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N-Carbamate-Assisted Stereoselective Synthesis of Chiral Vicinal Amino Sulfides

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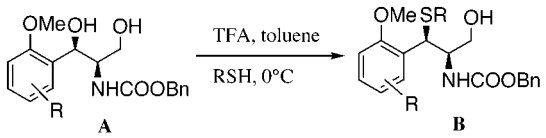
ABSTRACT



Simply mixing amino alcohol A and thiol in toluene and TFA provided the corresponding amino sulfide B in excellent chemical yield and diastereoselectivity. A double S_N2 process initiated by *O*-5 participation of the neighboring *N*-carbamate group was advanced to explain the overall retention of configuration at the chiral benzylic center.

Chiral benzyl sulfides have been found in a number of medicinally important compounds, such as diltiazem[1] (Figure 1) and SKF 104353, etc.[2] The chiral vicinal amino sulfide, on the other hand, has been used as chiral ligand in enantioselective synthesis[3] and is a key structural unit found in an ecteinascidine family marine alkaloid, an important class of anticancer agents isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[4]

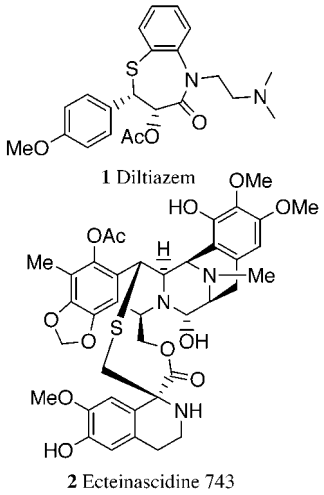


Figure 1.

The nucleophilic substitution at the benzylic position by a thiol is difficult to control stereoselectively due to the possible concurrent occurrence of both S_N1 and S_N2 processes.[5] Excellent diastereoselectivity was observed only in cases wherein the access of the nucleophile was anchimerically assisted[6] or conformationally biased, as, for example, in a polycyclic[7] or in a bridged ring system.[8] Alternatively,

(1) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851−856 and references therein.

(2) (a) Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem.* **1989**, *54*, 3487−3491. (b) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515−10530.

(3) (a) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010. (b) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31−34. (c) Jin, M. J.; Ahn, S. J.; Lee K. S. *Tetrahedron Lett.* **1996**, *37*, 8767−8770. (d) Christoffers, J. *Liebigs Ann.* **1997**, 1353−1358. (e) Fulton, D. A.; Gibson, C. L. *Tetrahedron Lett.* **1997**, *38*, 2019−2022. (f) Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans. I* **1999**, 2353−2365. (g) Jimeno, C.; Moyano, A.; Péricàs, M. A.; Riera, A. *Synlett* **2001**, 1155−1157.

(4) For a recent review, see: Rinehart, K. L. *Med. Res. Rev.* **2000**, *20*, 1−27.

(5) (a) Hashiyama, T.; Inoue, H.; Takeda, M.; Aoe, K.; Kotera, K. *J. Chem. Soc., Pekin Trans. I* **1985**, 421−427. (b) Showalter, H. D. H.; Winters, R. T.; Sercel, A. D.; Michel, A. *Tetrahedron Lett.* **1991**, *32*, 2849−2852. (c) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis, A. L.; Tillequin, F.; Koch, M.; Pierre, A.; Guilbaud, N.; Léonce, S.; Kraus-Berthier, L.; Rolland, Y.; Atassi, G. *J. Med. Chem.* **1996**, *39*, 4762−4766.

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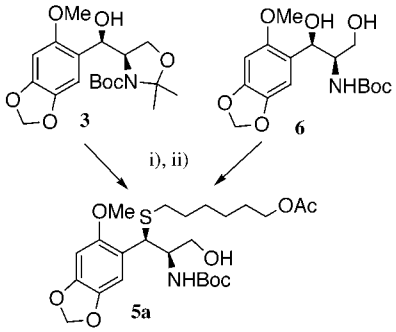
Michael addition of arenethiols to α,β-unsaturated carbonyl compounds has been reported to give excellent diastereo- and enantioselectivity.[9] An elegant enantioselective condensation of configurationally labile α-thiobenzyllithium with electrophile has recently been developed.[10]

A neighboring group participation could bypass the trigonal planar carbenium ion intermediate and give rise to stereocontrolled substitution products via a double S_N2 process.[11] In the case of β-amino alcohols, stereoselective transformation via aziridinium and aziridine intermediates is well documented.[12] We report herein a diastereoselective synthesis of amino sulfide and provide evidences for the formation of an iminocarbonate intermediate by way of the *O*-5 participation of the vicinal *N*-carbamate.[13]

While working on the hydrolysis of compound **3**,[14] we found that treatment of its methanol solution with aqueous HCl led to the stereoselective incorporation of the methoxy function at the benzylic position (yield = 40%, de = 10/1). Although the transformation itself can be understood on the solvolysis basis, a process involving *N*-3 and/or *O*-5 participation of the vicinal *N*-carbamate can also be advanced, leading to a stereoselective process. This assumption together with our interests in the synthesis of chiral amino sulfides prompted us to examine the thiolation of amino diol **3** using 6-acetoxyhexanethiol (**4**) as a sterically nonbiased nucleophile (Scheme 1). After a brief survey of reaction conditions,

Scheme 1



[a] i) toluene-TFA (v/v = 1/1), **4**, c = 0.03 M 0°C; ii) Boc_2O, $NaHCO_3$, THF

[a] i) toluene-TFA (v/v = 1/1), **4**, c = 0.03 M 0 °C; ii) Boc_2O, $NaHCO_3$, THF.

trifluoroacetic acid (TFA) was found to be the acid of choice. Thus, simply stirring a toluene−TFA (v/v = 1/1) solution of **3** and **4** (1.1 equiv relative to **3**) at 0 °C for 10 min provided the sulfide **5** in 95% yield after the reintroduction of the *N*-Boc function. The concentration was found to be an important factor that governs the diastereoseletivity of this reaction. While a de of 6/1 in favor of the *syn*-stereoisomer (vide infra) was obtained at 0.03 M, it decreased to 3/1 when the reaction was performed at 0.3 M. These results are indicative of the interplay between a simple nucleophilic substitution and a double S_N2 process via the participation of the *N*-carbamate function. Even better diastereoselectivity (10/1) was observed when the thiolation was performed on diol **6** under otherwise identical conditions.

The reaction conditions developed were found to be quite general, and various thiols including cysteine derivatives are effective reaction partners (Figure 2). The relative stereochemistry of **5** was determined to be *syn* by comparing the coupling constant (J = 8−10 Hz) with that of the starting material as well as the related sulfide derived from pseudoephedrine.[15] This stereochemical assignment was further corroborated by NMR analysis of thiomorpholinone (**7**) obtained from **5c** under classic conditions (i. TFA; ii. toluene, 2-hydroxypyridine). The benzylic proton resonanced at δ = 4.53 ppm with a coupling constant of 9.1 Hz clearly indicated the trans-diequatorial orientation of the 1-aryl and the 2-hydroxymethyl groups and hence the *syn*-stereochemistry of **5c**. Thus, thiolation occurred with overall retention of configuration at the benzylic position. The high diastereoselectivity observed made the S_N1 process unlikely and is in line with a double S_N2 process via neighboring group participation.

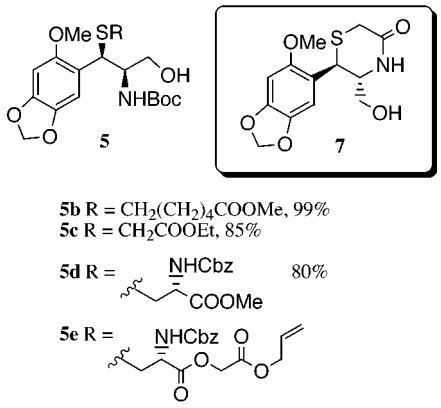
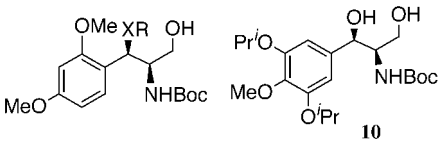


Figure 2.

(6) Lohray, B. B.; Jayachandran, B.; Bhushan, V.; Nandanan, E.; Ravindranathan, T. *J. Org. Chem.* **1995**, *60*, 5983−5985.
(7) (a) Allevi, P.; Anastasia, M.; Ciuffreda, P. *Tetrahedron Lett.* **1991**, *32*, 6927−6930. (b) Yin, S. F.; Ma, W. Y.; Wang, T. D.; Chen, X. H.; Zhang, C. N. *Acta Pharm. Sin.* **1993**, *28*, 668−672.
(8) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc*. **1996**, *118*, 9202−9203. (b) Zhou, B.; Guo, J.; Danishefsky, S. *Org. Lett*. **2002**, *4*, 43−46.
(9) (a) Nishimura, K.; Tomioka, K. *J. Org. Chem*. **2002**, *67*, 431−434 and references therein. (b) Diastereoselective intramolecular sulfur transfer, see: Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc*. **2001**, *123*, 5602−5603.
(10) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc*. **2000**, *122*, 11340−11347.
(11) Capon, B. *Q. Rev.* **1964**, *8*, 45−111.
(12) For recent reviews, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 599−619. (b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. (c) Atkinson, R. A. *Tetrahedron* **1999**, *55*, 1519−1559. (d) McCoull, W.; David, F. *Synthesis* **2000**, 1347−1365.
(13) For nomenclature, see Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1−13. (b) Reference 10, p 45.
(14) Compound **3** was synthesized by a phenolic aldol condensation between sesamol and Garner's aldehyde followed by selective *O*-methylation, see: Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem*. **1988**, *53*, 4919−4922.
(15) Poelert, M. A.; Hof, R. P.; Peper, N. C. M. W.; Kellog, R. M. *Heterocycles* **1994**, *37*, 461−475.

The 2,4-dimethoxyphenyl-substituted amino diol (**8**) participates as well in this process. It is interesting to note that even with sterically hindered *tert*-butylthiol, the corresponding sulfide **9b** (Figure 3) can still be isolated in reasonably



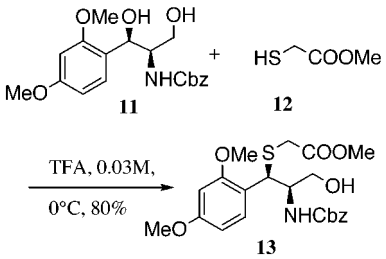
8 XR = OH
9a XR = SCH_2COOMe, 51%, *de* = 10/1
9b XR = SBu^t, 43%, *de* = 10/1

Figure 3.

good yield. On the other hand, compound **10** lacking the *o*-methoxy substituent did not react with the thiol and only deprotection of the *N*-Boc function was observed under identical conditions. The requirement of an *O*-methoxy group for thiolation is tentatively attributed to its inductive effect arising from the close proximity of the electronegative oxygen to the reaction center and is also in accord with the double S_N2 rather than S_N1 process.[16] Taft and co-workers have demonstrated that the inductive effect dominates over the resonance effect for *ortho* substituents by a factor of nearly two to one, while for *para* substituents the reverse is true.[17]

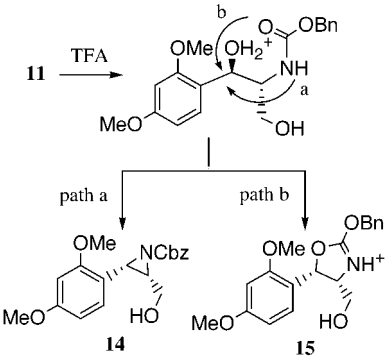
It is reasonable to hypothesize the neighboring group participation in view of the excellent diastereoselectivity obtained in such an acyclic system. Nevertheless, it is unclear whether the *N*-Boc was removed before or after the introduction of the thiol unit.[18] Indeed, the ring opening of *N*-unprotected aziridine by thiol in the presence of Lewis acid is known.[19] To clarify this point, the *N*-Cbz derivative **11** was synthesized. Reaction of **11** with methyl thioglycolate (**12**) under the standard conditions provided the sulfide **13** again in excellent diastereoselectivity (Scheme 2).

Scheme 2



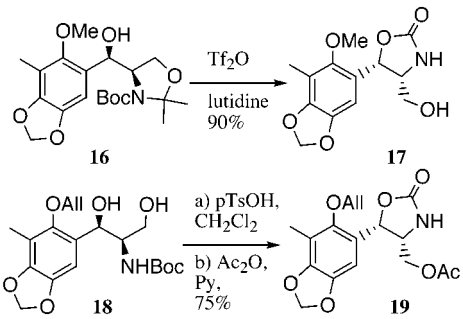
Starting from **11**, two reaction manifolds via either *N*-3 (path a, Scheme 3) or *O*-5 participation (path b) of the vicinal

Scheme 3



N-carbamate leading to aziridine **14** and iminocarbonate salt **15**, respectively, can be envisaged. Ring opening of **14** or **15** by thiol via a second S_N2 process then accounts for the overall retention of configuration at the benzylic position. We favored the pathway b based on the following arguments. First of all, the formation of the five-membered ring is kinetically and thermodynamically favored over the three-membered counterpart for both the entropy and the enthalpy factors. Indeed, ring closure of *N*-2-bromoethylbenzamide with methoxide gave exclusively the 2-oxazolines,[20] even though it is known that *N*-attack leading to the aziridine should be favored with an ionized (basic conditions) amide group.[21] Second, control experiments showed that formation of the 2-oxazolidinone from **16** is extremely facile. Thus, treatment of a dichloromethane solution of **16** with triflic anhydride (Tf_2O) in the presence of 2,6-lutidine provided directly the 2-oxazolidinone **17** whose stereochemistry was determined to be 4*R*,5*S* from detailed NMR studies (Scheme 4).[22] Even more relevant, treatment of a dichloromethane

Scheme 4



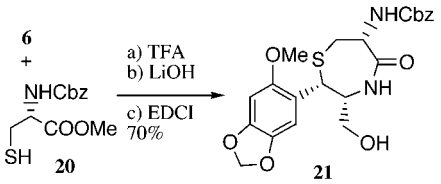
solution of **18** with *p*TsOH provided **19** in about 75% yield after acylation of the primary alcohol.[23] No trace amount of *N*-Boc aziridine was isolable from the reaction mixture under these conditions. Although these considerations did not

(16) Smith, M. B.; March, J. *Advances in Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; pp 436−437.
(17) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1−80.
(18) Neighboring group participation of *N*-*tert*-butyloxycarbamate can be a very fast process that is able to override the reduction of epoxide with a strong reductant such as LAH and Red-Al, see note 7 of: Urabe, H.; Aoyama, Y.; Sato, F. *Tetrahedron* **1992**, *48*, 5639−5646.

preclude the possibility of aziridine intermediate **14**, they are supportive of the iminocarbonate intermediate **15** in the present thiolation reaction. The preferential attack of thiol at the benzylic position rather than the C-2 position of **15** can be explained on the basis of the HSAB principle.[24]

The potential application of the present synthesis of chiral aminosulfide is illustrated in Scheme 5. Thus, condensation

Scheme 5



of **6** with *N*-Cbz-cysteine methyl ester (**20**) followed by saponification of the ester and lactamization provided the thiazepinone **21**. Compound **21** can also be considered as a reduced form of the ring-constrained dipeptide mimetic of β-aryl Ser-Cys whose potential as a dual ACE/NEP inhibitor has been demonstrated.[25]

In conclusion, we developed a stereoselective thiolation process of a vicinal amino alcohol via an iminocarbonate intermediate. To the best of our knowledge, it is the first example wherein the iminocarbonate was used as a transient aziridine equivalent for the introduction of thio unit with retention of configuration.[26]

Acknowledgment. We thank the CNRS for financial support. M. De Paolis thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a doctoral fellowship and J. Blankenstein thanks the Swiss National Science Foundation for a postdoctoral grant.

Supporting Information Available: Full experimental details and characterization data for compounds **5a**−**5d**, **7**, **9a**, **9b**, **13**, **17**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790−791.

(20) (a) Winstein, S.; Goodman, L.; Boschan, R. *J. Am. Chem. Soc.* **1950**, *72*, 2311. (b) Heine, H. W. *J. Am. Chem. Soc.* **1956**, *78*, 3708−3710.

(21) For a recent example of *N*-Cbz aziridine formation under specific conditions, see: Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045−2048.

(22) The (4*R*,5*R*) diastereoisomer of **17** was synthesized by reaction of **16** with NaH followed by acidic hydrolysis.

(23) While sulfide **5** was stable in TFA, the amino diols **3** and **6** decompose rapidly in TFA at 0 °C.

(24) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539. (b) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561−567.

(25) Crescenza, A.; Botta, M.; Corelli, F.; Santini, A.; Tafi, A. *J. Org. Chem.* **1999**, *64*, 3019−3025.

(26) (a) For bromide-mediated rearrangement of cyclic iminocarbonate to cyclic carbamate, see: Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745−8747. (b) For ring opening of oxazolidinone by thiolate, see: Ishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115−2120. (c) Imide carbonyl assisted thiolation of benzylic alcohol has also been postulated; see ref 2a.