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Aziridinium from *N,N*-Dibenzyl Serine Methyl Ester: Synthesis of Enantiomerically Pure β-Amino and α,β-Diamino Esters

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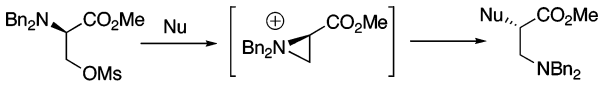
ABSTRACT

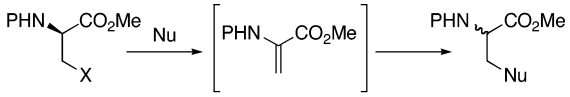


Nu = N_3, phthalimide, CN, $CH_2(COOMe)_2$, R_1R_2N

Reaction of *N,N*-dibenzyl-*O*-methylsulfonyl serine methyl ester with a variety of heteronucleophiles (sodium azide, sodium phthalimide, amines, thiols) and carbanions (sodium malonate) gave, via an aziridinium intermediate, the corresponding β-amino or α,β-diamino ester in good to excellent yield. A short synthesis of orthogonally protected and enantiomerically pure 2,3-diamino propionate (Dap) is described.

The high density of functionalization associated with its ready availability in both enantiomerically pure forms have made serine an ideal starting material in organic synthesis.[1] Several versatile serine-based synthons have been developed allowing regio- and stereoselective introduction of functional groups into the molecule. Among them, Garner's aldehyde[2] and Jackson's β-alanyl anion synthon[3] are notable examples and have been widely applied in the synthesis of complex natural products. On the other hand, earlier efforts aimed at synthesizing β-alanyl cation synthons for direct functionalization of serine have met with only limited success due to the competitive β-elimination process leading to racemic adducts (Scheme 1).[4] To avoid this undesired reaction, serine derivatives with reduced α-CH acidity have been synthesized. Indeed, by using the bulky electron-donating *N*-protecting groups such as *N*-phenylfluorenyl[5] and *N*-trityl[6] or by converting the carboxylic acid to the Weinreb amide,[7] the undesired β-elimination process can be effectively minimized.[8] However, the application scope of these synthons is still limited.

Scheme 1 β-Alanyl Cation Equivalent, Problem of β-Elimination



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(1) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*: *Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: New York, 1987.

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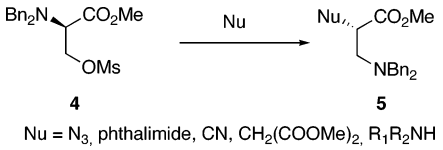
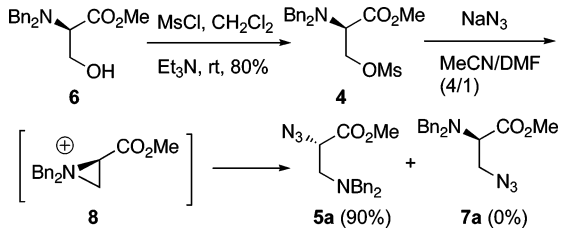
Scheme 2. Stereoselective Synthesis of Enantiomerically Pure β-Amino or α,β-Diamino Esters



The ability of the *N*,*N*-dibenzyl group to shield the α-CH of α-amino acid from deprotection has been amply demonstrated[9] and a variety of *N*,*N*-dibenzyl amino aldehydes, including serinal,[10] have been synthesized. We document herein that *N*,*N*-dibenzyl-*O*-methylsulfonyl serine methyl ester (**4**) is a stable α,β-alanyl double cation synthon. It reacts with a variety of heteronucleophiles (NaN_3, sodium phthalimide, amine, thiol) and carbanions (sodium malonate) to afford, via an aziridinium intermediate, the corresponding β-amino ester or α,β-diamino ester (**5**) in good to excellent yield (Scheme 2).

Compound D-**4** was obtained in 80% isolated yield by mesylation of the readily available D-*N*,*N*-dibenzyl serine methyl ester (**6**)[10b] under classic conditions (MsCl, Et_3N, CH_2Cl_2, rt, Scheme 3). We stress that formation of the chloro amine resulting from the attack of the chloride ion on the mesylate **4** was not observed.[11] Compound D-**4** in its pure form is stable at room temperature and can be stored for weeks in a refrigerator without detectable degradation.[12] This highly desirable stability can be ascribed to the bulky *N*-protecting group that protects the compound from the

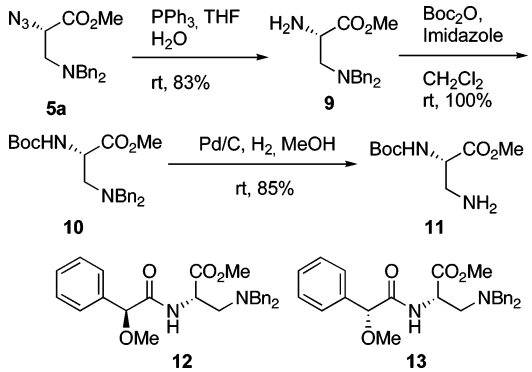
Scheme 3. Synthesis of (*S*)-α-Azido-β-*N*,*N*-dibenzylamino Propionate **5a**



β-elimination as well as from the formation of aziridinium.[13] As a prototypical transformation, reaction of **4** with sodium azide was first examined (Scheme 3). Under optimized conditions (MeCN/DMF = 4/1, 60 °C), a single product was isolated in 90% yield whose structure was determined to be (*S*)-methyl α-azido-β-*N*,*N*-dibenzyl propionate (**5a**). Methyl *N*,*N*-dibenzyl-β-azido alanate (**7a**) resulting from the formal direct nucleophilic substitution of mesylate by azide was not detected in the crude product by ^{1}H NMR analysis (Scheme 3). The formation of *N*,*N*-dibenzyl aziridinium-2-carboxylate **8** followed by regioselective ring opening by an S_N2 process could explain the formation of **5a**.

The structure of **5a** was determined by its transformation to the known compound **11** (Scheme 4). Staudinger reduction

Scheme 4. Structural Determination of Compound **5a**



of azide gave the diamine **9** in 83% yield. Protection of the resulting primary amine as *tert*-butyloxycarbamate gave **10**. The observed NH−CH_α correlation in the COSY spectrum of **10** is in accord with the structure of **5a**. Finally, removal of the *N*-benzyl group under hydrogenolysis conditions afforded the known (*S*)-N_α-Boc β-amino-alanine methyl ester. To further confirm the assignment of the stereochemistry of **5a**, both (*S*)- and (*R*)-*O*-methylmandelic acid derivatives **12** and **13** were synthesized. The calculated chemical shift differences [$\Delta\delta_{ArCH_2NBn_2(\mathbf{12-13})} = -0.09$ ppm; $\Delta\delta_{CO2Me(\mathbf{12-13})} = 0.04$ ppmp] were indicative of the *S* configuration of

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(6) (a) Dugave, C.; Menez, A. *J. Org. Chem.* **1996**, *61*, 6067−6070. (b) Dugave, C.; Menez, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1453−1465. (c) Mustapa, M. F. M.; Harris, R.; Bulic-Subanovic; Elliott, S. L.; Bregant, S.; Groussier, M. F. A.; Mould, J.; Schutz, D.; Chubb, N. A. L.; Gaffney, P. R. J.; Driscoll, P. C.; Tabor, A. B. *J. Org. Chem.* **2003**, *68*, 8185−8192. (d) Bregant, S.; Tabor, A. B. *J. Org. Chem.* **2005**, *70*, 2430−2438.

(7) Panda, G.; Rao, N. V. *Synlett* **2004**, 714−716.

(8) Other β-alanyl cation synthons: Serine β-lactone: (a) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237−2241. Cyclic sulfamidates, see: (b) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron*: *Asymmetry* **1990**, *1*, 881−884. Aziridine 2-carboxylate, for selected examples see: (c) Nakajima, K.; Tanaka, T.; Morita, K.; Okawa, K. *Bull. Chem. Soc.* **1980**, *53*, 283−284. (d) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc. Chem. Chem.* **1989**, 1852−1854. (e) Dauban, P.; Dubois, L.; Tran Huu Dau, M. E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035−2043. For recent reviews on the aziridine chemistry, see: (f) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347−1365. (g) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743. (h) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (i) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258.

(9) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

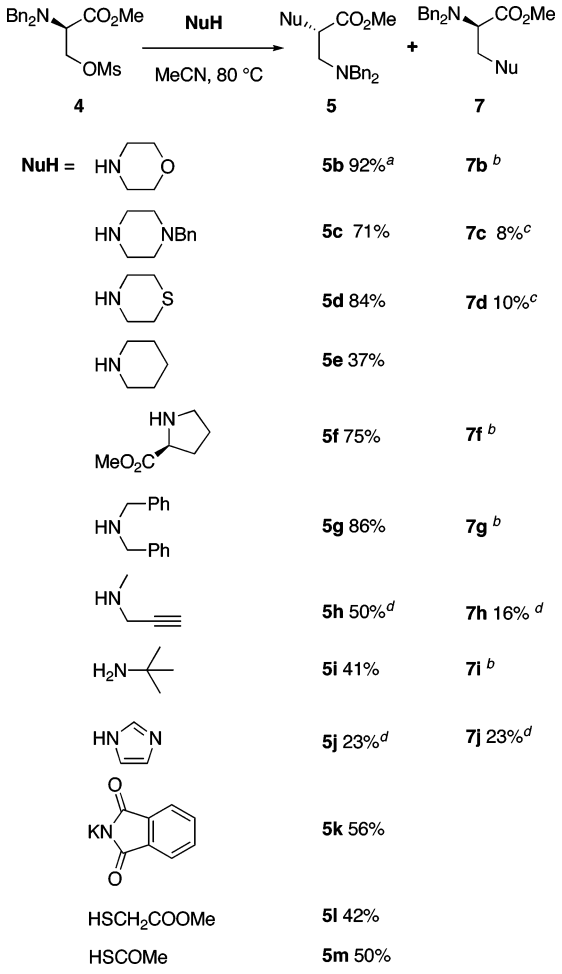
(10) (a) Laib, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1771−1772. (b) Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709−1713. (c) Andrés, J. M.; Pedrosa, R. *Tetrahedron* **1998**, *54*, 5607−5616. (d) East, S. P.; Shao, F.; Williams, F.; Jouillé, M. M. *Tetrahedron* **1998**, *54*, 13371−13390.

(11) See for example: (a) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766−6776. (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555−3557. (c) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435−1437.

(12) Certain mesylates derived from *N*,*N*-dibenzyl amino alcohol can be purified by low-temperature flash chromatography, see: Thomas, C.; Orecher, F.; Gmeiner, P. *Synthesis* **1998**, 1491−1496.

(13) (a) Lubell, W.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824−2831. (b) Temal-laïb, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583−590.

Table 1. Synthesis of β-Amino Ester and α,β-Diamino Ester[a]

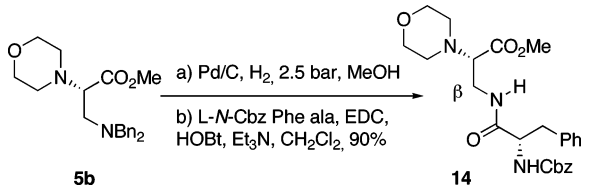


[a] Isolated yield. [b] Not observed in the ^{1}H NMR spectrum of the crude product. [c] Determined from the ^{1}H NMR spectrum of the crude product. [d] Inseparable mixture of two diastereoisomers.

compound **5a**.[14] Thus the configuration of the α-center was reversed in the course of this reaction. In addition, analysis of ^{1}H NMR spectra of compounds **12** and **13** indicated that the de of **12** and **13**, and hence the ee of their precursor **5a**, was higher than 95%. It is interesting to note that the transformation shown in Scheme 4 represents a new synthesis of selectively protected 2,3-diamino propionate (Dap), which is a key structural subunit in a number of natural products. Besides being shorter than other recently reported routes, the advantage of the present synthesis is the ready access to D-Dap from the cheaper L-serine.[15]

Whereas a number of *N*,*N*-dibenzyl amino alcohols have previously been synthesized and elegantly exploited as *N*,*N*-dibenzyl aziridinium precursors,[16,17] it is interesting to note that compound **4** was notably absent from these literature reports.[18] Encouraged by these results, the reaction of **4** with morpholine was next examined. Gratifyingly, simply heating an acetonitrile solution of morpholine with **4** to 80 °C afforded **5b** in 92% yield (Table 1). The structure of **5b** was determined by its transformation to the dipeptide **14** (Scheme 5). The NH−CH_β correlation in the COSY spectrum of **14** clearly indicated the structural identity of **5b**. Moreover, the de of **14**, hence the ee of **5b**, was determined to be higher than 95%.

Scheme 5. Synthesis of Dipeptide **14**



The reaction of **4** with other amines was next examined as a means for the syntheses of diversely substituted chiral diamines.[19] Although the degree of regioselectivity is sensitive to the nature of nucleophiles, the reaction is uniformly α-selective with a variety of cyclic as well as acyclic amines providing compound **5** as the major regioisomer (Table 1). Whereas *tert*-butylamine reacted with **4** to afford **5i** as a sole isolable regioisomer in moderate yield, other sterically less encumbered primary amines were poor substrates for this reaction due to the occurrence of a double alkylation reaction (results not shown). Imidazole also participated in this reaction to afford two regioisomers in a one-to-one ratio. Reaction of **4** with phthalimide anion worked under the identical conditions to provide the corresponding α-regioisomer **5k** in 56% yield. Thiols are also suitable nucleophiles. Thus reaction of **4** with methyl thioglycolate or the potassium salt of thiolacetic acid (MeCN, 80 °C) afforded **5*l*** and **5m** in yields of 42% and 50%, respectively. Due to the inherent

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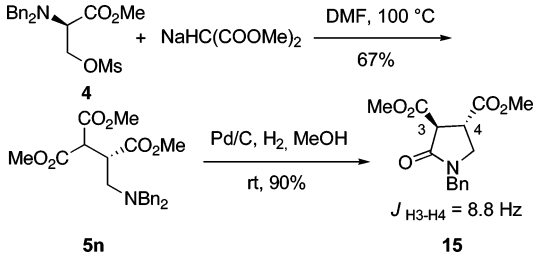
(16) (a) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717−5720. (b) Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem*, **1992**, *57*, 1663−1671. (c) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693−1699. (d) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647−649. (e) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304−307. (f) Graham, M. A.; Wadsworth, A. H.; Zahid, A.; Rayner, C. M. *Org. Biomol. Chem.* **2003**, *1*, 834−849. (g) McKay, C.; Wilson, R. J.; Rayner, C. M. *Chem. Commun.* **2004**, 1080−1081. (h) Couty, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2005**, *46*, 2253−2257.

(17) For interesting examples of ring opening of aziridine by a vicinal tertiary amine leading to aziridinium, see: (a) Concellón, J. M.; Riego, E. *J. Org. Chem.* **2003**, *68*, 6407−6410. (b) Concellón, J. M.; Riego, E.; Rivero, I. A.; Ochoa, A. *J. Org. Chem.* **2004**, *69*, 6244−6248. (b) Concellón, J. M.; Riego, E.; Suárez, J. R.; Garcia-Granda, S.; Diaz, M. R. *Org. Lett.* **2004**, *6*, 4499−4501.

(18) Compound **6** has been converted to the corresponding α-fluoro and α-bromo derivatives via an aziridinium intermediate, see: (a) Somekh, L.; Shanzer, A. *J. Am. Chem. Soc.* **1982**, *104*, 5836−5837. (b) Nagle, A. S.; Salvatore, R. N.; Chong, B.-D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011−3014.

(19) (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) Rondot, C.; Zhu, J. *Org. Lett.* **2005**, *7*, 1641−1644. (c) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835−4842. (d) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361−4364 and references therein.

Scheme 6. Reaction of Malonate Anion with **4**



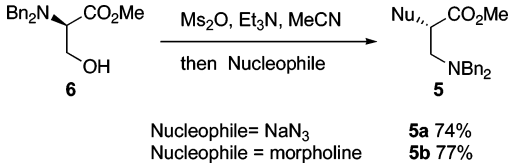
basicity of the malonate anion, its reaction with β-alanyl cation synthon usually led to the formation of racemic adduct via a sequence of β-elimination/Michael addition.[20] We were thus glad to observe that the reaction of **4** with sodium dimethyl malonate (DMF, 100 °C) provided cleanly the α-substituted product **5n** in 67% yield. The structure of **5n** was fully established by detailed spectroscopic studies and its chemical transformation to pyrrolidinone **15**. It is interesting to note that the lactamization displayed high group selectivity[21] to afford the 3,4 trans isomer as the only isolable product.

Finally, we found that **5** could be synthesized in a one-pot fashion from *N*,*N*-dibenzyl serine methyl ester without isolation of the mesylate **4**. Thus mesylation of **6** with Ms_2O in MeCN in the presence of Et_3N at room temperature followed by addition of NaN_3 and heating to 60 °C afforded **5a** in 74% isolated yield (Scheme 7). Similary, **5b** was prepared in 77% yield by using morpholine as a nucleophile.

(20) Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595−2598 and references therein.

(21) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17.

Scheme 7. One-Pot Synthesis of **5** from Alcohol **6**



The yield of this one-pot process was actually higher than the overall yield of the two-step process.

In summary, we demonstrated that optically pure *N*,*N*-dibenzyl-*O*-methylsulfonyl serine methyl ester (**4**) is a stable precursor of *N*,*N*-dibenzyl aziridinium-2-carboxylate (**8**). It reacts with a variety of heteronucleophiles (NaN_3, sodium phthalimide, amine, thiol) and carbanions (sodium malonate) to afford the corresponding β-amino ester or α,β-diamino ester (**5**) in good to excellent yield. Ring opening occurred preferentially at the sterically more hindered C_α position with inversion of configuration. A short synthesis of an important nonproteinogenic amino acid, the N_α-Boc-2,3-diamino propionate (Dap), has been developed.

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Supporting Information Available: Experimental details, physical data, and copies of ^1H and ^{13}C NMR spectra of compounds **4**, **6**, **5a**−**n**, **9**−**13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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