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# A Concise Enantioselective Synthesis of Allylamines and *N*-Boc-β-Amino Acids§

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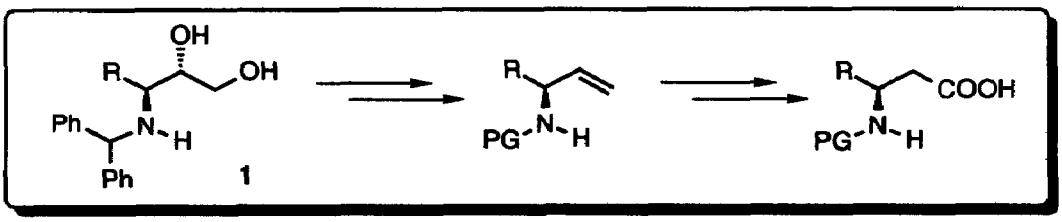
**Abstract:** A new and efficient enantioselective synthesis of allylamines and *N*-Boc-β-amino acids has been developed. Starting from enantiomerically enriched *N*-diphenylmethyl-3-amino-1,2-diols, allylamines are easily obtained by a Corey-Hopkins deoxygenative protocol. After a change in the nitrogen protecting group, the resulting *N*-Boc allylamines are converted into β-amino acids by hydroboration with 9-BBN followed by oxidation with PDC in DMF.

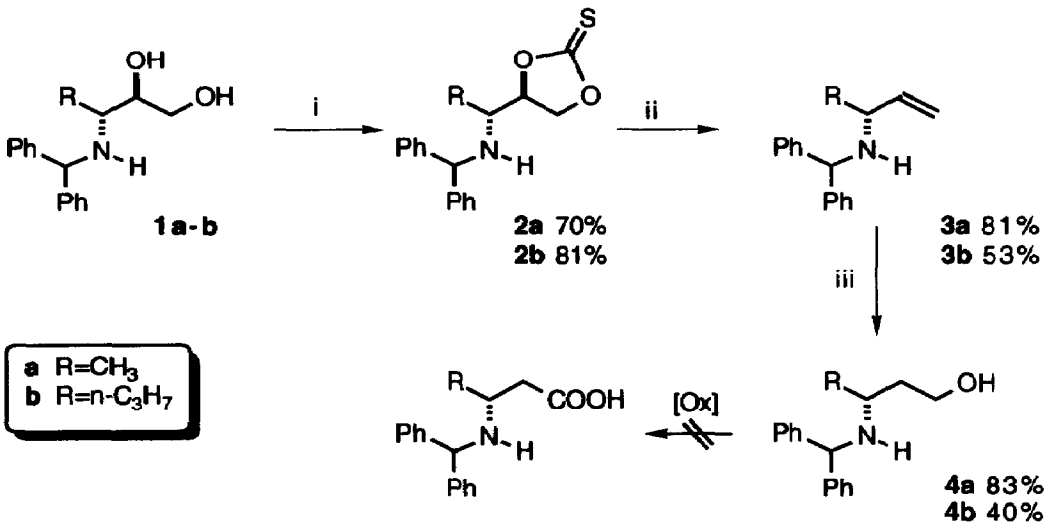
Enantiopure β-amino acids are emerging as an important class of organic compounds. They are in many instances suitable precursors to β-lactams[1] and are also components of natural and unnatural bioactive peptides[2] as well as of other natural products.[3] Notwithstanding, synthetic methodology allowing the enantioselective preparation of β-amino acids is scarce when compared to that devoted to their regioisomeric α congeners.[4] Only quite recently, several methods have been reported for the preparation of homochiral or enantioenriched β-amino acids, but they are mostly based on the chiral auxiliary strategy[5] or on the diastereoselective/chemoselective elaboration of chiral starting materials.[6] The need for efficient methodology where the asymmetric induction is achieved in a catalytic fashion[7] is thus clearly apparent.

We have recently reported the regioselective ring opening of chiral epoxy alcohols (arising from catalytic Sharpless epoxidation[8]) with primary amines,[9] and have employed the resulting scalemic *N*-diphenylmethyl-3-amino-1,2-diols (1) as starting materials for the enantioselective preparation of azetidinols,[10] aziridines[10] and α-amino acids.[11,12] We describe in the present communication the successful conversion of 1 into allylamines and, subsequently, into β-amino acids.



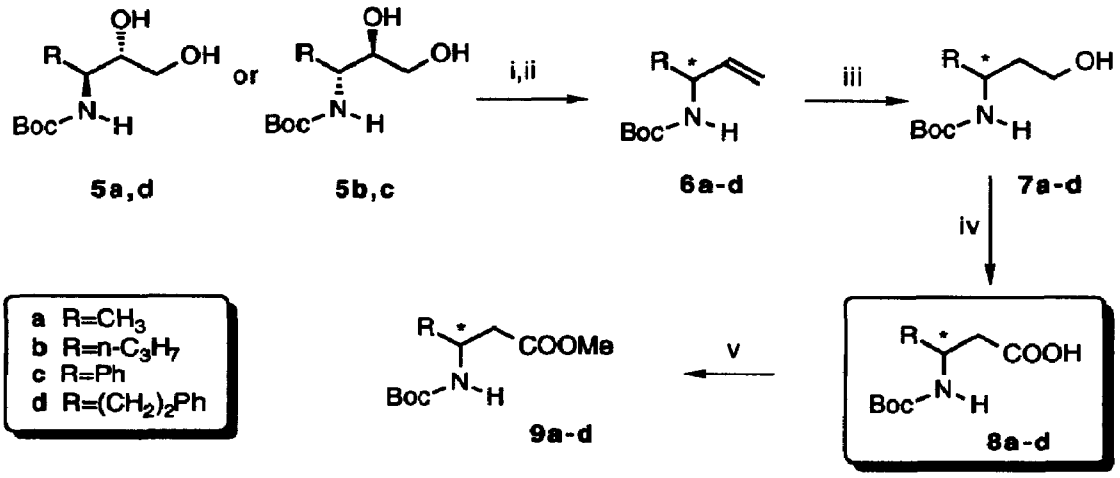

§ Dedicated to Professor Pedro Victory on the ocassion of his 65th birthday.

In our first approach (Scheme 1), *N*-diphenylmethyl-3-amino-1,2-diols (**1a-b**) were submitted to a variety of 1,2-diol deoxygenation procedures[13] with disappointing results. After much experimentation, it was finally found that the Corey-Hopkins protocol[14] afforded allylamines **3a-b** in satisfactory yield. Hydroboration of **3a** with $BH_3.SMe_2$ was non-regioselective providing, after oxidative work-up, a 5:4 mixture of primary and secondary alcohols. Moreover, the formation of the secondary alcohol took place without diastereoselectivity.[15] Most conveniently, hydroboration with 9-BBN followed by oxidation yielded exclusively the 1,3-aminoalcohols **4a-b**. A more direct route to **4a** was attempted by reduction of thionocarbonate **2a** with tri-n-butyltin hydride. Contrary to what is normally observed,[16] the process took place with low regioselectivity, affording a 3.4:1 mixture of primary and secondary alcohols in a modest 22% global yield. Final oxidative conversion of **4a-b** into the corresponding β-amino acids was attempted by a variety of methods (Jones, PDC in DMF, $RuCl_3$ cat./$NaIO_4$), but without success. It appears that, under oxidative conditions, scission of the benzhydryl group takes easily place giving rise to benzophenone and other by-products.




Scheme 1. *Reagents: i)* $Cl_2CS$, 4-DMAP, $CH_2Cl_2$; *ii)* 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine *iii)* 9-BBN, THF; $H_2O_2$, NaOH;

To avoid this problem, the nitrogen protecting group was changed to the more convenient *tert*-butoxycarbonyl at the beginning of the synthesis. Thus, *N*-Boc-3-amino-1,2-diols **5a-d**[17] were submitted to the above mentioned deoxygenative protocol[14] (Scheme 2) to afford in good yield the *N*-Boc-allylamines **6a-d** (Table 1). Hydroboration of the allylamines with 9-BBN followed by $H_2O_2$ oxidation afforded the *N*-Boc-3-aminoalcohols **7a-d**, which could be successfully oxidized to the corresponding *N*-Boc-β-amino acids **8** with PDC in DMF.[18] Final products were most conveniently isolated as the methyl esters **9a-d**, readily obtained by treatment of the crude acids with diazomethane.




Scheme 2. *Reagents: i)* $Cl_2CS$, 4-DMAP, $CH_2Cl_2$; *ii)* 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine *iii)* 9-BBN, THF; $H_2O_2$, NaOH; *iv)* PDC, DMF; *v)* $CH_2N_2$, $(C_2H_5)_2O$

Table 1. Yields and specific rotations of compounds **6-9**[a] according to Scheme 2.

| | R (configuration of 5) [% ee] | Yield(%) $[\alpha]_D$ (c in g/100mL, $CHCl_3$) | | | |
|---|---|---|---|---|---|
| | | **6** | **7** | **8** | **9**[b] |
| **a** | $CH_3$ (2*S*,3*S*) | 70 | 83 | 61 | 61 |
| | [91% ee] | -5.4°(1.6) | +9.0°(1.8) | -14.0°(1.4) | -22.0°(0.5) |
| **b** | n-$C_3H_7$ (2*R*,3*R*) | 68 | 74 | 66 | 73 |
| | [92% ee] | -14.3°(1.5) | +1.6°(1.5) | +27°(1.0) | +20.9°(1.9) |
| **c** | $C_6H_5$ (2*R*,3*R*) | 74 | 93 | n.d. | 55 |
| | [>99% ee] | -66°(1.9) | -55.4°(2.1) | n.d. | -29.0°(2.0) |
| **d** | $(CH_2)_2Ph$ (2*S*,3*S*) | 58 | 52 | n.d. | 51 |
| | [90% ee] | +22.5°(1.9) | +9.9°(1.5) | n.d. | +7.2°(1.8) |

[a] All new compounds gave satisfactory spectroscopic and/or analytical data. [b] Overall yields for the two-step conversion from **7**

In summary, we have developed an efficient procedure for the enantioselective synthesis of *N*-Boc protected β-amino acids and their methyl esters. The ultimate source of chirality in our approach is the catalytic Sharpless epoxidation.[8] Since a large number of epoxy alcohols are available in high enantiomeric purity and with completely defined configuration by the use of the Sharpless epoxidation, the present methodology appears to be of broad applicability. Moreover, since the chiral center is not subject to manipulation along the sequence, and no racemisation mechanism can be easily envisioned for any of the intermediates, the enantiomeric purity of the final products **7** and **8** is only conditioned by the efficiency of the catalytic Sharpless epoxidation. In fact, the specific rotations of the known compounds **7a**[19] and **9a**[20] are in perfect agreement with the enantiomeric purity of the starting epoxy alcohol (and hence, of the aminodiol **5a**).

On the other hand, enantioenriched allylamines **3a-b** and **6a-d**, which are early intermediates in our synthesis, represent also an actively pursued class of materials.[21] It is worth

noting that the Corey-Hopkins methodology,[14] when applied to aminodiols **1** or **5**, opens an straightforward route to this interesting class of compounds. Further applications of chiral allylamines are in development in our laboratories and will be reported in due course.

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