Asymmetric Synthesis of the β-Lactam Framework *via* a Three-component Coupling Reaction

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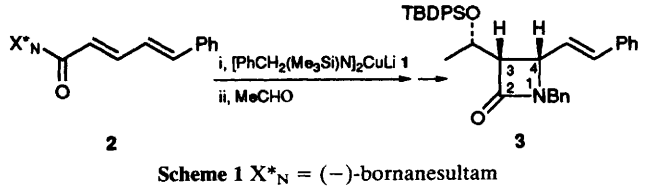
The reaction of the chiral lithium amide **4** with the dienoate **5a** provides regio- and stereo-selectively the β-amino ester **8** in essentially quantitative yield with >99% diastereoisomeric excess, which can be converted upon sequential treatment with $LiNPr^i_2$–$B(OMe)_3$–MeCHO to the key intermediate **6** for the β-lactam **7** having the correct absolute configuration.

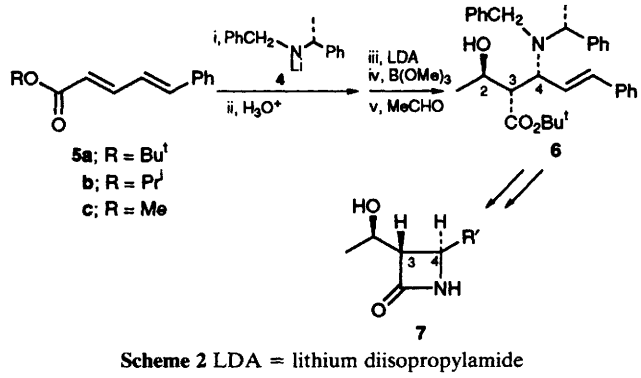
Since the discovery of 1β-methylcarbapenem, which possesses enhanced chemical and metabolic stability, much attention has been paid to the asymmetric synthesis of the β-lactam framework. We previously reported an entirely new approach to the synthesis of the β-lactam framework *via* a three-component coupling process;[1] the regioselective conjugate addition of the amide cuprate reagent **1** to α,β; γ,δ-unsaturated ester **2** having a sultam chiral auxiliary, followed by aldol condensation with acetaldehyde and subsequent manipulation gave the β-lactam **3** with high diastereoisomeric and enantiomeric excess (d.e. and e.e.) (Scheme 1).

The absolute stereochemistry at C-3 corresponds to that of natural β-lactams. The stereochemistry at C-4 and the hydroxyethyl unit, though opposite to that in the natural framework, can be converted to the correct configurations *via* the reported procedure.[2] However, it would be more desirable to directly construct the natural β-lactam framework *via* the three-component coupling method or a modification. We report that the following modified coupling process produces the correct absolute configurations at C-3, C-4 and the hydroxyethyl unit all at once: the conjugate addition of the chiral lithium amide **4** to α,β; γ,δ-unsaturated *tert*-butyl ester **5a**, followed by quenching the resulting enolate with saturated aqueous NH_4Cl solution and subsequent deprotonation of the β-amino ester with LDA, and addition of $B(OMe)_3$ and acetaldehyde gave **6**, which can be converted to **7**, with the stereochemistry of natural β-lactams, in high yield with high d.e. (Scheme 2). The success of this three-component coupling procedure is primarily due to the finding of Davies'



2 **3**

Scheme 1 X^*_N = (−)-bornanesultam



Scheme 2 LDA = lithium diisopropylamide

group that the conjugate addition of **4** to enoates proceeds with very high diastereoselectivity.[3]

First we examined the reaction of the lithium amide **4** with the dienoates **5**. Previously we observed that the reaction of certain lithium amides with enoates gave the conjugate addition product (1,4-adduct) along with the corresponding amide (1,2-adduct), and formation of the latter product was significantly diminished in the case of a sterically bulky ester group such as Pr^i.[1] However, the dienoates did not provide the 1,2-adducts (amides) upon treatment with **4**; regioselective 1,4-addition took place to give the corresponding β-amino esters in 98% isolated yield from **5a**, in 83% yield from **5b**, and in 81% yield from **5c**. In all cases only one diastereoisomer was produced. It should be noted that 1,6-addition does not take place; organocopper addition to dienoates often produces a mixture of 1,4- and 1,6-conjugate adducts.[4]

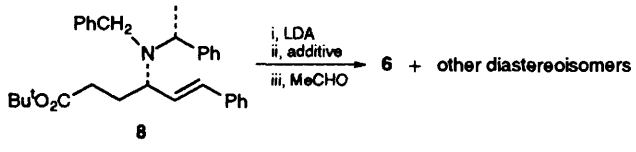
The β-amino ester **8**, obtained from **5a** in 98% yield with >99% d.e., was treated with 3 equiv. of LDA[5] in THF at 0 °C and the resulting mixture was stirred for 2 h at this temperature. The mixture was cooled to −78 °C and then acetaldehyde (10 equiv.) was added.[6,7] Although the aldol products, **6** and its diastereoisomers, were obtained in quantitative yield, the diastereoisomer ratio was not high (entry 1, Table 1). To enhance the diastereoselectivity of the aldol process, we examined several additives (Table 1; Scheme 3). The use of trialkylboranes[8] and butyl borate as an additive did not give a satisfactory result (entries 2–4). $Bu_2BOSO_2CF_3$, Et_3Al, Bu_3SnCl,[9] $ZnCl_2$ and $(C_5H_5)_2ZrCl_2$[10] also gave unsatisfactory results. Finally we found that the use of trimethyl borate produced the highest d.e. among the additives examined (entry 5). An attempt to generate *in situ* a boron enolate from **8** upon treatment with dibutylboron trifluoromethanesulfonate and triethylamine[11] resulted in failure.

The absolute stereochemistry at C-4 of **6** was determined as follows (Scheme 4). The reduction of **8** with $LiAlH_4$, followed by protection with the *tert*-butyldiphenylsilyl group, gave **9** in 86% yield. Hydrogenation in the presence of a catalytic amount of $Pd(OH)_2$ on carbon afforded **10**; $[\alpha]_D^{24}$ + 2.69 (*c* 1.16, $CHCl_3$). Authentic (3*R*)-benzylamino ester **11**[1] was reduced with $LiAlH_4$ and resulting alcohol was protected with TBDPSCl, giving **12** in 38% yield. Hydrogenation of **12** afforded **13**; $[\alpha]_D^{24}$ −2.81 (*c* 1.63, $CHCl_3$). Accordingly, it is clear that C-4 of **6** adopts the (*R*)-configuration.

Table 1 Reaction of **8** with acetaldehyde[a]

Entry	Additive (3 equiv.)	Product ratio **6**: other diastereomers	Isolated yield (%)
1	—	78:22	100
2	Bu_3B	81:19	72
3	Et_3B	86:14	82
4	$(BuO)_3B$	75:25	82
5	$(MeO)_3B$	91:9	89

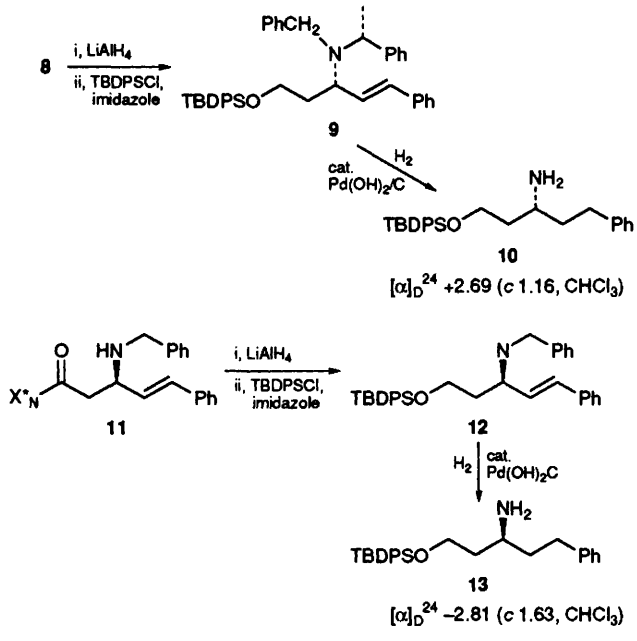
[a] The reaction was carried out on a 0.3 mmol scale. Treatment of **8** with 3 equiv. of LDA at 0 °C for 2 h, followed by cooling the reaction mixture at −78 °C produced the corresponding lithium enolate of **8**. The boron compounds were added at −78 °C and then the mixture was stirred for 30 min. Acetaldehyde was added at −78 °C, and the reaction was quenched after 15 min with sat. aqueous NH_4Cl solution.



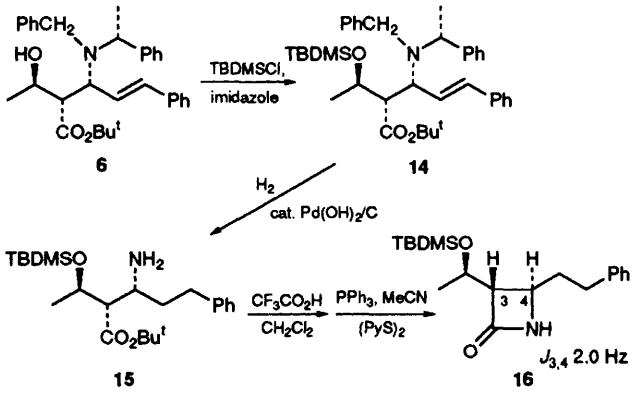
Scheme 3

The absolute stereochemistry at C-3 of **6** was determined unambiguously by derivatizing it to the β-lactam framework (Scheme 5). Protection of the hydroxy group of **6** with TBDMSCl gave **14** in 90% yield. Hydrogenation in the presence of a catalytic amount of $Pd(OH)_2$ on carbon produced **15** in 60% yield. Treatment with trifluoroacetic acid in CH_2Cl_2 followed by cyclization with PPh_3–$(PyS)_2$–MeCN[12] gave **16** in 55% yield. The coupling constant between H^3 and H^4 was 2.0 Hz, indicating *trans*-stereochemistry. The absolute stereochemistry of the hydroxyethyl unit (C-2 of **6**) was determined as follows (Scheme 6). The reduction of **6** with $LiAlH_4$ in ether gave **17** in 58% yield. Treatment with 2,2-dimethoxypropane in the presence of PPTS afforded **18** in 84% yield. NOEs were observed between H^b and H^a, H^b and H^c, H^b and H^d, and H^b and Me. The coupling constants between H^b and H^a, H^b and H^c, and H^b and H^d were 3.5 Hz (see **18'**). Accordingly, the H^b proton is assigned as equatorial. The Me group in **18'** is assigned to adopt an equatorial position to alleviate the 1,3-diaxial interaction with the acetonide methyl group.

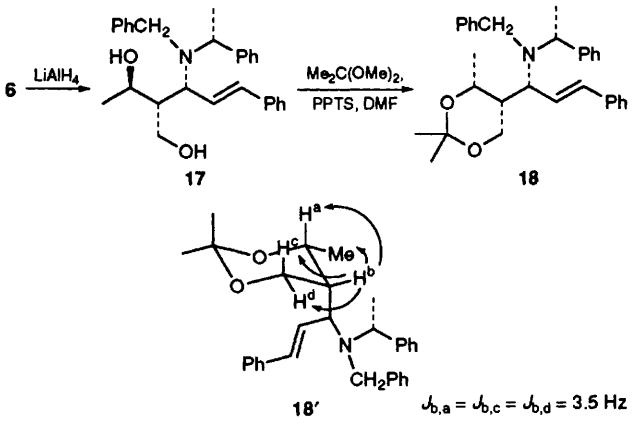
It is clear that the modified three-component coupling process *via* the chiral lithium amide **4** provides the β-lactam framework **7** having correct absolute configurations at C-3, C-4 and the hydroxyethyl unit. A remaining problem for the synthesis of 1β-methylcarbapenem key intermediates is to



Scheme 4 TBDPS = Bu^tPh_2Si; X^*_N = (−)-bornanesultam



Scheme 5 TBDMS = Bu^tMe_2Si; Py = 2-pyridyl



Scheme 6 PPTS = pyridinium toluene-*p*-sulfonate; DMF = dimethylformamide

accommodate an appropriate carbon chain in the R′ group of **7** and to control the diastereoselectivity in the 1,4-addition of metal amides. We are now pursuing such syntheses *via* the conjugate addition–aldol condensation.[13]

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