Note

Synthesis of (±)-4-Isocymobarbatol by Brominative Cyclization

Akira TANAKA and Takayuki ORITANI

Department of Applied Biological Chemistry, Faculty of Agriculture, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981, Japan

Received August 8, 1994

The brominative cyclization of 5-bromo-2-geranyl-1,4-benzenedioli bisthiooxymethyl ether (2) with 2,4,4,6-tetramethylcyclohexadienone was reexamined. This cyclization of 2 resulted in the formation of methoxymethyl ether 10 of 2,4,6-tribromophenol, together with previously described tricyclic compound 7, thus supporting the intervention of oxonium ion 12 in this reaction. An analogous reaction of bisthiooxymethyl ether 4 led to 8. Finally, 7 was converted to (±)-4-isocymobarbatol (6).

We have described in a previous paper the brominative cyclization of monoterpenoid hydroquinone dimethyl ether 3 with 2,4,4,6-tetramethylcyclohexadienone, leading to (±)-cycloemethyl dimethyl ether (5). In contrast, when thiooxymethyl ether 2 was submitted to the same reaction, we obtained the tricyclic compound 7 as the major product. In this interesting reaction, the formation of the intermediate oxonium ion such as 12 had been assumed. In this paper, we report a more detailed examination of the reaction leading to this type of tricyclic compound.

The brominative cyclization of 2 was affected according to the previously described procedure to yield 2,4,6-tribromophenol (9) and its methoxymethyl ether 10, together with tricyclic compound 7, supporting the intervention of oxonium ion 12 or its equivalent in this reaction. Next, we selected bisthiooxymethyl ether 4 as an appropriate derivative capable of forming analogous oxonium ion 13 in the brominative cyclization. In order to prepare this compound, 2 was first hydrolyzed with pyridinium p-toluensulphonate in tert-butyl alcohol to give (±)-cymopin (1) in an 80% yield, which after being treated with methoxysthio- methyl chloride and diisopropylethylamine in dichloromethane, afforded 4 in an 85% yield. Brominative cyclization of 4 provided tricyclic compound 8, although attempts to isolate methoxysthiooxymethyl ether 11 of 2,4,6-tribromophenol were unsuccessful due to its very unstable nature.

Finally, treatment of 2 with refluxing 80% acetic acid furnished almost quantitatively (±)-4-isocymobarbatol (6), an antimutagenic agent that has been isolated from the green alga, Cymopolia barbata. The IR and 1H-NMR spectra of synthetic 6 were in good agreement with those of natural 6, these data being kindly supplied by Dr. M. E. Wall.

Experimental

All melting point (mp) data are uncorrected. IR spectra were taken with a JASCO IR-810 infrared spectrometer, and 1H-NMR spectra were measured with a JEOL GSX-270 spectrometer. MS data were recorded with a JEOL JMX-DX-300 instrument.

Brominative cyclization of 2. This reaction was performed by using the bisthiooxymethyl ether 2 (100 mg) according to the previously described procedure. Purification of the crude product by preparative TLC furnished 9 (34 mg, 42%) and 10 (15 mg, 16%), together with 7 (40 mg, 35%). Sublimation of 9 gave a sample melting at 93°C, which was identical with authentic 2,4,6-tribromophenol in a mixed mp and IR spectral data. Recrystallization of 10 from hexane–AcOEt afforded a pure sample, mp 61–62°C. IR (KBr) νmax cm⁻¹: 3100, 3050, 2950, 2920, 1560, 1540, 1450, 1390, 1200, 1160, 920, 850, 730. 1H-NMR (CDCl₃) δ: 3.71 (3H, s), 5.16 (2H, s), 7.67 (2H, s). Anal. Found: C, 25.79; H, 2.04. Calcd. for C₇H₇Br₂O₂: C, 25.63; H, 1.88%.

(±)-Cymopin (1). A solution of 2 (1.00 g) and pyridinium p-toluensulphonate (2.4 g) in tert-ButOH (20 ml) was refluxed for 10 h and the mixture taken in ether, the ethereal solution then being washed with water, dried and concentrated to afford a crude product. Purification by column chromatography gave 1 (650 mg, 80%). Recrystallization from hexane provided a pure sample, mp 61–62°C (lit. 59–61°C).

(±)-Cymobarbatol bisthiooxymethyl ether (4). A solution of 1 (240 mg), methoxysthiooxymethyl chloride (0.36 ml) and iso-Pr₂EtN (1.5 ml) in CH₂Cl₂ (2 ml) was stirred at room temperature for 48 h, the mixture then being diluted with water and extracted with ether in the usual way. Purification of the crude product by preparative TLC yielded 4 (316 mg, 85%). IR (film) νmax cm⁻¹: 2910, 1600, 1480, 1370, 1190, 1100, 990, 850, 780. 1H-NMR (CDCl₃) δ: 1.58 (3H, s), 1.67 (3H, s), 1.68 (3H, s), 2.05 (4H, m), 3.26 (2H, d, J = 7.3 Hz), 3.38 (3H, s), 3.40 (3H, s), 3.56 (4H, m), 3.81 (2H, m), 3.88 (2H, m), 5.08 (1H, m), 5.21 (2H, s), 5.24 (2H, s), 5.25 (1H, m), 6.99 (1H, s), 7.31 (1H, s).

Brominative cyclization of 4. This reaction was effected utilizing 4 (106 mg) according to the previously reported procedure. Purification of the crude product by preparative TLC gave 8 (32 mg, 31%), together with 2,4,6-tribromophenol (9, 15 mg). Recrystallization of 8 from hexane afforded a pure sample, mp 80–81°C. IR (KBr) νmax cm⁻¹: 2950, 2930, 1660, 1575, 1480, 1380, 1160, 1120, 970, 860, 780. 1H-NMR (CDCl₃) δ: 1.01 (3H, s), 1.15 (3H, s), 1.20 (3H, s), 1.78 (2H, m), 1.97 (1H, dt, J = 3.8, 13.0 Hz). 2.12 (1H, dt, J = 3.8, 13.0 Hz), 2.28 (1H, dtt, J = 3.8, 13.8 Hz). 2.65 (1H, ddt, J = 12.4, 16.0 Hz), 2.75 (1H, dd, J = 5.6, 16.0 Hz), 3.40 (3H, s), 3.59 (2H, m), 3.90 (2H, m), 4.03 (1H, dd, J = 4.2, 13.0 Hz), 5.22 (2H, s), 6.93 (1H, s), 6.95 (1H, s). HREIMS: Found, 494.0327. Calcd. for C₁₂H₁₀Br₂O₄, 494.0313.

(±)-4-Isocymobarbatol (6). A solution of 7 (49 mg) in 80% ac. AcOH (1 ml) was stirred at refluxing temperature for 1.5 h. Evaporation of the solvent and preparative TLC of the resulting residue afforded 6 (44 mg, 99%). Recrystallization from MeOH–H₂O gave an analytical sample, mp 62–63°C. Anal. Found: C, 47.44; H, 4.90. Calcd. for C₁₂H₁₀Br₂O₄: C, 47.55; H, 4.99%. This synthetic sample was identical with natural 4-
isocymobarbatol in its IR and 1H-NMR spectra.

Acknowledgment. We thank Dr. M. E. Wall of Research Triangle Institute for sending us the IR and 1H-NMR spectra for natural 4-isocymobarbatol.

References