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(4*S*,5*S*)-4-Benzylamino-5-[((*tert*-butyl)diphenylsilyl)oxymethyl]-dihydro-2(3*H*)-furanone. A New Intermediate for the Enantiospecific Synthesis of β-Aminoesters and β-Lactams.

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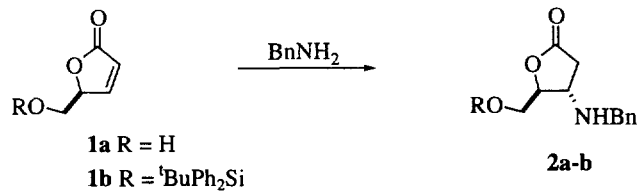
Abstract: Conjugate addition of benzylamine to (*S*)-5-hydroxymethyl-2(5*H*)-furanone generated the new aminolactone (**2b**) as a single diastereomer. The C4/C5 *trans* relationship was confirmed by X-ray crystal structure determination of the corresponding *t*-butyldiphenylsilyl ether. Elaboration of aminolactone (**2b**) to β-aminoesters and β-lactams is also described.

The wide range of biological activity that optically pure β-amino acids, esters and β-lactams possess ensures that their synthesis, chemistry and pharmacology remain areas of intense interest.[1] One direct method for the formation of β-amino acid derivatives is the conjugate addition of amines to α,β-unsaturated esters.[2] We were interested in adapting this approach through the conjugate addition of amines to enantiomerically-pure *α,β-unsaturated lactones* such as (**1**) (see Scheme 1). The product aminolactones might then serve as precursors to a variety of β-amino acid derivatives (including their corresponding esters and β-lactams). In this Letter we describe the enantiospecific synthesis and some chemical manipulations of one such aminolactone.



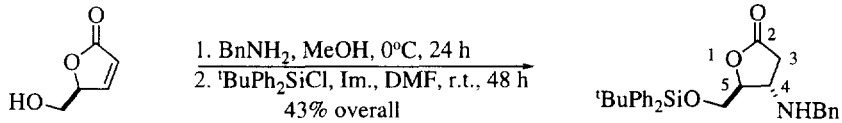
1a R = H
1b R = ^{t}BuPh$_2$Si

2a-b

Scheme 1.

Conjugate addition of carbon centred nucleophiles, (tris(methylthio))methyllithium and dimethylcopper lithium, to (**1b**) have been reported.[2b,3] Conjugate additions of amines (e.g. benzylamine) to (**1a**) or (**1b**) have not been reported but should occur at the less hindered face providing aminolactones such as (**2a**) or (**2b**) with high diastereoselectivity.

The lactone (**1b**) was prepared in 5 steps from D-mannitol.[4] Lactone (**1b**) was initially chosen as it bears a bulky silyl protecting group. Benzylamine was chosen as the amine nucleophile due to the relative ease with which the benzyl group could be removed at a later stage. Reaction of a methanol solution of (**1b**) with benzylamine produced a low yield (21%) of conjugate addition product (**2b**) as a single diastereomer as well as *t*-$BuPh_2SiOH$ (65%) although no desilylated lactone was recovered. Conducting the reaction at 0 °C gave slightly improved yields of (**2b**) (26%) with an accompanying decrease in silanol (55%). The reaction was attempted in a number of different solvents (CH_2Cl_2, THF and DMF) however in all these cases only starting material was recovered. It was found that addition of benzylamine to the unprotected lactone (**1a**) gave much improved yields of product as shown by analysis of the ^1H NMR spectrum of the crude reaction product. Isolation of the product (**2a**) proved to be extremely difficult so the crude reaction mixture was directly silylated giving (**2b**)[5] [mp 78-79 °C, $[\alpha]_D^{20}$ +15.3° (c 0.8, $CHCl_3$)] in 43% yield over two steps (see Scheme 2).[6]



1a **2b**

Scheme 2.

An X-ray crystal structure determination of (**2b**) confirmed the expected *trans* relationship of the C4/C5 substituents (see Figure 1 below).

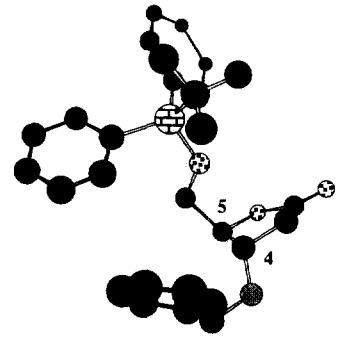
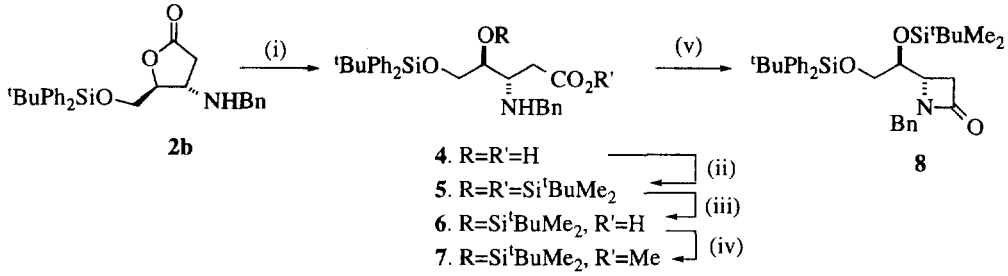


Figure 1. X-ray crystal structure of (**2b**) (hydrogens omitted for clarity).

We have also explored some of the chemistry of benzylaminolactone (**2b**). Hydrolysis of (**2b**) gave the β-amino acid (**4**). Silylation of (**4**) gave (**5**) which, after selective ester hydrolysis, provided the β-amino acid (**6**). Due to the zwitterionic character of intermediates (**4**) and (**6**) and the instability of (**5**), these products could not be completely purified. However, treatment of (**6**) with diazomethane gave β-amino ester (**7**) which

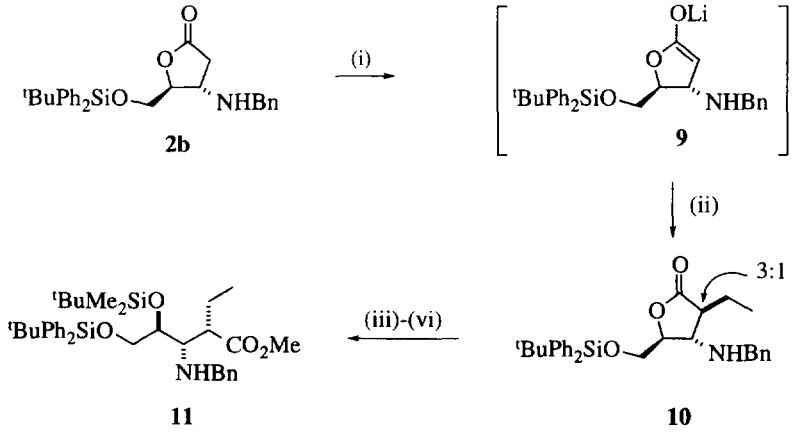
was fully characterized. Alternatively, treatment of (**6**) with triphenylphosphine and 2,2-dipyridyldisulfide[7] gave the enantiomerically pure β-lactam (**8**) [$[\alpha]_D^{20}$ -7.11° (c 1.11, $CHCl_3$)] in 60% yield (see Scheme 3).



(i) NaOH, MeOH, (ii) ^{t}BuMe$_2$SiCl, Et$_3$N, DMAP, DMF, (iii) HCl, MeOH (iv) CH_2N_2 (v) PPh_3, $(PyS)_2$, CH_3CN.

Scheme 3.

Benzylaminolactone (**2b**) could also be functionalised at C3 via its lithium enolate (**9**). Reaction of (**9**) with ethyl iodide gave (**10**) as a 3:1 mixture of diastereomers in 51% yield. The major diastereomer (shown) was subjected to the same hydrolysis,[8] silylation and esterification reactions as (**2b**) to provide β-amino ester (**11**) in 38% yield over four steps (see Scheme 4).

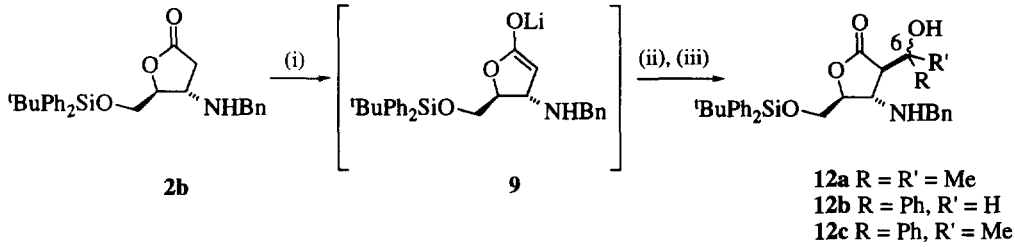


(i) LiHMDS, THF, -78°C, 30 min.; (ii) EtI, DMPU, 51%; (iii) NaOH, MeOH; (iv) ^{t}BuMe$_2$SiCl, Et$_3$N, DMAP, DMF; (v) HCl, MeOH; (vi) CH_2N_2, 38% overall from (**10**).

Scheme 4.

Much better levels of diastereoselectivity were obtained for aldol reactions of enolate (**9**) with acetone, acetophenone or benzaldehyde with C3/C4 *trans* products (**12a-c**) being obtained exclusively and in good yields. Where a new stereocentre was also generated at the product carbinol carbon (ie reaction with

acetophenone or benzaldehyde) little stereocontrol was observed (see Scheme 5). The elaboration of these and other adducts into the corresponding β-lactams will be the subject of a further communication.



2b **9**

12a R = R' = Me
12b R = Ph, R' = H
12c R = Ph, R' = Me

(i) LiHMDS, THF, -78°C, 30 min.; (ii) RCOR'; (iii) Aq. NH_4Cl.

Scheme 5.

Table 1. Results for aldol reactions of enolate (**9**).

Electrophile	Product	Yield %	C3/C4 (*trans/cis*)	Ratio C6 epimers
Acetone	**12a**	89	>95:5	-
Benzaldehyde	**12b**	77	>95:5	1:1.1
Acetophenone	**12c**	60	>95:5	1:1.4

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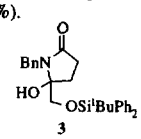
4. (a) Jackson, D. Y. *Synthetic Commun.* **1988**, *18*, 337. (b) Häfele, B.; Jäger, V. *Liebigs Ann. Chem.* **1987**, 85.
5. Unless otherwise stated, all new compounds discussed in this paper were fully characterised by ^1H NMR, ^{13}C NMR and IR spectroscopy; MS and microanalysis or high resolution mass spectrometry.
6. A 1,2-addition by-product (**3**) was also isolated (12%).



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8. It was found that during hydrolysis of (**2b**) and (**10**) some desilylation of the primary silyl ether occurs. This can be minimized by careful control of reaction time. Consequently the final product was sometimes contaminated by a small amount of the bis-^{t}BuMe$_2$Si ether. A small amount (≈5%) of epimerisation at C2 of (**10**) also occurred during hydrolysis.

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