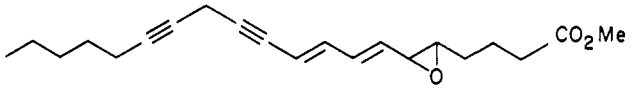
further purification in the condensation with methyl 4-formylbutyrate.[11] A solution of the salt **12** (24.2 g) in dichloromethane (100 mL) containing methyl 4-formylbutyrate (9.6 g) and benzyltriethylammonium chloride (0.5 g) was cooled to -30 °C and then treated with an aqueous solution of sodium hydroxide (75 mL, 10 M) over approximately 10 s. The dark colored reaction mixture was then stirred rapidly at -25 °C for 1 min and then cooled to -78 °C. The solvents were decanted, the residue was washed with ether, and the combined organic extracts were washed (water), dried (Na_2SO_4), and concentrated. The crude mixture of epoxides was then separated[12] (silica gel, 5:95:2 ethyl acetate-hexane-triethylamine) to yield the pure *trans*-epoxide[13] **13** (38% based on bromide **11**) and the cis isomer (12%). Hydro-

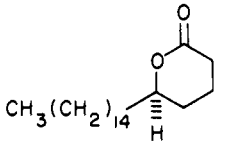


13

genation of the *trans*-epoxide **13** over a Lindlar catalyst in hexane gave racemic **3** (50%) [UV λ_{max} (hexane) 260, 280, 291 nm (ϵ 27 200, 35 400, 28 400)].

Addition of the methyl ester of L-cysteine in a mixture of methanol-water (6:1) and triethylamine[14] (to pH 8.5) to this racemate generated *one* pair of diastereomers (60%) which was separated on silica gel (ethyl acetate). Both materials were shown by ^1H NMR to be the products of 1,2-addition of the cysteine to the epoxide **3**.[15] The following reactions were carried out to establish the absolute stereochemistry at C-5 and confirm the regiochemistry of cysteine addition.

The compound with the longer retention time from the preparative high-performance liquid chromatogram was treated with Raney nickel in refluxing ethanol for 30 min, and the reaction product was then hydrogenated (Pd-ethyl acetate) to remove the remaining double bond. Hydrolysis (KOH, MeOH, H_2O, room temperature, 1 h) and acid cyclization (CF_3CO_2H, CH_2Cl_2, room temperature, 1 h) yielded a δ-lactone **14**; IR (film) 1739 cm^{-1}, $[\alpha]^{25}_D$ +20° (*c* 1, dioxane). The formation of a δ-lactone confirms



14

the regiochemistry of the cysteine addition to the epoxide **3**, and the sign of rotation[16] clearly establishes the absolute stereochemistry of **14** as 5*R*. If one assumes an S_N2 addition of cysteine to the epoxide, then the absolute stereochemistry of the dimethyl ester would be as shown by structure **6**. This isomer is of particular interest as the hydroxyl group in natural SRS-A has been shown to be 5*S*.[2]

Hydrolysis (KOH, MeOH-H_2O, room temperature, 30 min) of the ester groups of both diastereomers yielded the (5*R*,6*S*)- and (5*S*,6*R*)-SRS-A compounds, both of which were desalted and purified by reverse-phase chromatography[12] as the potassium salts (water and aqueous methanol, 7:3). Both compounds as the monopotassium salts showed marked spasmogenic activity in the guinea pig ileum assay,[1,17] the (5*S*,6*R*) isomer being more active.[18-20]

Acknowledgments. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ, in particular Ross Pitcher, for carrying out most of the spectral and microanalytical determinations. The authors also thank Dr. B. A. Pawson for her encouragement and support throughout this work.

(11) Burgstahler, A. W.; Weigel, L. O.; Schaefer, C. G. *Synthesis* **1976**, 767.

(12) High-performance liquid chromatography with a Waters Prep 500 was used throughout.

(13) ^1H NMR ($CDCl_3$) δ 6.46 (dd, 1, $J_{9,10}$ = 15 Hz, $J_{8,9}$ = 11 Hz, H-9), 6.30 (dd, 1, $J_{7,8}$ = 15 Hz, $J_{8,9}$ = 11 Hz, H-8), 5.52 (dd, 1, $J_{9,10}$ = 15 Hz, $J_{10,13}$ = 2 Hz, H-10), 5.37 (dd, 1, $J_{7,8}$ = 15 Hz, $J_{6,7}$ = 7.5 Hz, H-7), 3.58 (s, 3, CO_2CH_3), 3.18 (m, 2, H-13), 2.93 (dd, 1, $J_{6,7}$ = 7.5 Hz, $J_{5,6}$ = 2 Hz, H-6), 2.67 (d t, 1, $J_{5,6}$ = 2 Hz, $J_{4,5}$ = 8 Hz, H-5), 0.90 (t, 3, *J* = 6 Hz, H-20); UV λ_{max} (EtOH) 260, 272, 285 nm (ϵ 26 600, 35 500, 29 400).

(14) Boeckman, R. K., Jr.; Thomas, E. W. *J. Am. Chem. Soc.* **1979**, *101*, 987.

(15) The (5*S*,6*R*) isomer had the following data: ^1H NMR ($CDCl_3$) δ 6.53 (dd, 1, $J_{9,10}$ = 14.5 Hz, $J_{10,11}$ = 10 Hz, H-10), 6.0 (t, 1, $J_{11,12}$ = $J_{10,11}$ = 10 Hz, H-11), 5.62 (dd, 1, $J_{7,8}$ = 14.4 Hz, $J_{6,7}$ = 9.6 Hz, H-7), 5.3 (m, 1, $J_{14,15}$ = 10 Hz, $J_{13,14}$ = 9 Hz, H-14), 3.71 and 3.62 (2 s, 6, CO_2CH_3), 3.65 (m, 1, H-5), 3.4 (m, 1, H-6), 2.92 (t, 2, $J_{12,13}$ = $J_{13,14}$ = 9 Hz, H-13), 2.02 (m, 2, H-16), 0.86 (t, 3, *J* = 6 Hz, H-20); UV λ_{max} (ethanol) 269, 280, 291 nm (ϵ 28 200, 35 200, 28 900).

(16) Chiral δ-lactones of this type have been used by us in the synthesis of known 19-*nor*-steroids, and the absolute stereochemistry of the lactones is related to the sign of their specific rotations: Rosenberger, M.; Borer, R.; Saucy, G. *J. Org. Chem.* **1978**, *43*, 1550. Tuynenburg Muys, G.; van der Ven, B.; DeJonge, A. P. *Appl. Microbiol.* **1963**, *11*, 389.

(17) The (5*S*,6*R*) isomer had an EC_{50} of 4 × 10^{-9} M, and the (5*R*,6*S*) isomer had an EC_{50} of 8 × 10^{-9} M. These data were provided by Dr. A. Welton and H. Crowley in the Department of Pharmacology II at Hoffmann-La Roche Inc.

(18) After submission of this paper for publication, two other syntheses of leukotriene A methyl ester appeared in print: (a) Gleason, J. G.; Bryan, D. B.; Kinzig, C. M. *Tetrahedron Lett.* **1980**, *21*, 1129. (b) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J.; Larue, M.; Yound, R. N.; Masson, P.; Holme, G. *Ibid.* **1980**, *21*, 1485.

(19) The following papers pertinent to the isolation, structure determination, and biology of SRS-A were also recently published: (a) Piper, P. J.; Samhoun, M. N.; Tippins, J. R.; Morris, H. R.; Taylor, G. W. *Prostaglandins* **1980**, *19*, 185. (b) Örning, L.; Hammarström, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2014. These authors have shown that an important SRS-A contains the cysteinylglycine grouping. This probably results from the primary glutathione adduct of leukotriene A. Both these publications strongly support the original suggestions of Parker et al.[3]

(20) The addition of other sulfhydryl-containing molecules to leukotriene A methyl ester and their biological properties will be the subject of a future communication.

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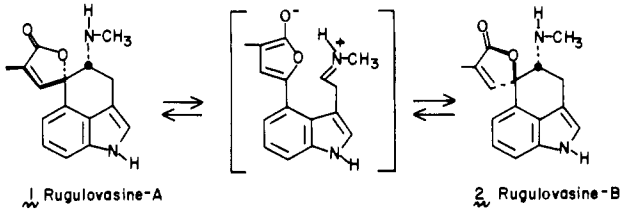
Total Synthesis of Rugulovasines

Sir:

The rugulovasines, isolated first[1] from strains of *Penicillium concavo-rugulosum* and subsequently[2] from *Penicillium islandicum*, were formulated as **1** and **2** on the basis of chemical



1 Rugulovasine-A 2 Rugulovasine-B

evidence[3] and crystallographic analysis.[4] That the alkaloids are isolated in racemic form and are observed to interconvert in polar media is most economically accommodated by the ingenious mechanism shown[4] and has led to the suggestion that the alkaloids may even be artifacts of the isolation procedure. One test of this mechanism requires the alkaloids in optically active form. While it may be unnatural to prefer synthesis to biosynthesis for such

(1) Abe, M.; Ohmomo, S.; Ohashi, T.; Tabuchi, T. *Agric. Biol. Chem.* **1969**, *33*, 469-471.

(2) Cole, R. J.; Kirksey, J. W.; Cutler, H. G.; Wilson, D. M.; Morgan-Jones, G. *Can. J. Microbiol.* **1976**, *22*, 741-744.

(3) Yamatodani, S.; Asahi, Y.; Matsukura, A.; Ohmomo, S.; Abe, M. *Agric. Biol. Chem.* **1970**, *34*, 485-487.

(4) Cole, R. J.; Kirksey, J. W.; Clardy, J.; Eickman, N.; Weinreb, S. M.; Singh, P.; Kim, D. *Tetrahedron Lett.* **1976**, 3849-3852.

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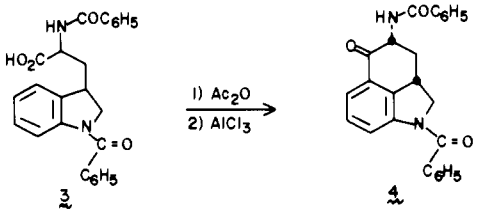
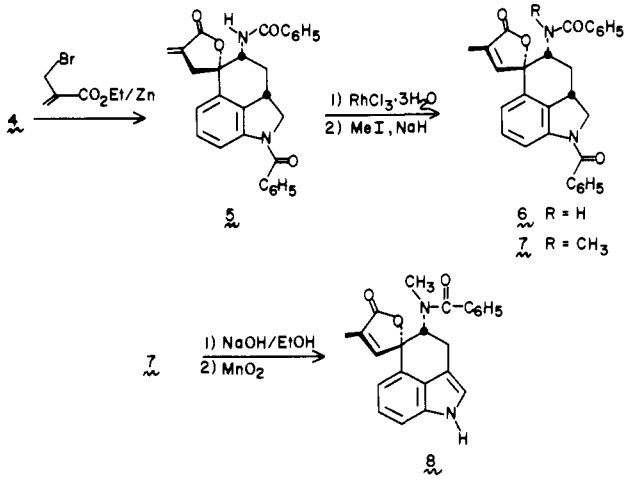
purposes, we have developed procedures which are quite compatible with this goal. Here we record the first total synthesis of the racemic rugulovasines.

As starting material, DL-tryptophan appeared likely, and a suitably blocked form was found in Witkop's[5] dihydro, dibenzoyl derivative **3**. Dehydration (Ac_2O, 100 °C, 15 min) afforded the



azlactone which cyclized[6] readily under Friedel-Crafts conditions ($AlCl_3$, $ClCH_2$-CH_2Cl, reflux, 30 min) to ketone **4**,[7] mp 172-173 °C (from MeOH).

Treatment of **4** with a solution derived from the action of Zn on ethyl α-(bromomethyl)acrylate[8] (THF, 50 °C, 14 h) gave the methylene lactone **5**, mp 218-219 °C, as a *single isomer* which



cleanly rearranged to the butenolide **6**, mp >275 °C, under the influence of $RhCl_3 \cdot 3H_2O$[9] ($CHCl_3$/EtOH/H_2O, 90 °C, 14 h). Alkylation (MeI/NaH, DMF, 25 °C, 30 min) gave **7**, mp 251-252 °C, mild hydrolysis (MeOH/HCl, 60 °C, 4 h or NaOH, H_2O/EtOH, 75 °C, 1 h) selectively exposed the indolene function, and oxidation[10] (MnO_2, CH_2Cl_2, 25 °C, 30 min) regenerated the indole. The monobenzoylrugulovasine **8**, mp 237-238 °C, was thus obtained in 25% overall yield from **3**.

Removal of the benzoyl group of **8** proved troublesome since decomposition was observed under acidic hydrolysis conditions, and only opening of the lactone occurred under the usual basic hydrolysis conditions. However, with a modification of Gassman's[11] procedure (*t*-BuOK, NaOH, THF/Me_2SO, 80 °C, 4 h) followed by neutralization, a single product, identical (physical properties, TLC, and published spectra[12]) to rugulovasine A (hydrate), was obtained. Hence, we assign the relative stereochemistry of **5** and subsequent compounds, as shown, and conclude that lactone opening protects the system from isomerization during the final deblocking step in the synthesis. Dissolution of this substance in MeOH at room temperature for 2 days gave a mixture of rugulovasines A and B from which **2** could be obtained by chromatography as previously described.[1-4]

Starting from L-tryptophan, a diastereomer of **3**[5] was obtained which was converted as described above to *optically active* **4**, $[\alpha]^{25}_D$ +176° (*c* 0.9, $CHCl_3$). Since the intermediate azlactone surely epimerizes at the α carbon, **4** owes its optical activity to the fixed chirality at the γ carbon and the stereospecificity of the Friedel-Crafts reaction. We have converted this substance to **8**, $[\alpha]^{25}_D$ -349° (*c* 0.5, $CHCl_3$), whose optical purity is >98% as determined by NMR with optically active shift reagents. We shall report on the racemization and interconversion of the rugulovasines at a later date; in the meantime, we note that **4** incorporates much of the functionality required for the synthesis of other ergot alkaloids.[6c,13]

Acknowledgments. We are pleased to acknowledge stimulating discussions and advice from Professor A. P. Kozikowski.

(5) Daly, J. W.; Mauger, A. N.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 648-654.

(6) (a) Intermolecular Friedel-Crafts acylations with azlactones have been reported: Balaban, A. T.; Bally, I.; Frangopol, P. T.; Bacescu, M.; Cioranescu, E.; Birladeanu, L. *Tetrahedron* **1963**, *19*, 169-176, and earlier work by these authors. (b) For intramolecular acylation of indole derivatives (anhydride): Szmuszkovicz, J. *J. Org. Chem.* **1964**, *29*, 843-849. (c) (Acid chloride) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087-3114.

(7) All new compounds were characterized by elemental analysis and showed the expected spectroscopic features. Stereochemical assignments were based on NMR spectra obtained at 300 or 600 MHz; in particular, the 1,3-cis relationship of the methine protons of **4** was evident from decoupling experiments at 600 MHz.

(8) Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457-458.

(9) We thank Professor P. A. Grieco for his advice concerning this reagent. See: Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102-7104. Biellmann, J. F.; Jung, M. J. *Ibid.* **1968**, *90*, 1673-1674. Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359-363.

(10) Jansen, A. B. A.; Surtees, J. R. *J. Chem. Soc.* **1964**, 5573-5577.

(11) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275-1276.

(12) We warmly thank Professor S. M. Weinreb for NMR spectra of these alkaloids.

(13) See, for examples: Floss, H. G. *Tetrahedron* **1976**, *32*, 873-912; the rugulovasines are, in fact, isomers of lysergic acid.

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Received March 25, 1980

Deuterium and Oxygen-18 Isotope Effects on Nucleophilic Displacement by Monomeric Water in Aprotic Solvents

Sir:

We report that the H_2O/D_2O rate-constant ratio for nucleophilic attack by water at a methyl carbon (eq 1) is reduced to very

$$L_2O + CH_3X \rightarrow L_2\overset{+}{O}CH_3 + X^- \quad (1)$$

near unity when the water is a dilute solute in a dipolar aprotic solvent. We have observed this for three leaving groups [CH_3X equals 1-methylthiophenium ion ($MeTh^+$),[1] methyl perchlorate ($MeOClO_3$),[2] and methyl trifluoromethanesulfonate (MeOTf)[3]] and for two aprotic solvents [acetonitrile (MeCN),[4] and tetrahydrothiophene 1,1-dioxide ($TMSO_2$; sulfolane)[5]]. We have also observed that the corresponding $H_2{}^{16}O/H_2{}^{18}O$ rate-constant ratio is 1.002 ± 0.004 (95% confidence limits) for the reaction of $MeTh^+$ with dilute H_2O in $TMSO_2$ at 35 °C. Although alternative explanations exist (vide infra), these observations are consistent with a mechanism in which no significant positive charge is present on the L_2O oxygen in the rate-determining transition state and thus in which the rate-determining process does not involve (and

(1) Used as the PF_6^- salt; prepared as described: Heldeweg, R. F.; Hogeveen, H. *Tetrahedron Lett.* **1974**, 75.

(2) Used as a stock solution in MeCN; prepared as described: Radell, J.; Connolly, J. W.; Raymond, A. J. *J. Am. Chem. Soc.* **1961**, *83*, 3958.

(3) Aldrich 99+% Gold Label, used without purification.

(4) Aldrich 99+% Spectrophotometric Gold Label, used without purification.

(5) Purified as described: Lewis, E. S.; Vanderpool, S. H. *J. Am. Chem. Soc.* **1977**, *99*, 1946.

0002-7863/80/1502-5427$01.00/0