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Synthesis of Orthogonally Protected Optically Pure β-Amino Acids: Constrained Phenylalanine Analogs 3-*tert*-Butoxycarbonylamino-1,2,3,4-tetrahydro-2-naphthoic acid benzyl ester

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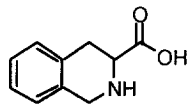
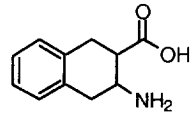
Abstract: *The synthesis of orthogonally protected* β-*amino acid 3-*tert-*butoxycarbonylamino-1,2,3,4-tetrahydro-2-naphthoic acid benzyl ester (Boc-*β*Atc-OBn) is described. The route to these constrained phenylalanine analogs features a SmI_2-mediated aziridine cleavage resulting in a* β-*amino ester. The stereochemistries have been determined by X-ray crystallographic analyses.*

Keywords: Amino acids and derivatives; aziridines; samarium and compounds; X-ray crystal structures

During the last several years, much effort has been focused on the development of structures designed to mimic naturally occurring amino acids and biologically active peptides.[1] Such efforts are intended to enhance potency, receptor selectivity and pharmacokinetic properties. Modifications which decrease conformational mobility have also been sought in order to gain insight into the relationship between the biological activity and the three dimensional topology. The imino acid analog Tic (1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid), characterized as a constrained phenylalanine analog, has been incorporated into several biologically active peptide and peptidomimetic sequences where a phenylalanine sidechain plays an integral role in the biological activity.[2] However, an amide bond formed at the nitrogen of Tic often results in *cis* and *trans* amide bond isomers that may complicate efforts to elucidate bioactive conformations. In order to minimize such complications, we initiated the synthesis of the β-amino acid 3-amino-1,2,3,4-tetrahydro-2-naphthoic acid (β-aminotetralin-2-carboxylic acid-βAtc) (**1**).



1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid (Tic)



3-amino-1,2,3,4-tetrahydro-2-naphthoic acid (βAtc) (**1**)

The stereoselective syntheses of β-amino acids have been recently reviewed [3] and shown to be attractive target structures. Our strategy utilizes a Sharpless asymmetric epoxidation [4] to establish chirality. The synthesis was initiated with the formation of the α,β-unsaturated ester (**2**) by trapping an *in situ* derived *o*-quinodimethane with ethyl propiolate.[5] Reduction of the ester (**2**) by DIBAL gave the allylic alcohol (**3**). Using (+)-diethyltartrate in the catalytic mixture gave the (2*S*,3*S*) epoxide (**4**) in high enantiomeric excess (as

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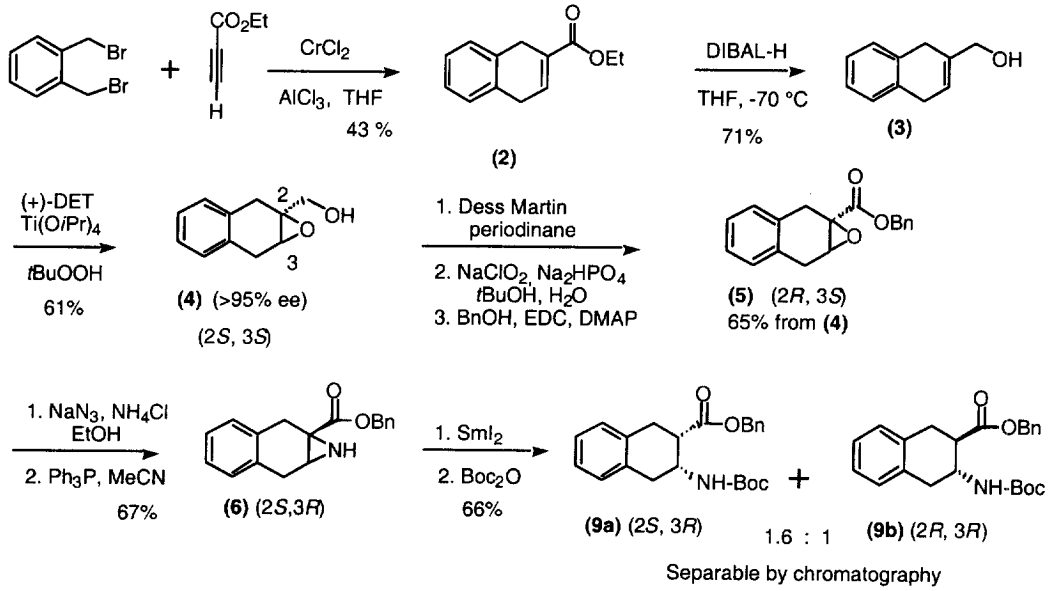
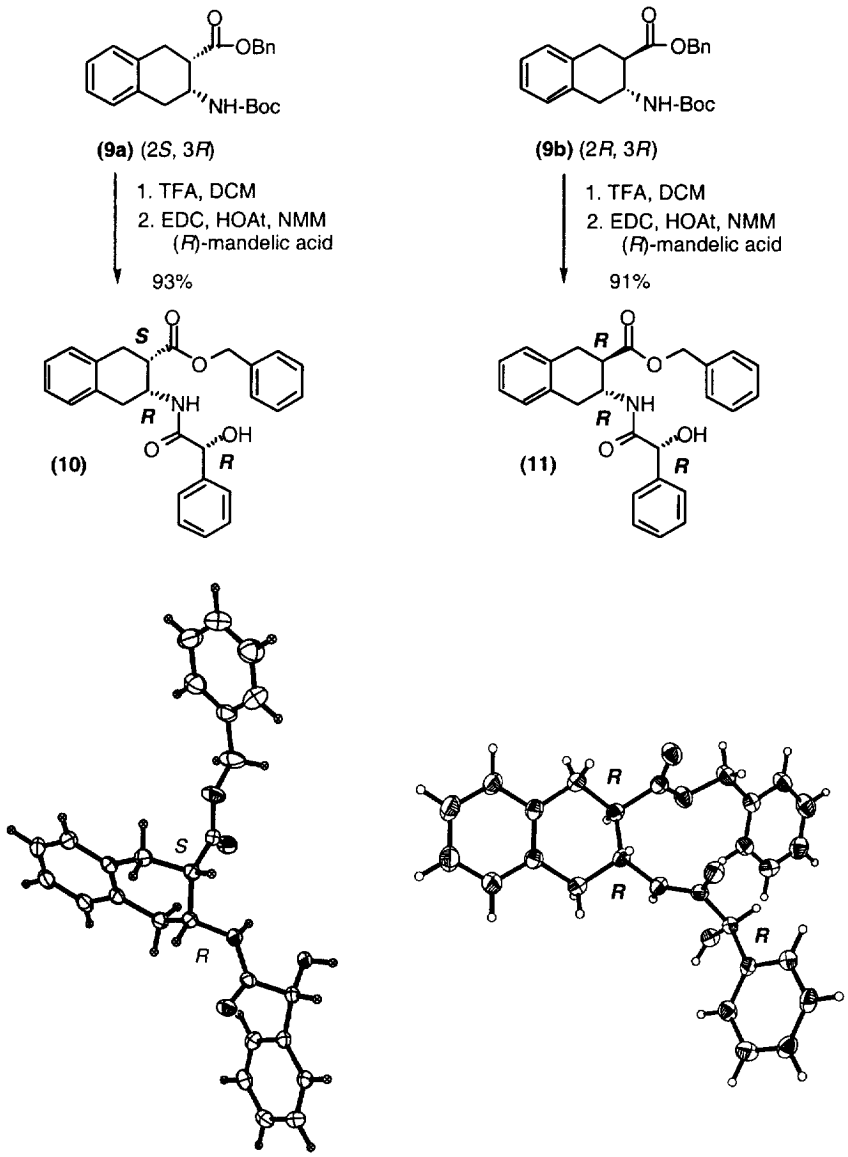
revealed by the syntheses and ^{1}H-NMR analyses of the Mosher esters [6]) after a single recrystallization. Oxidation of the alcohol of (2*S*,3*S*) epoxide (**4**) followed by esterification gave the (2*R*,3*S*) epoxy-benzyl ester (**5**). The chiral benzylaziridine-2-carboxylate (**6**) was obtained with complete retention of optical purity by opening the epoxide (**5**) with sodium azide followed by treatment with triphenylphosphine to reduce the azide and mediate the Staudinger ring closure.[7]



The addition of the aziridine (2*S*,3*R*) (**6**) to samarium iodide (SmI_2) gave the ring-opened β-amino ester.[8] After workup, the crude product was treated with di-*tert*-butyldicarbonate (Boc_2O) and two isomers of benzyl-3-*tert*-butoxycarbonylamino-1,2,3,4-tetrahydronaphthalene-2-carboxylate (Boc-βAtc-OBn) (**9a**) and (**9b**) were fully resolved by silica gel chromatography.[9] It was assumed from the proposed mechanism of the SmI_2-mediated aziridine ring opening that the two isomers possessed the same chirality at C(3) and different stereochemistry at C(2).[8] In order to unambiguously identify the stereochemistries, derivatives of compounds (**9a**) and (**9b**) were synthesized. The Boc-group of (**9a**) was removed and the resulting amine was coupled to (*R*)-mandelic acid using 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) to give the diastereomer (**10**) in high yields. The X-ray crystallographic analysis of the adduct (**10**) revealed a *cis* orientation of the nitrogen and the ester carbonyl of the β-amino ester.[10] Similarly, the (*R*)-mandelic acid adduct of (**9b**) was prepared giving the *trans* adduct (**11**) and successfully analyzed by X-ray crystallography.[10] The X-ray crystallographic analyses revealed the earlier eluting Boc-βAtc-OBn fraction to be the *cis* (2*S*,3*R*) isomer (**9a**) and the later eluting fraction to be the *trans* (2*R*,3*R*) isomer (**9b**). The *cis* to *trans* ratio is similar to those reported by Molander and Stengel.[8]



In conclusion, the four stereoisomers of the protected β-amino acid 3-*tert*-butoxycarbonylamino-1,2,3,4-tetrahydro-2-naphthoic acid benzyl ester have been synthesized and the absolute stereochemistry determined by X-ray crystallographic analyses. The (2*R*,3*S*) *cis* **(12a)** and (2*S*,3*S*) *trans* **(12b)** stereoisomers were also obtained in an analogous manner.[11] Incorporation of these novel β-amino acids into peptide sequences is currently underway and will be described in future reports.

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[6] The diastereomeric Mosher esters of the recrystallized epoxide **(4)** were synthesized according to the procedure in Gao *et al.*[4] The diastereomeric Mosher esters were measured by ^{1}H-NMR and the methylene protons (dd centered about about δ 4.4 ppm) adjacent to the epoxide and the ester were for comparison.

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[9] **(9a)** R_f EtOAc / hex (25%) 0.41; mp 101-102 °C; ^{1}H-NMR (360 MHz / $CDCl_3$) δ 7.32 (m, 4H); 7.15 (m, 4H); 7.07 (m, 1H); 5.12 (dd, *J* = 13, 18 Hz, 2H); 5.11 (m, 1H); 4.45 (m, 1H); 3.27 (dd, *J* = 9, 19 Hz, 1H); 3.07 (m, 3H); 2.86 (dd, *J* = 6.5, 17 Hz, 1H); 1.42 (s, 9H); $[\alpha]^{27}_D$ 7.25° (*c* = 5.1, $CHCl_3$); HRMS calcd for $C_{23}H_{28}NO_4$ (M + H^+) 382.2018, found m / z 382.2029.
(9b) R_f EtOAc / hex (25%) 0.34; mp 98-99 °C; ^{1}H-NMR (360 MHz / $CDCl_3$) δ 7.35 (m, 5H); 7.10 (m, 4H); 5.15 (dd, *J* = 9, 21 Hz, 2H); 4.69 (m, 1H); 4.27 (m, 1H); 3.28-3.14 (m, 2H); 3.03 (dd, *J* = 5.4, 17 Hz, 1H); 2.94 (m, 1H); 2.69 (dd, *J* = 8.3, 17 Hz, 1H); 1.41 (s, 9H); $[\alpha]^{27}_D$ 0.62° (*c* = 1.3, $CHCl_3$); HRMS calcd for $C_{23}H_{28}NO_4$ (M + H^+) 382.2018, found m / z 382.2004.

[10] The X-ray crystallographic data have been deposited in the Cambridge Crystallographic Database.

[11] The (2*R*,3*S*)-Boc-βAtc-OBn **(12a)** and (2*S*,3*S*) Boc-βAtc-OBn **(12b)** stereoisomers were obtained from the enantiomer of epoxide **(4)** which was derived from the use of (-)-diethyltartrate in the catalytic mixture. The syntheses of the dipeptide Boc-Tyr(O*t*Bu)-βAtc-OBn using the four stereoisomers of Boc-βAtc-OBn resulted in four spectroscopically distinct products in high diastereomeric purity. These results provide further evidence that the aziridine ring opening reaction results in single *cis* and single *trans* stereoisomers.