present work. This allows an absolute value of $D(F^-–HF)$ of 39.1 kcal mol^{-1} to be established. Second, Kebarle's[13] value of 23.3 kcal mol^{-1} for $D(F^-–H_2O)$ and the ladder of fluoride transfer equilibrium measurements of the present work establish an absolute value of $D(F^-–HF)$ of 38.6 kcal mol^{-1}. These two independent methods of rendering our relative scale an absolute one are thus seen to be in excellent agreement.

We thus suggest that a new completely experimental value for $D(F^-–HF)$ of 39 ± 1 kcal mol^{-1} (163 ± 4 kJ mol^{-1}) be adopted. It is interesting to note that this value is in best agreement with the lowest of the previous experimental determinations[8] based on crystal lattice energy assumptions and in excellent agreement with the ab initio quantum chemical calculations by Noble and Kortzeborn.[11]

Acknowledgment. Financial support of the Natural Sciences and Engineering Research Council Canada is gratefully acknowledged. We thank M. Roy for the synthesis of ketene.

Registry No. FHF^-, 18130-74-0.

Opening of Epoxides with Trimethylsilyl Cyanide To Produce β-Hydroxy Isonitriles. A General Synthesis of Oxazolines and β-Amino Alcohols

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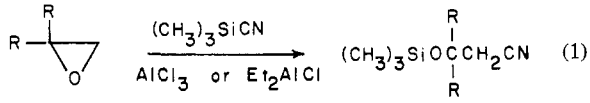
Recently, trimethylsilyl cyanide has been reported to react with epoxides under catalysis by aluminum chloride[1] or diethylaluminum chloride[2] to produce the trimethylsilyl ethers of β-hydroxy nitriles (eq 1). A type of general Lewis acid catalysis



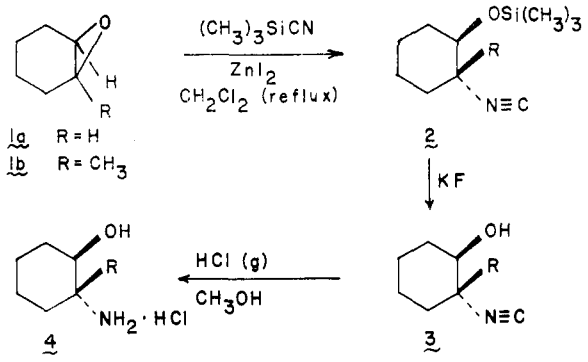
(1)

has been invoked to explain these transformations.[2] We now report (a) that catalysis of the addition of trimethylsilyl cyanide to epoxides with zinc iodide gives an entirely different product, namely, the trimethylsilyl ether of β-hydroxy isonitriles, and (b) that this highly stereospecific synthesis of β-hydroxy isonitriles provides ready access to stereospecifically substituted oxazolines and β-amino alcohols.

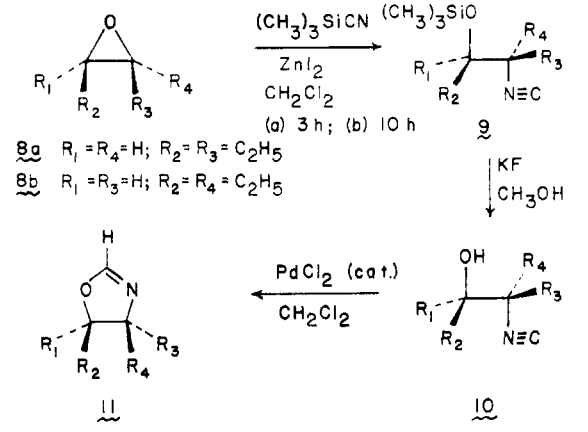
In a typical procedure, 1 equiv of cyclohexane epoxide (**1a**), Scheme I, was treated with 2 equiv of trimethylsilyl cyanide and a catalytic amount (0.5 mol%) of zinc iodide in refluxing methylene chloride for 4 h to give 73% of **2a**.[3] Removal of the trimethylsilyl protecting group from **2a** was accomplished with 3 equiv of potassium fluoride in methanol to give 98% of **3a**. The stereochemistry of the epoxide opening was shown to be trans through the hydrolysis of **3a** to the known amine hydrochloride, **4a**, in 88% yield, mp 174–175 °C (lit.[4] mp 176–177 °C).[5,6]

The same sequence of reactions that had been carried out on **1a** was performed on 1-methylcyclohexene epoxide (**1b**) in order to evaluate the regiospecificity of this useful isonitrile synthesis. Under the reaction conditions described above, **1b** gave 79% of **2b**. Both the stereospecificity and the regiospecificity of the

Scheme I



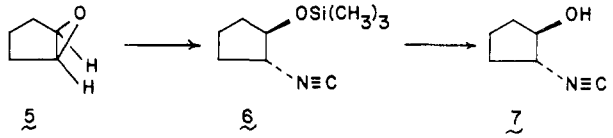
Scheme II



opening of the epoxide moiety of **1b** were very clean. The regiospecificity was established through careful analysis of the proton-decoupled ^{13}C NMR spectrum of **2b**, which showed the quaternary carbon as a triplet of equal intensity peaks due to the coupling of this carbon with the nitrogen of the isonitrile group.[7] It is of particular significance that the regiospecificity of the zinc iodide catalyzed reaction[8] is the opposite of that reported[2] for the aluminum trichloride promoted reaction.[9]

Deprotection of **2b** with potassium fluoride gave an 81% yield of **3b**. Hydrolysis of **3b** with methanolic hydrogen chloride produced **4b**, mp 199–202 °C, in 80% yield. The formation of the β-amino alcohol having the amino group on the tertiary carbon illustrates the synthetic potential of our reaction sequence for this class of compounds.

In a general extension of this new synthetic method, we treated cyclopentene epoxide (**5**) (eq 2) with trimethylsilyl cyanide in the



(2)

presence of zinc iodide for 12 h to yield 77% of **6**. Deprotection of the hydroxyl moiety of **6** with potassium fluoride gave a 92% yield of **7**. The stereochemistry of **7** was established through the hydrolysis of **7** to the known *trans*-β-amino alcohol hydrochloride salt, mp 192.5–194.0 °C (lit.[10] mp 193–194 °C). In a similar series of reactions, *cis*-3-hexene epoxide (**8a**), was treated with trimethylsilyl cyanide in the presence of zinc iodide to give 82%

(1) Lidy, W.; Sundermeyer, W. *Tetrahedron Lett.* **1973**, 1449.
(2) Mullis, J. C.; Weber, W. P. *J. Org. Chem.* **1982**, *47*, 2873.
(3) Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds. In all cases the spectral data (IR, NMR, etc.) were consistent with the assigned structures. All yields reported are of isolated, purified material.
(4) McCasland, G. E.; Clark, R. K.; Carter, H. E. *J. Am. Chem. Soc.* **1949**, *71*, 637.
(5) The overall yield of **4a** from **1a** was 63%. This offers a very simple and highly stereospecific path to β-amino alcohols.
(6) Schöllkopf, U.; Böhme, P. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 491.
(7) Stephany, R. W.; de Bie, M. J. A.; Drenth, W. *Org. Magn. Reson.* **1974**, *6*, 45. Koole, N. J.; Knol, D.; de Bie, M. J. A. *J. Magn. Reson.* **1976**, *21*, 499. Kuntz, I. D., Jr.; Schleyer, P. von R.; Allerhand, A. *J. Chem. Phys.* **1961**, *35*, 1533. Spiesecke, H. *Z. Naturforsch., A* **1968**, *23A*, 467.
(8) It should be noted that the opening of **1b** occurred faster than the opening of **1a**. With **1b** the reaction was complete in 3 h.
(9) This reversal of regiochemistry firmly established that very different mechanisms are involved in the presence of the two different catalysts.
(10) McCasland, G. E.; Smith, D. A. *J. Am. Chem. Soc.* **1950**, *72*, 2190.

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of **9a** (Scheme II).[11] Treatment of **9a** with methanolic potassium fluoride gave 75% of **10a**. When **10a** was treated with a catalytic amount of palladium chloride[12] (0.8 mol %), an 80% yield of **11a** was obtained. In an analogous series of reactions **8b** gave 74% of **9b**; **9b** yielded 81% of **10b**; and **10b** gave 75% of **11b**. Spectroscopic and/or chromatographic comparisons of **9a** and **9b**, **10a** and **10b**, and **11a** and **11b** showed that in each case the isomers were uncontaminated by the epimer. Thus, very epimerically pure β-amino alcohols and oxazolines can be synthesized from the isonitriles prepared by our method.

In summary, we have shown that the addition of trimethylsilyl cyanide to epoxides is extremely dependent on the nature of the Lewis acid catalyst. With zinc iodide, a new synthetic route to isonitriles has been developed. These isonitriles are extremely useful intermediates for the synthesis of β-amino alcohols and oxazolines.

Acknowledgment. We are indebted to the National Science Foundation for Grant CHE81-14772, which supported this investigation.

Registry No. 1a, 286-20-4; **1b**, 1713-33-3; **2a**, 83152-87-8; **2b**, 83152-88-9; **3a**, 83152-97-0; **3b**, 83152-89-0; **4a**, 5456-63-3; **4b**, 5456-63-3; **5**, 285-67-6; **6**, 83152-90-3; **7**, 83152-98-1; **8a**, 36611-94-6; **8b**, 36611-93-5; **9a**, 83152-91-4; **9b**, 83152-94-7; **10a**, 83152-92-5; **10b**, 83152-95-8; **11a**, 83152-93-6; **11b**, 83152-96-9; $(CH_3)_3SiCN$, 7677-24-9; ZnI_2, 10139-47-6; *trans*-β-amino alcohol hydrochloride salt, 31775-67-4.

(11) The stereochemistry of the ring opening of **8a** and **8b** has not been rigorously established. The assignments of the stereochemistry of **9a** and **9b** were made by analogy to the stereochemistry of the ring opening of **1** and **5**.

(12) Bartel, K.; Fehlhammer, W. P. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 599.

Synthesis of Nanaomycin A and Deoxyfrenolicin by Alkyne Cycloaddition to Chromium–Carbene Complexes

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Deoxyfrenolicin (**1**)[2] and nanaomycin A (**2**)[3] are members of a group of naphthoquinone antibiotics based on the isochroman skeleton. The significant antibiotic activity[2,4] and potential antitumor activity[5] of members of this group have prompted numerous recent synthesis efforts.[6] As part of a general study in naphthoquinone synthesis directed toward granaticin (**3**), we have developed a strategy (Scheme I) that relies on two key steps: cycloaddition of an alkyne (ideally **4**) with a carbene–chromium complex (**5**)[7] and intramolecular alkoxycarbonylation of an hydroxy alkene (**6**) to form the pyran ring. High regioselectivity and functional group compatibility are required in the alkyne cycloaddition. Since regioselectivity in the alkyne cycloaddition appears to be strongly influenced by steric effects of the alkyne substituents and since the few *di*substituted alkynes that have been tested show poor regioselectivity,[7,8] we studied intermolecular reaction with a very simple *mono*substituted alkyne, allylacetylene.[9]

Scheme I. Strategy

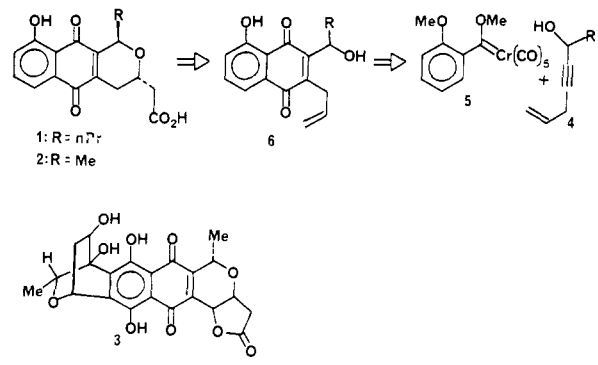
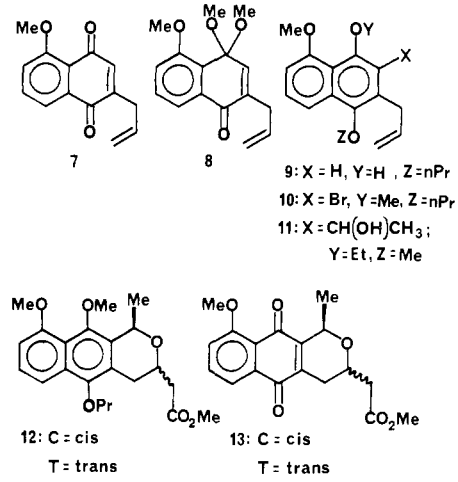


Chart I



The first target was nanaomycin A (**2**). Reaction of *o*-lithioanisole[10] with $Cr(CO)_6$ (equimolar) in ether at 25 °C for 2 h followed by addition of methyl fluorosulfonate (3-fold excess) gave the known[11] complex, **5**, as red crystals in 77% yield overall from *o*-bromoanisole. Heating a solution of complex **5** (10 mmol) and allylacetylene (15 mmol) in THF at 45 °C for 36 h led to a red solution. After removal of the volatiles at reduced pressure, the residue was oxidized with ceric ammonium nitrate (aqueous acetonitrile; 25 °C/0.5 h) to give a mixture which was partitioned between ether and water. From the ether was isolated 2-allyl-5-methoxy-1,4-naphthoquinone (**7**, 52% (Chart I)).[12] Alternatively, oxidation of the crude product in methyl alcohol led directly to the monoketal **8** (54% yield). Only one regioisomer was de-

(1) Recipient of an NIH Postdoctoral Fellowship: (a) 1978–1981; (b) 1980–1982.

(2) Deoxyfrenolicin (**1**) is a degradation product of a natural epoxy naphthoquinone, frenolicin: Ellestad, G. Z.; Kunstmann, M. P.; Whaley, H. A.; Patterson, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 1325.

(3) (a) Omura, S.; Tanaka, H.; Koyana, Y.; Oiwa, R.; Katagiri, M. *J. Antibiot.* **1974**, *25*, 363. (b) Tanaka, H.; Koyama, Y.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *Ibid.* **1975**, *28*, 860. (c) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Omura, S. *Ibid.* **1975**, *78*, 868.

(4) Deoxyfrenolicin shows antibacterial activity in vitro and antifungal activity against a variety of fungi in vivo: (a) van Meter, J. C.; Cann, M.; Bohonos, N. "Antibacterial Agents Annual, 1960"; Plenum Press: New York, 1961; p 77. (b) Iwai, Y.; Kora, A.; Takahashi, Y.; Awaya, T.; Masuma, R.; Oiwa, R.; Omura, S. *J. Antibiot.* **1978**, *31*, 959

(5) For a discussion and leading references, see: Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527.

(6) (a) Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 609–612. (b) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans 1* **1981**, 1197–1202. (c) Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, *22*, 4469–4477. (d) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923–4924. (e) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978** *100*, 6263–6265. (f) Pyrek, J. St.; Achmatowica, O.; Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673–680.

(7) (a) Dotz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644–645. (b) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449–1457. (c) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4–C6 and references therein.

(8) Wulff, W. D.; Tang, T. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677–7678.

(9) While this work was in progress, Dr. Dötz reported a series of similar reactions with allylacetylene and other enynes; see ref 7b.

(10) This compound can be prepared either by bromine–lithium exchange with *n*-butyllithium in hexane [according to the procedure: Glaze, W. H.; Ranade, A. C. *J. Org. Chem.* **1971**, *36*, 3331] or by direct metalation of anisole with *n*-butyllithium in ether [see: Ronald, R. C. *Tetrahedron Lett.* **1975**, 3973–3977 and references therein].

(11) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Muller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237.

(12) Eisenhuth, W.; Schmid, H. *Helv. Chim. Acta* **1958**, *41*, 2021.

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