

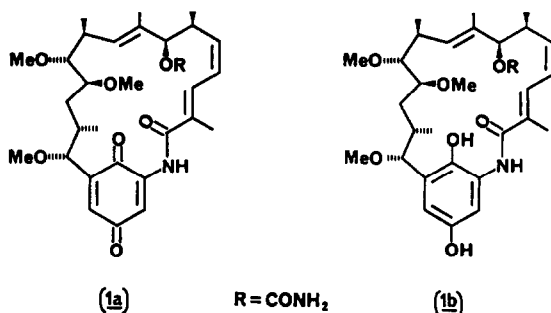
THE STEREOSSELECTIVITY OF DIRECTED ALDOL REACTIONS WITH 3-NITRO-2-METHOXYBENZALDEHYDES IS AFFECTED BY THE AMINE EMPLOYED AS BASE.

Raymond Baker, Jose L. Castro and Christopher J. Swain

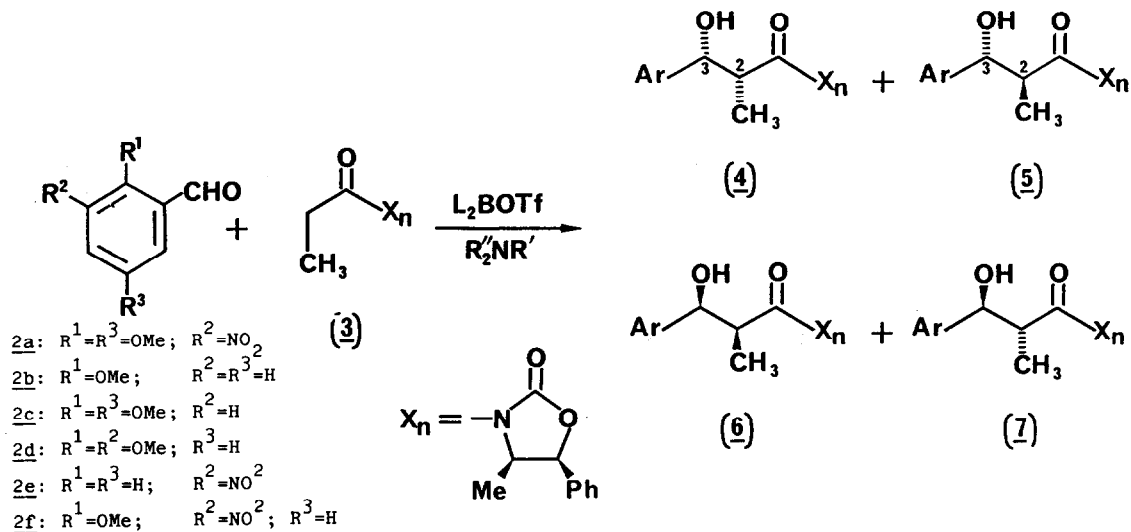
Merck Sharp and Dohme Research Laboratories,
 Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR

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*-Pr₂NEt as base whereas the use of Et₃N 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 C₂₀ and C₂₁. Amongst a number of available alternatives⁴ the Evans aldol methodology⁵ 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 a 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.

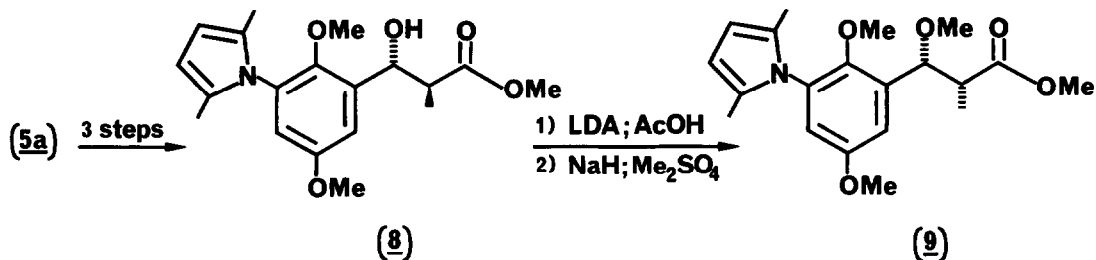


In our initial experiments reaction of 3-nitro-2,5-dimethoxybenzaldehyde (**2a**) with (**3**) in the presence of 9-BBN-trifluoromethanesulfonate (-OTf), *i*-Pr₂NEt in dichloromethane at -78°C for 0.5 h followed by 1 h at room temperature gave a 56:43 ratio of *erythro*:*threo* compounds with all four possible diastereomers being formed. The products were



separated by flash chromatography on silica gel (CH_2Cl_2 -3% Et₂O) 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), $[\alpha]_D^{22} + 82^\circ$ ($c=2.0, \text{CH}_2\text{Cl}_2$); δ H (CDCl₃) 7.45-7.27 (m, 7H, ArH); 5.69 (d, 1H, $J=7.4\text{Hz}$, PhCH-O); 5.41 (t, 1H, $J=3.0\text{Hz}$, 3-H), 4.82 (qn, 1H, $J=6.8\text{Hz}$, N-CH-); 4.05 (dq, 1H, $J=7.1$ and 3.0Hz , 2-H); 3.88 (d, 1H, $J=2.4\text{Hz}$, -OH); 3.86 (s, 3H, Ar-OMe); 3.85 (s, 3H, Ar-OMe); 1.19 (d, 3H, $J=7.1\text{Hz}$, 2-Me) and 0.91 (d, 3H, $J=6.6\text{Hz}$, N-CH-Me) ppm. Its erythro configuration was established on the basis of the small $H_{2,3}$ coupling constant, $J=3.0\text{Hz}$ ⁶, and its absolute stereochemistry confirmed by X-ray spectroscopic studies. The other major isomer (5a), was concluded to have a threo configuration on the basis of $J_{2,3}=8.2\text{Hz}$ and a ¹H n.m.r. (CDCl₃), δ 7.45-7.29 (m, 7H, ArH), 5.69 (d, 1H, $J=7.2\text{Hz}$, PhCH-O); 5.18 (t, 1H, $J=8.2\text{Hz}$, 3-H), 4.79 (qn, 1H, $J=6.8\text{Hz}$, N-CH-); 4.32 (dq, 1H, $J=7.0$ and 8.3Hz , 2-H); 3.91 (s, 3H, Ar-OMe); 3.83 (s, 3H, Ar-OMe); 3.42 (d, 1H, $J=8.0\text{Hz}$, -OH); 1.12 (d, 3H, $J=7.0\text{Hz}$, 2-Me); 0.91 (d, 3H, $J=6.6\text{Hz}$, N-CH-Me) ppm. Further conclusive chemical evidence was obtained in that (5a) was converted to (9), a further intermediate in our synthesis of Macbecin unambiguously prepared from (4a). The minor isomers, (6a) and (7a) were characterised on the basis of their ¹H n.m.r. spectra⁷.

The use of other dialkylboron triflates such as the commercially available *n*-Bu₂BOTf⁸ and the freshly prepared Et₂BOTf gave predominantly the threo-isomer (5a) although significant amounts of the erythro 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 erythro selectivity. The loss of diastereoselectivity in these reactions was examined further by a study of reactions of



Table^a

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

a) All reactions were carried out according to reference 5 using CH₂Cl₂ as solvent except for entry 4 where a 4:1 mixture of THF-CH₂Cl₂ was used. b) 9-BBN-OTf and Et₂BOTf were freshly prepared according to references 10 and 11 respectively. n-Bu₂BOTf was purchased as a 1M solution in CH₂Cl₂ 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 ≥ 98%. e) not detected by ¹H-NMR. f) Isolated yield either by flash chromatography or crystallisation; Correct C,H,N elemental analysis (≤ 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 unambiguously assigned because of its relatively large H₂-H₃ coupling constant, J=5.7Hz, however chemical correlation⁹ 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 Et₃N 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 Et₃N (entry 7). Parallel results were observed with 2-methoxy-3-nitrobenzaldehyde (entries 13 and 14).

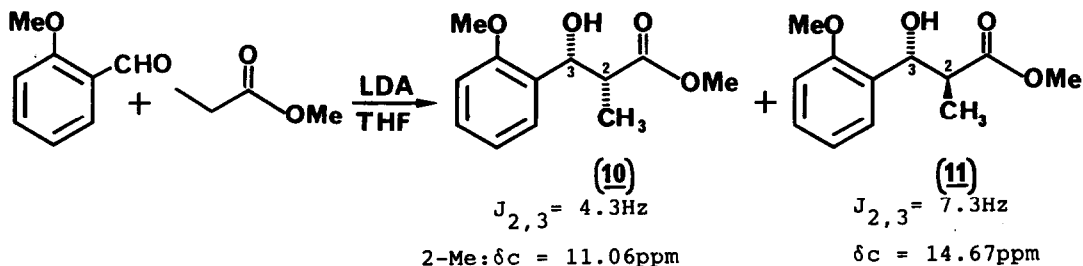
Our experiments therefore indicate that in aldol reactions with aromatic aldehydes substituted with an ortho-methoxy and a meta-nitro group (entries 1-4, 13, 14) selectivity can only be obtained with the appropriate choice of conditions. Replacement of i-Pr₂NEt with Et₃N or N-ethyl piperidine results 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-Pr₂NEt and Et₃N 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-Pr₂NEt. After cooling to -78°C, Et₃N-HCl (1 eq) in CH₂Cl₂ 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.

References and Notes

1. S. Tanida, T. Hasegawa and E. Higashide, *J. Antibiot.*, **1980**, 33, 199.
2. M. Muroi, M. Izawa, Y. Kasai and M. Asai, *J. Antibiot.*, **1980**, 33, 205.
3. M. Muroi, K. Haibara, M. Asai, K. Kamiya and T. Kishi, *Tetrahedron*, **1981**, 37, 1123.
4. For an excellent review on the subject see: C.H. Heathcock in "Asymmetric Synthesis", J.D. Morrison Ed. Vol. 3, Academic Press 1984, pp 111-212. See also T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, **1985**, 26, 5807; M. Nerz-Stormes and E.R. Thornton, *Tetrahedron Lett.*, **1986**, 27, 897.
5. D.A. Evans, J. Bartroli and T.L. Shih, *J. Am. Chem. Soc.*, **1981**, 103, 2127.
6. See C.H. Heathcock in reference 4, and references therein.
7. (**6a**): ^1H n.m.r. (CDCl_3), δ 7.45-7.28 (m, 7H, Ar-H); 5.72 (d, 1H, $J=7.2\text{Hz}$, PhCH-O); 5.42 (t, 1H, $J=3.0\text{Hz}$, 3-H); 4.76 (qn, 1H, $J=6.8\text{Hz}$, N-CH-); 4.22 (dq, 1H, $J=7.1$ and 3.4Hz , 2-H); 3.88 (s, 3H, Ar-OMe); 3.84 (s, 3H, Ar-OMe); 3.76 (d, 1H, $J=2.8\text{Hz}$, -OH); 1.19 (d, 3H, $J=7.1\text{Hz}$, 2-Me); 0.90 (d, 3H, $J=6.6\text{Hz}$, N-CH-Me) ppm.
(**7a**): ^1H n.m.r. (CDCl_3), δ 7.45-7.28 (m, 7H, Ar-H); 5.69 (d, 1H, $J=7.3\text{Hz}$, PhCH-O); 5.24 (t, 1H, $J=7.2\text{Hz}$, 3-H); 4.82 (qn, 1H, $J=6.7\text{Hz}$, N-CH-); 4.25 (qn, 1H, $J=7.1\text{Hz}$, 2-H); 3.91 (s, 3H, Ar-OMe); 3.86 (s, 3H, Ar-OMe); 3.20 (d, 1H, $J=6.8\text{Hz}$, -OH); 1.16 (d, 3H, $J=7.0\text{Hz}$, 2-Me); and 0.92 (d, 3H, $J=6.6\text{Hz}$, N-CH-Me) 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 ($\text{MeOH}-\text{CH}_2\text{Cl}_2$, 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:



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.

10. T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **1980**, 53, 174.
11. D.A. Evans, J.V. Nelson, E. Vogel and T.R. Taber, *J. Am. Chem. Soc.*, **1981**, 103, 3099.

Acknowledgements

We wish to acknowledge the contribution of Prof. D.A. Evans, (Harvard) for providing experimental details of studies of aldol reactions with aldehyde (**2a**). We also thank Dr. J.P. Springer (MSD, Rahway) for X-ray structure determinations on (**4a**) and (**4b**). J.L.C. wishes to thank MSDRL (Harlow) for the provision of facilities and the Ministry of Education and Science (Spain) and the British Council for a grant.

(Received in UK 26 February 1988)