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A Stereocontrolled Approach to 1β-Methylcarbapenem

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Abstract: Conjugate addition of lithium *N*-allyl-*N*-α-methylbenzylamide to chiral α,β-unsaturated esters is subject to double stereodifferentiation, the mismatched pair reaction allowing access to an intermediate for 1β-methylcarbapenem synthesis.

Since the discovery that the 1β-methyl substituent on the carbapenem skeleton enhances chemical and metabolic stability,[1] many stereocontrolled routes to key intermediates possessing the required four contiguous stereogenic centres have appeared.[2] We describe here the preliminary results of a double stereodifferentiation[3] approach to a key intermediate **9**.[4] The pivotal reaction in this strategy involves the 1,4-conjugate addition of lithium *N*-allyl-*N*-α-methylbenzylamide **2** to a homochiral α,β-unsaturated ester (Figure). This reaction involving two chiral participants is generally subject to double stereodifferentiation, having a matched and mismatched pair of reagents. It has already been demonstrated that the conjugate addition of the homochiral lithium amide proceeds in a predictable fashion,[5] with a single enantiomer of the lithium amide **2** always attacking the same face of the α,β-unsaturated ester, however the effects of further chirality in the ester had not been investigated. The desired synthetic target **9** possesses the (6*S*,5*R*) configuration, consequently an asymmetric synthesis of this based upon a conjugate addition of **2** necessitates the use of the (*R*)-enantiomer.

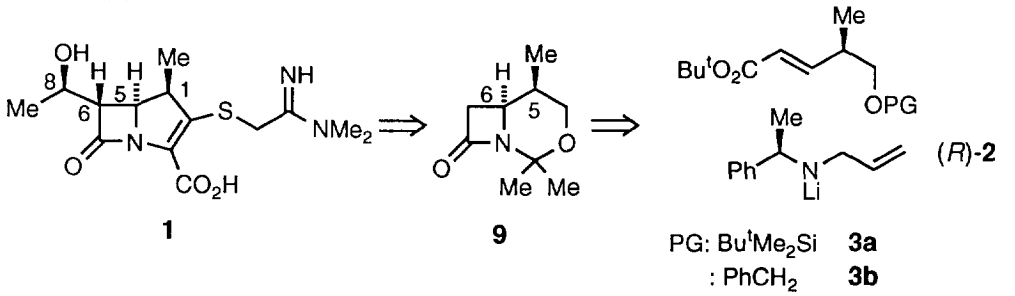
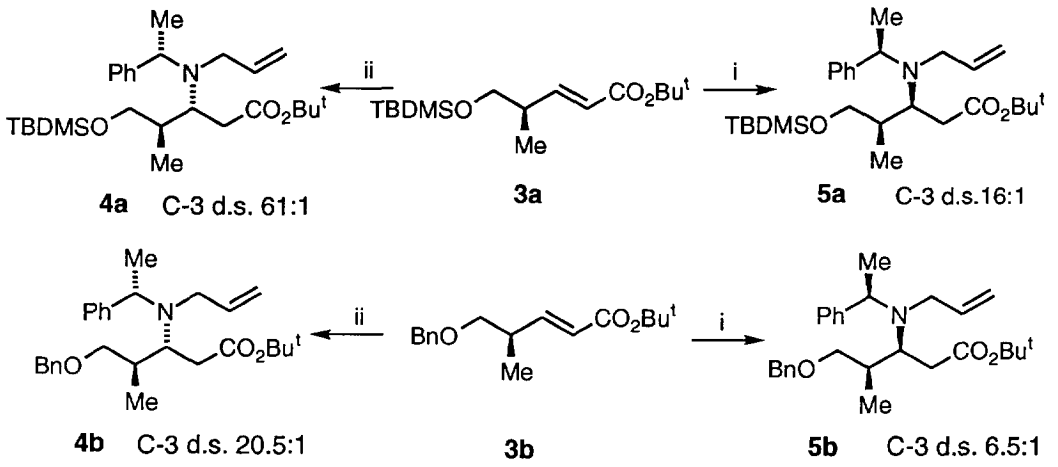


Figure.

The hydroxyl group of the chiral α,β-unsaturated ester **3** was protected as its silyl and benzyl ethers, the latter being preferred since it would allow concomitant deprotection of both the N and O benzyl groups at a late stage in the synthesis. Formation of the ester **3b** {$[\alpha]_D^{23}$ +12.3 (*c* 1.95, $CHCl_3$)}was completed efficiently by benzylation of methyl (*S*)-3-hydroxy-2-methyl propionate, followed by $LiAlH_4$ reduction and tandem Swern oxidation-Wittig reaction at low temperature;[6] the silyl variant **3a** {$[\alpha]_D^{23}$ +21.1 (*c* 1.02, EtOH; lit.,[7])}was synthesised in an analogous fashion using a literature procedure.[7] The stereodirecting effects of both ester and lithium amide were investigated by the conjugate addition of both enantiomers of the lithium amide **2** to a

single enantiomer of each ester (Scheme 1), the observed diastereoselectivities are summarised in Table 1 (the figures shown in parentheses are for the isolated major diastereoisomer following chromatographic separation). The dominant stereodirecting effect in both reactions of each substrate was predicted to be that of the lithium amide, overriding any stereodirecting effect of the ester.



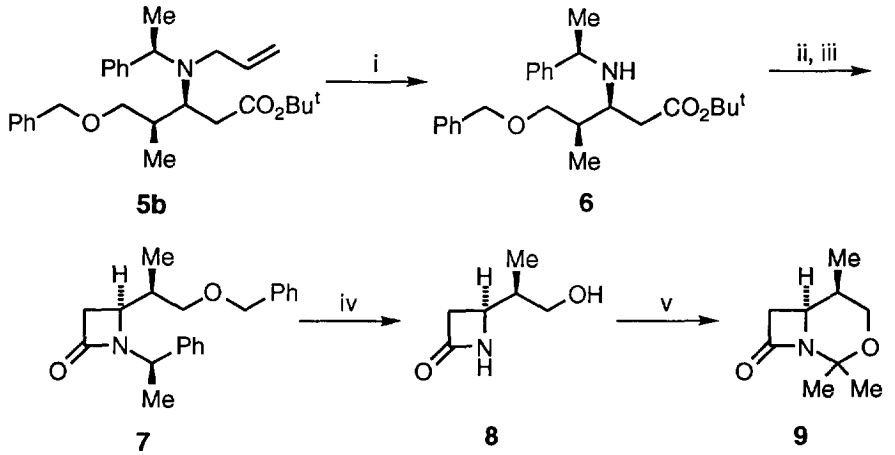
Scheme 1: *Reagents*: i) (*R*)-**2**, NH_4Cl; ii) (*S*)-**2**, NH_4Cl.

Lithium amide	Substrate	Protecting group	C-3 d.s., d.e. (%)	Major isomer	Yield (%)
(*S*)-**2**	**3a**	Bu^tMe_2Si-	61:1, 97	(3*R*,α*S*,4*R*)-**4a** $[\alpha]_D^{23}$ +35.1 (*c* 1.22, $CHCl_3$)	84
(*S*)-**2**	**3b**	$PhCH_2$-	20.5:1, 91	(3*R*,α*S*,4*R*)-**4b** $[\alpha]_D^{23}$ +38.1 (*c* 1.25, $CHCl_3$)	77
(*R*)-**2**	**3a**	Bu^tMe_2Si-	16:1, 88 (65:1, 97)	(3*S*,α*R*,4*R*)-**5a** $[\alpha]_D^{23}$ -46.6 (*c* 1.55, $CHCl_3$)	84 (79)
(*R*)-**2**	**3b**	$PhCH_2$-	6.5:1, 73 (70:1, 97)	(3*S*,α*R*,4*R*)-**5b** $[\alpha]_D^{23}$ -53.8 (*c* 2.00, $CHCl_3$)	80 (60)

Table 1.

After separation of the major diastereoisomer **5b** {$[\alpha]_D^{23}$ -53.8 (*c* 2.00, $CHCl_3$)}, arising from the mismatched reaction of the benzyloxy ester, transformation of this β-amino ester to the desired bicyclo[4.2.0]octan-8-one **9** was efficiently carried out (Scheme 2). Following deallylation[8] yielding **6** {$[\alpha]_D^{23}$ +11.5 (*c* 1.60, $CHCl_3$)} and cleavage of the *tert*-butyl ester,[9] subsequent cyclisation[10] of the resulting β-amino acid {$[\alpha]_D^{23}$ -53.3 (*c* 1.00, $CHCl_3$)} yielded the dibenzylated β-lactam **7** {$[\alpha]_D^{23}$ -57.5 (*c* 1.19, $CHCl_3$)}. Birch reduction[11] removed both benzyl groups in excellent yield giving **8** {$[\alpha]_D^{23}$ -4.6 (*c* 1.02, $CHCl_3$)}, with acetonide formation then being accomplished under standard conditions. Analysis of the ^1H nmr spectrum, in particular observation of characteristic chemical shifts and coupling constants confirmed

both the relative and hence absolute configuration of **9** {$[\alpha]_D^{23}$ +48.0 (*c* 0.52, $CHCl_3$;lit.,[4c-e])}.[4a] Consequently, following confirmation of the absolute configuration of **5b**, from the reaction exhibiting least diastereoselectivity, the configuration of the remaining 1,4-adducts were determined assuming this proven domination of the asymmetric induction of the lithium amide.



Scheme 2: *Reagents*: i) $RhCl(PPh_3)_3$, H_2O, CH_3CN (98%); ii) CF_3CO_2H, CH_2Cl_2 (91%); iii) PPh_3, $(PyS)_2$, CH_3CN (85%); iv) Na, NH_3 (l), EtOH (92%); v) $Me_2C(OMe)_2$, $BF_3.Et_2O$ (69%).

When comparing the results of silyl and benzyl ethers it can be seen that the silyl group dramatically increases the diastereoselectivity observed. The reason for this difference in diastereoselectivities is not obvious. However, the reduced availability of the oxygen atom for lithium chelation in the case of the bulkier silyl ether may account for the results. The magnitude of this increase in diastereoselectivity is such that the mismatched reaction of silyl ether **3a** is comparable to that for the matched reaction of the benzyl ether **3b**. The increased diastereoselectivity in both matched and mismatched reactions of the silyl ether **3a**, indicates that the stereodirecting effect of the γ-methyl group is not accounting for this anomalous behaviour. Consequently, a disrupted transition state can be invoked to account for the disparate results involving either enantiomer of lithium amide and the benzyl ether. Separation of the major diastereoisomer **5a** from the mismatched reaction involving silyl ether **3a** was accomplished in excellent yield, consequently transformation of this to **9** could easily be realised.[4d]

Indeed, two similar approaches to β-amino adducts, **5a** and its ethyl ester analogue have been reported. The first approach[4d] involved a thermal addition of benzylamine to the ethyl ester analogous to **3a**; a separable 2.3:1 mixture of two diastereoisomers was obtained, with the major diastereoisomer subsequently transformed to **9**. The second report by Hawkins and Lewis,[7] involved the conjugate addition of an azepine derived homochiral lithium amide to **3a**. Once again, this combination of chiral reactants represented a mismatched reaction.

In conclusion, following the mismatched yet highly diastereoselective conjugate addition of (*R*)-lithium *N*-allyl-*N*-α-methylbenzylamide to (*R*)-*tert*-butyldimethylsilyloxy-ester **3a** and subsequent isolation of a single

diastereoisomer in high yield forms the basis of an asymmetric synthesis of a key intermediate to 1β-methylcarbapenem. The ease of separation, high yield and diastereoselectivity of the reaction offers distinct advantages over the previous related approaches to this intermediate.

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Note added in proof: Since submission of this manuscript a similar approach to **9** via **3a** and lithium (α-methylbenzyl)benzylamide has been reported N. Tsukada, T. Shimada, Y.S. Gyoung, N. Asoa and Y. Yamamoto, *J. Org. Chem.*, 1995, **60**, 143.

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