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Communications

Solvolytic Rearrangement of Silphin-2α-yl Methanesulfonate to α-Terrecyclene: A Probable Biogenetic Relationship between Silphinene and Quadrone

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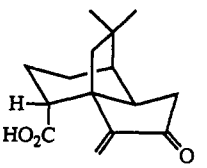
Summary: The solvolytic rearrangement of silphin-2α-yl methanesulfonate (**4b**) to tricyclic olefin **5** named α-terrecyclene suggests the occurrence of similar rearrangements in the biosynthesis of quadrone and its *Aspergillus terreus* co-metabolites.

The biosynthesis of the carbon skeleton of the sesquiterpenes terrecyclic acid (**1**),[1] quadrone (**2**),[2] and related metabolites produced by *Aspergillus terreus* has remained obscure despite elaborate labeling studies to elucidate the cyclization pathway.[3] The structure of the initial unoxidized product of cyclization is also unknown.[3a,4] We have discovered a novel skeletal rearrangement of methanesulfonate **4b** derived from silphinene (**3**)[5] to tricyclic olefin **5** which is named α-terrecyclene for its apparent structural relationship to quadrone and its co-metabolites. We propose that silphinene and quadrone are biogenetically related, that **5** (or its exocyclic isomer) is the unknown sesquiterpene precursor to quadrone, and that similar rearrangements occur during quadrone biosynthesis in *A. terreus* cells.

(±)-Silphinene (**3**), prepared by the intramolecular arene photoannulation approach of Wender and Ternansky,[6] was



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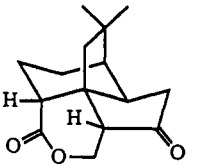

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epoxidized,[5a] and the 3:1 mixture of isomeric epoxides was reduced ($LiAlH_4$, THF) as reported previously to the known[5a] major isomer, silphinan-2α-ol (**4a**, mp 51–52.5 °C), and its 2β epimer which are separable by chromatography (Scheme I). A single-crystal X-ray diffraction analysis[7] of **4a** proved the stereochemistry shown which was previously assigned incorrectly on the basis of inferences from NMR spectral data.[5a]

The unstable methanesulfonate **4b** (CH_3SO_2Cl, pyr, 0 °C, 1 h) underwent solvolysis in formic acid (2 equiv of NaO_2CH, rt, 15 min) to give an 8:1 mixture (81%) of α-terrecyclene (**5**)[8,9] and silphinene (**3**). Aqueous solvolysis

(1) (a) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *J. Antibiotics* **1982**, *35*, 778. (b) Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *Ibid.* **1982**, *35*, 783.

(2) (a) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiotics* **1978**, *31*, 38. (b) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499.

(3) (a) Cane, D. E.; Whittle, Y. G.; Kiang, T.-C. *Biorg. Chem.* **1986**, *14*, 417. (b) Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A.; Furihata, K.; Seto, H. *Tetrahedron Lett.* **1985**, *26*, 3845. (c) Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *Agric. Biol. Chem.* **1984**, *48*, 835. (d) Beale, J. M., Jr.; Chapman, R. L.; Rosazza, J. P. *J. Antibiotics* **1984**, *37*, 1376. (e) Cane, D. E.; Whittle, Y. G.; Liang, T.-C. *Tetrahedron Lett.* **1984**, *25*, 1119.

(4) Cane, D. E.; Rawlings, B. J.; Yang, C. C. *J. Antibiotics* **1987**, *40*, 1331.

(5) (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. (b) Teresa, J. de P.; San Feliciano, A.; Barrero, A. F.; Medarde, M.; Tome, F. *Ibid.* **1981**, *20*, 166.

(6) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625.

(7) Colorless monoclinic crystals (space group $C2/c$) were grown from pentane at −10 °C. Data were collected at −75 °C. The final agreement factor was $R = 0.043$. Successful convergence was indicated by the maximum shift/error for the last cycle. The final difference Fourier map had no significant features, and a final analysis of variance between observed and calculated structure factors showed no systematic errors. We thank Drs. Teresa Prussak-Wieckowski and Scott Wilson for carrying out the X-ray diffraction analysis.

(8) Characterization data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 6.9 Hz, 3 H), 1.08 and 1.16 (2s, 6 H, $2CH_3$), ~1.16–1.21 (1 H), 1.60 (d, J = 1.4 Hz, 3 H, CH_3), 1.39–1.64 (m, 4 H), 1.76–1.78 (m, 1 H), 1.83–2.0 (m, 2 H), 2.25–2.35 (m, 2 H), 1.43–2.55 (m, 1 H), 5.12 (sextet, J = 12.6 Hz, 1 H, vinyl H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.68, 17.49, 26.23, 27.01, 28.83, 34.18, 35.78, 35.85, 40.93, 49.45, 51.64, 53.70, 63.50, 122.45, 146.74; MS(EI, 70 ev) m/z (rel intensity) 204 (M^+, 6.5), 147 (100), 105 (25.5), 41 (16).

(9) All new compounds reported except the unstable methanesulfonate **4b** were fully characterized by appropriate ^{1}H NMR, ^{13}C NMR, IR, and mass spectra, and elemental compositions were verified by satisfactory combustion analyses (**5**, **7**, and **8**) or by MS (**6**). Methanesulfonate **4b** was characterized by its ^{1}H NMR spectrum in pyridine-d_5.

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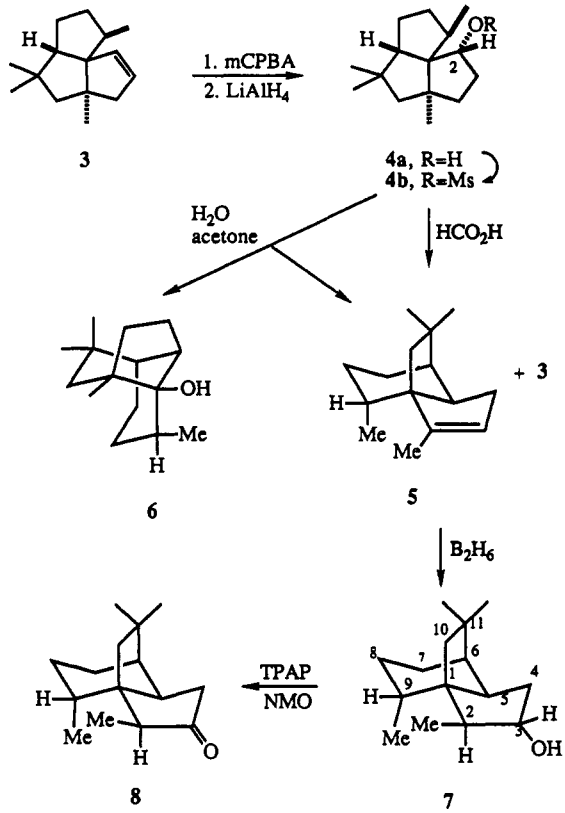
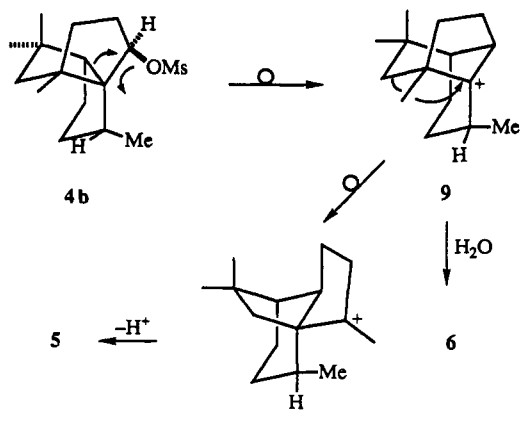
Scheme I



(1:3 H_2O/acetone v/v, 1.5 equiv of pyridine; rt, 1 h) of **4b** afforded the same two olefins (60:40, 60%) together with recovered **4a** (3%) and a tertiary alcohol (13%) for which structure **6** is proposed.

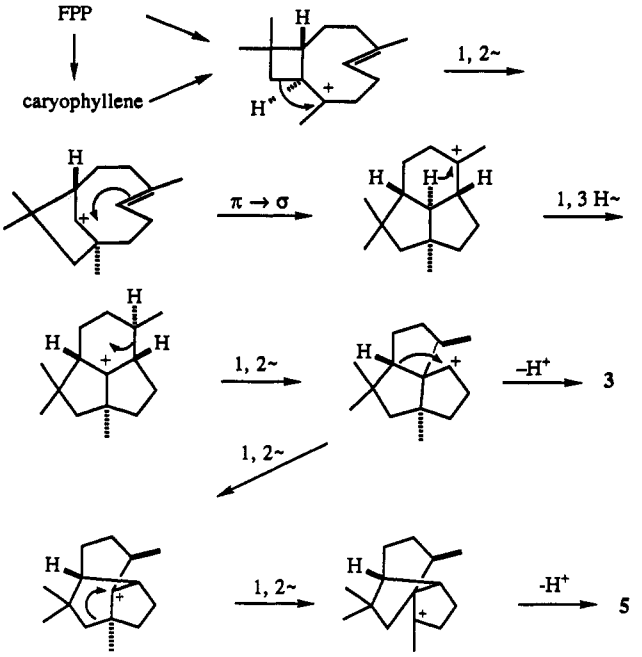
Hydroboration (BH_3, THF; rt, 1.5 h; H_2O_2, NaOH) of the 8:1 mixture of **5** and **3** gave rise to secondary alcohol **7** (mp 92–94 °C) in 83% yield after chromatographic purification. Oxidation of **7** to the corresponding ketone **8** (96%; IR $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}) was accomplished with tetrapropylammonium perruthenate (TPAP, 0.05 equiv) and *N*-methylmorpholine *N*-oxide (NMO, 1.5 equiv) (CH_2Cl_2, rt, 30 min).[10]

The structures assigned to the rearranged olefin **5** and tertiary alcohol **6** are based upon the mechanism shown below together with comprehensive spectroscopic analyses (^1H NMR, ^{13}C NMR, IR, and MS). ^1H–^1H COSY and



(10) (a) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13. (b) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

Scheme II



^1H–^{13}C HETCOR NMR plots of alcohols **6** and **7** are consistent with the structures.[11] The IR stretching frequency for the carbonyl group of **8** confirms that the double bond of **5** is situated in a 5-membered ring. The rearrangement of **4b** to α-terrecylene requires two successive Wagner–Meerwein rearrangements via bridgehead carbocation **9**. The tertiary alcohol results from interception of **9** by water capture.

This rearrangement suggests a reasonable biogenetic pathway to the carbon skeleton of quadrone and its congeners (Scheme II).[12] The biogenetic relationship of silphinene to caryophyllene and the basic steps in the scheme up to the silphinyl carbocation were proposed previously by Bohlmann.[5a,13] Evidence supporting the occurrence of a 1,3-hydride shift in the biosynthesis of dihydrobotrydial has been reported.[14] It seems likely that α-terrecyclene **5** (or its exocyclic double isomer) is the sesquiterpene hydrocarbon precursor to quadrone and the related *A. terreus* metabolites.

The pathway shown in Scheme II is consistent with the results of the labeling patterns observed in investigations on the biosynthesis of quadrone and terrecyclic acid.[3] It is amusing to note that the last of the four carbon skeletal rearrangements in this biogenesis reconnects the two carbon atoms that were disconnected in the initial ring expansion step. Thus, two of the four rearrangements

(11) The two-dimensional NMR maps prove the presence of a CH_2 flanked by quaternary carbons in **6** and **7** and most of the other C–C bonds in the continuous chain of CH and CH_2 groups from C2 to C9 in **7**. However, the $CH_2CHCHCH_2$ connectivity in the C4–C5–C6–C7 segment of **7** could not be proven unequivocally owing to overlap of resonances in the ^1H NMR spectra. Attempts to obtain crystals of **7** or its dinitrobenzoate derivative suitable for X-ray diffraction analysis have been unsuccessful thus far.

(12) An alternative biogenesis via a bicyclo[6.3.0]undecenyl carbocation intermediate and 1,2- and 1,3-hydride shifts has been proposed.[3b] However, the two hydride shifts in this scheme appear to be rather unfavorable for stereoelectronic reasons.

(13) (a) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. *Phytochem.* **1981**, *20*, 2239. (b) The same biogenetic pathway was developed independently by Dr. H. Shirahama of Hokkaido University. We are grateful to Dr. Shirahama for bringing this unpublished scheme to our attention.

(14) Bradshaw, A. P. W.; Hanson, J. R.; Nyfeler, R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2187.

remain unexposed in the ^{13}C NMR spectra of quadrone and terrecyclic acid biosynthesized from doubly ^{13}C-labeled compounds such as [1,2-$^{13}C_2$]acetate.

Acknowledgment. We thank Drs. M. F. Leopold and Vera Mainz for invaluable assistance in obtaining the two-dimensional NMR plots. This research was supported in part by a grant from the National Institutes of Health (GM 13956).

Supplementary Material Available: Tables of ^1H and ^{13}C NMR data for **6** and **7**, ^1H and ^{13}C NMR spectra of **5** and **7**, and ^1H–^1H COSY, ^1H–^{13}C HETCOR, and APT plots for **7** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Novel Thermolytic Annulation of an Oxazolidinone: An Enantiospecific Synthesis of (−)-Slaframine[1]

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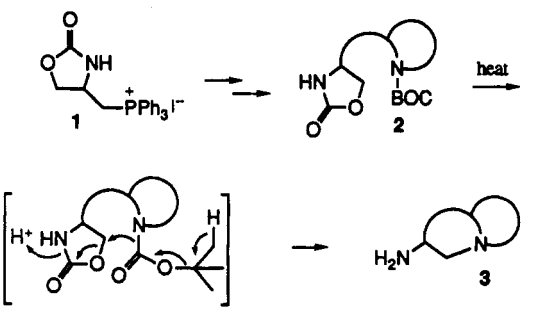
Summary: Optically pure β-aminopiperidines can be prepared in high yields through a thermolytic annulation sequence involving ring opening of an oxazolidinone.

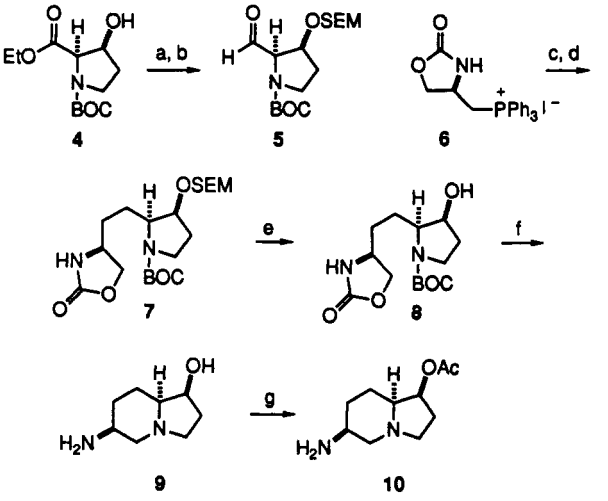
Hydroxylated indolizidine and piperidine alkaloids isolated from plants and microorganisms[3] have attracted considerable attention due to their diverse biological activity.[4] Therefore, the development of efficient methods for the synthesis of both the natural products and their analogs is important for the establishment of structure–bioactivity relationships of these compounds. We have developed a novel thermolytic annulation sequence for the construction of piperidines by intramolecular nucleophilic ring opening of oxazolidinones at the 5-position. The methodology provides ready access to β-amino piperidines (Scheme I). This structural unit is present in biologically active natural products such as slaframine,[5] pseudodistomines,[6] and unnatural amino azasugars.[7]

Indolizidine alkaloid slaframine (**10**) [(1*S*,6*S*,8a*S*)-1-acetoxy-6-aminooctahydroindolizine], a mycotoxin produced by the fungus *Rhizoctonia leguminicola*, has been shown to be responsible for excess salivation in cattle when they graze on fungus infested feeds.[8] Several synthetic approaches to racemic slaframine,[9] and two very recent syntheses leading to optically active material,[10] have been reported in the literature.

Scheme I



Scheme II[a]



[a] Key: (a) SEMCl, DIEA, CH_2Cl_2, rt, 18 h, 94%; (b) DIBALH, toluene, −78 °C; (c) 1.95 equiv of *n*-BuLi, 2 h, −78 °C, add **5**, 52%; (d) 10% Pd on C, EtOAc, H_2, 97%; (e) TBAF, HMPA, 80 °C, 3 h, 90%; (f) 270 °C, 5 min, 92%; (g) ref 9d.

We herein report enantiospecific syntheses of (−)-slaframine and (−)-8a-epidesacetoxyslaframine to illustrate the utility of our ring closure method. The key features of our approach include the following: (i) a novel annulation of an oxazolidinone under thermolytic conditions to furnish

(1) Presented in part at the 201st National Meeting of the American Chemical Society; Atlanta, GA, Abstr. No. 184.

(2) Undergraduate research participant 1988–90, NSF-REU participant 1988.

(3) (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 6863. (c) Clevestine, E. C.; Broquist, H. P.; Harris, T. M. *Biochemistry* **1979**, *18*, 3658.

(4) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1.

(5) Cartwright, D.; Gardiner, R. A.; Reinhart, K. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 7615.

(6) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450.

(7) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187 and references cited therein.

(8) Gardiner, R. A.; Rinehart, Jr., K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639.

(9) (a) Cartwright, D.; Gardiner, R. A.; Reinhart, K. L.; Jr., *J. Am. Chem. Soc.* **1970**, *92*, 7615. (b) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848. (c) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065. (d) Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681. (e) Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695. (f) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368.

(10) (a) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. (b) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469.

0022-3263/92/1957-4329$03.00/0