Use of lithium (α-methylbenzyl)allylamide for a formal asymmetric synthesis of thienamycin

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The highly stereoselective conjugate addition of lithium (α*R*)-(α-methylbenzyl)allylamide 3 to (*E*)-*tert*-butyl penta-2,4-dienoate 4, followed by a stereoselective aldol reaction with acetaldehyde, are the key steps in the synthesis of the known β-lactam intermediate, (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinylazetidin-2-one 2, for elaboration to thienamycin and its derivatives.

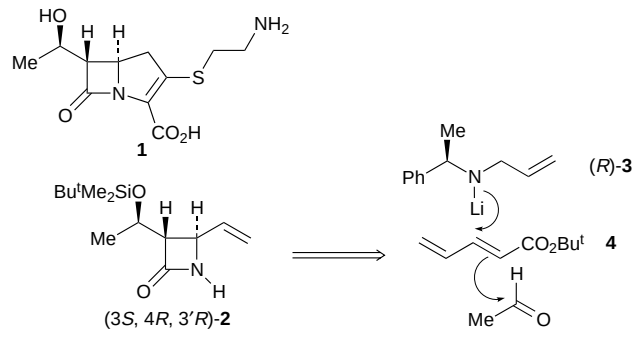
The carbapenems are an important class of β-lactam antibiotics with broad-spectrum potency and stability to β-lactamases. (+)-Thienamycin **1**, the first member of the family to be discovered,[1] has been the subject of numerous syntheses, with the *trans* stereochemistry of the protons in the β-lactam ring and the 3-[(*R*)-1-hydroxyethyl] side chain presenting a considerable synthetic challenge.[2] This key β-lactam framework is also found in the 1β-methylcarbapenems[3] and the tribactams,[4] antibiotics of current interest due to their enhanced chemical and metabolic stabilities.

A concise approach to this β-lactam framework is *via* a conjugate addition-aldol condensation strategy. Yamamoto *et al*. have used lithium *N*-benzyltrimethylsilylamide to give a key β-lactam intermediate as a single diastereomer,[5] but with the wrong absolute stereochemistry, and lithium (α-methylbenzyl)benzylamide,[6] developed in our laboratories, to give a β-lactam with the correct absolute stereochemistry but, due to the requirement of removing the *N*-benzyl groups by hydrogenation, without the possibility of incorporating an unsaturated side chain necessary for further synthetic elaboration.[7]

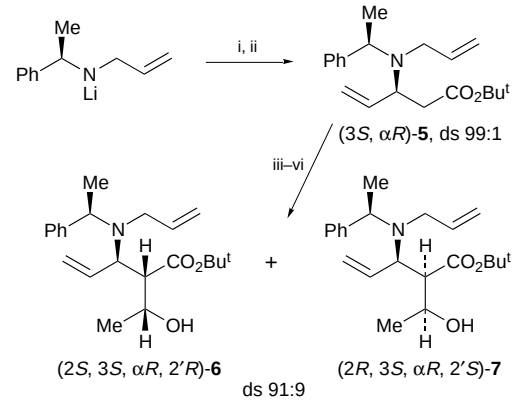
We have recently developed lithium (α*R*)-(α-methylbenzyl)allylamide **3** specifically for the synthesis of homochiral β-amino acids and β-lactams[8] and its application to the synthesis of carbapenem intermediates has already been demonstrated.[9] In particular, the use of this reagent to generate β-lactams with unsaturated side chains suggested its application in the synthesis of the known β-lactam intermediate, (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinylazetidin-2-one **2**[10,11] for the synthesis of thienamycin, *via* a conjugate addition–aldol condensation approach (Scheme 1).

Addition of lithium (α-methylbenzyl)allylamide (*R*)-**3** to (*E*)-*tert*-butyl penta-2,4-dienoate **4**,† followed by quenching with aqueous ammonium chloride, gave the β-amino adduct (3*S*,α*R*)-**5** in 87% yield with no 1,2- nor 1,6-addition being observed (Scheme 2). Analysis of the 500 MHz ^{1}H NMR spectrum of the crude addition product showed the diastereoselectivity (ds) to be 99 : 1. Treatment of the adduct (3*S*, α*R*)-**5** with LDA in THF at 0 °C for 2 h followed by cooling to −78 °C and quenching with acetaldehyde gave only two of the four possible diastereomeric aldol products, (2*S*,3*S*,α*R*,2′*R*)-**6** and (2*R*,3*S*,α*R*,2′*S*)-**7**, in a 4 : 1 ratio by analysis of the 500 MHz ^{1}H NMR spectrum of the crude reaction mixture. To improve the stereoselectivity of the aldol reaction a series of transmetallating reagents were investigated. The best selectivity was achieved using trimethyl borate, giving the same two diastereomers but with an improved ratio of 91 : 9 (Scheme 2), in accordance with the results from Asao *et al*. using lithium (α-methylbenzyl)benzylamide,[7] attesting to the structural similarity of the intermediate enolates. These were separable by flash chromatography to give (2*S*,3*S*,α*R*,2′*R*)-**6** as a single diastereomer in 75% yield.

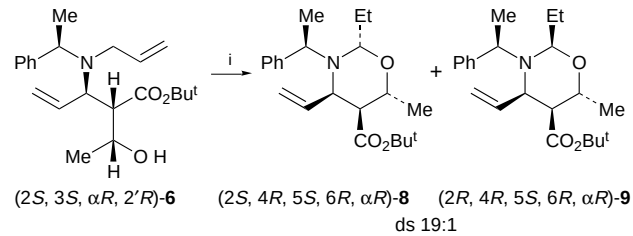
The absolute stereochemistry of (2*S*,3*S*,α*R*,2′*R*)-**6** was determined by treatment with tris(triphenylphosphine)rhodium(i) chloride in toluene under anhydrous conditions. This gave cyclisation to a 19:1 mixture of the perhydro-1,3-oxazines, (2*S*,4*R*,5*S*,6*R*,α*R*)-**8** and (2*R*,4*R*,5*S*,6*R*,α*R*)-**9**, diastereomeric at the newly formed C2 aminol centre, in 90% yield (Scheme 3). The cyclisation presumably occurs by intramolecular trapping of an intermediate imminium species, in equilibrium with the enamine generated in the isomerisation of the allyl double bond, by the 2′-hydroxy group.‡ Analysis of the coupling constants in the 500 MHz ^{1}H NMR spectrum of the major diastereomer



Scheme 1



Scheme 2 *Reagents and conditions*: i, CH_2=CHCH=$CHCO_2Bu^t$ **4**, ii, aq. NH_4Cl, 87%; iii, LDA, iv, $B(OMe)_3$, v, MeCHO, vi, aq. NH_4Cl, 82%



Scheme 3 *Reagents and conditions*: i, $(PPh_3)_3RhCl$, 90%

(2*S*,4*R*,5*S*,6*R*,α*R*)-**8** allowed determination of the two stereocentres formed in the aldol reaction (H_B-H_C, *J* 10.9 Hz, ax–ax coupling; H_C-H_D *J* 6.2 Hz, ax–eq coupling) and NOE analysis verified the expected equatorial stereochemistry of the ethyl group at the aminol centre (H_A–H_B, 16.4%) (Fig. 1).

Although treatment of this mixture of perhydro-1,3-oxazines with aqueous hydrochloric acid gave only the desired β-amino acid (2*S*,3*S*,α*R*,2′*R*)-**10** in 92% yield, verifying that they were diastereomeric only at C2, it proved more efficient to first remove the allyl group from the aldol product (2*S*,3*S*,α*R*,2′*R*)-**6** with tetrakis(triphenylphosphine)palladium(0) and *N*,*N*-dimethylbarbituric acid[12] to give the deallylated product in 98% yield. Since the deprotection proceeds *via* a π-allyl cation there is no opportunity for cyclisation to a perhydro-1,3-oxazine. Hydrolysis of the *tert*-butyl ester with trifluroacetic acid then gave the β-amino acid (2*S*,3*S*,α*R*,2′*R*)-**10** in 97% yield (Scheme 4). Despite its polar nature and the possibility of a zwitterionic form the acid was readily extracted into ethyl acetate, presumably because of its ability to intramolecularly hydrogen bond.

Treatment of β-amino acid (2*S*,3*S*,α*R*,2′*R*)-**10** with 2,2′-dipyridyl disulfide and triphenylphosphine[13] gave cyclisation to the β-lactam (3*S*,4*R*,α*R*,3′*R*)-**11** in 98% yield (Scheme 4). Protection of the hydroxy group with *tert*-butyldimethylsilyl chloride proceeded in 98% yield and was followed by removal of the *N*-α-methylbenzyl group using sodium in liquid ammonia[14] to give the known intermediate (3*S*,4*R*,3′*R*)-**2** in 95% yield. The specific rotation, $[\alpha]_D^{22}$ −25.9 (*c* 1.06, $CHCl_3$), of (3*S*,4*R*,3′*R*)-**2**, was in excellent agreement with the literature value, $[\alpha]_D^{25}$ −24.5 (*c* 1.05, $CHCl_3$), as was the spectroscopic data.§

In summary, the key β-lactam intermediate (3*S*,4*R*,3′*R*)-**2** for the synthesis of thienamycin and its derivatives has been synthesised in seven steps and 58% overall yield from lithium (α-methylbenzyl)allylamide (*R*)-**3** and (*E*)-*tert*-butyl penta-2,4-dienoate **4**. The highly diastereoselective conjugate addition of the lithium amide (*R*)-**3** to the unsaturated ester **4**, followed by a selective aldol reaction with acetaldehyde, constructed all three stereocentres with the correct absolute stereochemistry in two steps. Since the conjugate addition of the lithium amide has been shown to be highly selective to a wide range of α,β-unsaturated esters this methodology can be applied to the synthesis of the key β-lactam frameworks of a variety of carbapenems.

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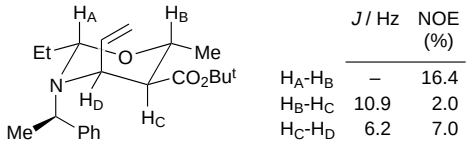
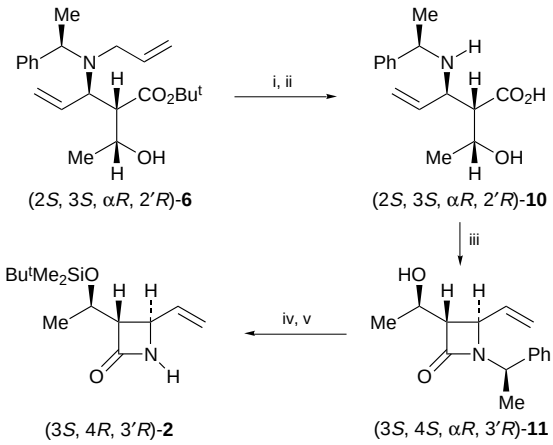


	J / Hz	NOE (%)
H_A-H_B	–	16.4
H_B-H_C	10.9	2.0
H_C-H_D	6.2	7.0

(2*S*, 4*R*, 5*S*, 6*R*, α*R*)-**8**

Fig. 1



(2*S*, 3*S*, α*R*, 2′*R*)-**6**

(2*S*, 3*S*, α*R*, 2′*R*)-**10**

(3*S*, 4*R*, 3′*R*)-**2**

(3*S*, 4*S*, α*R*, 3′*R*)-**11**

Scheme 4 *Reagents and conditions*: i, $Pd(PPh_3)_4$, NDMBA, 98%, ii, TFA, 97%; iii, $(PyS)_2$–PPh_3, 98%; iv, Bu^tMe_2SiCl, 98%; v, Na, NH_3 (l), 95%

Footnotes

† (*E*)-penta-2,4-dienoic acid was prepared by the Knoevenagel-type reaction of malonic acid with acrolein in the presence of pyridine, see: P. J. Jessup, C. B. Petty, J. Roos and L. E. Overman, *Org. Synth.*, 1988, **Coll. Vol. 6**, 95. The *tert*-butyl ester **4** was preapred from the acid using isobutylene and a catalytic amount of concentrated sulfuric acid. This bulky ester group prevents 1,2-addition of the lithium amide.

‡ An analagous cyclisation to form acetals has been observed in the isomerisation of allyl ethers to prop-1-enyl ethers using tris(triphenylphosphine)rhodium(i) chloride, R. Gigg and C. D. Warren, *J. Chem. Soc. C*, 1968, 1903.

§ (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinylazetidin-2-one **2** was isolated as a white crystalline solid; mp 62–63 °C; $[\alpha]_D^{21}$ −25.9 (*c* 1.06, $CHCl_3$); (Found: C, 61.24; H, 9.85; N, 5.17. $C_{13}H_{25}NO_2Si$ requires C, 61.13; H, 9.87; N, 5.48%); $\nu_{max}(CHCl_3/cm^{-1}$ 3415m (N–H), 2957m (C–H), 1762s (C=O); δ_H (300 MHz; $CDCl_3$) 6.02 (1 H, br s, NH), 5.96 (1 H, ddd, *J* 17.1, 10.3 and 6.8, C*H*=CH_2), 5.32 (1 H, d, *J* 17.1, *trans* CH=C*H*$_2$), 5.17 (1 H, d, *J* 10.3, *cis* CH=C*H*$_2$), 4.10–4.30 (2 H, m, CHOSi, NC*H*CH), 2.89 (1 H, dd, *J* 4.4 and 2.4, NCHC*H*), 1.22 (3 H, d, *J* 6.3, CH_3CO), 0.88 [9 H, s, $(CH_3)_3CSi$], 0.08 [6 H, s, $(CH_3)_2Si$]; δ_C (50 MHz) 169.1 (C=O), 137.8 (*C*H=CH_2), 116.5 (CH=*C*H$_2$), 65.8, 65.3 (CHOSi, NCH), 52.2 (CHCO), 25.6 [C(*C*H$_3$)$_3$], 22.2 (*C*H$_3$CO), 17.8 [*C*(CH$_3$)$_3$], −4.4, −5.2 [Si(CH$_3$)$_2$]; *m*/*z* (CI, NH_3) 256 (MH^+, 100%). For comparative data see ref. 11. All other compounds exhibited satisfactory analytical and spectroscopic data.

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