Pergamon

Tetrahedron Letters 41 (2000) 2851–2854

TETRAHEDRON LETTERS

Diastereoselective amination of vinylic sulfoximines: application to the asymmetric synthesis of functionalized β-substituted and β,β-disubstituted β-amino acids, and of γ-amino alcohols

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Received 2 February 2000; accepted 15 February 2000

Abstract

An asymmetric synthesis of protected β-substituted and β,β-disubstituted β-amino acids, which carry a hydroxyalkyl side chain, from sulfonimidoyl functionalized homoallylic alcohols is described. The method allows for an asymmetric synthesis of γ-amino alcohols as well.

β-Peptides are currently of high interest because of their structure and biological activities.[1] Recently, β,β-disubstituted β-peptides have attracted attention due to novel secondary structures hitherto not observed for β-peptides.[2] Besides the β,β-disubstituted β-peptides, those carrying a hydroxy group in the side chain would be of particular interest because of the synthesis of glyco-β-peptides as analogs of glyco-α-peptides which are of high biological relevance.[3] Whereas numerous methods exist for the asymmetric synthesis of β-substituted β-amino acids,[4,5] we are aware of only one method giving access to β,β-disubstituted β-amino acids.[5c,5f,6] We now describe a method for the asymmetric synthesis of β-substituted and β,β-disubstituted β-amino acids of type **A**[5a,5g] and **B**, which carry a hydroxyalkyl side chain, from sulfonimidoyl functionalized *anti*-homoallylic alcohols of type **C**[7] and **D**[7] (Scheme 1). The δ-hydroxy β-amino acids **A** and **B** may not only serve as starting materials for the synthesis of β-peptides and their glycosides but also for that of analogs of sperabillin and negamycin which are peptide-like natural products with interesting biological activities.[8] An additional feature of the method described is that it also provides for an asymmetric synthesis of substituted γ-amino alcohols which have found much use in the synthesis of biologically active compounds.[9]

Treatment of the enantio- and diastereopure hydroxy sulfoximines **1a**[7] and **1b**[7] with trichloroacetyl isocyanate followed by the cleavage of the corresponding intermediate *N*-trichloroacetyl carbamates with aqueous NH_3 gave the carbamates **2a** (90%) and **2b** (85%),[10a] respectively (Scheme 2). A similar successive treatment of the enantio- and diastereopure hydroxy sulfoximine **4**[7] with trichloroacetyl isocyanate and NH_3 furnished the carbamate **5** (94%). Reaction of carbamates **2a** and **2b**[10b] with

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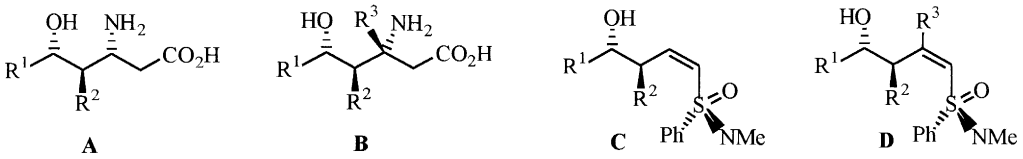
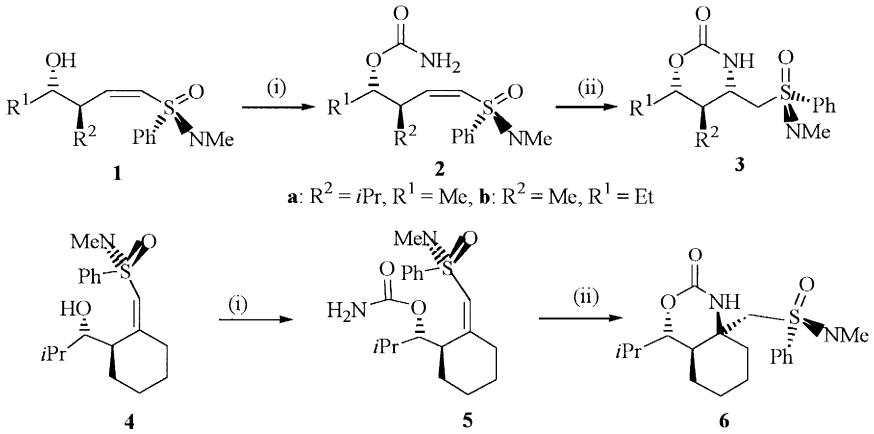
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00307-5



Scheme 1.

*n*BuLi at low temperatures and warming the reaction mixtures to room temperature led to a smooth Hirama–Itô[11] cyclization to afford, after aqueous work-up, the cyclic carbamates **3a** (94%)[12] and **3b** (93%),[12] respectively, each as a single diastereomer (≥98% de).[13,14] A similar cyclization of the β,β-disubstituted carbamate **5** also proceeded readily and gave after aqueous work-up the bicyclic carbamate **6** (92%)[12] as a single diastereomer (≥98% de). The configurations of carbamates **3a**, **3b** and **6** were determined by ^{1}H NMR spectroscopy in combination with NOE experiments and X-ray structure analysis of derivatives thereof (vide infra).

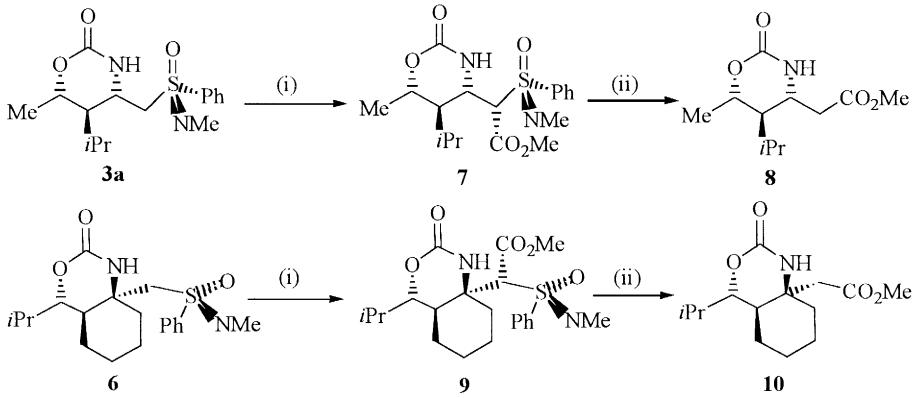


Scheme 2. (i) 1. $Cl_3CCONCO$, THF, 22°C, 2 h; 2. NH_3 (aq), 22°C, 10−18 h. (ii) 1. 1.1 equiv. of *n*BuLi, THF, −78°C→22°C, 10−18 h; 2. H_3O^+

For the synthesis of amino acids from **3a**, **3b** and **6** the introduction of a carboxyl group at the α-position of the sulfonimidoyl group was required. Key to the realization of this transformation was the observation that the double lithiation of **3a**, **3b** and **6** with *n*BuLi proceeded readily to give quantitatively the dilithium salts Li_2-**3a**, Li_2-**3b** and Li_2-**6**, respectively, being stable at low temperatures in solution.

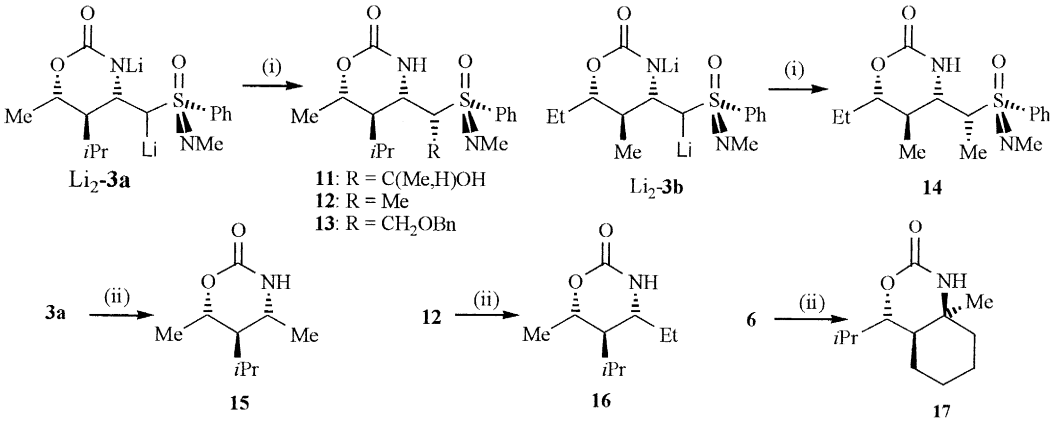
The reaction of Li_2-**3a** and Li_2-**6** with ClCOOMe[15] gave the ester **7** (66%) as a mixture of diastereomers (84:16) and the ester **9** (70%)[12] as a single diastereomer, respectively (Scheme 3). The configurations of the new stereogenic center of esters **7** and **9** were provisionally assigned as depicted based on NMR spectroscopic investigations. The conversion of sulfoximines **7** and **9** to the protected amino acids **8** and **10**, respectively, called for a reductive removal of the sulfonimidoyl group, which was best accomplished with Raney nickel.[16] Thus, reaction of **7** and **9** with Raney nickel furnished the protected β-substituted β-amino acid **8** (90%)[12] and the β,β-disubstituted β-amino acid **10** (86%),[12] respectively (Scheme 3). The configuration of the ester **10** was established by X-ray structure analysis.[17]

The above results prompted us to also investigate the synthesis of functionalized γ-amino alcohols from sulfoximines of type **3a** and **6**. Thus, reaction of Li_2-**3a** with MeCHO afforded the hydroxy sulfoximine **11** (67%, 28% de) as a mixture of only two diastereomers which are presumably epimers in regard to the C atom bearing the hydroxy group. Treatment of Li_2-**3a** with MeI and $BnOCH_2Cl$ furnished with modest diastereoselectivities the substituted sulfoximines **12** (68% de) and **13** (de not



Scheme 3. (i) 1. 2.2 equiv. of *n*BuLi, THF, −78°C; 2. $ClCO_2Me$, −78°C, 4 h. (ii) Ra-Ni, THF, H_2O, 22°C, 8 h

determined), respectively. The methylation of the dilithium salt Li_2-**3b** with MeI proceeded with a higher diastereoselectivity and gave the methylated sulfoximine **14** (80% de). Sulfoximines **12**–**14**[12] were easily obtained diastereomerically pure by chromatography in 75%, 70% and 68% yield, respectively, based on the starting sulfoximines. The configurations of the newly generated stereogenic center of **11**–**14** were determined by NOE experiments. This assignment was verified in the case of **12** by X-ray structure analysis.[17] Finally, treatment of **3a**, **12** and **6** with Raney nickel under similar conditions as used above afforded the protected γ-amino alcohols **15** (88%),[12] **16** (79%)[12] and **17** (90%),[12] respectively (Scheme 4).



Scheme 4. (i) MeCHO, MeI or $BnOCH_2Cl$, THF, −78°C. (ii) Ra-Ni, THF, H_2O, 22°C, 5−18 h

In summary, the sulfoximine route provides for a new access to enantio- and diastereopure β-substituted and β,β-disubstituted δ-hydroxy β-amino acids and to γ-amino alcohols. The starting hydroxy sulfoximines are readily available enantio- and diastereopure through hydroxyalkylation of the corresponding allylic sulfoximines which in turn are easily prepared from (+)- or (−)-*N*,*S*-dimethyl-*S*-phenylsulfoximine.[7] Although in the final reduction step the chirality of the sulfonimidoyl group is lost, as it is the case in the other route to β,β-disubstituted β-amino acids,[5c,5f] this disadvantage is compensated for by the ready accessibility of the enantiopure starting material either from commercial sources, by catalytic asymmetric synthesis or by an efficient resolution amendable to large scale.[18] The synthesis of acyclic amino acids of type **B** is now underway in our laboratories.[19]

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 11 and Sonderforschungsbereich 380).

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