron enolate[11] of methyl isopropyl ketone with **6c**. The 1,3-syn stereochemistry was established by conversion into the acetonides **15a** and **15b**,[10] followed by NMR analysis (*cf.* **12**).

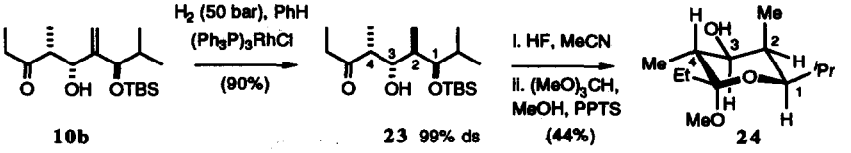
Taken together, these results demonstrate that stereoselectivity increases with the size of the protecting group on the β-oxygen (TBDPS > TBS > Bn) in **6**. Whilst the sense of asymmetric induction for the syn aldol additions is the same as that expected from chelation,[12] this cannot be the origin of the stereocontrol here. Boron enolates are incapable of reacting by way of internally chelated cyclic transition states and bulky silyl protecting groups usually[13] disfavour chelation.[14]

The results for α-methylene-β-alkoxy aldehydes of type **6** suggest that the 1,3-asymmetric induction is influenced by several factors, including the nature of the β-hydroxy protecting group. We therefore returned to the aldehyde **3** used in our etheromycin work,[3] which now has an acetonide protecting group. Reaction of **3** with the titanium enolate of diethyl ketone (**Scheme 4**) gave a 70 : 30 mixture of the two syn adducts **16** and **17**.[15] Thus, showing a small degree of *si*-face selectivity in favour of formation of the 1,3-syn-3,4-syn adduct **16**. This result shows that the cyclic protecting group and/or the more remote stereocentres in **3** act to reverse the diastereoface selectivity in comparison to **6**.



Scheme 4 Aldol conditions: (*a*) Et_2CO, $TiCl_4$, CH_2Cl_2, –78 °C, 30 min; $^iPr_2NEt$, 1 h; **3**, 1 h; (*b*) (*R*)- or (*S*)-**18**, $TiCl_4$, CH_2Cl_2, –78°C, 30 min; $^iPr_2NEt$, 1 h; **3**, 1 h.

Double stereodifferentiation experiments[16] were then performed on **3**, using the titanium enolates derived from (*R*)- and (*S*)-**18**.[3,17] The titanium aldol reaction with (*R*)-**18** gave the 1,3-syn-3,4-syn adduct **19** via *si*-face attack on **3** as the major adduct with 95% ds. While this was anticipated to be the matched combination,[3,17] an unexpectedly high level of diastereoselectivity was obtained based on the low intrinsic facial biases of the two reactants. In comparison, the reaction of **3** with the enantiomeric ketone (*S*)-**18** led to the formation of an 88 : 12 mixture of the two syn aldol adducts **21** and **22** (62%; some 1,4-addition products were also obtained). This corresponds to the mismatched combination. The titanium enolate from (*S*)-**18**, which shows a small preference for *re*-face attack on aldehydes (*ca.* 2 : 1),[17] was now able to completely override the low *si*-facial bias of **3**.



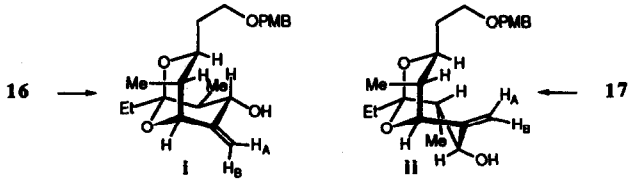
Scheme 5

Whilst the precise origins of π-face selectivity are presently obscure, α-methylene aldehydes having a remote β-stereocentre such as **6a–d**, and to a lesser extent **3**, are shown to be capable of undergoing highly stereoselective aldol reactions. This is especially useful as the allylic alcohol products can be stereoselectively reduced or otherwise functionalised. For example, the hydroxyl-directed, homogeneous hydrogenation using $(Ph_3P)_3RhCl$,[18] **10b** → **23** (**Scheme 5**), proceeded in 90% yield with 99% ds. The product stereochemistry (1,2-syn-2,3-anti) was confirmed by ^1H NMR decoupling and NOE experiments on the derived acetal **24**. Applications of these novel methods for acyclic stereocontrol to the total synthesis of natural products of polyketide origin are now being explored.

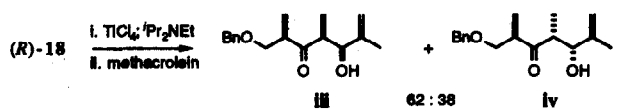
Acknowledgement: We thank the SERC (Postdoctoral Award to RDT; GR/F43505) and EC (SCI*.0324.C) for support.

References and Notes

1. Reviews: (a) Heathcock, C. H. in *Asymmetric Synthesis*; Vol 3, p 111, Morrison J. D., Ed.; Academic Press, New York (1984); (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. in *Topics in Stereochemistry*, Vol.13, p 1, Wiley-Interscience, New York, (1982).
2. For the aldol reactions of chiral α-methyl aldehydes, see: (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151; (b) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439.
3. Paterson, I.; Tillyer, R. D.; Ryan, G. R. *Tetrahedron Lett.* **1993**, *34*, 0000 (preceding paper in this issue).
4. (a) Review: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653; (b) Hoffman, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849; (c) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113 (1972); *Chem. Abs.* **1972**, *77*, 34174q; (d) Asymmetric Baylis-Hillman reactions: Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 969.
5. All new compounds gave spectroscopic data in agreement with the assigned structures.
6. The aldehydes **6a–d** were prepared as follows: (*i*) $MeO_2CCH{=}CH_2$, $^{i}PrCHO$ or $^{n}PrCHO$, DABCO (0.5 eq.), MeOH, 20 °C (68–99%); (*ii*) Bn protection: $BnOC(CCl_3){=}NH$, cat TfOH, CH_2Cl_2/*c*-C_6H_{12} (86%); or TBS/TBDPS protection: $^{t}BuMe_2SiCl$ or $^{t}BuPh_2SiCl$, imidazole, cat DMAP, DMF (88–94%); (*iii*) DIBAL, Et_2O, –78 °C (71–94%); (*iv*) $(COCl)_2O$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 → 0 °C (84–91%).
7. (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866; (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047; (c) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381; (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099; (e) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.
8. The isomer ratios shown were all determined by 400 MHz ^{1}H NMR spectroscopy and by weighing after HPLC separation (3,4-anti aldol adducts usually comprised 5–7% of the product mixture).
9. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
10. The acetonides in **Scheme 3** were prepared by initial reduction of the ketone to the anti 1,3-diol followed, for **12a** and **15b**, by: (*i*) selective TBDPS mono-protection; (*ii*) TBS deprotection by AcOH; (*iii*) $(MeO)_2CMe_2$, PPTS; for **15a**, by: (*iv*) TBAF; (*v*) $(MeO)_2CMe_2$, PPTS; (*vi*) HPLC separation of the regioisomeric acetonides; and for **12b**, by steps (*iv*), (*v*), then (*vii*) TBSCl, imidazole; step (*vi*). For **10a** and **10c**, the stereochemistry was determined by correlation with the free triol corresponding to **12a**.
11. Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.
12. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
13. (a) Che, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130; (b) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgenson, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.
14. For an apparent exception, where silyl ether chelation in a tin(II) enolate aldol reaction is proposed, see: Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.
15. The stereochemistry of **16** and **17** was assigned from NOE studies performed on the derived bicyclic acetals **i** and **ii** (*cf.* ref 3).



16. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. The stereochemical results in **Scheme 4** cannot be satisfactorily explained by the multiplicativity rules for double asymmetric synthesis.
17. These chiral titanium enolates show only low levels of facial bias in their aldol reactions with simple aldehydes, typically *ca* 2:1 in favour of formation of the syn-syn isomer **iii** over **iv** for methacrolein (see also ref 14). We thank Dr R. D. Norcross for this result.



iii 62 : 38 iv

18. (a) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 109; (b) Nakata, M.; Akiyama, N.; Kamata, J.; Kojima, K.; Masuda, H.; Kinoshita, M.; Tatsuta, K. *Tetrahedron* **1990**, *46*, 4629.

(Received in UK 30 April 1993)