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THE STEREOSELECTIVITY OF DIRECTED ALDOL REACTIONS WITH 3-NITRO-2-METHOXYBENZALDEHYDES IS AFFECTED BY THE AMINE EMPLOYED AS BASE.

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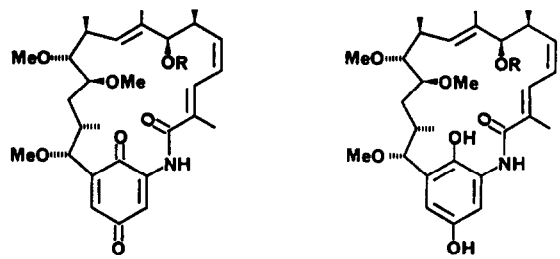
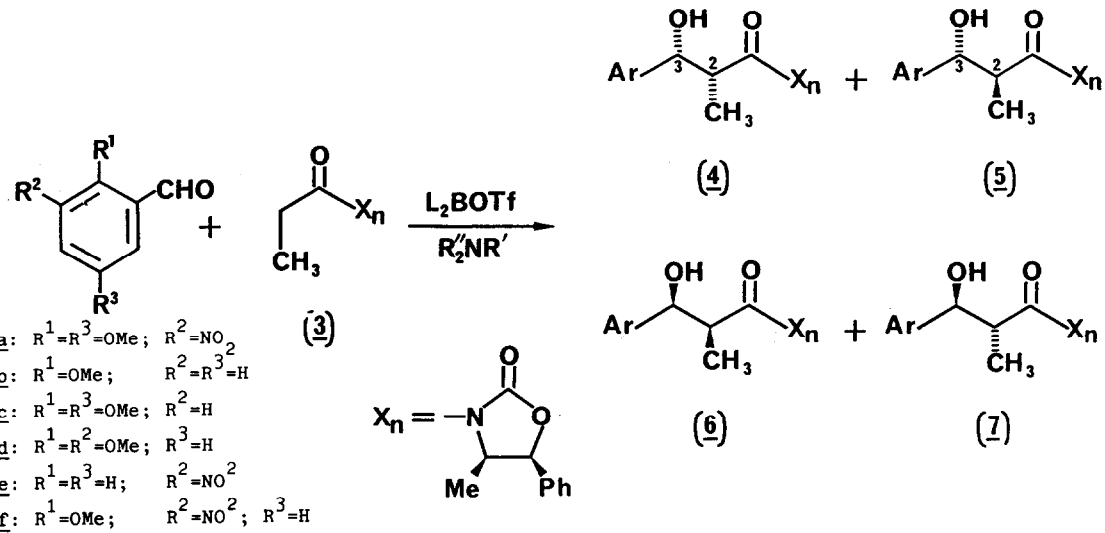
Reactions of 3-nitro-2-methoxybenzaldehydes with the boron enolate of a chiral propionyl oxazolidone has been demonstrated to yield poor diastereoselection in the presence of i-Pr_2NEt as base whereas the use of Et_3N results in 98% diastereoselection. The nature of the ammonium salt formed on production of the enolate appears to play some role in the transition state for reaction with the aldehyde.

Macbecin I (1a) and II (1b) are new antibiotics isolated from the fermentation broth of Nocardia sp (No C-14919) exhibiting antibacterial, antifungal, antiprotozoal and antitumour activities[1,2]. Their structure and absolute stereochemistry were determined by Muroi et al[3] and the two compounds assigned to the ansamycin group of antibiotics. In the course of our synthetic studies we required to establish the syn-stereochemistry at C_{20} and C_{21}. Amongst a number of available alternatives[4] the Evans aldol methodology[5] appeared to be particularly suitable in view of the high degree of enantio- and diastereo-selection demonstrated in its application. In our synthetic strategy we were required, therefore, to undertake reaction between 3-nitro-2,5-dimethoxybenzaldehyde (2a) and the chiral propionyl oxazolidone (3). In this communication we report the disappointing levels of diastereoselection observed under standard conditions and demonstrate that with certain substituted aromatic aldehydes the levels of diastereoselectivity are determined by the choice of amine.



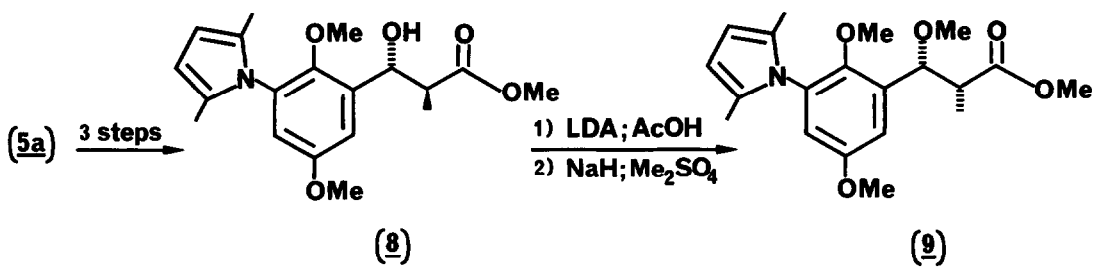
(1a) R=CONH$_2$ (1b)

In our initial experiments reaction of 3-nitro-2,5-dimethoxybenzaldehyde (2a) with (3) in the presence of 9-BBN-trifluromethanesulfonate (-OTf), i-Pr_2NEt in dichloromethane at -78°C for 0.5 h followed by 1 h at room temperature gave a 56:43 ratio of erythro: threo compounds with all four possible diastereomers being formed. The products were



separated by flash chromatography on silica gel (CH_2Cl_2–3% Et_2O) and the structures assigned by consideration of their 360MHz ^1H n.m.r. The major product (entry 1, Table) (4a) had the properties, mp 201-3°C (CH_2Cl_2), $[\alpha]_D^{22}$ + 82° (c=2.0,CH_2Cl_2); δH ($CDCl_3$) 7.45-7.27 (m, 7H, ArH); 5.69 (d, 1H, J=7.4Hz, PhC<u>H</u>-O); 5.41 (t, 1H, J=3.0Hz, 3-H), 4.82 (qn, 1H, J=6.8Hz, N-C<u>H</u>-); 4.05 (dq, 1H, J=7.1 and 3.0Hz, 2-H); 3.88 (d, 1H, J=2.4Hz, -OH); 3.86 (s, 3H, Ar-<u>OMe</u>); 3.85 (s, 3H, Ar-<u>OMe</u>); 1.19 (d, 3H, J=7.1Hz, 2-Me) and 0.91 (d, 3H, J=6.6Hz, N-CH-<u>Me</u>) ppm. Its <u>erythro</u> configuration was established on the basis of the small $H_{2,3}$ coupling constant, J=3.0Hz[6], and its absolute stereochemistry confirmed by X-ray spectroscopic studies. The other major isomer (5a), was concluded to have a <u>threo</u> configuration on the basis of $J_{2,3}$=8.2Hz and a ^1H n.m.r. ($CDCl_3$), δ 7.45-7.29 (m, 7H, ArH), 5.69 (d, 1H, J=7.2Hz, PhC<u>H</u>-O); 5.18 (t, 1H, J=8.2Hz, 3-H), 4.79 (qn, 1H, J=6.8Hz, N-C<u>H</u>-); 4.32 (dq, 1H, J=7.0 and 8.3Hz, 2-H); 3.91 (s, 3H,Ar-<u>OMe</u>); 3.83 (s, 3H, Ar-<u>OMe</u>); 3.42 (d, 1H, J=8.0Hz, -O<u>H</u>); 1.12 (d, 3H, J=7.0Hz, 2-Me); 0.91 (d, 3H, J=6.6Hz, N-CH-<u>Me</u>) ppm. Further conclusive chemical evidence was obtained in that (5a) was converted to (9), a further intermediate in our synthesis of Macbecin unambigously prepared from (4a). The minor isomers, (6a) and (7a) were characterised on the basis of their ^1H n.m.r. spectra[7].

The use of other dialkylboron triflates such as the commercially available <u>n</u>-Bu_2BOTf[8] and the freshly prepared Et_2BOTf gave predominantly the <u>threo</u>-isomer (5a) although significant amounts of the <u>erythro</u> products (4a) and (6a) were also formed (entries 2 and 3). It was also shown (entry 4) that a more coordinating solvent such as THF has only a small effect in decreasing the <u>erythro</u> selectivity. The loss of diastereoselectivity in these reactions was examined further by a study of reactions of



Table[a]

ENTRY	ALDEHYDE	L_2BOTf[b]	AMINE[c]	RATIO[d] 4 : 5 : 6 : 7	YIELD[f] of 4 %
1	2a	9-BBN	DIPEA	47 : 29 : 9 : 14	30
2	2a	n-Bu	DIPEA	18 : 75 : 7 : 0[e]	13
3	2a	Et	DIPEA	20 : 73 : 7 : 0[e]	14[g]
4	2a	n-Bu	DIPEA	10 : 85 : 5 : 0[e]	-
5	2a	Et	TEA	>98	87
6	2a	n-Bu	TEA	>98	76
7	2a	n-Bu	NEP	>98	83
8	2b	n-Bu	DIPEA	>98	82
9	2b	n-Bu	TEA	>98	83
10	2c	n-Bu	DIPEA	>98	64
11	2d	n-Bu	DIPEA	>98	80
12	2e	n-Bu	DIPEA	>98	82[g]
13	2f	n-Bu	DIPEA	68 : 26 : 6 : 0[e]	-
14	2f	n-Bu	TEA	>98	88
15	2a	n-Bu	1) DIPEA 2) TEA-HCl	>98	85

a) All reactions were carried out according to reference 5 using CH_2Cl_2 as solvent except for entry 4 where a 4:1 mixture of THF-CH_2Cl_2 was used. b) 9-BBN-OTf and Et_2BOTf were freshly prepared according to references 10 and 11 respectively. n-Bu_2BOTf was purchased as a 1M solution in CH_2Cl_2 from the Aldrich Co. c) DIPEA: diisopropylethylamine; TEA: triethylamine; NEP: N-ethylpiperidine. d) Determined by 360 MHz ^1H n.m.r: where other isomers were not detected the purity was assumed $\geq$ 98%. e) not detected by ^1H-NMR. f) Isolated yield either by flash chromatography or crystallisation; Correct C,H,N elemental analysis ($\leq$ 0.1%) was obtained for all compounds. g) Not determined.

a range of substituted benzaldehydes with the acyl oxazolidinone (3). Thus, reaction of o-methoxybenzaldehyde (2b) (entry 8) gave a single product whose stereochemistry could not be unambigously assigned because of its relatively large H_2-H_3 coupling constant, J=5.7Hz, however chemical correlation[9] and X-ray analysis showed it to be the erythro compound (4b). Indeed high stereoselectivity was observed in all cases (entries 10-12) except with aldehydes with a ortho-methoxy, meta-nitro substitution pattern (entries 1-4, 13). Surprisingly when Et_3N was used as base (entries 5,6) the required erythro aldol product (4a) was formed with more than 98% diastereoselection (limit of ^1H n.m.r. detection) and good chemical yield. It is noteworthy that this reaction was repeated on a 80 mmol scale without loss in either diastereoselection or yield and that a similar base such as N-ethylpiperidine gave the same result as Et_3N (entry 7). Paralell results were observed with 2-methoxy-3-nitrobenzaldehyde (entries 13 and 14).

Our experiments therefore indicate that in aldol reactions with aromatic aldehydes substituted with an ortho-methoxy and a meta-nitro group (entries 1-4, 13, 14) selectivity can only be obtained with the appropriate choice of conditions. Replacement of i-Pr_2NEt with Et_3N or N-ethyl piperidine results in a striking improvement in stereoselectivity High selectivity with the other substituted benzaldehydes appears to be much less dependent on the choice of amine (entries 8-12). Since both i-Pr_2NEt and Et_3N have been used for generating the (Z)-boron enolate of (3) the loss of selectivity observed in the cases of (2a) and (2f) does not appear to be associated with the enolisation process but rather in the second stage of reaction of the aldehyde with the intermediate enolate. These results suggest that the ammonium salt plays a significant role in the transition state for reaction of the aldehyde with the boron enolate. This hypothesis was confirmed by the following experiment in which the (Z)-boron enolate of (3) was generated under standard conditions using i-Pr_2NEt. After cooling to -78°C, Et_3N-HCl (1 eq) in CH_2Cl_2 was added followed immediately

by the aldehyde (2a). After being stirred for 0.5h at -78°C and 1h at 0°C usual work up afforded (4a) with > 98% diastereoselectivity and 85% isolated yield (entry 15).

We suspect that there may be other cases where the loss of total stereo-control in aldol reactions might be solved by a careful choice of experimental conditions.

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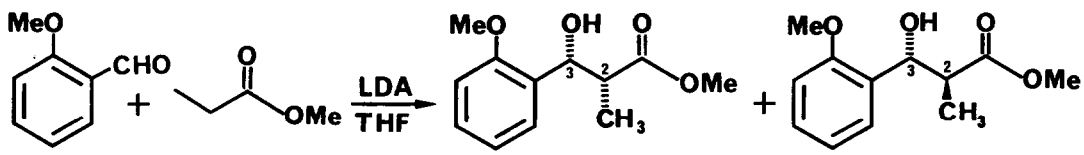
6. See C.H. Heathcock in reference 4, and references therein.
7. (6a): ^{1}H n.m.r. ($CDCl_3$), δ 7.45-7.28 (m, 7H, Ar-H); 5.72 (d, 1H, J=7.2Hz, PhC<u>H</u>-O); 5.42 (t, 1H, J=3.0Hz, 3-H); 4.76 (qn, 1H, J=6.8Hz, N-C<u>H</u>-); 4.22 (dq, 1H, J=7.1 and 3.4Hz, 2-H); 3.88 (s, 3H, Ar-O<u>Me</u>); 3.84 (s, 3H, Ar-O<u>Me</u>); 3.76 (d, 1H, J=2.8Hz, -O<u>H</u>); 1.19 (d, 3H, J=7.1Hz, 2-Me); 0.90 (d, 3H, J=6.6Hz, N-CH-<u>Me</u>) ppm.
(7a): ^{1}H n.m.r. ($CDCl_3$), δ 7.45-7.28 (m, 7H, Ar-H); 5.69 (d, 1H, J=7.3Hz, PhC<u>H</u>-O); 5.24 (t, 1H, J=7.2Hz, 3-H); 4.82 (qn, 1H, J=6.7Hz, N-C<u>H</u>-); 4.25 (qn, 1H, J=7.1Hz, 2-H); 3.91 (s, 3H, Ar-O<u>Me</u>); 3.86 (s, 3H, Ar-O<u>Me</u>); 3.20 (d, 1H, J=6.8Hz, -O<u>H</u>); 1.16 (d, 3H, J=7.0Hz, 2-Me); and 0.92 (d, 3H, J=6.6Hz, N-CH-<u>Me</u>) ppm.
8. Dibutylboron triflate (1M solution in CH_2Cl_2) is available from the Aldrich Chemical Co. Ltd. In our hands no significant differences were observed between this Aldrich borane and the freshly prepared Et_2BOTf.
9. Compound (4b) was treated with NaOMe (MeOH-CH_2Cl_2, 0°C) to give the methyl ester whose spectroscopic properties were identical with those of the racemic erythro aldol product (10) prepared as shown below:



(10) $J_{2,3}$ = 4.3Hz; 2-Me: δc = 11.06ppm

(11) $J_{2,3}$ = 7.3Hz; δc = 14.67ppm

For a correlation of ^{13}C chemical shifts with erythro-threo geometry see : C.H. Heathcock, M.C. Pirrung, and J.E. Sohn, J. Org. Chem., 1979, 44, 4294.
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