ORGANIC LETTERS

2000
Vol. 2, No. 16
2423−2425

Syntheses of Optically Active Trifluoronorcoronamic Acids

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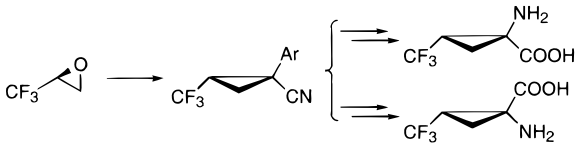
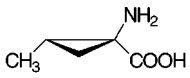
Received April 28, 2000

ABSTRACT



Syntheses of optically active trifluoronorcoronamic acid 6 and its diastereomer 9 are described. Highly stereospecific and diastereoselective S_N2 cyclization of γ-cyanohydrins 3a and 3b gave cyclopropyl nitriles 4a and 4b. Hydrolysis of the cyano group and deprotection of the amino group of 4a provide trifluoronorcoronamic acid 6. Hofmann rearrangement of the amide which was generated by hydrolysis of the cyano group and oxidative cleavage of the aryl ring of 4b to provide trifluoro-*allo*-norcoronamic acid 9.

The cyclopropyl amino acids, 1-aminocyclopropane-1-carboxylic acid, and its derivatives have been of interest to scientists for their roles and reactions in vivo,[1] which include roles as intermediates in the biosynthesis of the fruit ripening hormone ethylene,[2] as components of bacterial phytotoxins,[3] and as intermediates in the biosynthesis of cyclic amino acid azetidine-2-carboxylic acid.[4] Norcoronamic acid **1** is such a naturally occurring cyclopropyl amino acid which was isolated after hydrolysis of bacterial toxin norcoronatine from *Pseudomonas syringae*.[5]



norcoronamic acid **1**

The conformationally constrained nature of the cyclopropyl amino acids is of interest and may affect the conformation of peptides containing the amino acid, controlling interactions with enzymes and receptors.[1a] Fluorination of the compound could result in a further change of properties, via electronic effects and by modifying chemical stability.[6] Although there are many published examples of the synthesis of cyclopropyl amino acids, there have been few reports on the fluorinated analogues of cyclopropyl amino acids.[7] To date there has been no report on the fluorinated analogue of norcoronamic acid, 2-trifluoromethyl-1-aminocyclopropane-1-carboxylic acid.

Herein, we wish to report stereoselective syntheses of trifluorinated norcoronamic acid **6** and its diastereomer **9**, 2-trifluoromethyl-1-aminocyclopropane-1-carboxylic acid,

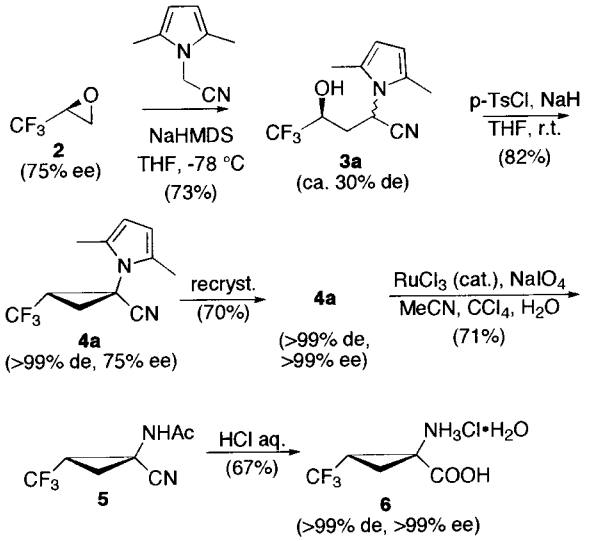
(1) (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575 and references therein.
(2) Burroughs, L. F. *Nature* **1957**, *179*, 360. Baldwin, J. E.; Adlington, R. M.; Lajoie, G. A.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1496.
(3) Mitchell, R. E. *Phytochemistry* **1985**, *24*, 1485.
(4) Leete, E.; Louters, L. L.; Rao, H. S. P. *Phytochemistry* **1986**, *25*, 2753.
(5) Ichihara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.
(6) (a) *Fluorine-containing Amino Acids Synthesis and Properties*; Kukhar', V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: New York, 1995. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (c) *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; American Chemical Society: Washington, DC, 1995.
(7) Sloan, M. S.; Kirk, K. L. *Tetrahedron Lett.* **1997**, *38*, 1677.
(8) The compound having *S* configuration of 75% ee is commercially available: (a) Furuhashi, K. *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons: New York, 1992; p 167. Optically pure 2,3-epoxy-1,1,1-trifluoropropane and its synthon are also available in laboratory scales: (b) Bussche-Hunnefeld, C. von der; Cescato, C.; Seebach, D. *Chem, Ber.* **1992**, *125*, 2795. (c) Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41. (d) Shimizu, M.; Sugiyama, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2655. (e) Katagiri, T.; Obara, F. *Jpn. Kokai Tokkyo Koho* **1994**, Jp06-247953. (f) Vanhessche, K. P. M.; Sharpless, K. B. *Chem. Eur. J.* **1997**, *3*, 517.

10.1021/ol0059955 CCC: $19.00
Published on Web 07/13/2000

from an optically active epoxide. Our approach is based on a cyclization of optically active 4-hydroxy-5,5,5-trifluoronorvaline cyanide derivatives **3**, which were derived from the reaction between optically active 2,3-epoxy-1,1,1-trifluoropropane **2**[8] with substituted acetonitriles.[9] The key cyclization step to cyclopropane **4** involved an S_N2 reaction (inversion of configuration at the electrophilic center) with high diastereoselectivity and created the amino acid α-carbon as a new stereogenic center.[10] Thus, the configuration of the epoxide controls the stereochemistry of the final product in our strategy.

Preparation of the cyanohydrin **3a** as a diastereomeric mixture was conducted in a manner similar to that described in our previous reports.[9] The yield of **3a** was 73%, while the diastereomeric excess of **3a** was ca. 30% de. The diastereomeric mixture of cyanohydrin **3a** was then cyclized to cyclopropyl cyanide **4a** without further purification. In the course of this intramolecular nucleophilic substitution, one of the chiral centers was epimerized via a planar cyano-stabilized carbanion. Then, highly diastereoselective cyclization occurred to yield cyclopropyl cyanide **4a**, controlled by the steric effect exerted by the trifluoromethyl group attached to the chiral carbon. The yield of **4a** was 82%, and the diastereomeric excess of **4a** was found to be >99%. Recrystallization of **4a** gave optically pure **4a** in 70% yield.[8] Oxidative degradation of the pyrrole ring of **4a** gave amino nitrile **5** (71%); then hydrolysis of the cyano group afforded the optically pure trifluoronorcoronamic acid **6** in 67% yield (Scheme 1).[11]

Scheme 1



Configuration of cyclopropylcyanide **4a** was confirmed by X-ray crystallographic analysis; the ORTEP diagram of **4a** is shown in Figure 1.[12]

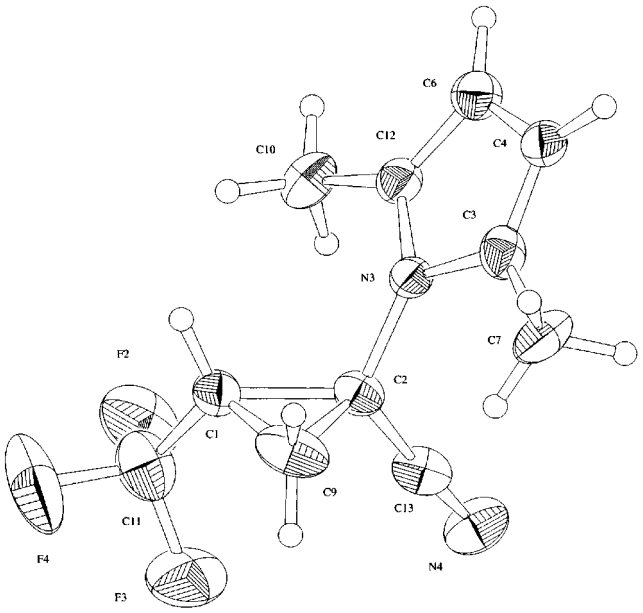


Figure 1. X-ray structure of **4a**.

A similar preparation of the diastereomeric mixture of cyanohydrins **3b** followed by cyclization gave cyclopropyl cyanide **4b** in 67% yield and 90% diastereomeric excess. Recrystallization of **4b** gave enantiomerically pure cyclo-

(9) Katagiri, T.; Akizuki, M.; Kuriyama, T.; Shinke, S.; Uneyama, K. *Chem. Lett.* **1997**, 549.

(10) Katagiri, T.; Irie, M.; Uneyama, K. *Tetrahedron: Asymmetry* **1999**, *10*, 2583.

(11) Spectroscopic data for trifluoronorcoronamic acid hydrochloride monohydrate (**6**): white powder, mp 200 °C (dec); $[\alpha]^{20}_D$ +13.6 (*c* 1.2, H_2O); IR (KBr) 3448, 3040, 1618 cm^{-1}; ^1H NMR (D_2O) δ 1.58 (ddq, J = 10, 8, 1, 1H), 1.90 (dd, J = 8, 7, 1H), 2.17−2.38 (ddq, J = 10, 7, 7, 1H); ^{19}F NMR ($CDCl_3$, C_6F_6 internal standard) δ 106.9 (d, J = 7). Anal. Calcd for $C_5H_9ClF_3NO_3$: C, 26.86; H, 4.06; N, 6.26. Found: C, 27.08; H, 4.32; N, 6.47.

(12) Crystal data for cyclopropyl cyanide **4a**: $C_{11}H_{11}F_3N_2$; M_r = 228.22; orthorhombic; $P2_12_12_1$; a = 8.1846(6), b = 19.407(2), and c = 7.0250(6) Å, V = 1115.8400 $Å^3$, Z = 4, D_x = 1.358 g/cm^3; μ = 1.17 cm^{-1} for Mo Kα radiation (λ = 0.7107 Å). The structure was solved by a direct method (SIR 92) and refined by a full-matrix least-squares method. Final R was 0.078 and R_w was 0.107 for 916 reflections with $I_0 > 3.00\sigma(I_0)$. Reflection/parameter ratio was 5.87. Goodness of fit indicator was 3.70. Max shift/error in final cycle was 0.06.

(13) Spectroscopic data for *N*-Boc-trifluoro-*allo*-norcoronamic acid (**9**): white solid, mp 158−159 °C; $[\alpha]^{20}_D$ −25.5 (*c* 3.2, $CDCl_3$); IR (KBr) 3370, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.81 (m, 1H), 2.00 (m, 1H), 2.52 (m, 1H), 5.15 (br, 1H); ^{19}F NMR ($CDCl_3$, C_6F_6 internal standard) δ 100.5 (d, J = 6); EI-MS (rel int) 169 (17, M^+ − Boc), 59 (33), 57 (100), 41 (27). Anal. Calcd for $C_{10}H_{14}F_3NO_4$: C, 44.61; H, 5.24; N, 5.20. Found: C, 44.69; H, 5.05; N, 5.58.

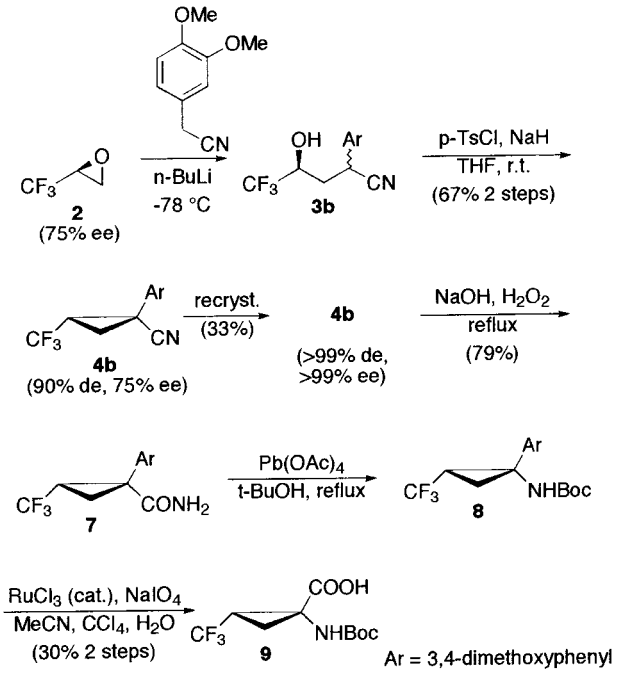
(14) Present diastereomeric configurations of the cyclopropanes **4a** and **4b** are consistent with our previous X-ray crystallographic results of the derivative from 1-phenyl-1-cyano-2-trifluoromethylcyclopropane having (1*S*,2*S*) configuration, see ref 10.

(15) Crystal data for cyclopropyl cyanide **4b**: $C_{13}H_{12}F_3NO_2$; M_r = 271.24; orthorhombic; $P2_12_12_1$; a = 12.9184(5), b = 14.0537(5), and c = 7.0743(2) Å, V = 1284.35(8) $Å^3$, Z = 4, D_x = 1.403 g/cm^3; μ = 1.23 cm^{-1} for Mo Kα radiation (λ = 0.7107 Å). The structure was solved by a direct method (SIR 92) and refined by a full-matrix least-squares method. Final R was 0.065 and R_w was 0.084 for 1343 reflections with $I_0 > 3.00\sigma(I_0)$. Reflection/parameter ratio was 7.30. Goodness of fit indicator was 3.12. Max shift/error in final cycle was 0.09.

(16) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, A., Ed.; Wiley-VCH: New York, 1993; p 103. Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, A., Ed.; Wiley-VCH: New York, 1993; p 159.

propyl cyanide **4b** in 33% yield. Hydrolysis of the cyano group gave amide **7** (79%); then Hofmann rearrangement followed by oxidative degradation of aromatic ring of amine **8** gave Boc-protected trifluoro-*allo*-norcoronamic acid **9** in 30% yield (two steps) (Scheme 2).[13]

Scheme 2



Configuration of the cyclopropyl nitrile compound **4b** was also confirmed by X-ray crystallographic analysis; the ORTEP diagram of compound **4b** is shown in Figure 2.[14,15]

The present strategies for the preparation of cyclopropyl amino acids are characterized by utilization of the chiral center from epoxide, which controls the stereochemistry of the amino acid α-carbon in the course of the cyclization. The α-carbon of the amino acid was epimerized upon becoming a cyano-stabilized carbanion and did not therefore influence the stereochemistry of the final cyclopropane at all. Also, the cyano group is convenient for the preparation of amino acids, because it can be converted both to an amino group via Hofmann-type rearrangement and to a carboxyl group via simple hydrolysis. Because of recent advances in

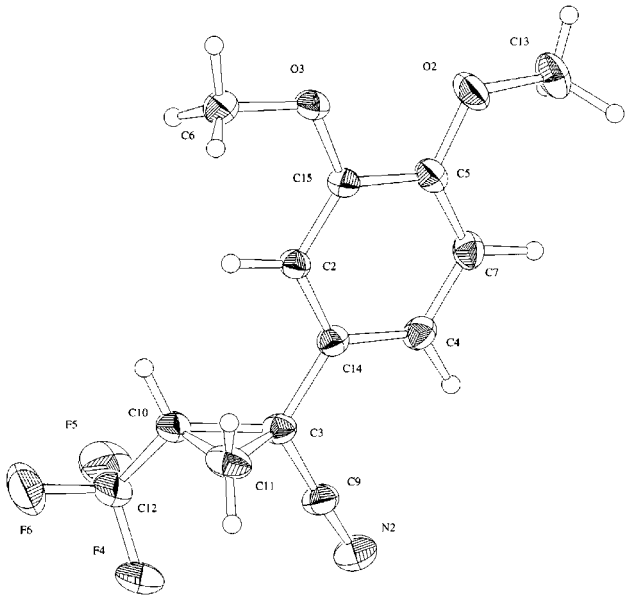


Figure 2. X-ray structure of **4b**.

chiral epoxidation,[16] the optically active epoxide has become a reliable class of chiral building blocks. Our present strategy would therefore be a highly reliable method for stereocontrolled preparation of cyclopropyl amino acids. Studies on the scope of the present strategies for the preparation of other cyclopropyl amino acids are now in progress.

Acknowledgment. We thank SC-NMR Laboratory of Okayama University for ^{19}F and ^{1}H NMR analyses and the Venture Business Laboratory of Graduate School of Okayama University for X-ray crystallographic analysis. This work was partly support by Monbusho (Grant-in-Aid for Scientific Research on Priority Areas, No. 706 (Dynamic Control of Stereochemistry) and No. 12650854) and by The Shorai Foundation for Science and Technology.

Supporting Information Available: Full experimental details and characterization data for compounds **3a**, **4a**, **4b**, **5**, **6**, **7**, and **9** and CIF files for **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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