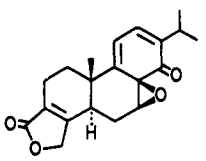
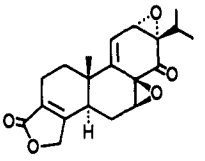


17



18

20 °C), giving bisoxide **18**, along with the 12,13-β-epoxy isomer. The mixture was immediately further oxidized with 3,5-$(NO_2)_2C_6H_3CO_3H$-Na_2HPO_4 (CH_2Cl_2, 20 °C), forming *l*-triptonide (15% from **17**; mp 251-252 °C) purified by chromatography (Porasil T, EtOAc-hexane). The synthetic material was identical in all respects (IR, NMR, UV, CD; mmp 250-252 °C) with a sample of authentic triptonide. In view of the reported[1,2b] reconstitution of the triptolide system by sodium borohydride reduction of **2**, the above synthesis embraces the former natural product as well.

Acknowledgments. The authors are grateful to the American Cancer Society for grant support (CH-48), the National Science Foundation for NMR facilities (GP-28142), R. G. Hoffmann and F. Donovan of the Resins Division of the Organic Department, Hercules, Inc., for a generous gift of pine rosin, and Dr. M. Suffness, National Cancer Institute (DHEW), and Professor J. M. Cassady, Purdue University, for a sample of triptonide.

E. E. van Tamelen,* J. P. Demers, E. G. Taylor, K. Koller[20]

Department of Chemistry, Stanford University
Stanford, California 94305

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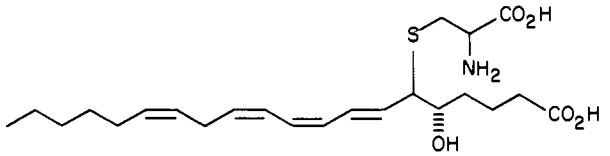
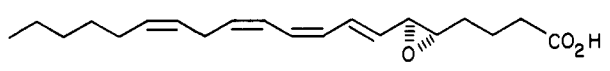
Total Synthesis of (5*S*,6*R*,7*E*,9*E*,11*Z*,14*Z*)-5-Hydroxy-6-[(2*R*)-2-amino-2-(carboxyethyl)thio]-7,9,11,14-eicosatetraenoic Acid, a Potent SRS-A

Sir:

The slow-reacting substance of anaphylaxis (SRS-A) is a highly spasmogenic material and possibly plays an important role in asthma and other diseases of the respiratory system.[1] A structure for the SRS-A had been proposed by Samuelsson et al.[2] as **1** and

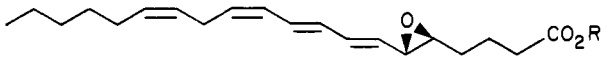


1



2

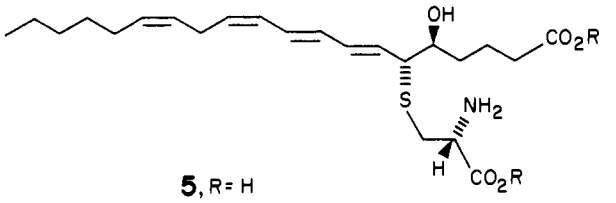
was thought to arise by the addition of cysteine to the epoxide **2**, which is derived from arachidonic acid. Other publications[3,4] suggested that there may be a family of compounds exhibiting SRS-A properties, one member of this group being the product resulting from ring opening of the epoxide **2** by glutathione. Until quite recently, there was still some doubt as to the stereochemical nature of the double bonds in the SRS-A, and while some authors[2] preferred structure **2** for the epoxide, others[5] favored **3**. This



3, R = H
4, R = CH_3

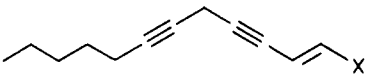
problem has been resolved by the elegant synthesis of the glutathione adduct of **3**, by Corey and his group,[6] which was shown to be the same material as the SRS-A derived from a mouse mast cell tumor line (UV spectrum and high-performance liquid chromatography).

In this communication, we report the synthesis of (5*S*,6*R*)-**5**, a potent spasmogenic agent, via the racemic *trans*-epoxide **4**. As



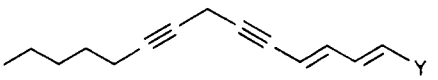
5, R = H
6, R = CH_3

in the case of the recently reported syntheses,[5,18b] our approach also employed a polyene sulfonium salt for the construction of the desired epoxide. The key sulfonium salt **12** was prepared as follows. The copper-catalyzed coupling of 1-bromo-2-octyne[7] with the ethyl vinyl ether adduct of (*E*)-1-hydroxy-2-penten-4-yne[8] gave **7** (EtMgBr, CuCl, THF, 60 °C, 1 h), and subsequently the alcohol

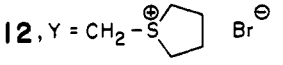


7, X = $CH_2OCH(CH_3)OC_2H_5$
8, X = CH_2OH
9, X = CHO
10, X = $CH(OH)CH{=}CH_2$

8 after acid hydrolysis[9] (acetone, 0.2 N H_2SO_4, room temperature, 3 h, 84% overall yield). Oxidation of this material with pyridinium dichromate[10] (CH_2Cl_2, room temperature, 3 h) gave the aldehyde **9** which was converted to the vinyl carbinol **10** with vinylmagnesium chloride (THF, -40 °C, 30 min, 58% from **8**). Exposure of **10** to phosphorus tribromide (ether, -30 → 0 °C, 1 h, 70%) gave the *all-trans*-bromide **11**, which on treatment with



11, Y = CH_2Br



12, Y = CH_2-S⊕ Br⊖

tetrahydrothiophene yielded the salt **12** [MeOH-H_2O (9:1), room temperature, 1 h, 100%]. This material was used directly without

(1) Orange, R. P.; Austen, K. F. *Adv. Immunol.* **1969**, *10*, 105.
(2) Borgeat, P.; Hammarström, S.; Samuelsson, B., presented at the 1979 International Conference on Prostaglandins, Washington, D.C., May 1979. See: *Chem. Eng. News* **1979**, *57* (24), 19.
(3) Parker, C. W.; Huber, M. M.; Hoffman, M. K.; Falkenhein, S. F. *Prostaglandins* **1979**, *18*, 673.
(4) Hammerström, S.; Murphy, R. C.; Samuelsson, B.; Clark, D. A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1266.
(5) Corey, E. J.; Yoshinobu, A.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748.
(6) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436.
(7) Brandsma, L. "Preparative Acetylenic Chemistry", Elsevier: Amsterdam, 1971.
(8) Available from Farchan, Division Chemsampco, Inc.; see also ref 7.
(9) Satisfactory ultraviolet, ^1H NMR, mass spectra, and elemental analyses were obtained for all intermediates.
(10) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

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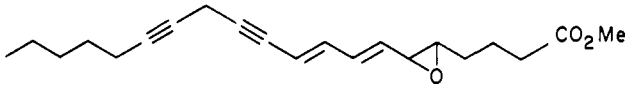
further purification in the condensation with methyl 4-formylbutyrate.[11] A solution of the salt **12** (24.2 g) in dichloromethane (100 mL) containing methyl 4-formylbutyrate (9.6 g) and benzyltriethylammonium chloride (0.5 g) was cooled to -30 °C and then treated with an aqueous solution of sodium 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-

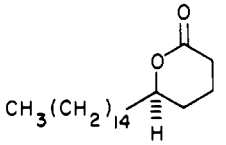


13

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.

Michael Rosenberger,* Christian Neukom

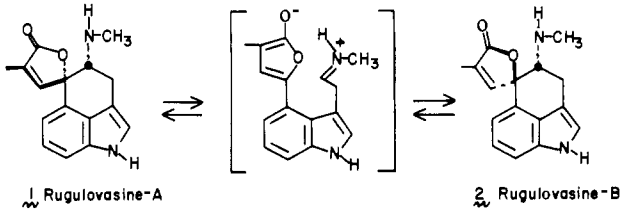
Chemical Research Department, Hoffmann-La Roche Inc. Nutley, New Jersey 07110

Received March 28, 1980

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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