Tetrahedron Letters,Vol.23,No.45,pp 4643-4646,1982 0040-4039/82/454643-04$03.00/0
Printed in Great Britain

CHIRAL, BIOMIMETIC TOTAL SYNTHESIS OF (-)-APLYSISTATIN

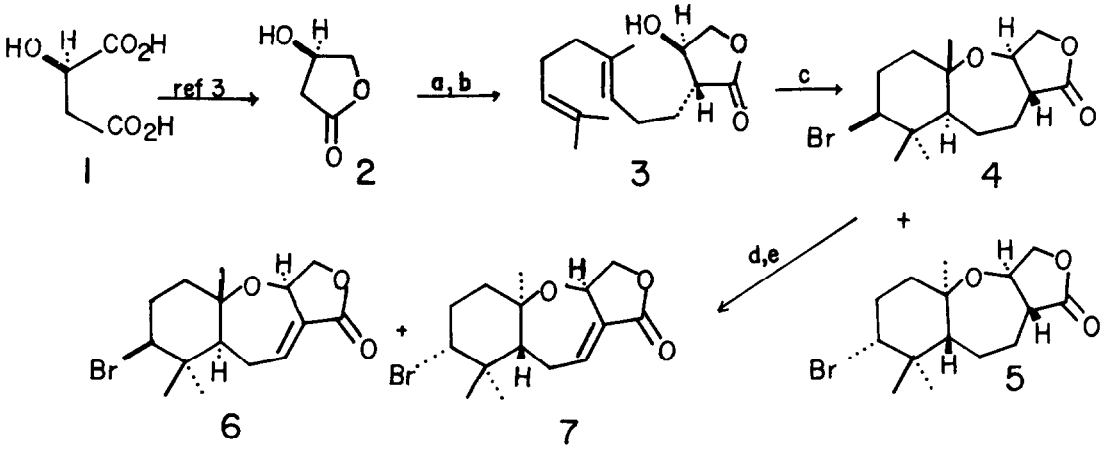
Hong-Ming Shieh and Glenn D. Prestwich*
Department of Chemistry
State University of New York at Stony Brook
Stony Brook, New York 11794 U.S.A.

SUMMARY. The marine antineoplastic agent aplysistatin (6) has been prepared enantiospecifically. The key step is the biomimetic cyclization of (2R, 3R)-2-homogeranyl-3,4-dihydroxybutanoic acid 1 4 lactone (3) with 2,4,4,6-tetrabromocyclohexa-2,5-dienone in nitromethane.

The anticancer agent aplysistatin (6) was isolated from the sea hare Aplysia angasi by Pettit and co-workers,[1] and total syntheses of this natural product in racemic form have been achieved by Hoye[2a,2b] and by White.[2c] The structure of this cyclic ether suggested to us a biomimetic synthesis in which all four chiral centers could be introduced stereospecifically by the cyclization of a diene alcohol such as 3, in which the absolute configuration at the carbinol carbon would uniquely determine the remaining three stereocenters. We now report the first enantiospecific total synthesis of natural (-)-aplysistatin, synthetically derived from R-(+)-malic acid.

The chiral β-hydroxy-γ-butyrolactone (R)-2 was prepared from the corresponding R-(+)-malic acid (1).[3,4] The dianion of 2 was generated by treatment with 2 equiv. of lithium diisopropylamide at -78°C in THF and was alkylated[4] with homogeranyl iodide[5] in THF-HMPA at -78 to -45° to give the desired substrate 3 in 35% yield after flash chromatography. As observed in the alkylation of acyclic β-hydroxyesters,[6] only the trans-2,3- disubstituted lactone is obtained[4,7] (Scheme I). At temperatures above -45°C, elimination of HI from the iodide to give the conjugated diene occurred more rapidly than alkylation of 2. Brominative cyclization[8] of 3

*Fellow of the Alfred P. Sloan Foundation (1981-83) and Camille and Henry Dreyfus Teacher-Scholar (1981-86).



Scheme I. Synthetic scheme for chiral 6 and 7, shown only for the natural (-)-6. Reagents and conditions : (a) LDA (2 equiv.), THF, -78°C, 1 hr; (b) homogeranyl iodide, THF-HMPA (2:1), -78°(5 hr), -40°(16 hr); (c) 2,4,4,6-tetrabromocyclohexa-2,5-dienone, CH_3NO_2, 20°, 2 hr; (d) LDA (1 equiv.), THF, -78°, 1 hr; C_6H_5SeBr, -78°(1 hr), then -40°(2 hr); (e) H_2O_2, THF, cat. CH_3CO_2H, 0°, 0.5 hr.

was effected using 1.2 equiv. of 2,4,4,6-tetrabromocyclohexa- 2,5-dienone in dry nitromethane[9] at ambient temperature for 2 hr. The high R_f fraction (cyclic ethers) was isolated from the crude cyclization mixture by flash chromatography to afford a 12% yield of a 19:81 mixture[7] of 7,8-dihydroaplysistatin 4 and the enantiomeric 12-epi isomer 5. The conformations of 3 required for synchronous cyclization via diastereomeric transition states [8,10] to give 4 and 5 are shown in Figure 1. The approximately 5:1 preference for cyclization to the undesired enantiomeric 12-epi isomer 5 indicates 1-2 kcal difference in the coiled transition states corresponding to 3A and 3B. We believe this arises from the steric interactions of the incipient angular methyl with H-8 in 3A, which is avoided in 3B.

The mixture of cyclic ethers 4 and 5 was converted in 93% yield to (-)-aplysistatin (6) and (+)-12-epiaplysistatin (7) by phenylselenation of the lactone enolates at -78°C followed by oxidative elimination of phenylselenic acid to introduce the 7,8- double bond. Analysis of this mixture of diastereomers by GC on a 50-m fused silica capillary clearly showed a 12:88 mixture of 6:7, which co-eluted with authentic samples of (dl)- aplysistatin and (dl)-12-epiaplysistatin furnished by Prof. T. Hoye. This mixture of 6 and 7 was separated by HPLC[7] to give homogeneous samples of chiral 6 ($[\alpha]^{20}_{589}$ (CH_3OH) = -421°(lit.[1]-375°); CD in methanol $[\theta]^{20}_{259}$ + 8460 (lit.[1] +8580)). The 12-epi isomer 7 had $[\alpha]^{20}_{589}$ (CH_3OH) = +25°; CD (CH_3OH), $[\theta]^{20}_{259}$ = +3522. The 80 MHz

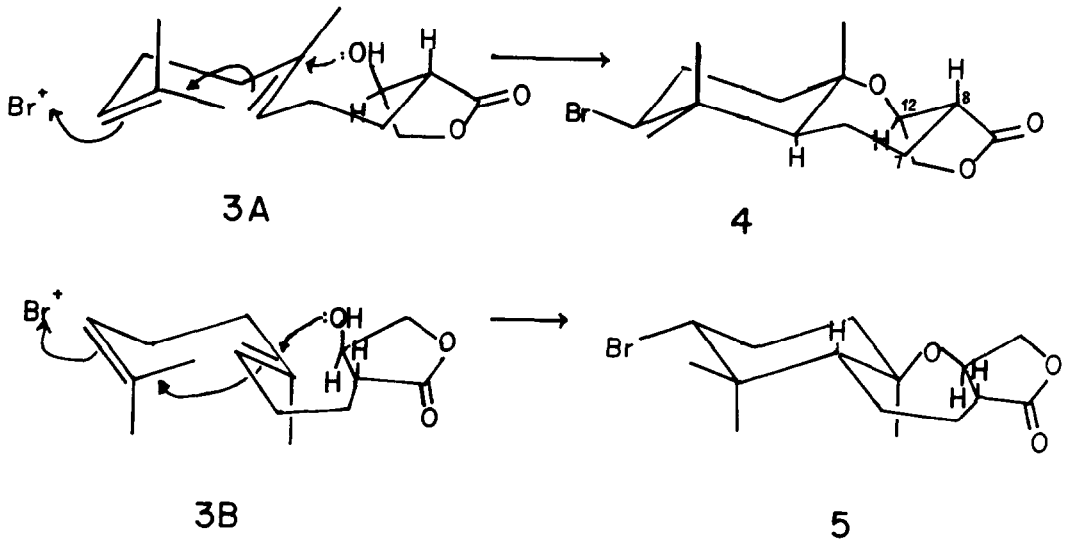


Figure 1. Conformations of 3 required for cyclization to 7,8-dihydroaplysistatin (3A→4) and 12-epi-7,8-dihydroaplysistatin (3B→5).

^{1}H-NMR and EI-mass spectra of 6 and 7 were indistinguishable from those for the racemic samples provided by Hoye[2a,b] and for the chiral 6 provided by Pettit.[1]

The sequence described above was initially developed using the more available S-(-)-malic acid. In this way, the unnatural isomer (+)-aplysistatin and (-)-12-epiaplysistatin were obtained in a 12:88 ratio following the same synthetic sequence. In both enantiomeric series, it is important to note that only a single pair of chiral, diastereomeric bicyclic ethers is obtained out of the 32 possible stereoisomers of 4.

A number of marine natural products are based on the bromonium ion-initiated cyclizations of sesquiterpenes. The chamigrenes,[11] snyderols,[12] and bromoepicaparrapi oxides[8,13] have been prepared by biomimetic electrophile-induced cyclizations. These routes offer high stereoselectivity in the simultaneous construction of several new chiral centers, thereby mitigating otherwise unacceptably low yields in the penultimate steps of the total syntheses. Indeed, haloethers such as 6 lacking derivatizable functional groups would be difficult to obtain in chiral form from synthetic racemic materials.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We thank Profs. J. White and T. R. Hoye for communicating their results[2b,2c] with us prior to publication. We thank Profs. Hoye and Pettit also for authentic samples as mentioned in the text.

References and Notes

1. Pettit, G.R.; Herald, C.L; Allen, M.S.; Von Dreele, R.B.; Vanell, L.D.; Kao, J.P.Y.; Blake, W., J. Am. Chem. Soc. 1977, 99, 262-263.

2. a) Hoye, T.R.; Kurth, M.J., J. Am. Chem. Soc. 1979, 101, 5065-5067; b) Hoye, T.R.; Caruso, A.J.; Dellaria, F.F. and Kurth, M.J., J. Am. Chem. Soc., in press (1982); c) Nishiguchi, T., Skeean, R.W., and White, J.D., J. Am. Chem. Soc., in press (1982).

3. R-(+) isomer: Mori, K.; Takigawa, T. and Matsuo, T., Tetrahedron 1979, 35, 933-940. S-(-) isomer: a) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J., J. Am. Chem. Soc. 1973, 95, 8749-8755; b) Corey, E.J., Niwa, H.; Knolle, J., J. Am. Chem. Soc. 1978, 100, 1942-1944. The Corey method was employed for the synthesis of both isomers.[4]

4. Shieh, H.M.; Prestwich, G.D., J. Org. Chem. 1981, 46, 4319-4321.

5. Homogeranyl iodide was prepared by homologation of geranyl bromide with phenylthiomethylcopper followed by treatment with CH_3I/NaI/DMF: Corey, E.J. and Jautelat, M., Tetrahedron Lett. 1968, 5787-5788.

6. Frater, G., Helv. Chim. Acta 1979, 62, 2825-2828.

7. All structures were consistent with spectral data (IR, 80 MHz ^{1}H-NMR, 20 MHz ^{13}C-NMR, LRMS, and HRMS). Homogeneity was assessed by TLC (Polygram Sil G 4x8 cm) and by capillary gas chromatography (Varian 3700 GLC, 12 m x 0.8 mm glass OV-101 column or 50 m x 0.25 mm vitreous silica OV-101). HPLC was performed on a Waters system using a Lichrosorb SI-60, 10 m (250 mm x 4.5 mm) column by elution with 1.5 ml/min of 10% ethyl acetate in hexane and with detection at 254 nm.

8. Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T., J. Chem. Soc. Chem. Comm. 1980, 1106-1108. The chiral allylic alcohol of nerolidol almost completely controlled the generation of three new asymmetric centers of 3β-bromo-8-epicaparrapi oxide.

9. The cyclization is only successful when performed using nitromethane freshly distilled from CaH_2 and by addition of the solid, sparingly-soluble TBCD to a dilute solution of the dienol 3 in nitromethane (1 mg 3 per ml). All other conditions lead to more polar monocyclic compounds; in the (dl)-8-thiophenyl compound corresponding to 3, White found no reaction with TBCD.[2c]

10. Prestwich, G.D.; Labovitz, J.N., J. Am. Chem. Soc. 1974, 96, 7103-7105.

11. Faulkner, D.J., Pure Appl. Chem. 1976, 48, 25-28.

12. Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y., J. Chem. Soc. Chem. Comm. 1976, 518-519.

13. Hoye, T.R.; Kurth, M.J., J. Org. Chem. 1979, 44, 3461-3467.

(Received in USA 14 July 1982)