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THE SYNTHESIS OF TRISNORCYBRODOLIDE, A METABOLITE OF CYATHUS BULLERI BRODIE.

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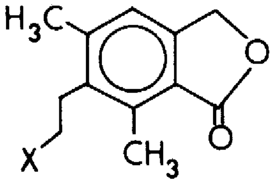
Abstract: The synthesis of trisnorcybrodolide (1) from mesitylene is described.

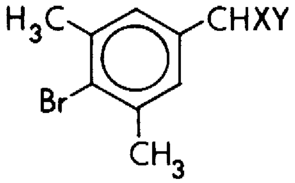
In the preceding paper we described the isolation of trisnorcybrodolide (1) from cultures of the bird's nest fungus *Cyathus bulleri*. Trisnorcybrodolide (1) plays an important role in the assignment of the structures of the new *seco*-illudalane sesquiterpenes cybrodol and isocybrodol[1]. We report herein an unambiguous synthesis of 1 from mesitylene.

Chromyl acetate oxidation[2] of 2-bromomesitylene[3] provided the diacetoxymethyl compound 2[4,5] in $\sim$50% yield. Reduction (LAH) of 2 provided the alcohol 3, which has been prepared previously by a more circuitous route[6]. Methylation (NaH, CH_3I) gave the ether 4 which on treatment with butyllithium (THF/hexane, -78°) followed by oxirane gave the β-hydroxyethyl compound 5[4]. Bromination (Br_2, CH_3NO_2, 0°) and protection of the alcohol function (dihydropyran, pyridinium tosylate, CH_2Cl_2) furnished 6[4]. The Grignard reagent derived from 6 could not be induced to react with carbon dioxide or methyl chloroformate but the lithium derivative 7, prepared by treating 6 with butyllithium (THF/hexane, -78°), reacted with methyl chloroformate to give the ester 8[7] in 51% yield.

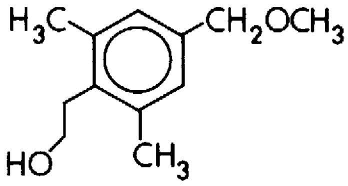
We deemed it worthwhile to investigate the action of chlorotrimethylsilane-sodium iodide in acetonitrile on the ester 8 since it has been reported[8] that this reagent will bring about the cleavage of methyl ethers and methyl esters and will convert benzylic alcohols to iodides. Thus 8 might be converted to the intermediate 9 which is well suited for lactonization. At this point, it was not clear what the fate of the tetrahydropyranyl ether protecting group would be. In the event, treatment of 8 with the Olah reagent[8] gave a mixture of trisnorcybrodolide (1, 11%) and the corresponding iodide 10 (60%). In order to avoid the side reaction associated with the THP protecting group in 8, it was removed (pyridinium tosylate, CH_3OH) and replaced with an acetyl group (Ac_2O, pyridine) to give 11[4]. Treatment of 11 with chlorotrimethylsilane-sodium iodide followed by methanolysis (Na_2CO_3, CH_3OH) of the resulting acetyltrisnorcybrodolide (12) gave trisnorcybrodolide (1) in good yield (75% overall from 8). The synthetic compound was identical (mp, ir, ^{1}H nmr, ms) with that isolated from *C. bulleri*, confirming the structural assignment[1,9].



1 X=OH
10 X=I
12 X=OAc



2 X=Y=OAc
3 X=OH, Y=H
4 X=OCH_3, Y=H



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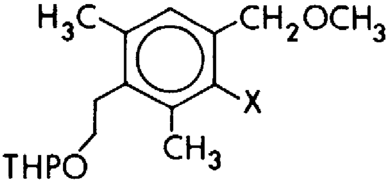
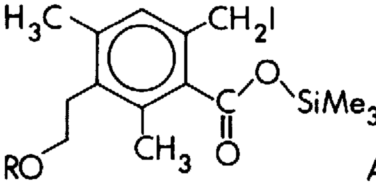


6 X=Br
7 X=Li
8 X=$COOCH_3$



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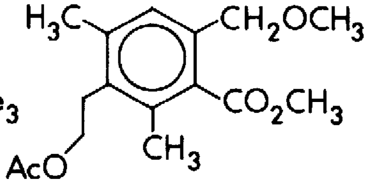

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References and Notes

1. W.A. Ayer and R.H. McCaskill. Tetrahedron Letters, preceding paper.
2. K.B. Wiberg, in "Oxidation in Organic Chemistry, Part A." ed. K.B. Wiberg, Academic Press, New York. 1965. pp 92-94. The conditions used were those of S.V. Lieberman and R. Connor, Org. Syn. Coll. Vol. **2**, Wiley, New York. 1943. pp 441-443.
3. L.I. Smith. Org. Syn. Coll. Vol. **2**, Wiley, New York. 1943. p 95.
4. All new compounds gave analytical and spectral (^{1}H and ^{13}C nmr, ir) data consistent with the assigned structures.
5. That oxidation had occurred <u>para</u> to the bromine was apparent from the equivalence displayed in the ^{1}H and ^{13}C nmr spectra.
6. P.J. Grisdale, J.L.R. Williams, M.E. Glogowski and B.E. Babb. J. Org. Chem., **36**, 544 (1971).
7. Ir (film): 1729 cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 1.4-1.8 (6H, m), 2.33 (3H, s), 2.37 (3H, s), 3.00 (2H, t, J = 7 Hz), 3.30 (3H, s), 3.50 (2H, m), 3.70 (2H, t, J = 7 Hz), 3.87 (3H, s), 4.38 (2H, s), 4.56 (1H, bs), 7.00 (1H, s).
8. G.A. Olah, S.C. Narang, B.C.B. Gupta and R. Malhotra. J. Org. Chem., **44**, 1247 (1979).
9. We thank the Natural Sciences and Engineering Research Council Canada for financial support and a scholarship (to R.H.M.).

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