Tetrahedron Letters,Vol.28,No.11,pp 1229-1232,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

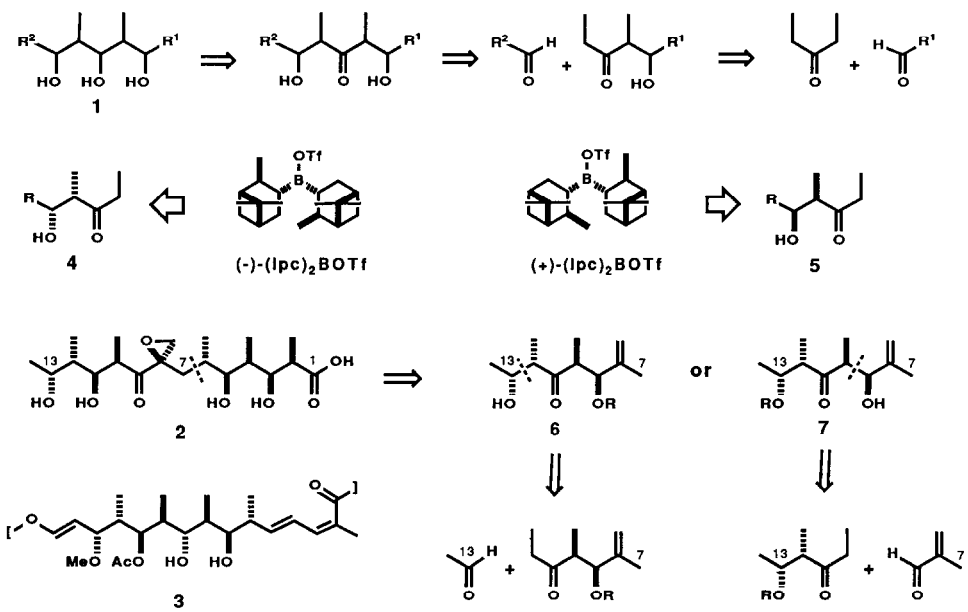
STUDIES IN MACROLIDE SYNTHESIS: ALDOL CONDENSATIONS OF CHIRAL ETHYLKETONES VIA BORON ENOLATES.

Ian Paterson* and Cynthia K. McClure
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Summary *Aldol condensation of chiral ethylketones **8** and **9**,via their 9-BBN or $^{n}Bu_2B$ enolates,with methacrolein and acetaldehyde gives mainly the anti-syn adduct, **8**→**14** or **9**→**18**. The chiral reagent (+)-$(Ipc)_2BOTf$, in the presence of Et_3N, is used to enhance the formation of **14** and **18**, while (-)-$(Ipc)_2BOTf/Et_3N$ leads to reduced selectivity.*

The generalised chiral sequence **1** is a common structural feature of the macrolide antibiotics, e.g. the secoacid structure **2** of oleandomycin and the ansa chain **3** of rifamycin S, as well as other polypropionate-type natural products. The synthesis of fragments corresponding to specific stereoisomers of **1** has been achieved by starting from carbohydrates, by the use of iterative propionate enolate aldol condensations, or by other tactics.[1] In connection with our own work on macrolide synthesis,[2] we were attracted by the simplicity and directness of an approach using the sequential aldol condensation of diethylketone[3] with suitable simple aldehydes followed by a reduction step (Scheme 1). Control of the absolute as well as the relative stereochemistry in the direction desired, however, is essential for this strategy to be useful. Using the chiral boron enolate of diethylketone prepared with (-)- or (+)-$(Ipc)_2BOTf/{}^{i}Pr_2NEt$, we were able to obtain on condensation with aldehydes *syn* α-methyl-β-hydroxy ethylketones **4** or **5** with good enantioselectivity (66-90% ee with ≥90% diastereoselectivity).[4] Control of the two new chiral centres generated on the other side of the ketone carbonyl group in a second aldol condensation[5a] with prochiral[3] aldehydes was now required.

Scheme 1.



For the synthesis of a C_7-C_{13} fragment, **6** or **7**, corresponding to target **2**[2], we chose to look first at the sequential aldol condensation of diethylketone with methacrolein and acetaldehyde. We now report our findings for this second aldol condensation using boron enolates (Scheme 2). The simple dialkylboron *Z* enolates of chiral ketones **8** and **9**

(BL_2=9-BBN or $^nBu_2B$) are found to show high stereoselectivity in the formation of the *all-syn* aldol adduct, **8** →**14** and **9** →**18**. The degree of enolate diastereoface selectivity in **10*Z*** and **11*Z*** appears to be much higher than some previously reported examples of this type of ketone aldol condensation.[5b,c,6] The chiral boron triflate reagent (+)-Ipc_2BOTf (prepared from (-)-α-pinene) can be used cooperatively both to control the stereoselectivity of the enolisation step (*Z vs E*) and enhance the *Z* enolate face selectivity in addition to the aldehyde to give **14** or **18**. In contrast, use of (-)-Ipc_2BOTf (prepared from (+)-α-pinene) opposes the strong chiral induction from the simple enolate to give **15** or **19** as well.

The tert-butyldimethylsilylethers **8**[7] (90%ee; $[\alpha]_D^{20}$=-1.0° (c 2.1, $CHCl_3$)) and **9**[7] (82%ee; $[\alpha]_D^{20}$=+25.0° (c 2.4, $CHCl_3$)) were prepared from the previously described β-hydroxyketones[4] ($^tBuMe_2SiOTf$, lutidine, CH_2Cl_2, -78°C; 97%). Use of acetaldehyde in aldol condensation with **8** (R^1= isopropenyl), mediated by different dialkylboron triflate reagents, gave varying amounts of the four possible aldol diastereoisomers **14**, **15**, **16**, and **17** (entries 1-4 in Table). Di-n-butylboron triflate (entry 1) gave a substantial amount of the *anti* adducts, **16** and **17**, indicating that under normal conditions the enolisation stereoselectivity was low. Examination of the enolisation step in CD_2Cl_2 (0°C, 0.2 - 20h) by ^1H NMR spectroscopy clearly showed initial formation of the *E* and *Z* enolates in roughly equal amounts which did not change with time. In the aldol condensation, one *syn* adduct was formed (presumably mainly via **10*Z***) with high selectivity (>20:1) over the other *syn* isomer. This major isomer was found to be **14**.[8,9] Changing to 9-BBNOTf/Et_3N (entry 2) improved the enolisation stereoselectivity (91% **10*Z*** by ^1H NMR) and a smaller amount of *anti* products was obtained. Again **14** was the major *syn* product. In contrast to the high selectivity observed between the two *syn* isomers, both possible *anti* isomers, **16** and **17**, were formed in more equal amounts indicating that **10*E*** showed much lower facial selectivity.The chiral boron triflate reagent (+)-$(Ipc)_2BOTf$ (which should also favour **14**)[4] was then tried to see if this already high substrate-derived selectivity could be further increased.[10] When this reaction was carried out *in the presence of excess triethylamine*[11] (the ^1H NMR spectrum showed clean formation of the *Z* enolate), **14** was obtained with 94% overall stereoselectivity (entry 4). However, when the chiral influences of the ketone and the ligands were conflicting, as with (-)-$(Ipc)_2BOTf/Et_3N$ (entry 3), the **14**:**15** ratio was reduced to 3:1. The chiral influence of the Ipc ligands on boron are therefore not strong enough to completely override the dominant intrinsic facial bias of this ketone enolate.[10]

We have also examined the diethylketone aldol condensation with methacrolein and acetaldehyde in the reverse order. Aldol condensation of ethylketone **9** (R^1= methyl) with methacrolein was carried out using the same range of dialkylboron triflates (entries 5-8 in Table). Again a pronounced facial bias of the *Z* enolate was found without using chiral ligands on boron. High selectivity between the two possible *syn* adducts[8,9], **18** and **19**, was obtained with both $^nBu_2BOTf$ (entry 5) and 9-BBNOTf (entry 6). Remarkably enolisation of **9** with $^nBu_2BOTf$ was now just as stereoselective as with 9-BBNOTf (*cf* entry 1). However, noticeable amounts of *anti* isomers, **20** and **21**, were still formed. When (+)-$(Ipc)_2BOTf/Et_3N$ was now used, **18** was obtained with 91% overall stereoselectivity (entry 8). While use of the enantiomeric reagent (entry 7) gave a 3.4:1 mixture of **18** and **19**. It should be pointed out that in the matched runs (entries 4 and 8), the formation of 2-3% of the minor *syn* isomer is probably due to the starting ketone not being enantiomerically-pure.

The high stereoselectivity obtained for **10*Z*** →**14** and **11*Z*** →**18** without resorting to chiral ligands on boron is remarkable (Scheme 2). A reasonable rationalisation directs H_A (rather than Me or R_L) in towards the ligand on boron, the most crowded position, as the new bond is starting to form. This leads to two major transition state arrangements **12** and **13** based on the conventional chair-type model.[5a] The bulky R_L , i.e. CHR^1OTBS, is then best oriented away from the ligand on boron with the smaller methyl group eclipsing the double bond as in **13**, rather than **12** which suffers R_L interactions with H_B and H_C. For the analogous *E* enolate, however, such allylic eclipsing is disfavoured since it involves replacing H_B with a methyl group on the enolate and the reaction is more finely balanced. Additional results are required to assess the generality of these trends and more fully understand their origins.[12] Overall, the stereochemical outcome of boron enolate aldol condensations of ketones can be influenced by many variables[5]: the substitution of the enolate partner, the aldehyde, the amine, the solvent, the enolisation time/temperature, and the size of the ligands on boron. To this list can also be added the chirality of the ligands on boron and the chirality of the ketone. The present work shows that suitable matching of these last two variables can lead to

Scheme 2.

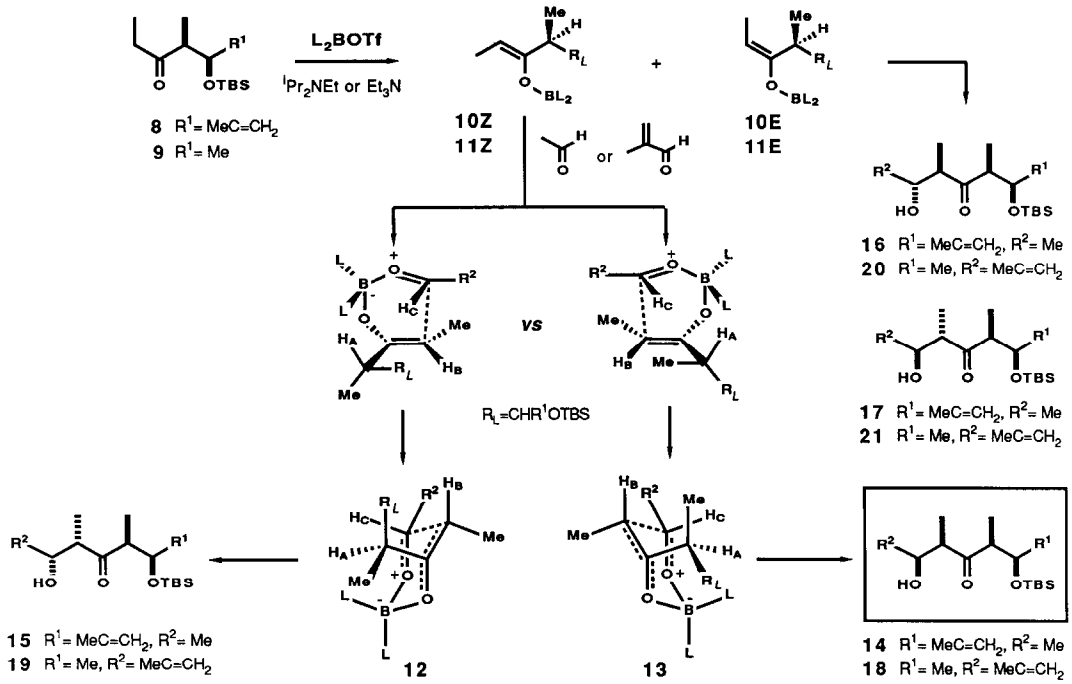


Table.

Aldol condensations of ethylketones 8 with acetaldehyde and 9 with methacrolein: effect of the reagent.

entry		reagent[a]	10Z : 10E[b]	14[c]	15	16+17	syn/anti[e]	14/15	% yield[d]
1		$^nBu_2BOTf/^iPr_2NEt$	55:45	63	3	34	2/1	21/1	85
2	R^1= MeC=CH_2	9-BBNOTf/Et_3N	91:9	83	7	10	9/1	12/1	97
3	R^2= Me	(-)-$(Ipc)_2BOTf/Et_3N$	97:3	72	24	4	24/1	3/1	67(81)
4		**(+)-$(Ipc)_2$BOTf/Et_3N**	97:3	94	2	4	24/1	47/1	65(78)
				18[c]	**19**	**20+21**	**syn/anti[f]**	**18/19**	
5		$^nBu_2BOTf/^iPr_2NEt$		84	5	11	8/1	17/1	90
6	**R^1= Me**	9-BBNOTf/$^iPr_2NEt$		85	5	10	9/1	17/1	70(90)
7	**R^2= MeC=CH_2**	(-)-$(Ipc)_2BOTf/Et_3N$		72	21	7	13/1	3.4/1	50(80)
8		**(+)-$(Ipc)_2$BOTf/Et_3N**		91	3	6	16/1	30/1	62(70)

[a] Enolisation (0°C, 2-5h) and condensation (0°C,2-5h) conditions are standard. Method is described in ref 4 [b] Determined by ^{1}H-NMR spectroscopy. [c] Isomer ratios determined by weighing isolated components after HPLC separation [d] Yields in parenthesis allow for recovered starting ketone. [e] Ratio for (14+15)/(16+17) [f] Ratio for (18+19)/(20+21).

high levels of stereocontrol producing useful polypropionate-type fragments. The mismatched case is still a problem though, which needs to be solved for our oleandomycin synthesis. Finally, if chiral ketones are used where the ketone chiral centre(s) are further removed from the carbonyl group, the chiral ligands on boron alone are expected to control the stereochemistry of the aldol reaction.

Acknowledgements We thank the SERC for support and Roussel Laboratories Ltd. for a Research Fellowship (to C.K.M.). We also thank Drs. R. Westwood and P. D. Kennewell for their interest in this work.

References and Notes

(1) Reviews: I. Paterson and M. M. Mansuri, *Tetrahedron*, **41**, 3569 (1985); S. Masamune and P. A. McCarthy, *Macrolides Antibiotics: Chemistry, Biology, and Practice* (Ed. S. Omura), Ch. 4, Academic Press, New York (1984).

(2) (a) I. Paterson, *Tetrahedron Lett.* **24**, 1311 (1983); (b) I. Paterson, S. K. Patel, and J. R. Porter, *Ibid.* **24**, 3395 (1983).

(3) This sequential aldol strategy has also been very effectively used by Masamune and coworkers in the synthesis of a rifamycin S fragment, but the stereochemical control came from the aldehyde component by starting with two enantiomerically-pure β-alkoxy chiral aldehydes and exploiting chelation control using Li enolates, see: S. Masamune, B. Imperiali, and D. S. Garvey, *J. Am. Chem. Soc.* **104**, 5528 (1982); S. Masamune, J. W. Ellingboe, and W. Choy, *Ibid.* **104**, 5526 (1982).

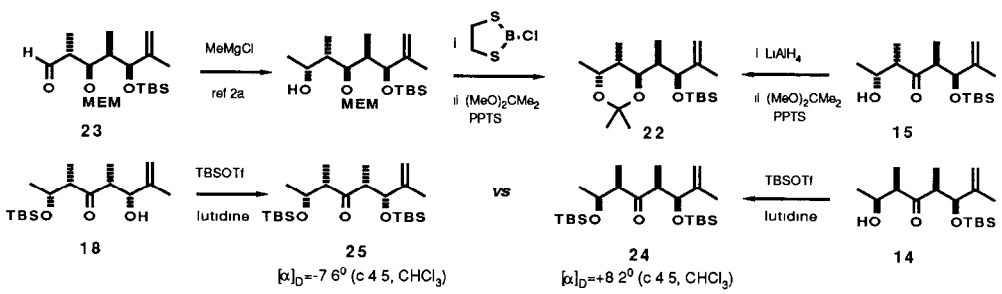
(4) I. Paterson, M. A. Lister, and C. K. McClure, *Tetrahedron Lett.* **27**, 4787 (1986).

(5) (a) Reviews: C. H. Heathcock, *Asymmetric Synthesis* **3**, (Ed. J. D. Morrison), Ch. 2, Academic Press, New York (1984); D. A. Evans, J. V. Nelson, and T. R. Taber, *Topics in Stereochemistry* **13**, 1 (1982); (b) S. Masamune, *Organic Synthesis Today and Tomorrow* (Ed. B. M. Trost and C. R. Hutchinson), pp 199-215, Pergamon Press, New York (1981); (c) D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.* **103**, 3099 (1981); (d) S Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperiali, *J. Am. Chem. Soc.* **103**, 1566 (1981); (e) T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **53**, 174 (1980).

(6) High diastereoface selectivities in aldol condensations of boron enolates of α-chiral ethylketones with achiral aldehydes, as far as we are aware, have only previously been found with α-siloxy-[5d] and α-tosylamino-[5c] ketones

(7) For analytical purposes, the small amount (3-5%) of *anti* isomer obtained in the first aldol[4] was removed at this point by HPLC separation.

(8) The stereochemistry of the *syn* isomers in these aldol condensations was established as follows (all new compounds gave spectroscopic data in agreement with the assigned structures). The minor *syn* isomer obtained by condensation of **8** with acetaldehyde was found to be **15** by its correlation with the acetonide **22** independently prepared from the previously described[2a] aldehyde **23**. The major *syn* isomer was compared as its *bis*-TBS ether **24** with **25** (from the major *syn* by the other aldol route from **9**). These were identical except for the ***opposite*** sign of their specific rotations (i.e. they are enantiomers) leading to the assignment of the major *syn* isomers as **14** and **18** respectively.



(9) NMR data and rotations for compounds. **14**: $[\alpha]_D$=+59.0° (c=4.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 4.78 (2H, br. s), 4.10 (1H, d, *J*=8.4 Hz), 4.05 (1H, qd, *J*=6.6, 2.2 Hz), 2.96 (1H, dq, *J*=8.4, 6.8 Hz), 2.44 (1H, qd, *J*=7.3, 2.6 Hz),1.70 (3H, s), 1.11 (3H, d, *J*=7.3 Hz), 1.10 (3H, d, *J*=6.6 Hz), 1.08 (3H, d, *J*=6.6 Hz), 0.87 (9H, s), 0.04 (3H,s), -0.02 (3H,s); ^{13}C NMR (100.6 MHz, $CDCl_3$) 219.2, 145.9, 113.5, 78.7, 66.2, 66.1, 51.9, 50.2, 25.9, 19.7, 18.3, 17.2, 14.3, 8.9. **15**: $[\alpha]_D$=+5.0° (c=1.5, $CHCl_3$); ^{1}H NMR (250MHz, $CDCl_3$) 4.81 (1H, m), 4.79 (1H, m), 4.22 (1H, d, *J*=8.4 Hz), 4.07 (1H, qd, *J*=6.4, 3.1 Hz), 2.92 (1H, dq, *J*=8.4, 6.9 Hz), 2.58 (1H, qd, *J*=7.1, 2.8 Hz), 1.13 (3H, d, *J*=6.2 Hz), 1.12 (3H, d, *J*=6.9 Hz),1.01 (3H, d, *J*=7.3 Hz), 0.87 (9H, s), 0.05 (3H, s), -0.01 (3H, s). **18**: $[\alpha]_D$=+56.7° (c=4.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 5.10 (1H, m), 4.94 (1H, m), 4.42 (1H, br.s), 3.92 (1H, quintet, *J*=6.2 Hz), 3.35 (1H, br. s), 2.96 (1H, qd, *J*=7.5, 2.3 Hz), 2.89 (1H, dq, *J*=6.8, 5.7 Hz),1.67 (3H, s), 1.08 (3H, d, *J*=7.2 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=7.3 Hz), 0.87 (9H, s), 0.06 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) 219.1, 143 5, 111.6, 72.8, 70.9, 52.3, 48.1, 25.9, 21.1, 19.8, 18.2, 13.8, 9.0. **19**: $[\alpha]_D$=+33.9° (c=1.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 5.05 (1H, m), 4.93 (1H, m), 4.32 (1H, br. s), 3.94 (1H, quintet, *J*=6.2 Hz), 2.93 (1H, qd, *J*=6.9, 3.3 Hz), 2.82 (1H, quintet, *J*=6.9 Hz), 1.72 (3H, s), 1.07 (3H, d, *J*= 6.9 Hz), 1.06 (3H, d, *J*=6.2 Hz), 1.00 (3H, d, J=6.9 Hz), 0.87 (9H, s), 0.05 (6H, s). **22**: ^{1}H NMR (250 MHz, $CDCl_3$) 4.85 (1H, m), 4.81 (1H, m), 3.97 (1H, dq, *J*= 6.6, 5.8 Hz), 3.90 (1H, d, *J*=9.9 Hz), 3.07 (1H, dd, *J*=8.0, 1 2 Hz), 1.71 (1H, m), 1.64 (3H, s), 1.57 (1H, m), 1.27 (3H, s), 1.19 (3H, s), 1.05 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.6 Hz), 0.86 (9H, s), 0.73 (3H, d, *J*=6.6 Hz), 0.04 (3H, s), -0.01 (3H, s).

(10) For a review on double asymmetric synthesis, see: S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed.* **24**, 1 (1985).

(11) The use of triethylamine proved to be critical for the clean enolisation of ethylketones **8** and **9**. Use of the more hindered amine ^{i}Pr$_2$NEt led to competing reduction of the ketone by the boron reagent. Analogous reductions by $(Ipc)_2BCl$ have been described, see: J. Chandrasekharan, P. V. Ramachandran, and H. C. Brown, *J. Org. Chem.* **50**, 5446 (1986).Triethylamine, however, gives comparable results to ^{i}Pr$_2$NEt in the enolisation of diethylketone.[4]

(12) For a theoretical treatment of boron enolate aldol condensations, see: C. Gennari, R. Todeshini, M. G. Beretta, and C. Scolastico, *J. Org. Chem.* **51**, 612 (1986).

(Received in UK 8 January 1987)