h and the reaction mixture was concentrated to give a solid. Sublimation of the solid [70–80 °C (20 mmHg)] gave a 61% yield of 7: mp 61–63 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (3 H, s, CH_3), 2.50 (3 H, s, SCH_3), 3.91 (3 H, s, OCH_3), 7.6–8.7 (2 H, br s, 2 NCH); IR ($CHCl_3$) 1550, 1455, 1410, 1275, 1040 cm^{-1}.

Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55; N, 8.28. Found: C, 56.68; H, 6.49; N, 8.36.

3-Methoxy-4-methyl-5-(phenylseleno)pyridine (8). A solution of isopentyl nitrite (140 mg, 1.36 mmol) was added to a stirred solution of **6** (42 mg, 0.34 mmol) in diphenyl diselenide (189 mg, 0.68 mmol) at 80 °C. Workup of the reaction mixture as described above gave a 50% yield of **8** as a syrup: bp 150 °C (2.5 mmHg) (bath temperature); ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s, CH_3), 3.92 (3 H, s, OCH_3), 7.29 (5 H, s, C_6H_5), 8.13 (1 H, s, Ar H), 8.24 (1 H, s, ArH); IR ($CHCl_3$) 1570, 1540, 1460, 1400, 1280, 1190, 1025 cm^{-1}; exact mass calcd for $C_{13}H_{13}NOSe$ 279.0148 and 277.0174, found 279.0159 and 277.0171.

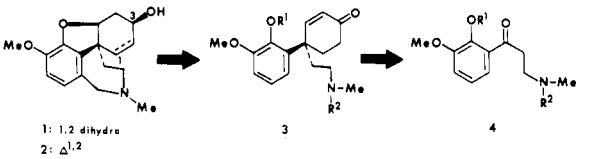
Registry No. 1, 64436-92-6; 2, 77903-25-4; 4, 77903-26-5; 5, 77903-27-6; 6, 77903-28-7; 7, 77903-29-8; 8, 77903-30-1; 9, 77903-31-2; 10, 77903-32-3; 11, 77903-33-4; 12, 77903-34-5; 13, 77903-35-6; 14, 77903-36-7; pivaloyl chloride, 3282-30-2; dimethyl disulfide, 624-92-0; diphenyl diselenide, 1666-13-3.

Communications

Total Synthesis of Racemic Lycoramine

Summary: The application of a general methodology for the construction of quaternary carbon atoms to the efficient total synthesis of the Amaryllidaceae alkaloid lycoramine (1) is described.

Sir: Inasmuch as the quaternary carbon atom is an important structural element found in numerous natural products, a variety of synthetic methods have been developed for the construction of such centers.[1] We have recently invented a general procedure for the formation of fully substituted carbon atoms by an efficient process that results in the net geminal acylation–alkylation of the carbonyl function of ketones.[2] In order to establish its practical utility, we report the successful implementation of this methodology as a key step in an efficient synthesis of lycoramine (1),[3] an Amaryllidaceae[4] alkaloid that is closely related to galanthamine (2).[5] The salient feature of our synthetic strategy is the preparation of a 4,4-disubstituted cyclohexenone such as **3**, which is suitably functionalized for elaboration to lycoramine (1), from a precursor ketone **4** by employing a new method for the annelation of a cyclohexenone ring at a carbonyl carbon atom.



After conducting a series of preliminary studies with several protected β-aminoethyl aryl ketones of type **4**, the *O*-allyl keto urethane **8** emerged as the starting material of choice. The preparation of **8** from commercially available *o*-vanillin (**5**) may be conveniently accomplished in 67% overall yield by a straightforward sequence of reactions. (See Scheme I.) Thus, alkylation of the sodium salt of *o*-vanillin with allyl bromide (2 equiv, DMF, 25 °C, 12 h) gave *O*-allyl-*o*-vanillin (**6**) (92%).[6] Addition of vinylmagnesium bromide (4 equiv, THF, 25 °C, 5 min) to **6** followed by Jones oxidation (0 °C, 30 min) of the intermediate alcohol afforded the α,β-unsaturated ketone **7** (81%). When **7** was allowed to react with benzyl *N*-methylcarbamate (1 equiv, 25 °C) in the presence of a catalytic amount (7%) of camphorsulfonic acid,[7] the requisite ketone **8** was produced (90%).

The next stage of the synthesis involves the transformation of **8** to the key intermediate cyclohexenone **11**, and our general procedure for introducing two dissimilar alkyl appendages at carbonyl carbon atoms via intermediate metalloenamines[2] seemed ideally suited to the task. In the event, sequential reaction of **8** with diethyl [(*N*-benzylidenamino)lithiomethyl]phosphonate (1.2 equiv, THF, −78 °C → reflux, 3 h) and *n*-butyllithium (1.2 equiv, THF, −78 °C, 1 h) provided the metalloenamine **9** which was treated in situ with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[8] (3 equiv, 20% HMPA–THF, −78 °C → 25 °C, 18 h) and then aqueous acid (1 N HCl, 6 h), yielding the intermediate δ-keto aldehyde **10**. When **10** was treated with base (0.5 N KOH, 30% aqueous MeOH, 25 °C, 2 h), facile cycloaldolization and dehydration ensued to give **11** in 40–45% overall yield from **8**.[9]

(1) For a review, see Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) Martin. S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.*, **1980**, *102*, 5866.

(3) For previous syntheses of lycoramine, see (a) Hazama, N.; Irie, H.; Mizutani, T.; Shingur, T.; Takada, M.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 2947. (b) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *Ibid.* **1968**, 2954. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065.

(4) For a review of the Amaryllidaceae alkaloids, see Funganti, C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New Yrok, 1975; Vol. 15, Chapter 3.

(5) For previous syntheses of galanthamine and related compounds, see (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Franck, B.; Lubs, H. J. *Justus Liebigs Ann. Chem.* **1968**, *720*, 131. (c) Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 2602. (d) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (e) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, R.; Hiiragi, M.; Hayasaka, T. *J. Chem. Soc. C* **1971**, 1043. (f) Kametani, T.; Yamaki, K.; Terui, T.; Shibuya, S.; Fukumoto, K. *Ibid.* **1972**, 1513. (g) Kametani, T.; Yamaki, K.; Terui, T. *J. Heterocycl. Chem.* **1973**, *10*, 35.

(6) The structure assigned to each compound was in accord with its spectral (^{1}H NMR, IR, mass) characteristics. Analytical samples of all new compounds were obtained by chromatography (HPLC) and gave satisfactory combustion analyses (C, H, N) and/or parent ion identification by high-resolution mass spectrometry. All yields are based upon isolated materials which were >95% pure.

(7) Cf. (a) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (b) Mohrle, H.; Engelsing, R. *Monatsh. Chem.* **1971**, *102*, 233.

(8) Brown, E.; Dhal, R. *Bull. Soc. Chim. Fr.* **1972**, 4292.

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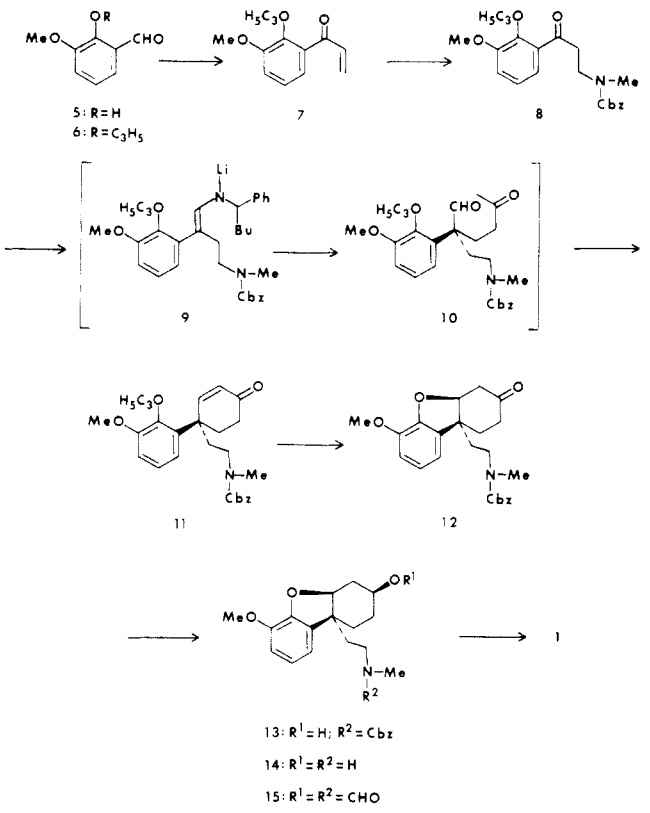
Scheme I



Subsequent removal of the *O*-allyl protecting group from **11** with a catalytic amount (7%) of rhodium trichloride[10] in refluxing ethanol was accompanied by spontaneous cyclization of the intermediate phenol to give **12** in 86% yield. The hydride reduction of the carbonyl functional group of **12** ($LiAlH_4$, glyme, -78 °C) proceeded with a high degree of stereoselectivity (>95%) to afford the alcohol **13**, which was then converted to the amino alcohol **14** by catalytic hydrogenolysis (H_2, 5% Pd-C, HCl/EtOH) in 84% overall yield.

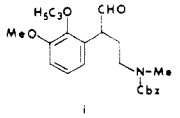
Although it might be possible to convert **14** directly into lycoramine (**1**) by a classical Pictet-Spengler reaction, numerous attempts to effect such a conversion using formaldehyde under a variety of acidic reaction conditions failed to produce significant quantities of lycoramine.[11] Consequently, we turned our attention to the transformation of **14** to lycoramine via a Bischler-Napieralski reaction which has previously been employed for the construction of hydrobenzazepines.[12] Reaction of the amino alcohol **14** with excess acetic formic anhydride in pyridine (80 °C, 6 h) afforded **15** (95% yield), which was smoothly converted to racemic lycoramine (**1**) [as needles, mp 101-102 °C (lit. mp 98-99 °C,[3a] 94-97 °C,[3c])] in 68% yield by cyclization with phosphorus oxychloride (85 °C, 20 h) followed by hydride reduction [$NaBH_4$ (20 equiv), MeOH, -78 °C → 0 °C, 3 h] of the intermediate iminium salt. The synthetic lycoramine, which was thus obtained in 14% overall yield from *o*-vanillin has spectral properties (90 MHz ^1H NMR, IR, low-resolution mass spectra, TLC, VPC) identical with an authentic sample of *dl*-lycoramine.[13]

The application of our general methodology for the construction of quaternary carbon atoms to the syntheses of other natural products is in progress and will be reported independently.

Acknowledgment. We thank the National Cancer Institute, DHEW (Grant CA 21860), and the Robert A. Welch Foundation for their generous support of this work.

Registry No. (±)-**1**, 18797-70-1; **5** sodium salt, 78166-97-9; **6**, 23343-06-8; **7**, 78166-98-0; **8**, 78166-99-1; (±)-**9**, 78167-00-7; (±)-**10**, 78167-01-8; (±)-**11**, 78167-02-9; (±)-**12**, 78167-03-0; (±)-**13**, 78167-04-1; (±)-**14**, 78167-05-2; (±)-**15**, 78167-06-3; (±)-**i**, 78167-07-4; allyl bromide, 106-95-6; vinyl bromide, 593-60-2; benzyl *N*-methylcarbamate, 30379-59-0; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; diethyl [(*N*-benzylidenamino)lithiomethyl]phosphonate, 78167-08-5.

(9) The unalkylated aldehyde **i** was also obtained 10-20% yield from this sequence. Despite numerous attempts, we have not yet found



reaction conditions which would allow complete alkylation of the intermediate metalloenamine **9**.

(10) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

(11) However, we know of only one example of the formation of a seven-membered ring by a Pictet-Spengler reaction: Kametani, T.; Terui, T.; Ogino, T.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 874. For a related process, see Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495.

(12) Cf. (a) Kanaoka, Y.; Sato, E.; Yonemitsu, O.; Ban, Y. *Tetrahedron Lett.* **1964**, 2419. (b) Fushimi, T.; Ikuta, H.; Irie, H.; Nakadachi, K.; Uyeo, S. *Heterocycles* **1979**, *12*, 1311. (c) Sanchez, I. H.; Mendoza, M. T. *Tetrahedron Lett.* **1980**, 3651.

(13) We thank Professor A. G. Schultz for the 90-MHz ^1H NMR and IR spectra and also an authentic sample of racemic lycoramine.

(14) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

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Azetidinone Antibiotics. 22. A Rearrangement of Oxoazetidinesulfinic Acids to Haloazetidinones[1]

Summary: Treatment of the oxoazetidinesulfinic acid **3** with a positive halogen source gave trans and cis 4-haloazetidinones **5**; the trans isomers of **5** are easily converted to oxazoline **6** by chromatography on silica gel, while the cis isomers are transformed into **6** by reacting with PbF_2 in Me_2SO.

Sir: Earlier reports have shown that sulfinic acid **3** is a useful intermediate in the synthesis of 3-methylenecepham sulfoxide **4**.[2] We now report that further investigation into the chemistry of this sulfinic acid has demonstrated a unique reactivity which leads to the formation of other synthetically useful azetidinone derivatives.

Treatment of the penicillin sulfoxide **1** in refluxing toluene with NCS (1 equiv. 90 min) gave the sulfinyl chloride **2**[2] (Scheme I), which upon hydrolysis (aqueous 1 N HCl, toluene, 1 h) provided sulfinic acid **3** in 70% yield as a colorless amorphous solid; NMR ($CDCl_3$) δ 1.9 (s, 3, CH_3), 4.46 (s, 2, side-chain CH_2), 4.88 (d, 1, J = 5.0 Hz,

(1) Paper 21. Kukolja, S.; Spitzer, W. A.; Scott, J. K. *J. Org. Chem.* **1981**, *46*, 1934.

(2) Kukolja, S.; Lammert, S. R.; Gleissner, M. R.; Ellis, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 5040. Kukolja, S. In "Recent Advances in the Chemistry of β-Lactam Antibiotics"; Elks, J., Ed.; The Chemical Society, Burlington House: London, 1977; p 181.

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