Diastereoselective Addition to an α-Alkoxyaldehyde under Dipolar (Cram–Felkin) and Chelation (Cram–Cyclic) Controlled Conditions; A Stereocontrolled Synthesis of (+)-Blastmycinone

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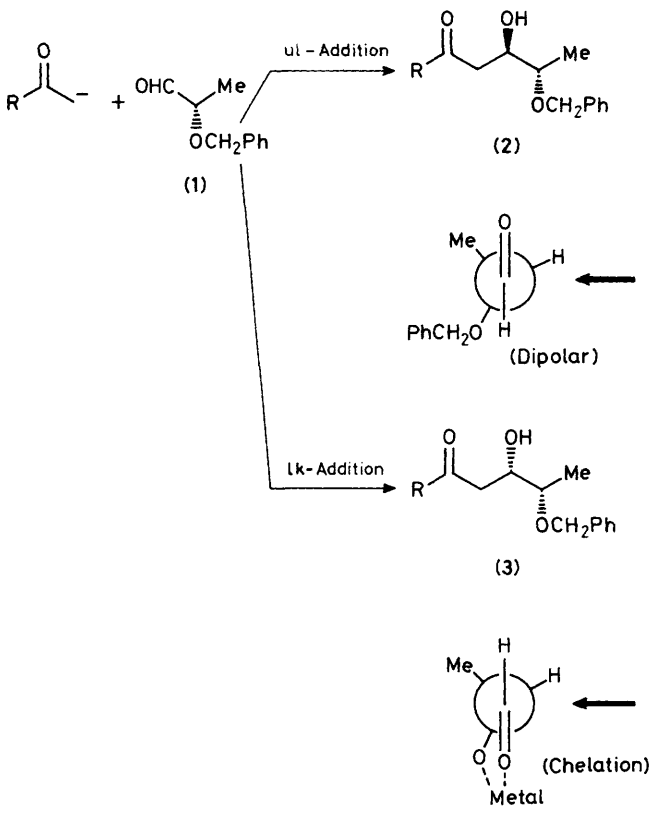
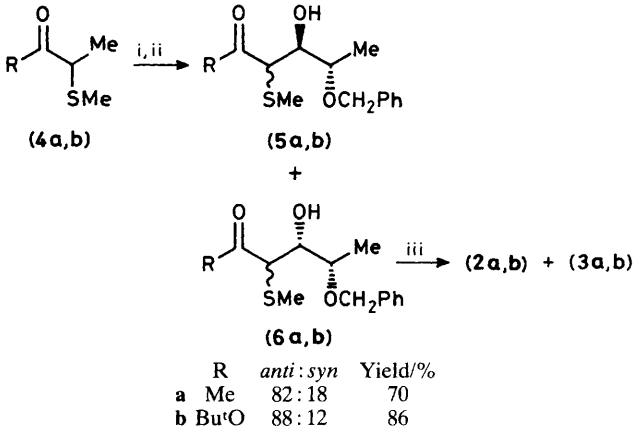
Stereoselective synthesis of *anti* (**2**) and *syn* (**3**) diols by addition of an acetyl anion equivalent to 2-benzyloxypropanal (**1**) and stereocontrolled synthesis of (+)-blastmycinone (**11**) are described.

Stereochemical studies of nucleophilic additions to the diastereotopic face of α-chiral aldehydes have been the focus of much current interest in aldol and organometallic addition reactions.[1] In particular, the stereoselective nucleophilic additions to α-alkoxyaldehydes have received much attention[2] especially in the synthesis of complex polyoxygenated natural products. There have been recent reports of stereoselective control in the synthesis of *syn* diols[3] (lk-addition), but there is still no reliable method for controlling the stereochemistry of these reactions with high selectivity for both *anti* and *syn* diols (ul- and lk-additions).[4] These additions are classified as the dipolar (Cram–Felkin)[5] and chelation (Cram–cyclic)[6] models,

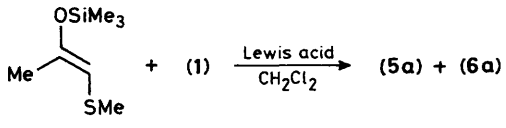


Scheme 1



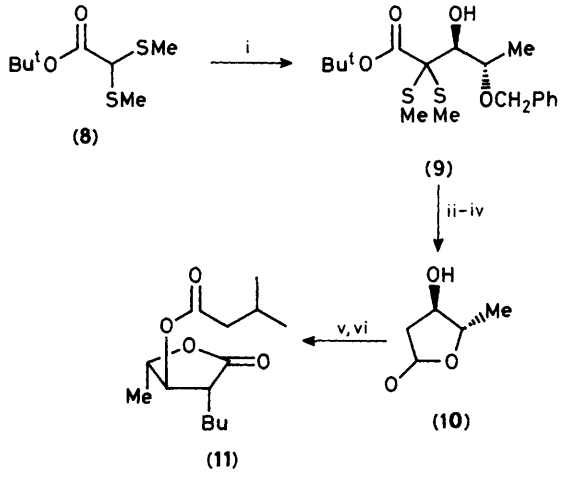
	R	*anti* : *syn*	Yield/%
a	Me	82 : 18	70
b	Bu^{t}O	88 : 12	86

Scheme 2. *Reagents:* i, lithium di-isopropylamide (LDA), tetrahydrofuran (THF); ii, (**1**); iii, Raney-Ni(W-2).



Lewis acid	Temp./°C	*anti* : *syn*	Yield/%
$MgBr_2$	0	1 : 99	70
$ZnCl_2$	0	6 : 94	55
$SnCl_4$	−78	20 : 80	58

Scheme 3



Scheme 4. *Reagents and conditions:* i, LDA, THF, −78 °C, then (**1**); ii, Raney-Ni(W-2), H_2, EtOH, room temp., 30 min; iii, Pd–C, H_2, EtOH; iv, catalytic amount of CF_3CO_2H, toluene, reflux, 30 min; v, Bu^{n}Li (2.1 equiv.), THF : hexamethylphosphoramide 9 : 1, −78 °C, then Bu^{n}I (1.2 equiv.); vi, isovaleryl chloride (1.2 equiv.), dimethylaminopyridine, pyridine.

as illustrated in Scheme 1. In this communication we report the highly stereocontrolled addition of an acetyl anion equivalent [(**4**) or (**7**)] to 2-benzyloxypropanal (**1**) leading to the *anti* and *syn* diols, (**2**) and (**3**).

Aldol reaction of the lithium salt of (**4a**) with (**1**) gave a mixture of diastereoisomers (**5a**) and (**6a**) which upon desulphurization by Raney-Ni afforded two diastereoisomers (**2a**) and (**3a**) with an excellent selectivity (82 : 18).† In this addition reaction, the *anti* compound was preferred.‡ Similarly (**4b**) showed good selectivity (88 : 12), Scheme 2.

However, Lewis acid-promoted reaction[3] of the silyl enol ether (**7**) displayed a reversal of stereoselectivity. The silyl enol ether *E*-(**7**) (*E* : *Z*, 4 : 1) was treated with (**1**) in the presence of the Lewis acids, $MgBr_2$, $ZnCl_2$, or $SnCl_4$. These reactions were highly *syn* selective (Scheme 3), with $MgBr_2$ being the most effective (1 : 99). The reaction of the other isomer, *Z*-(**7**) (*E* : *Z*, 1 : 5) with (**1**) and $SnCl_4$ showed similar *syn* selectivity (20 : 80).

Using this reaction we were able to carry out a short and highly stereocontrolled synthesis of (+)-blastmycinone (**11**) as shown in Scheme 4. Aldol addition of (**8**) with (**1**) gave the aldol (**9**) with high *anti* selectivity (over 35 : 1) in 85% yield. This high selectivity is probably due to the larger size of the nucleophilic centre, substituted with two methylthio groups. After reductive desulphurization and removal of the benzyl group, cyclization furnished the optically pure hydroxylactone (**10**), $[\alpha]_D^{18}$ −8.1° (*c* 1.6, MeOH), in 62% yield (three steps). Alkylation of this lactone with n-butyl iodide followed by acylation with isovaleryl chloride provided (+)-blast-

† Satisfactory spectroscopic (i.r., ^{1}H n.m.r., and mass) and optical rotation data were obtained for all new compounds. The diastereoisomeric ratios were determined by n.m.r. spectroscopy and g.c. after derivatisation to the corresponding silyl compounds. All yields are isolated yields.

‡ Analogous high *anti* selective addition of β-dimethylaminopropionate to α-alkoxyaldehyde was achieved. See L. Bamfi, A. Bernard, L. Colombo, C. Gennari, and C. Scolastico, *J. Org. Chem.*, 1984, **49**, 3784.

mycinone, $[\alpha]_D^{18}$ +10.1° (*c* 1.3, $CHCl_3$), in 32% yield (two steps), which was identical in all respects including optical rotation ($[\alpha]_D^{26}$ +10°) to the natural product reported in the literature.[7]

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