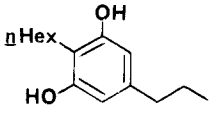
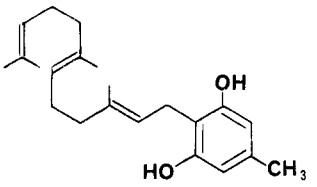
1-4[9-11] provides efficient regiocontrolled routes to a variety of differentially protected resorcinol and phloroglucinol derivatives. The synthesis of the antifungal antibiotics DB-2073 (**26**)[15] and grifolin (**27**)[16] demonstrates the utility



26



27

of this approach. Thus, exposure of **17** to 4 equiv of trimethylsilyl iodide[17] in acetonitrile (reflux, 24 h) produced DB-2073 in 89% yield, while cleavage of the methyl ether in annulation product **20** was achieved by treatment with excess methylmagnesium iodide[18] at 165 °C for 15 min (49-83% yield). Pure grifolin was obtained in 21-43% overall yield (from (*E,E*)-farnesol) in this manner.[19]

Both alkynyl thioethers[20] and ynamines[21] participate as reactive ketenophiles in the regiocontrolled phenol annulation. The thioethers function in these reactions as ketenophilic equivalents for unactivated acetylenes, since the resulting annulation products readily undergo desulfurization to yield *monooxygenated* benzene derivatives. Thus, treatment of aryl sulfide **21** with excess Raney nickel[22] in methanol (reflux, 2 h) furnished 2,4,5-trimethylphenol[23] in 99% yield after chromatographic purification.

Finally, annulations employing 4,4-dichlorocyclobutenone derivatives[24] generate highly substituted 2-chlorophenols, presumably via intermediate 6,6-dichlorocyclohexadienones which undergo radical-mediated dechlorination at the elevated reaction temperature.

Further studies are underway in our laboratory to demonstrate the utility of this methodology in the total synthesis of antitumor antibiotics.[3]

Acknowledgment. Annulation experiments involving dichlorocyclobutenones were carried out by Katherine S. Takaki. We thank the National Institutes of Health and Eli Lilly and Co. for generous financial support.

Supplementary Material Available: Full characterization (250-MHz ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data and/or elemental analyses) for all new compounds (7 pages). Ordering information is given on any current masthead page.

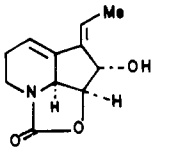
Rick L. Danheiser,*[2] Stephen K. Gee
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received February 29, 1984

(9) Preparation of 1: Jones, E. R. H.; Eglington, G.; Whiting, M. C.; Shaw, B. L. In "Organic Syntheses"; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 404.
(10) Acetylenes **2** and **3** were prepared by using the general method of Newman: (Newman, M. S.; Geib, J. R.; Stalick, W. M. *Org. Prep. Proc. Int.* **1972**, *4*, 89). For earlier syntheses, see: Nooi, J. R.; Arens, R. F. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 284.
(11) Alkynyl ether **4** was prepared in one step in 67-76% yield from (*E,E*)-farnesol[12] by sequential treatment in THF with 1.1 equiv of CH_3Li (-78 °C, 35 min), 1.1 equiv of MsCl (-78 °C, 1 h), and 1.4 equiv of MeOC≡CMgBr in the presence of 0.05 equiv of Li_2CuCl_4[13] (-78 → 25 °C).
(12) Pure (*E,E*)-farnesol was prepared from (*E*)-geranylacetone by reaction with (a) $(i\text{-PrO})_2POCH_2CO_2Et$-KO-*t*-Bu[14] (THF, 0 → 50 °C; 87% yield as a 93:7 mixture of *E* and *Z* isomers) and (b) DIBAL in CH_2Cl_2-hexane at -78 °C (50% yield, isomers separated on a Waters Prep LC-500).
(13) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(14) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(15) Kitahara, T.; Kanda, H. *J. Anbibiotics* **1975**, *28*, 943. For an earlier synthesis, see: Achenbach, H.; Kohl, W.; Kunze, B. *Chem. Ber.* **1979**, *112*, 1841.
(16) Goto, T.; Kakisawa, H.; Hirata, Y. *Tetrahedron* **1963**, *19*, 2079.
(17) Olah, G. A.; Narang, S. C.; Gupta, B. G.; Malhorta, R. *J. Org. Chem.* **1979**, *44*, 1247.
(18) Mechoalam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6159 and references cited therein.
(19) This constitutes the first total synthesis of grifolin that is both regio- and stereoselective. For previous approaches, see: Marquet, J.; Moreno-Manas, M. *Chem. Lett.* **1981**, 173 and references cited therein.
(20) Preparation of **5**: Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes, and Cumulenes"; Elsevier: Amsterdam, 1981; pp 106-107.
(21) Ynamine **6** was prepared in 56% yield by the method of Montijn et al. (Montijn, P. P.; Harryvan, E.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1211).
(22) Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356.
(23) Mp 63.5-64 °C (lit. mp 62 °C: Morgan, G. T.; Pettit, A. E. J. *J. Chem. Soc.* **1934**, 418).
(24) Readily available via the addition of dichloroketene to alkynes: Hassner, A.; Dillon, J. L. *J. Org. Chem.* **1983**, *48*, 3382. See also: Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23.

Synthesis of 2-Substituted Δ^3-Piperidines: The Nitrogen Analogue of the Ferrier Rearrangement. An Approach to Streptazolin

Summary: The Lewis acid induced reaction of *N*-carbethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine (**6**) with various carbon nucleophiles has been studied as a route to 2-substituted Δ^3-piperidines.

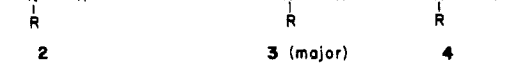
Sir: In our efforts to synthesize the structurally unique antimicrobial agent streptazolin, [2a*S*-(2aα,3α,4*Z*,7bα)]-4-ethylidene-2a,3,4,6,7,7b-hexahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent[*cd*]inden-1-one (**1**),[1] we needed to have



Streptazolin (1)

access to a 2-substituted-1,2,5,6-tetrahydropyridine. While the metal hydride reduction of substituted pyridinium salts represents a well-known technique for the production of tetrahydropyridines, it has generally been observed that the presence of a substituent at the 2-position leads to generation of the 2-substituted-1,2,3,6-tetrahydropyridine **3** as the major product.[2]

It thus became of interest to ascertain whether one could obtain access to compounds like **4** through an S_N2' (or S_N1') like reaction on the tetrahydropyridinol **6**. Such a



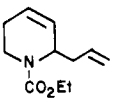
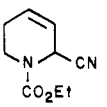
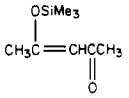
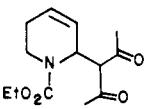
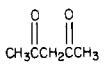
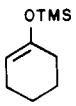
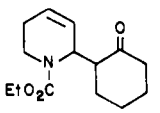
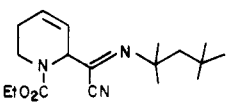
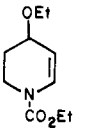
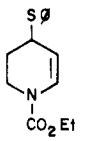
2 3 (major) 4

reaction does, of course, bear close resemblance to the well-known Ferrier rearrangement process of glycals.[3] The known 4-oxo-1,2,3,4-tetrahydropyridine **5**[4] was reduced to the alcohol **6** by using $NaBH_4/CeCl_3$.[5] On exposure of this alcohol in turn to allyltrimethylsilane in the presence of

(1) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.
(2) (a) Ferles, M.; Pliml, J. *Adv. Heterocycl. Chem.* **1970**, *12*, 43. (b) Lyle, R. E.; Anderson, P. S. *Ibid.* **1966**, *6*, 45.
(3) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180.
(4) Haider, A.; Cornuz, G.; Wyler, H. *Helv. Chim. Acta* **1975**, *58*, 1287.
(5) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

0022-3263/84/1949-1674$01.50/0

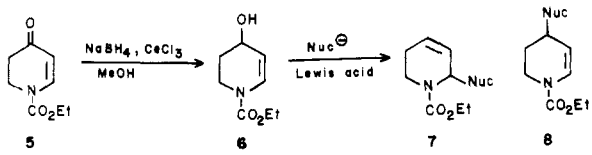
Table I. Reactions of 6 with Various Carbon and Heteroatom Nucleophiles

nucleophile (amount)	reaction conditions	product (yield, %)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$SnCl_4$ (1.2 equiv), CH_2Cl_2, -78 °C, 30 min	 7a (90)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$SnCl_4$ (1.2 equiv), CH_3CN, -78 °C → rt,[c] 20 min	7a (64)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$TiCl_4$ (1.3 equiv), CH_2Cl_2, -78 °C, 30 min	7a (89)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	$BF_3{\cdot}OEt_2$ (1.1 equiv), CH_3CN, 0 °C → rt, 30 min	7a (43)
$H_2C{=}CHCH_2SiMe_3$ (2 equiv)	Me_3SiOTf (1.3 equiv), CH_2Cl_2, -78 °C, 1 h	7a (51)
Me_3SiCN (6 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, -78 °C, 3 h	 7b (70)
 (2 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, -78 °C, 2 h	 7c (47)
 (solvent)	$BF_3{\cdot}OEt_2$ (1.5 equiv), 0 °C, 1.5 h	7c (24)
 (2 equiv)	Me_3SiOTf (1.5 equiv), CH_2Cl_2, -78 °C, 2.5 h	 7d (84)[a]
$(CH_3)_3CCH_2C(CH_3)_2N{\equiv}C$	Me_3SiOTf (1.3 equiv), CH_2Cl_2, -78 °C, 1.5 h	 7e (44)[b]
EtOH (solvent)	PPTS (1 equiv), rt, 1.5 h	 7f (67)
EtOH (solvent)	Me_3SiOTf (1.1 equiv), -78 °C, 3 h	7f (+ 5% diaddition product) (54)
C_6H_5SH (2 equiv)	PPTS (1.2 equiv), C_6H_6, rt, 1.5 h	 7g (46)
C_6H_5SH (1 equiv)	Me_3SiOTf (1 equiv), CH_2Cl_2, -78 °C, 3 h	7g (65)

[a] This compound was contaminated by an unidentified impurity and was thus further characterized by preparing its 2,4-dinitrophenylhydrazone derivative (mp 128-130 °C). [b] The assignment of structure to this product was based on its ^{13}C NMR. Its mechanism of formation is presumably related to that postulated in the Lewis acid catalyzed oligomerization of isocyanides: Saegusa, T.; Taka-ishi, N.; Ito, Y. *J. Org. Chem.* **1969**, *34*, 4040. [c] rt = room temperature.

a variety of Lewis acids (Table I),[6] **7a** was indeed formed in high yield. The 4-substituted product **8a** was detected as a relatively minor component in the crude reaction mixture (ratio ≃ 50:1). The reactions of **6** with several other nucleophiles were examined as well. As can be seen from the accompanying table, the 2-substituted products were formed predominantly, or exclusively, by using carbon nucleophiles, a result in line with the known kinetic preference for addition at the α-site of a conjugated imi-

(6) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, *24*, 1563.



5 6 7 8

nium ion system (e.g., pyridinium ions).[2]

When **6** was exposed to thiophenol or ethanol with use of pyridinium *p*-toluenesulfonate as catalyst, the 4-substituted-Δ^2-piperidines **7f** and **7g** (Table I) resulted. Apparently, the regiochemical orientation observed here represents a thermodynamic result. While initial kinetic addition may occur at the 2-position, an anomeric effect weakened by nitrogen lone-pair interaction with the carbethoxy substituent and the consequent nonbonded interactions between the ortho-related substituents as well as the resonance stabilization of the enamido system lead to migration of the heteroatom nucleophile to the 4-position. With trimethylsilyl triflate as catalyst, **6** likewise reacted with ethanol to afford **7f** plus a small amount of the diaddition product, *N*-carbethoxy-2,4-diethoxypiperidine.[7]

The work described herein thus provides a useful entry to 2-substituted-Δ^3-piperidines (for carbon nucleophiles) via the nitrogen analogue of the Ferrier rearrangement process. The chemistry further reveals the importance of iminium salts as reactive intermediates for organic synthesis.[8,9]

Experimental procedures for the preparation of **6** and its transformation to **7a** and **7b** follow.

***N*-Carbethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine (6).** To a stirred solution of the *N*-carbethoxy-4-oxo-1,2,3,4-tetrahydropyridine (**5**, 2.97 g, 17.6 mmol) and cerium(III) chloride hexahydrate (6.24 g, 17.6 mmol) in 44 mL of methanol was added sodium borohydride (678 mg, 17.6 mmol) in small portions at 0 °C over 20 min. The reaction mixture was diluted with 40 mL of water, concentrated in vacuo to ~40 mL, and extracted with ether (4 × 40 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated to afford 2.81 g (93%) of the alcohol **6** as a colorless oil. This compound was used in all subsequent reactions without further purification. Attempted chromatographic purification of **6** resulted in decomposition: IR (thin film) 3439, 3023, 2930, 2884, 1708, 1648, 1462, 1415, 1377, 1344, 1335, 1326, 1296, 1228, 1164, 1059, 997, 948, 878, 859, 834, 770, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, CH_3, J = 7.1 Hz), 1.60 (d, 1 H, OH, J = 5.5 Hz), 1.70–1.98 (m, 2 H, -CH_2CH_2N<), 3.41 (br t, 1 H, >CH_{ax}–N<, J = 11.1 Hz), 3.92 (m, 1 H, >CH_{eq}–N<), 4.10–4.32 (overlapping q and m, 3 H, CH_2CH_3, J = 7.1 Hz, >CHOH), 5.02 and 5.11 (two br s, 1 H, -CH=CHCHOH, collapsed to two d on irradiation at 4.22, J = 6.7 Hz), 6.98 (two br d, 1 H, -CH=CHCHOH, J = 8.1 Hz); mass spectrum (15 eV), m/z 171 (M^+), 154, 153, 152, 142, 124, 108, 102, 98, 80 (base), 74, 59, 45, 31, 29; exact mass calcd for $C_8H_{13}NO_3$ 171.0895; found 171.0887.

***N*-Carbethoxy-2-allyl-1,2,5,6-tetrahydropyridine (7a).** To a stirred solution of the allylic alcohol **6** (2.01 g, 11.8 mmol) and allyltrimethylsilane (3.79 mL, 23.3 mmol) in 20 mL of methylene chloride cooled to −78 °C was added stannic chloride (1.70 mL, 14.5 mmol) dropwise over 5 min. After 30 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, warmed to room temperature, and extracted with ether (4 × 50 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel with 3% ethyl acetate–hexanes as eluent to afford **8a** (30 mg) and a mixture of **7a** and **8a** (21 mg). On further elution, 2.06 g (90%) of **7a** was obtained as a colorless liquid: IR (thin film) 2904, 1695, 1456, 1352, 1326, 1243, 1195, 1103, 1034, 912, 767, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3 H, CH_3, J = 7.1 Hz), 1.89–2.02 (m, 1 H, >NCH_2CH_{ax}—), 2.20 (br s, 1 H, >NCH_2CH_{eq}—), 2.34 (t, 2 H, -CH_2CH=CH_2, J = 6.9 Hz), 2.90 (br s, 1 H, -$(CH_2)CH_{ax}N$<), 4.11–4.18 (m, 3H, -$CH_2CH_{eq}NC(O)OCH_2$-), 4.43 (br s, 1 H, >$NCHCH_2CH$=CH_2), 5.02–5.10 (m, 2 H, -CH_2CH=CH_2), 5.62–5.93 (m, 3 H, -CH=CH-, -CH=CH_2); mass spectrum (15 eV), m/z 196 (M^+ + 1), 154 (M^+ − CH_2CH=CH_2, base), 126, 82, 58, 43; exact mass calcd for $C_8H_{12}NO_2$ (M^+ − CH_2CH=CH_2) 154.0868, found 154.0868.

***N*-Carbethoxy-2-cyano-1,2,5,6-tetrahydropyridine (7b).** A stirred solution of the allylic alcohol **6** (34.2 mg, 0.200 mmol) and trimethylsilyl cyanide (160 μL, 1.20 mmol) in 8 mL of methylene chloride under a nitrogen atmosphere was cooled to −78 °C and treated with trimethylsilyl triflate (58.0 μL, 0.300 mmol). After 3 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, warmed to room temperature, and extracted with ether (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with 5% ethyl acetate–hexanes as eluent to give 25.2 mg (70%) of **7b** as an oil: IR (thin film) 2917, 1704, 1461, 1420, 1376, 1335, 1300, 1275, 1259, 1236, 1203, 1168, 1111, 1056, 1037, 987, 899, 770, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, CH_3, J = 7.1 Hz), 2.06–2.40 (m, 2 H, CH_2CH=CH-), 2.95–3.21 (m, 1 H, >$CH_{ax}N$<), 4.10–4.40 (m, 3 H, -CH_2CH_3, >$CH_{eq}N$<), 5.25 and 5.38 (two br s, 1 H, >CHCN), 5.70 (br s, 1 H, -CH=CHCHCN), 6.11 (br s, 1 H, -CH=CHCH(CN)-); mass spectrum (15 eV), m/z 180 (M^+), 152, 151 (base), 135, 125, 108, 107, 81, 80, 68, 42, 29; exact mass calcd for $C_9H_{12}N_2O_2$ 180.0899; found 180.0897.

Acknowledgment. This work was supported by National Institutes of Health and the Camille and Henry Dreyfus Foundation.

Supplementary Material Available: Characterization data for **7c–g** (2 pages). Ordering information is given on any current masthead page.

Alan P. Kozikowski,* Pyeong-uk Park
Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received November 14, 1983

(7) Natsume, M.; Sekine, Y.; Soyagimi, H. *Chem. Pharm. Bull.* **1978**, *26*, 2188.

(8) For some other examples of the trapping of iminium salts by allylsilanes, see: Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, *22*, 1567. Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

(9) For a report concerning the use of 2-cyano-Δ^3-piperidines as 5,6-dihydropyridinium salt equivalents, see: Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683 and references cited therein.

Intramolecular Reactions of Azidoalkenes. The 2-(Azidoalkyl)quinone Rearrangement

Summary: Rearrangements of 2-(azidopropyl)-1,4-benzo- and -1,4-naphthoquinones give 2-(2-Δ^1-pyrrolinyl)-4-cyclopentene-1,3-diones and pyrrolidino[2,1-*b*]azepine-1,5-diones via intermediate triazolines. Acid-catalyzed triazoline isomerization to an isolable diazo enedione is reported.

0022-3263/84/1949-1676$01.50/0