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Selective Deprotection Strategies to *N*-(α-methylbenzyl)-β-amino Esters and Derived β-Lactams

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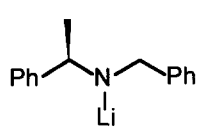
Abstract: A variety of *N*,*N*-diprotected β-amino esters, prepared by highly diastereoselective conjugate addition of chiral lithium amides, were selectively mono-deprotected under either reductive (hydrogenolysis) or oxidative (DDQ or CAN) conditions. Combined with these deprotection methods, lithium (α-methylbenzyl)(3,4-dimethoxybenzyl) amide **2** can be used as an efficient differentially protected chiral ammonia equivalent for the asymmetric synthesis of β-amino acid and β-lactam derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

Previously, we have demonstrated that lithium (α-methylbenzyl)benzylamide **1** and lithium (α-methylbenzyl)(3,4-dimethoxybenzyl)amide **2** are extremely useful chiral ammonia equivalents for the asymmetric synthesis of β-amino acids and derivatives.[2,3] The two benzyl groups attached to the β-amino nitrogen could be readily removed by hydrogenolysis and, if required, the resulting free amino position can be re-protected for further synthetic transformation. However, for the asymmetric synthesis of β-lactams, a range of methods compatible with a variety of functional groups is desirable for the selective removal of one of the two benzyl groups so that *N*-protected β-lactams can be formed directly. For this purpose, we have reported lithium (α-methylbenzyl)allylamide **3** as a differentially protected chiral ammonia equivalent, whose allyl group can be readily removed by either a palladium or rhodium catalysed deallylation reaction.[4,5] Herein, we wish to describe convenient alternative procedures to the asymmetric synthesis of *N*-protected β-lactams.



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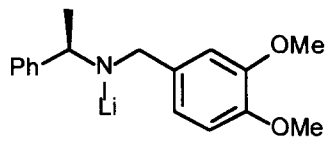

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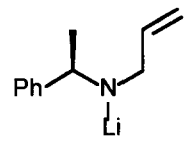

3

The β-amino butanoate derivatives **4** (95% de), **5** (94% de) and **6** (>99% de) were prepared by highly diastereoselective conjugate addition of the corresponding lithium amides.[2] During the attempts on debenzylation of these adducts by hydrogenolysis using $Pd(OH)_2/C$ (Pearlman's catalyst), we found that the reaction was highly selective, if carried out under mild conditions. Treatment of **4**, **5** and **6** with the catalyst (<10 wt%) under atmospheric pressure of hydrogen in methanol cleaved only one of the two benzyl groups highly selectively to give **7** and **8** (Scheme 1).[16] One similar observation has been noted recently by Kocienski.[6] Generally, the ease of hydrogenolysis of a benzyl group increases in the series: primary < secondary < tertiary amine.[7-9] The remarkable selectivity we observed is in accordance with this trend and is explained in terms of strain release in the formation of the π-benzyl complexes on the catalyst surface.[8] The ease of the cleavage from the tertiary amines was found to be benzyl > α-methylbenzyl > 3,4-

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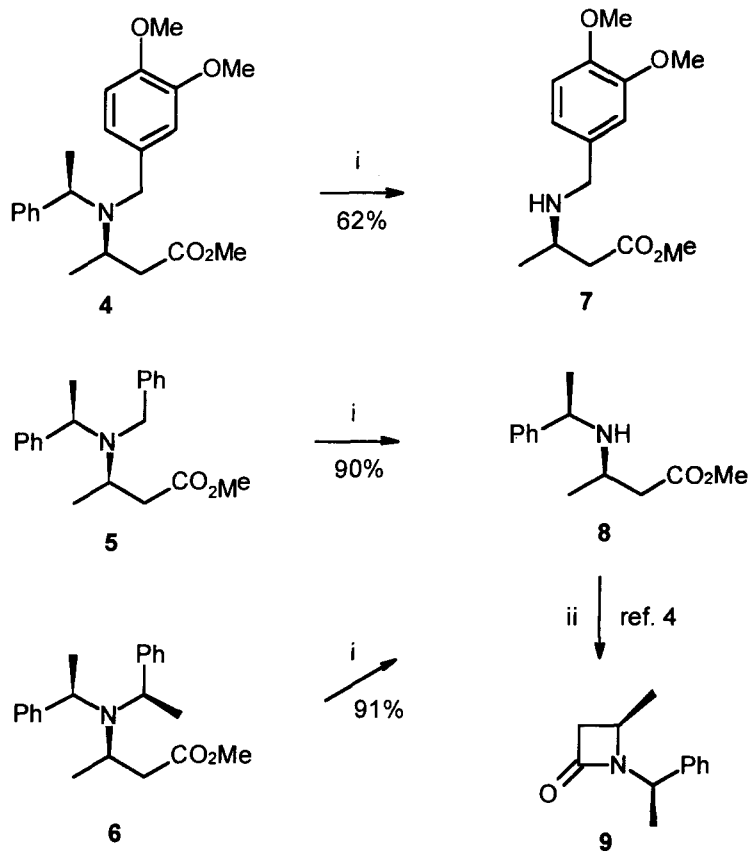


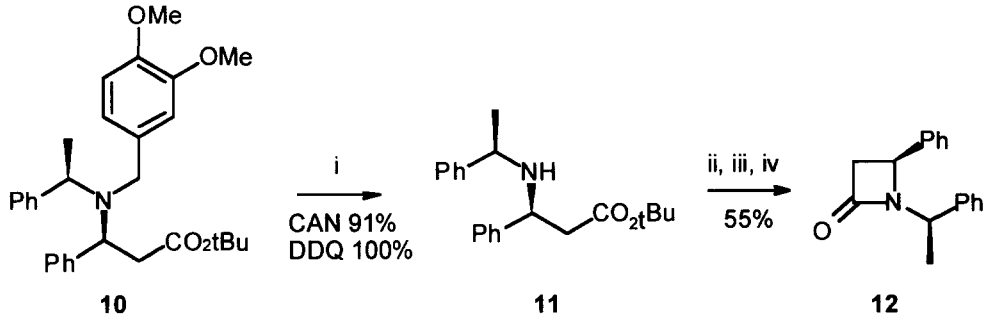
Scheme 1. *Reagent:* i) H_2 1atm, $Pd(OH)_2/C$, methanol; ii) ref 4 (MeMgBr)

dimethoxybenzyl. Strong deactivation effects of alkoxy groups on hydrogenolysis of benzyl groups have also been reported by Bringmann and co-workers.[10] Higher catalyst load and hydrogen pressure were required for cleavage of both benzyl groups. The β-amino ester **8** can be readily converted to the *N*-protected β-lactam **9** by treatment with methylmagnesium bromide.[4]

Although selective mono-debenzylation of the conjugate adducts could be readily achieved, this method can not be applied to the compounds with functionalities that are incompatible with hydrogenolysis conditions. Methoxy-substituted benzyl groups are widely used for protection of alcohols, and can be cleaved in the presence of benzyl ether by oxidative treatment with ceric ammonium nitrate (CAN) or DDQ.[11] Therefore, the 3,4-dimethoxybenzyl groups of the conjugate adduct might be removed oxidatively to afford the β-amino derivatives, cyclization of which would give the *N*-protected β-lactams. Although removal of 4-methoxybenzyl protecting groups from carboxamides or sulphonamides under acidic or oxidative conditions has been described in the literature,[12-15] the oxidative removal of methoxybenzyl groups from alkyl amines which are not activated by electron withdrawing groups is apparently less common.

Thus, oxidative removal of the dimethoxybenzyl group of **10** (97%de) using DDQ was examined. DDQ was added to a solution of **10** in dichloromethane-water (5:1) and the resulting dark red solution stirred at room temperature overnight, during which time a pale yellow hydroquinone derivative was precipitated. After workup, column chromatography on alumina afforded a nearly quantitative yield of de-methoxybenzylated product **11** and 3,4-dimethoxybenzaldehyde. Treatment with CAN in acetonitrile/water 5:1 also cleaved the 3,4-dimethoxybenzyl group in excellent yield. The *t*-butyl ester **11** was then transformed into its methyl ester

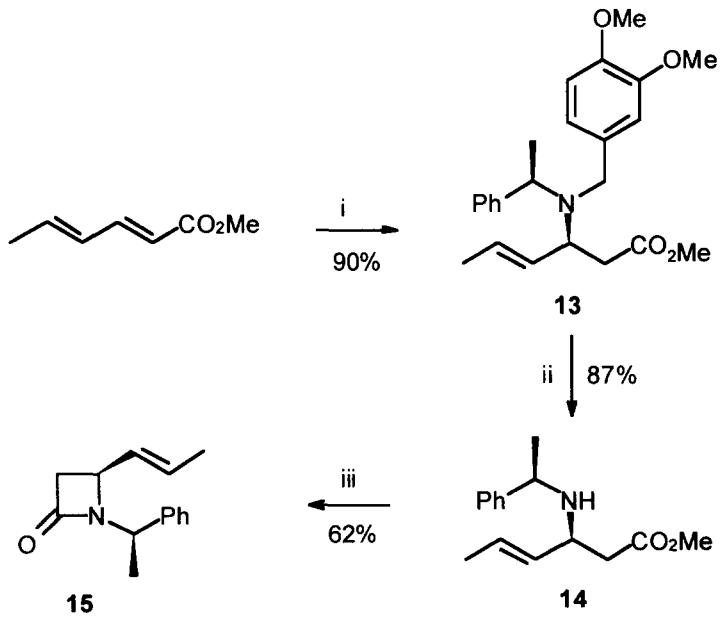
by acid hydrolysis followed by esterification using thionyl chloride in methanol. Cyclization of the methyl ester was effected by treatment with methylmagnesium bromide to afford *N*-protected β-lactam (4*S*,α*R*)-**12** {$[\alpha]_D^{20}$ -55.9 (c 1.06, $CHCl_3$), lit.[4] for (4*R*,α*S*)-**12** $[\alpha]_D^{20}$ +57.9 (c 1.06, $CHCl_3$)} as a single diastereoisomer in 55% yield for the three steps (Scheme 2).



Scheme 2. *Reagents*: i) DDQ, DCM/water 5:1, or CAN MeCN/water 5:1; ii) TFA; iii) $SOCl_2$, MeOH; iv) MeMgBr

β-Lactams containing functional groups, such as alkenes, which are incompatible with hydrogenolysis conditions should be accessible using these procedures. This was demonstrated by the synthesis of the β-lactam **15**. The conjugate addition of the lithium amide **2** to methyl sorbate was highly selective giving **13** with 96% de. The conjugate adduct **13** was then transformed into **14** in good yield (87%) by CAN-promoted de-methoxybenzylation. Cyclization of **14** by treatment with methylmagnesium bromide provided the β-lactam (4*S*,α*R*)-**15** in 62% yield {$[\alpha]_D^{20}$ +38.7 (c 0.98, $CHCl_3$), lit.[4] for (4*R*,α*S*)-**15** $[\alpha]_D^{20}$ -39.4 (c 1.02, $CHCl_3$)} as a single diastereoisomer.

In conclusion, we have found that the β-amino ester derivatives **4**, **5** and **6**, obtained *via* diastereoselective conjugate addition of chiral lithium amides, could be selectively mono-debenzylated by hydrogenolysis to afford the β-amino ester derivatives, cyclization of which gives *N*-protected β-lactams. We have also shown that the 3,4-dimethoxybenzyl group of the conjugate adducts **10** and **13** can be readily removed in an oxidative



Scheme 3. *Reagent:* i) (*R*)-**2**; ii) CAN, MeCN/Water; iii) MeMgBr

manner using CAN or DDQ in excellent yield. These selective deprotection methods enable the lithium (α-methylbenzyl)(3,4-dimethoxybenzyl)amide **2** to be used as an efficient differentially protected chiral ammonia equivalent for the asymmetric synthesis of β-amino acid and β-lactam derivatives *via* the conjugate addition strategy.

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