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The use of lithium (α-methylbenzyl)allylamide for the asymmetric synthesis of unsaturated β-amino acid derivatives

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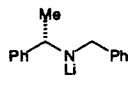
Abstract: The unsaturated β-amino acid derivatives (3*R*)-(*E*)-3-(*N*-*tert*-butoxycarbonyl)aminohex-4-enoate and methyl (2*S*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)-amino-2-hydroxyhex-4-enoate have been synthesised from lithium (*S*)-(α-methylbenzyl)allylamide and (*E*,*E*)-*tert*-butyl hex-2,4-dienoate. After a highly stereoselective conjugate addition of the lithium amide to the α,β-unsaturated ester, or a highly stereoselective conjugate addition–electrophilic hydroxylation, the adducts are deallylated and the resulting secondary amines converted to either a benzoyl amide or oxazolidinone. The *N*-α-methylbenzyl group is then removed with either formic acid or using a dissolving metal reduction. These deprotection procedures leave unsaturation in the molecules intact. © 1997 Elsevier Science Ltd

One of the more versatile approaches for the synthesis of homochiral β-amino acids is via the stereoselective conjugate addition of lithium amides to α,β-unsaturated acceptors.[1] We have demonstrated the utility of the highly stereoselective conjugate addition of lithium (α-methylbenzyl)benzylamide **1** (Figure 1) to α,β-unsaturated esters for the synthesis of a wide range of β-amino acid derivatives.[2] However, since removal of the benzyl groups from the addition products requires hydrogenolysis, the amide **1** cannot be used for the synthesis of unsaturated β-amino acid derivatives. Since unsaturated β-amino acids occur in nature, such as ADDA **2** (Figure 1) in the antibiotics cyanovirifin RR, nodularin and microcystin LR,[3] it was desirable to bring their synthesis within the scope of our lithium amide methodology.



(*S*)-**1**

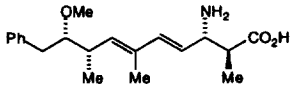


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Figure 1.

More recently we have demonstrated the use of lithium (α-methylbenzyl)allylamide (*S*)-**3** (Figure 2) for the synthesis of homochiral β-amino acids and β-lactams.[4–6] In the addition products resulting from its highly stereoselective conjugate addition, the *N*-allyl group is removable in the presence of the *N*-α-methylbenzyl group by treatment with tris(triphenylphosphine)rhodium(I) chloride and the resulting secondary β-amino esters can be cyclised to β-lactams. The *N*-α-methylbenzyl group can then be removed from the β-lactams using a dissolving metal reduction, even in the presence of unsaturated side chains, and the resulting deprotected β-lactams can be potentially hydrolysed to unsaturated β-amino acid derivatives. However, we desired a more efficient approach to these β-amino acid derivatives and also a methodology for the synthesis of unsaturated α-hydroxy-β-amino acid derivatives. In this communication we demonstrate the use of lithium (α-methylbenzyl)allylamide (*S*)-

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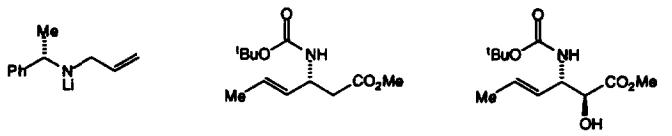
3 for the synthesis of (3*R*)-(*E*)-3-(*N*-*tert*-butoxycarbonyl)aminohex-4-enoate **4** and methyl (2*S*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)-amino-2-hydroxyhex-4-enoate **5** (Figure 2).

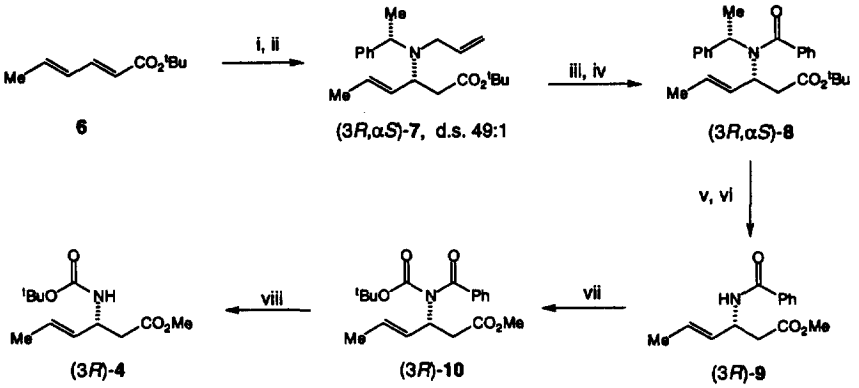


(*S*)-**3** (3*R*)-**4** (2*S*,3*S*)-**5**

Figure 2.

Addition of the lithium amide (*S*)-**3** to (*E*,*E*)-*tert*-butyl hex-2,4-dienoate **6**[7] in THF at −78°C for 1 hour gave the β-amino ester (3*R*,α*S*)-**7** in 78% yield, with no 1,2- or 1,6-addition being observed (Scheme 1). The diastereoselectivity was determined by analysis of the 500 MHz ^{1}H NMR spectrum of the crude addition product with integration of the ABX system for the α-methylene protons of each diastereoisomer showing the de to be 96%. Treatment of the adduct (3*R*,α*S*)-**7** (de 96%) with tris(triphenylphosphine)rhodium(I) chloride in acetonitrile–water[8] cleanly gave the deallylated product in 92% yield which was then converted into the amide (3*R*,α*S*)-**8** in 95% yield using benzoyl chloride, triethylamine and a catalytic amount of DMAP. Although the β-amino ester (3*R*,α*S*)-**7** possesses two double bonds in an allylic disposition to the nitrogen atom, no isomerisation of the main chain double bond was observed. This is in accord with the observation that an allyl ether can be selectively isomerised in the presence of a but-2-enyl ether.[9] Removal of the *N*-α-methylbenzyl group from (3*R*,α*S*)-**8** was first attempted by treatment with sodium in liquid ammonia, in an analogous fashion to the deprotection of *N*-benzyl β-lactams,[10] but was unsuccessful. However, heating (3*R*,α*S*)-**8** in neat formic acid at 60°C for 16 hours[11] gave clean removal of the *N*-α-methylbenzyl group and the *tert*-butyl ester, but left the double bond intact. Rather than isolate the intermediate water soluble acid it was converted to the methyl ester (3*R*,α*S*)-**9** with thionyl chloride and methanol in 89% overall yield for the two steps (Scheme 1). Although the benzoyl amide was required for removal of the *N*-α-methylbenzyl group it is not a convenient protecting group for the amine because of the harsh conditions required for deprotection. However, conversion of the amide to a carbamate enables the benzoyl group to be removed using milder conditions. Treatment of the amide (3*R*)-**9** with di-*tert*-butyl dicarbonate, triethylamine and DMAP gave the carbamate (3*R*)-**10** in 93% yield from which the benzoyl group could be removed by treatment with sodium methoxide in methanol to give the unsaturated β-amino acid derivative (3*R*)-**4** in 87% yield, protected with the synthetically more useful *tert*-butoxycarbonyl group (Scheme 1).[12]

Addition of the lithium amide (*S*)-**3** to (*E*,*E*)-*tert*-butyl hex-2,4-dienoate **6** in THF at −78°C for 1 hour followed by the addition of solid (+)-(camphorsulfonyl)oxaziridine gave the α-hydroxy-β-amino adduct (2*S*,3*S*,α*S*)-**11** in 72% yield (Scheme 2). The diastereoselectivity was determined by analogy with previous hydroxylations performed using this methodology.[13] Analysis of the 500 MHz ^{1}H NMR spectrum of the crude addition product showed only two diastereoisomers and integration of the doublets for the C_α protons showed the de to be 96%. The adduct (2*S*,3*S*,α*S*)-**11** (de 96%) was then deallylated using tetrakis(triphenylphosphine)palladium(0) and *N*,*N*-dimethylbarbituric acid[14] in 96% yield. The use of tris(triphenylphosphine)rhodium(I) chloride in acetonitrile–water for the deallylation is not appropriate in this case since intramolecular quenching of the intermediate imminium species by the 2-hydroxyl group to give an oxazolidine is faster than hydrolysis by water to give the deprotected secondary amine.[15] Although the deallylated adduct could now be dibenzoylated and the *N*-α-methylbenzyl group removed by treatment with formic acid, the opportunity also exists for its conversion to an oxazolidinone and removal of the *N*-α-methylbenzyl group by a dissolving metal reduction, as for *N*-benzylated β-lactams. Thus treatment of the deallylated adduct with 1,1′-carbonyldiimidazole gave the oxazolidinone (4*S*,5*S*,α*S*)-**12** in 96% yield (Scheme 2). Since



Scheme 1. *Reagents and conditions*: i, (*S*)-**3**, ii, aq. NH_4Cl, 78%; iii, $(PPh_3)_3RhCl$ 92%; iv, PhCOCl, Et_3N, DMAP, 95%; v, HCO_2H, 60°C, vi, $SOCl_2$, MeOH, (89% for v and vi); vii, $(^tBuOCO)_2O$, Et_3N, DMAP, 93%; viii, NaOMe, MeOH, 87%.

the coupling constant of vicinal ring protons in oxazolidinones has been shown to be reliably characteristic of both *cis* and *trans* stereochemistry,[16] the coupling constant between the C4 and C5 protons in (4*S*,5*S*,α*S*)-**12** of *J* 9.0 Hz corresponds to *cis* vicinal ring protons, confirming the *anti* selectivity of the hydroxylation step. In an attempt to remove the *N*-α-methylbenzyl group the oxazolidinone (4*S*,5*S*,α*S*)-**12** was treated with lithium in liquid ammonia. Analysis of the crude ^1H NMR spectrum, however, showed a product still containing the *N*-α-methylbenzyl group but without the *tert*-butyl ester and with cleavage of the oxazolidinone ring, suggesting that the ester group was acting as a more efficient electron acceptor than the benzyl group. The oxazolidinone (4*S*,5*S*,α*S*)-**12** was therefore[17] first treated with trifluoroacetic acid, hydrolysing the *tert*-butyl ester to the acid in 98% yield. Treatment of this acid with lithium in liquid ammonia would be expected to generate a lithium carboxylate thereby preventing the carbonyl group from acting as an electron acceptor. Indeed, treatment of the acid with lithium in liquid ammonia gave clean removal of the *N*-α-methylbenzyl group and left the prop-1-enyl side chain intact. The intermediate water soluble acid was then converted to the methyl ester (4*S*,5*S*)-**13** with thionyl chloride and methanol, in 89% overall yield for the two steps (Scheme 2). Classical methods for the hydrolytic conversion of cyclic carbamates to their corresponding amino alcohols are harsh and generally lead to undesirable side reactions such as β-elimination and epimerisation. However, a very mild method of cleaving *N*-(*tert*-butoxycarbonyl)oxazolidinones has been reported using caesium carbonate in methanol at room temperature.[18] The oxazolidinone (4*S*,5*S*)-**13** was therefore treated with di-*tert*-butyl dicarbonate to give the *N*-(*tert*-butoxycarbonyl)oxazolidinone (4*S*,5*S*)-**14** in 92% yield followed by treatment with caesium carbonate in methanol to give the desired methyl (2*S*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)-amino-2-hydroxyhex-4-enoate **5** in 86% yield (Scheme 2).[19]

In summary, we have demonstrated the application of lithium (α-methylbenzyl)allylamide **1** for the synthesis of the homochiral unsaturated β-amino acid derivatives (3*R*)-(*E*)-3-(*N*-*tert*-butoxycarbonyl)aminohex-4-enoate **4** and methyl (2*S*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)-amino-2-hydroxyhex-4-enoate **5** previously inaccessible using lithium (α-methylbenzyl)benzylamide **1**.

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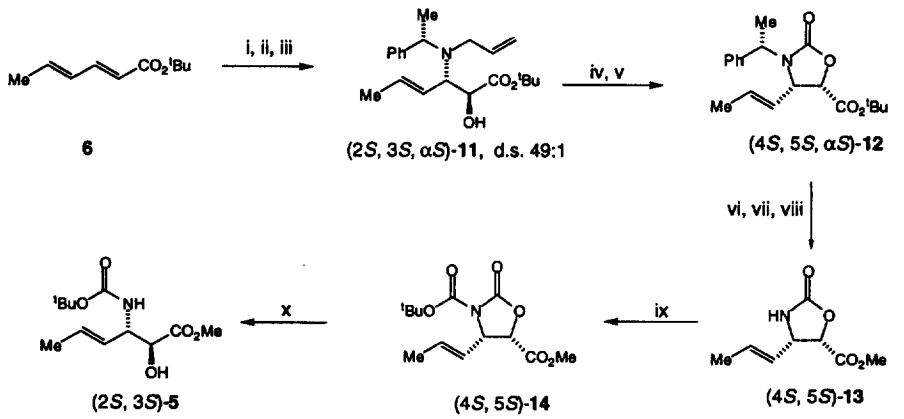

Scheme 2. *Reagents and conditions*: i, (*S*)-**1**, ii, (+)-(camphorsulfonyl)oxaziridine, iii, aq. NH_4Cl, 72%; iv, $Pd(PPh_3)_4$, NDMBA, 96%; v, 1,1′-carbonyldiimidazole, 96%; vi, TFA, 98%, vii, Li, NH_3 (l), EtOH, viii, $SOCl_2$, MeOH, 86%; ix, $(^tBuOCO)_2O$, Et_3N, DMAP, 92%; x, Cs_2CO_3, MeOH, 86%.

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12. (3*R*)-(*E*)-3-(*N*-*tert*-butoxycarbonyl)aminohex-4-enoate **4** was isolated as a colourless oil; $[\alpha]_D^{24}$ −8.5 (*c* 1.73, $CHCl_3$); (Found: C, 59.67; H, 8.50; N, 5.89. $C_{12}H_{21}NO_4$ requires C, 59.24; H, 8.70; N, 5.76%); ν_{max} (film)/cm^{-1} 3359bm (NH), 2978s (CH), 1714s (C=O), 1515s (NC=O); δ_H (300 MHz; $CDCl_3$) 5.64 (1H, ddq, *J* 15.3, 6.6 and 1.1, CH_3CH=CH), 5.44 (1H, ddq, *J* 15.3, 6.1 and 1.5, CH_3CH=C*H*), 5.09 (1H, br s, N*H*), 4.46–4.41 (1H, m, NC*H*CH_2), 3.67 (3H, s, CO_2CH_3), 2.58 (1H, d, *J* 5.7, CH_2CO_2), 1.67 (3H, dd, *J* 7.6 and 1.1, CH_3CH=CH), 1.43[9H, s, $C(CH_3)_3$]; δ_C (50 MHz; $CDCl_3$) 172.0, 155.3 (NCOPh, CO_2CH_3), 130.2, 127.0 (CH_3CH=CH), 79.3 [$C(CH_3)_3$], 51.5 (CO_2CH_3), 48.9 (NCH), 39.5 (CH_2CO), 28.2 [$C(CH_3)_3$], 17.4 (CH_3CH=CH); *m/z* (CI) 244 (MH^+, 10%), 144 (100%). All other compounds in Scheme 1 exhibited satisfactory spectroscopic and analytical data.
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19. Methyl (2*S*,3*S*)-(*E*)-3-(*N*-*tert*-butoxycarbonyl)amino-2-hydroxyhex-4-enoate **5** was isolated as a white, crystalline solid; m.p. 75–76°C; $[\alpha]_D^{23}$ +15.5 (*c* 1.50, $CHCl_3$); (Found: C, 55.70; H, 8.39; N 5.17. $C_{12}H_{21}NO_5$ requires C, 55.58; H, 8.16; N, 5.40); ν_{max} (KBr disc)/cm^{-1} 3400bm (OH), 3356s (NH), 1740s, 1687s, 1531s (C=O); δ_H (300 MHz; $CDCl_3$) 5.71 (1H, ddq, *J* 15.2, 6.6 and 1.1, CH_3CH=CH), 5.33 (1H, ddq, *J* 15.2, 7.2 and 1.6, CH_3CH=C*H*), 5.04 (1H, br d, *J* 7.6, N*H*), 4.56–4.45 1H, br m, NC*H*CHO), 4.37 (1H, d, *J* 3.1, NCHC*H*O), 3.79 (3H, s, CO_2CH_3), 1.68 (3H, d, *J* 6.6, CH_3CH=CH), 1.45 [9H, s, $C(CH_3)_3$]; δ_C (50 MHz; $CDCl_3$) 173.2 (CO_2CH_3), 155.4 (OCON), 130.1 (CH_3CH=*C*H), 125.2 (CH_3CH=CH), 79.8 [$C(CH_3)_3$], 73.2 (*C*HO), 55.0, 52.6 (OCH_3, NCH), 28.2 [$C(CH_3)_3$], 17.7 (CH_3CH=CH); *m/z* (CI, NH_3) 260 (MH^+, 10%), 70 (100%). The resonances due to the C2, C3 and NH protons were all broadened in the ^1H NMR spectrum due to restricted rotation about the amide bond, even at 70°C. All other compounds in Scheme 2 exhibited satisfactory spectroscopic and analytical data.

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