Pergamon

Tetrahedron Letters 39 (1998) 9389–9392

TETRAHEDRON
LETTERS

Facile synthesis of D-amino acids from an L-serine-derived aziridine

Jeremy M. Travins and Felicia A. Etzkorn*
University of Virginia, Department of Chemistry

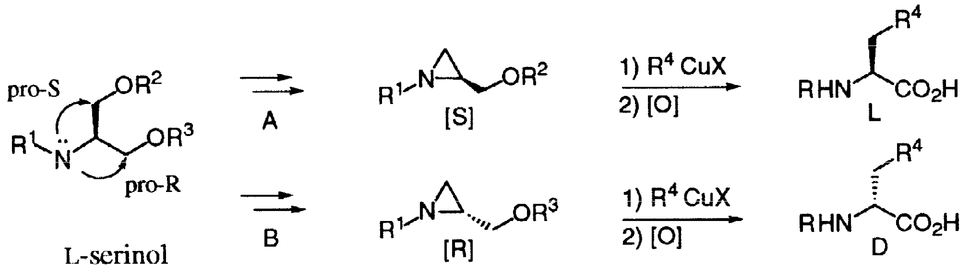
Received 2 September 1998; accepted 6 October 1998

Abstract

Using the concept that L-serine can be converted into a desymmetrized γ-diol derivative, five D-amino acids were synthesized from a common aziridine intermediate by a general, high-yielding three-step process. The key 2-*t*-butyldimethylsiloxymethyl N-*t*-butoxycarbonyl aziridine intermediate was synthesized in four steps and 65% overall yield.

Keywords: amino acids and derivatives; aziridines; copper and compounds; asymmetry

Stereoselective syntheses of unnatural amino acids are increasingly important for peptidomimetics and rational drug design. The stereoselective synthesis of α-amino acids was thoroughly reviewed in 1994 and 1989 [1,2]. Stereoselective transformations of aziridines have also been reviewed [3]. The conversion of L-serine (Ser) into D-amino acids using methods not involving aziridine intermediates has been described [4,5]. Organometallics have been reacted with aziridine electrophiles to give L-α-amino acids or alcohols previously [6-14]. *t*-Butyl ester has been used to circumvent attack of the organometallic reagent on the carboxyl group of the aziridine, but the non-orthogonal Boc group was used on the amine [10,6]. In another case, the free carboxylate of the aziridine was inert to nucleophilic attack [8], though the N-pentamethyl-chromanyl protecting group is expensive and the N-tosyl group requires harsh cleavage conditions. The diphenylphosphinoyl group is a promising



Scheme 1: Prochirality of L-serinol and conversion to amino acids.

---

*University of Virginia, Department of Chemistry, McCormick Rd., Charlottesville, VA 22903 USA
Tel: 804-924-3135, FAX: 804-924-3567, Email: fae8m@virginia.edu

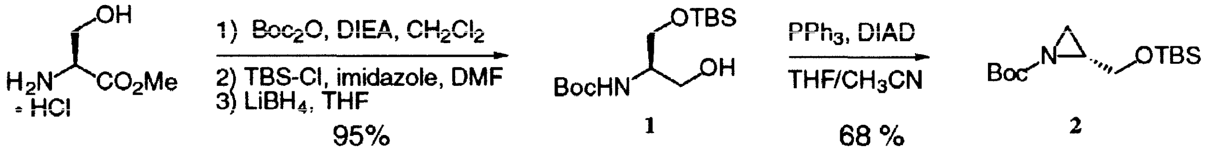
PII: S0040-4039(98)02198-4

aziridine activating group stable to many nucleophiles and easily cleaved by TFA [9]. We now report an economical and facile synthesis of D-amino acids via nucleophilic ring opening of an L-serine-derived aziridine.

Ring opening of Ser-derived aziridines is essentially the conversion of Ser to a different amino acid. Interestingly, derivatives of serine can be thought of as desymmetrized γ-diols and used as the chiral precursor for either L- or D-amino acids, Scheme 1. Reducing the acid of Ser to the alcohol gives a meso-compound with two reaction sites, potentially pro-R and pro-S. In route B, the final D-amino acid has the inverse stereochemistry of the starting Ser.

The aziridine used in the ring-opening reactions was synthesized in four steps from L-serine methyl ester, Scheme 2. The amine was protected as the *t*-butylcarbamate and the alcohol was silylated with TBSCl. Reduction of the methyl ester with $LiBH_4$ gave alcohol **1** in 95% yield over four steps without chromatography.[1] Mitsunobu ring closure [6,16] and the single chromatographic step of the sequence gave 68% yield of intermediate aziridine **2**.[2] This high-yielding sequence allowed us to prepare multigram quantities of **2** quickly.

Copper-mediated ring opening of the aziridine with Grignard or organolithium reagents gave the amino-alcohol TBS-ethers generally in high yield, Scheme 3 and Table 1. $CuBr_2$-SMe_2 complex efficiently catalyzed reaction of Grignard reagents with the aziridine [6,9]. The higher-order cuprate derived from methyllithium also reacted in high yield leading to Boc-D-Abu. Boc-L-Abu has been synthesized by a highly efficient route from L-Met [17]. Allylmagnesium halides were somewhat problematic reagents, giving lower yields and purity. Fmoc-L-homoallylglycine has been prepared via alkylation of glycine [18].



Boc = *t*-butoxycarbonyl, DIEA = diisopropylethylamine, TBS = *t*-butyldimethylsilyl,
DMF = N,N-dimethylformamide, DIAD = diisopropylazodicarboxylate, THF = tetrahydrofuran

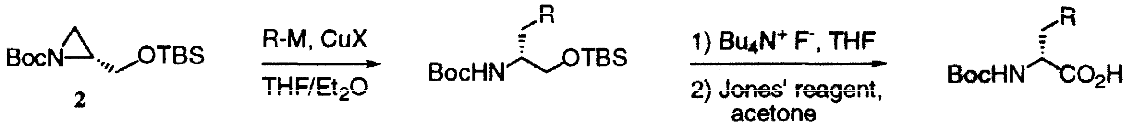
Scheme 2: Synthesis of 2-*t*-butyldimethylsiloxymethyl N-*t*-butoxycarbonyl aziridine.

---

[1] **N-Boc-Serin-(O-*t*-butyldimethylsilyl)-ol (1).** DIEA (8.05 mL, 46.2 mmol) was added to a stirred suspension of serine methyl ester hydrochloride (6.58 g, 42.3 mmol) in CH_2Cl_2 (150 mL). Boc_2O (9.23 g, 42.3 mmol) was added and the reaction was stirred for 2h. Aqueous workup (1N HCl, $NaHCO_3$, CH_2Cl_2) yielded 9.15 g of product which was dissolved in DMF (150 mL) and cooled to 4° C. Imidazole (8.53 g, 125.3 mmol, 3 eq.) was added followed by TBSCl (6.92 g, 45.9 mmol, 1.1 eq) and the reaction was stirred for 6 h. DMF was removed with high vacuum/rotary evaporator. Aqueous workup (NH_4Cl, $NaHCO_3$, EtOAc) yielded 13.61 g of product. The crude material was dissolved in THF (120 mL) and $LiBH_4$ (1.36 g, 62.6 mmol, 1.5 eq) was added. The exothermic reaction warmed to ~35° C and was stirred for 1.5 h. Slow NH_4Cl quench followed by aqueous workup (NH_4Cl, $NaHCO_3$, EtOAc) yielded 12.40 g (96% overall) of alcohol **1** which was used crude in the next reaction. A sample was purified for analysis. $[\alpha]^{25}_D$ = +17.7° (c 2.12, $CHCl_3$). lit. $[\alpha]_D$ = +13° (c 1.1, $CHCl_3$) [15] ^1H NMR ($CDCl_3$) δ 5.12 (br s, 1H), 3.63 (m, 5H), 3.35 (br s, 1H), 1.39 (s, 9H), 0.84 (s, 9H), 0.02 (s, 6H).

[2] **2-t-Butyldimethylsiloxymethyl N-t-butoxycarbonyl aziridine (2).** Ph_3P (8.13 g, 31 mmol) was dissolved in 9:1 THF/CH_3CN (300 mL) and cooled to 4° C. DIAD (6.08 mL, 31 mmol) was added over 10 min. After stirring 15 min., a solution of Boc-amino-alcohol **1** (6.31 g, 20.7 mmol) in THF (40 mL) was added over 15 min. The solution was allowed to warm to rt and stirred for 24 h. Aqueous workup followed by silica chromatography (pet. ether:EtOAc, 95:5) yielded 4.02 g (68%) of azirdine **2** as a colorless oil. $[\alpha]_D^{25}$ +58.0° (c=1.96 MeOH). ^1H NMR ($CDCl_3$) δ 3.72 (dd, 1H, *J*=4.8,11.4), 3.57 (dd, 1H, *J*=4.8,11.4), 2.49 (m, 1H), 2.18 (d, 1H, *J*=6.2), 2.00 (d, 1H, *J*=3.5), 1.39 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

The TBS group was removed with fluoride and the resulting Boc-amino alcohol was oxidized with Jones' reagent. The Boc-amino acid was purified by simple aqueous work up. Yields of the final two steps were around 70%, while the overall yields were generally 60-65%.[3] The yields from the Jones' oxidations were reasonably good, though generally the lowest yielding steps in the sequence. The use of other oxidants in schemes to invert serine has been discussed [ref 1, *cf.* pp. 1616-1617]. The optical rotations for the chromatographically-purified Boc-D-amino acids were of the same magnitude and opposite sign to the corresponding known Boc-L-amino acids, Table 1. The short reaction times and facile purification procedure allowed most amino acids to be synthesized in under eight hours. Though this route has more steps than other aziridine routes, it is similar in actual preparation time. The potential for racemization is vastly reduced at the alcohol oxidation state and eliminates the possibility of addition to the carboxyl by strong nucleophiles. The protecting group strategy is orthogonal and allows more product diversity.



Scheme 3: Synthesis of Boc-D-amino acids from aziridine **2**.

Table 1
Reaction Conditions, Yields, and Optical Rotations for D-Amino Acid Syntheses.

R-M	(eq)	CuX	(eq)	yield %	overall yield %	Boc-D-Amino acids $[\alpha]_D^{25}$/ Boc-L-Amino acids $[\alpha]_D$[a]	
PhMgBr	(2.5)	CuBrSMe2	(0.10)	100	65	-24.8	(c=1.00 EtOH)/
						L +24.9	(c=1.20 EtOH)
*i*PrMgCl	(3.0)	CuBrSMe2	(0.15)	93	69	+22.7	(c=1.24 CH_2Cl_2)/
						L -22.8	(c=1.04 CH_2Cl_2)[b]
MeLi		CuCN	(2.50)	93	70	+18.8	(c=1.62 MeOH)/
(5.0)						L -18.8	(c=2 MeOH) [19]
cyclopentylMgCl	(2.5)	CuBrSMe2	(0.15)	96	71	+7.3	(c=0.90 MeOH)
allylMgCl	(1.2)	CuBrSMe2	(0.15)	61	43	+1.5	(c=1.36 MeOH)

[a] Novabiochem Boc-L-Phe and Boc-L-Leu rotations were measured. [b] Boc-Leu values are reported as the monohydrate. Boc-D-Leu previously synthesized gave $[\alpha]_D = 19.7°$ (c 1.545, CH_2Cl_2), but $[\alpha]$ was not calculated as the monohydrate [20].

---

[3] **General procedure for Boc-amino acids.** The Grignard reagent (1.5-2.5 eq) was added to a suspension of CuBr-SMe_2 (15 mol %) in THF (8 mL/mmol aziridine) at -40°C. Alternatively, MeLi (5 eq) was added to a suspension of CuCN (2.5 eq) in THF (3 mL/mmol CuCN) at -40°C. The cuprate was stirred for 20 min and a 4° C solution of aziridine **2** in Et_2O (0.25-0.5M) was added over 3-5 min, and stirred ~ 1 hr. After sat'd $NaHCO_3$, sat'd NH_4Cl, EtOAc workup, the TBS ether (0.1 M in THF) was treated with 1M nBu_4NF/THF (3 eq) for 1 hr at 4° C. After aq. workup, the crude alcohol (83 mM in acetone) was cooled to 4° C, 2-3 eq. of Jones reagent (2.67M) were added and the reaction was stirred for 20 min. *i*-PrOH was added followed by aq. workup (1N HCl, EtOAc). The Boc-amino acid was extracted from EtOAc with dilute aq. $NaHCO_3$. Reacidification and EtOAc extraction of the aq. basic solution yielded the Boc-amino acid.

In conclusion we have developed a general synthesis of optically pure D-amino acids from a single L-Ser derived aziridine. This methodology provides a useful complement to previous work, adding side chain diversity and orthogonally protected intermediates. The short and economical synthesis of both the aziridine and the subsequent amino acids makes this a practical methodology.

Acknowledgements. This work was supported in part by ACS-PRF Grant 28634-G4 and by NIH Grant 1 R29 GM52516-01.

References

1. Duthaler, RO. Tetrahedron 1994;50:1539-1650.
2. Williams, RM *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989; Vol. 7.
3. Tanner, D. Angew. Chem. Int. Ed. Engl. 1994;33:599-619.
4. Sibi, MP, Rutherford, D, Sharma, R. J. Chem. Soc. Perkin Trans. 1 1994:1675-1678.
5. Maurer, PJ, Takahata, H, Rapoport, H. J. Am. Chem. Soc. 1984;106:1095-.
6. Baldwin, JE, Farthing, CN, Russell, AT, Schofield, CJ, Spivey, AC. Tetrahedron Lett. 1996;37:3761-3764.
7. Tanner, D, Gautun, OR. Tetrahedron 1995;51:8279-8288.
8. Church, NJ, Young, DW. Tetrahedron Lett. 1995;36:151-154.
9. Osborn, HMI, Sweeney, JB. Tetrahedron Lett. 1994;35:2739-2742.
10. Baldwin, JE, Spivey, AC, Schofield, CJ, Sweeney, JB. Tetrahedron 1993;49:6309-6330.
11. Tanner, D, Birgersson, C, Dhaliwal, HK. Tetrahedron Lett. 1990;31:1903-1906.
12. Baldwin, JE, Adlington, RM, O'Neil, IA, Schofield, C, Spivey, AC, Sweeney, JB. J. Chem. Soc., Chem. Commun. 1989:1852-1854.
13. Duréault, A, Tranchepain, I, Depezay, J-C. J. Org. Chem. 1989;54:5324-5330.
14. Baldwin, JE, Adlington, RM, Robinson, NG. J. Chem. Soc., Chem. Commun. 1987:153-.
15. Gonda, J, Helland, A-C, Ernst, B, Bellus, D. Synthesis 1993:729-733.
16. Wipf, P, Miller, CP. Tetrahedron Lett. 1992;33:6267-6270.
17. Jiang, J, Schumacher, KK, Joullié, MM. Tetrahedron Lett. 1994;35:2121-2124.
18. Myers, AG, Gleason, JL, Yoon, T, Kung, D. J. Am. Chem. Soc. 1997;119:656-673.
19. Kubik, A, Siemian, IZ, Stachowiak, W, Szewczuk, A, Klis, W. Polish J. Chem. 1980;54:435-441.
20. Oppolzer, W, Tamura, O, Deerberg, J. Helv. Chim. Acta 1992;75:1965-1978.