A Trilactone Related to Anemonin

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In memory of Professor Nicholas Alexandrou

Treatment of Anemonin sequentially with two equivalents of the anion **2** and iodine gave the monoalkylated monoiodinated iodolactone *t*-butyl ester **3**. Ester cleavage in anhydrous acedic media followed by treatment with sodium hydrogen carbonate transformed **3** to trilactone **4**.

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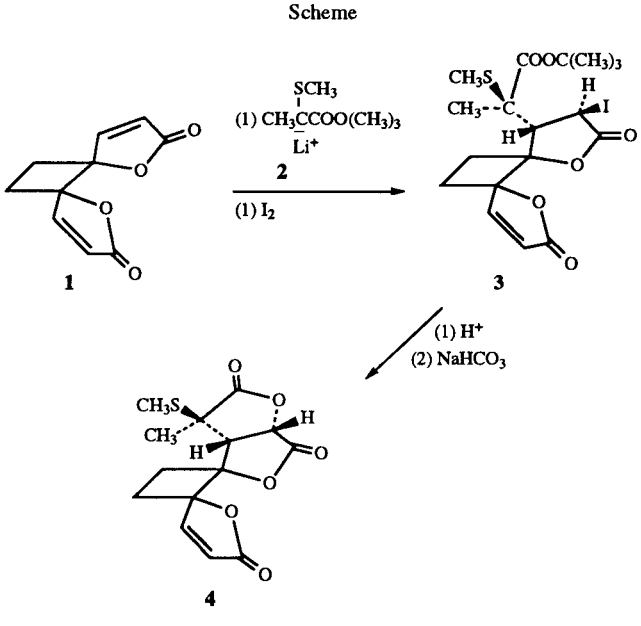
Protoanemonin, 5-methylene-5*H*-furan-2-one, is a well known antibacterial principle released by maceration of the plant tissue of *Anemona pulsatilla L.* and several other *Ranunculaceae* [2]. Both protoanemonin, a monolactone, and its cyclodimerization product anemonin **1**, a dilactone, were determined in the flowering aerial parts of *P. alpina apiifolia.* Anemonin is the primary compound responsible for antipyretic activity and both anemonin and protoanemonin participate in a sedating effect [3]. Therefore, the construction of an additional lactone moiety on the molecule of anemonin would produce an attractive novel compound carrying three crowded lactone functional groups of which the pharmacological properties would be interesting to evaluate.

Thus, the synthesis of such a trilactone, namely the *trans*-1,7-Dioxadispiro[4.0.4.2]dodec-3-ene[*cis*-9-hydroxy-10-[2-(2β-methylthiopropanoic acid)]-γ-lactone]-2,8-dione **4** was undertaken and herewith we describe our results. The required anion **2** was generated from the ester 1,1-dimethylethyl 2-methylthiopropanoate with lithium diisopropylamide at dry ice-acetone temperature [4]. This ester in turn was prepared by the reaction of the 2-chloropropanoyl chloride with 2-methyl-2-propanol in the presence of triethylamine and 4-dimethylaminopyridine to produce the 1,1-dimethylethyl 2-chloropropanoate, which was subsequently reacted with sodium thiomethoxide. Conjugate addition of the anion **2** to anemonin **1** [5] followed by quenching with iodine produced the *trans* adduct *t*-butyl ester: trans-1,7-Dioxadispiro[4.0.4.2]dodec-3-ene-*trans*-3-iodo-4-[2-(2-methylthio-*t*-butoxypropanoyl)]-2,8-dione **3** in 71% yield.

Scheme



Although two equivalents of the anion **2** were used in the reaction and both the conjugated double bonds of anemonin are equally exposed, since the two lactone rings are installed in a fixed *trans* configuration, only one of them underwent the addition. It is well known that *t*-butyl esters are cleaved by moderately acidic media under anhydrous conditions [6]. Consequently the *t*-butyl ester **3** was heated in benzene solution in the presence of catalytic amounts of *p*-toluenesulfonic acid and trifluoroacetic acid to afford the corresponding iodolactone acid which was not isolated. Instead this reaction mixture was subsequently treated with aqueous sodium hydrogen carbonate at room temperature [7] to give the trilactone **4** in 58% yield as the single isomer. The structural assignment of trilactone **4** illustrated in the Scheme was deduced on the basis of spectral data and by comparison with previously reported assignments of comparable compounds [4] It shows a methyl singlet at δ 1.74 and a methylthio singlet at δ 2.17. A chemical shift of δ 4.85 (d) was observed for the H_A with J_{BA} = 8 Hz and a chemical shift of δ 3.91 for the H_B with J_{BA} = 8 Hz. These data, as well as simple Dreiding stereomodels supported the structure depicted in the Scheme.

EXPERIMENTAL

1,1-Dimethylethyl 2-Chloropropanoate.

A solution of 2-chloropropanoyl chloride (25.4 g, 0.2 mole) in 100 ml of dry toluene was added dropwise to a stirred solution of 2-methyl-2-propanol (freshly distilled from potassium permaganate and dried over calcium hydride, 29.6 g, 0.4 mole), 4-dimethylaminopyridine (24.4 g, 0.2 mole) and triethylamine (freshly distilled from lithium aluminum hydride, 20.2 g, 0.2

mole) in 200 ml of dry toluene. The reaction mixture was stirred at room temperature for ten hours, washed with water, dried (sodium sulfate), and the solvent was rotary evaporated under reduced pressure. The residual oil was distilled *in vacuo* to give 25.7 g (78%) of colorless oil, bp 49-51°/14 mm, lit [8a] bp 52-53°/12 mm, [8b] bp 48°/15 mm.

1,1-Dimethylethyl 2-Methylthiopropanoate.

Sodium metal (3.68 g, 0.16 mole) was carefully dissolved in 150 ml of absolute ethanol under argon. Excess methanethiol was slowly bubbled through this solution by cooling the reaction flask in an ice bath, followed by the slow addition of 1,1-dimethyl 2-chloropropanoate (23.03 g, 0.14 mole). The reaction mixture was stirred at room temperature for a half hour and refluxed for two hours. The inorganic material was filtered and the solvent was evaporated under reduced pressure. The residual oil was distilled *in vacuo* to give 18.5 g (75%) of a colorless oil, bp 68-70°/14 mm, lit [4] bp 70-72°/16 mm.

trans-1,7-Dioxadispiro[4.0.4.2]dodec-3-ene-*trans*-9-iodo-10-[2-(2-methylthio-*t*-butoxypropanoyl)]-2,8-dione **3**.

To a solution of lithium diisopropylamide (0.02 mole) in 35 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) cooled with a dry ice-acetone bath under argon atmosphere was added dropwise with stirring a solution of 1,1-dimethylethyl 2-methylthiopropanoate (3.52 g, 0.02 mole) in 25 ml of tetrahydrofuran. After fourty fiye minutes stirring, a solution of anemonin (1.92 g, 0.01 mole) in 15 ml of tetrahydrofuran and 50 ml of hexamethylphosphoramide was added dropwise over a one half hour period, at dry ice-acetone temperature. This mixture was stirred for two hours at this temperature, and a solution of iodine (3 g, 0.02 mole) in 30 ml of tetrahydrofuran was then added dropwise. The reaction mixture was stirred for one half hour at dry dry ice-acetone temperature, quenched with a little water, and the mixture was diluted with dichloromethane while stirring was continued. It was acidified with dilute hydrochloric acid, saturated with sodium chloride and the organic layer was washed with ice-water and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed through a silica gel column using ether-hexane mixtures. The product was crystallized from the ether-hexane fraction to give 3.3 g (71%) of solid mp 169-170°; ir (potassium bromide): ν 1750 (lactone C=O), 1690 (ester C=O), 1590 (C=C) cm^{-1}; ^1H nmr (Varian EM 360, deuteriochloroform): δ 1.20 (s, 3H, CH_3), 1.55 (s, 9H, CMe_3), 2.20 (s, 3H, CH_3S), 2.35 (m, 4H, CH_2CH_2), 3.97 (d, 1H, CH), 5.22 (d, 1H, CHI), 6.15 (d, 1H, C=CH-C=O), 7.70 (d, 1H, CH=C).

Anal. Calcd. for $C_{18}H_{23}IO_6S$; C, 43.73; H, 4.66; I, 25.71. Found; C, 44.02; H, 4.86; I, 25.85.

trans-1 7-Dioxadispiro[4.0.4.2]dodec-3-ene[*cis*-9-hydroxy-10-[2-(2β-methylthiopropanoic Acid)]-γ-lactone]-2,8-dione **4**.

A solution of iodolactone *t*-butyl ester **3** (2.6 g, 5.26 mmoles) and anhydrous *p*-toluenesulfonic acid (0.52 g, 3 mmoles) in 150 ml of anhydrous benzene containing a few drops of trifluoroacetic acid was refluxed for three hours. After cooling the solution at room temperature, 2.5 g of sodium hydrogen carbonate powder and 50 ml of ethyl acetate were added and the mixture was stirred overnight. The reaction mixture then was applied to a column of silica gel and the product was initially eluted with ether containing ethyl acetate (9:1, v/v). Considerably more product was obtained by continuing elution of the column with acetone-ethyl acetate mixtures. The product was crystallized from ether-ethyl acetate and the mother liquor was chromatographed again on silica gel using initially ethyl acetate:ether:hexane (1:1:1, v/v) to separate unreacted starting material (50 mg). The product was obtained as white crystals, mp 259-260°, 950 mg (58%); ir (potassium bromide): ν 1755, 1770, 1790 (lactone carbonyls), 1590 (CH=C-) cm^{-1}; ^1H nmr (JEOL-PFT-100, deuteriochloroform): δ 1.74 (s, 3H, CH_3), 2.17 (s, 3H, CH_3S), 2.20-3.05 (m, 4H, CH_2CH_2), 3.91 (d, 1H, C-CH(C)-C, J = 8 Hz), 4.86 (d, 1H, OCHC-O, J = 8 Hz), 6.13 (d, 1H, O=CHCO, J = 6 Hz), 7.66 (d, 1H, HC=C-C=O, J = 6 Hz); hrms: Calcd. for $C_{14}H_{14}O_6S$: m/z 310.051. Found: m/z 310.048.

Anal. Calcd. for $C_{14}H_{14}O_6S$: C, 54.19; H, 4.52. Found: C, 54.40; H, 4.61.

REFERENCES AND NOTES

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