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A NEW STEREOSELECTIVE SYNTHESIS OF (±)-DEBROMOAPLYSIN AND (±)-APLYSIN

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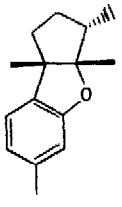
During the course of an investigation of ortho-metallated aryl methoxymethyl ethers[1] with some α-chlorocyclopentenones a very unexpected participation of the methoxymethyl group occured which resulted in structures very similar to the marine sequiterpene debromoaplysin 1. Debromoaplysin 1, as well as the related bromo-compounds aplysin 2 and aplysinol 3 were first isolated from the sea hare Aplysia kurodai by Japanese workers, who also reported the first synthesis, albeit in low yield[2,3]. These sesquiterpenes are thought to occur in these organisms through their diet of red algae, a rich source of marine natural products[4]. This report describes a new efficient synthesis of 1 and the first reported direct conversion of 1 to 2.



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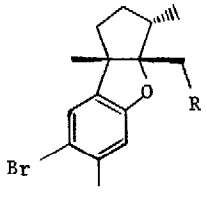
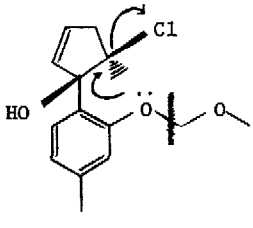


2 R=H, 3 R=OH

Initial work involved the condensation of 6-lithio-3-methylphenol methoxymethyl ether, 4[1], with 5-chloro-5-methyl-2-cyclopentenone, 5[5], which resulted in the formation of chlorohydrin 6. Prolonged treatment with base at room temperature failed to have any effect on 6; a strong indication that it is a cis-chlorohydrin. Bartlett has shown that under more drastic conditions cyclic cis-chlorohydrins rearrange to form cyclic ketones[6]. However, when 6 was refluxed with methanolic KOH, it reacted slowly to form a product which lacked the carbonyl band and methoxymethyl resonances expected for the rearrangement product 8, and was shown instead to be the tricyclic alcohol 7 which has the aplysin type structure.



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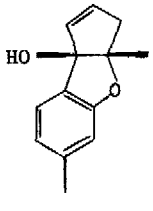

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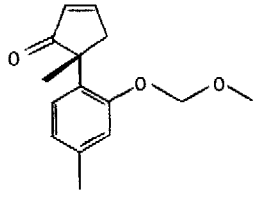

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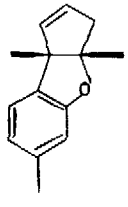

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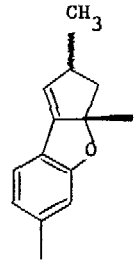

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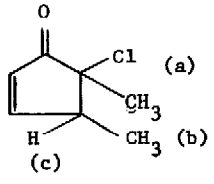
The conversion of 6 to 7 is noteworthy as it is formally a base-catalyzed methanolysis of a mixed formaldehyde acetal. Most probably the formation of 7 involves solvolysis of the tertiary chloride with internal trapping by the phenolic ether oxygen to form a tricyclic oxonium ion which collapses to 7 and an O-methylated formaldehyde cation. The failure of 6 to form 7 when treated with NaH in dimethylformamide suggests that the base serves principally to prevent the buildup of HCl from the solvolysis. Indeed, compound 6, was shown to be extremely sensitive to acid. It decomposes on standing or when dissolved in alcohols in the absence of base with the liberation of HCl and is rapidly converted to a dark tarry mass.

For a tertiary allylic, benzylic alcohol, compound 7 is remarkably insensitive to acid catalyzed reactions. It remains unchanged when treated with acetic acid for extended periods, and will not oxidize with allylic rearrangement to an enone with Cr^{VI} oxidizing agents. It can, however, be converted to a single highly reactive bromide upon treatment with either concentrated hydrobromic acid or PBr_3 in ether. This bromide, which is stable only in solution, has an nmr spectrum almost identical to the alcohol 7, to which it rapidly reverts upon exposure to water.

Examination of molecular models of the tricyclic system indicates that the double bond in conjugation with the aromatic ring is considerably more strained than in the unconjugated, or disubstituted position. This suggested that substitution reactions of 7 should preferentially occur without allylic rearrangement, and that the key benzylic methyl group required for an aplysin synthesis could be introduced via an organometallic coupling reaction. An investigation of coupling reactions of 7 or the derived bromide with several magnesium, copper, and nickel[7] methyl complexes established that simple Grignard coupling of the bromide would produce the desired methylated tricyclic ether 9. Interestingly, copper reagents substituted with extensive migration of the double bond to the conjugated position affording compounds, i.e. 10, which, as predicted from the aforementioned model studies, were highly reactive and polymerized in a few days at room temperature.

An aplysin synthesis requires a secondary methyl group in the cyclopentene ring derived from the chlorocyclopentenone. Fortunately, the requisite 5-chloro-4,5-dimethyl-2-cyclopentenone 11 is readily available as a 2:3 mixture of cis and trans isomers from the aluminum chloride catalyzed condensation of acetylene and tigoyl chloride[5]. These ketones decomposed extensively upon distillation, but could readily be separated by preparative liquid chromatography on a 50.8 mm x 50 cm column containing 500g of Merck Silica Gel PF eluted with 25% ethyl ether in petroleum at 610 ml/hr. As much as 7g of the ketone mixture could be separated at one time; the minor isomer eluted first. Preliminary structural assignments of the cis and trans isomers were made on the basis of the nmr spectra and were confirmed by the conversion, without alteration of the secondary methyl stereochemistry, of the trans isomer of 11 into compound 16 which is isomeric with debromoaplysin.

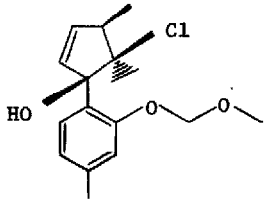


Characteristic PMR Resonances* of the Isomeric Cyclopentenones 1

proton	a	b	c
cis dimethyl	1.56	1.28	3.45
trans dimethyl	1.63	1.32	3.05

*Chemical shifts in ppm relative to TMS.

Treatment of the trans-ketone 11 with the lithium reagent 4 afforded after base treatment a modest yield of tricyclic alcohol along with significant amounts of unreacted m-cresol methoxymethyl ether and a yellow-orange polymeric substance, apparently derived from deprotonation and subsequent self-condensation of the chlorocyclopentenone. Thus, a suspension of 24.4 mmoles of 4, prepared as previously described[1], was slowly added over a 1 h period to a solution of 3.37g (23.2 mmoles) of trans-cyclopentenone 11 in 450 ml of dry ether at 0°. The mixture was allowed to warm to ambient temperature overnight, then quenched with water and filtered through Celite to remove the aforementioned polymeric material. After drying and concentrating, the crude adduct 12 was dissolved in a solution of 3.0g KOH in 150 ml of dry methanol and heated to reflux for 28 hr. The crude product was then chromatographed on a 500g silica gel column to afford 2.10g (42%) of alcohol 14 as a yellow oil, which was shown to be >85% pure by gas chromatography (GC)[8]. Unlike the trans-ketone 11, the cis isomer reacts to form trans-chlorohydrin 13 that is rapidly cyclized by mild base treatment at room temperature to an epoxide which resisted further cyclization to form 14.



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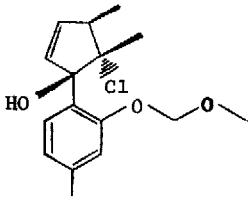

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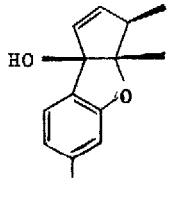

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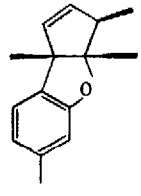

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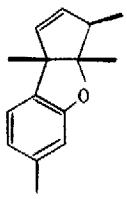
The methylation of the bromide derived from tricylcic alcohol 14 formed the ether 15 which appears to be the exclusive methyl coupling product. This reaction is most conveniently carried out by quenching the alcohol bromination mixture in an excess of Grignard reagent. Thus, a solution of alcohol 14, 2.40g (9.4 mmoles), in 300 ml of dry ether was treated with an excess of PBr_3 (16 mmoles) at room temperature. After conversion to the bromide was complete, 1½ h, the solution was added to a large excess of CH_3MgBr in ether (105 mmoles) over a 1 h period. The mixture was stirred overnight with an excess of CH_3I to remove phosphines, then quenched with water and extracted with petroleum. After chromatography on silica gel and bulb to bulb distillation (75°/0.025 mm), 407 mg (20%) of tricyclic ether 15 was obtained in >99% purity. Thus, in two steps from 11 the entire carbon structrue of aplysin has been completely assembled.

Conversion of 15 to aplysin 2 requires epimerization of the secondary methyl group and introduction of the bromine substituent. The epimerization was accomplished in two steps by isomerization to the trisubstituted olefin 17 followed by catalytic hydrogenation from the face of the cyclopentene away from the aromatic ring. To insure that the initial stereochemical assignments of the ketone 11 had been correct, 15 was hydrogenated, without isomerization, to 16 which was shown to be isomeric with an authentic sample of debromoaplysin[9].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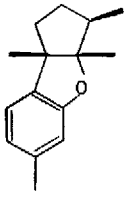
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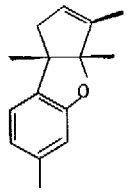
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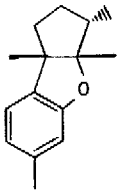
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Of the several reagents for the double bond isomerization that were investigated Wilkinson's catalyst appears to be the most effective. Refluxing a solution of 268 mg of 15 in the 4 ml of toluene-isobutanol (1:1) containing 15 mg triphenylphosphine and 10 mg Wilkinson's catalyst for 70 h in the presence of air[10] afforded a 95:5 mixture of 17 and 15. This was readily separated by liquid chromatography on silica gel to yield 202 mg (75%) of 17 which was >98% pure by GC.

Hydrogenation of 17 with Adam's catalyst in ethanol produced a 95:5 mixture of debromoaplysin 1 and the isometric hydrocarbon 16. Separation of the mixture was conveniently accomplished by liquid chromatography on silica gel and after bulb to bulb distillation (70%/ 0.05 mm) an 81% yeild of pure (+) debromoaplysin (>99% by GC) was obtained. The constitution of the synthetic material was established by comparison with natural debromoaplysin[9] and by conversion to aplysin.

Contrary to published reports[3] debromoaplysin can be selectively brominated in excellent yield to form aplysin. Treatment of a solution of 1, 22 mg (0.1 mmoles) in 1 ml of hexane, in which was suspended 11 mg dry Na_2CO_3, with a slight excess of bromine (5 µl) resulted in rapid (within 5 min) decolorization. After filtration through a short column of silica gel the crude product was recrystallized from methanol to afford 24 mg (80%) of aplysin 2, mp 98.5-100° (sealed capillary). An analytical sample melted 100-101° (lit 101-102°)[3] and its constitution was established by comparison (ir, nmr, GC, tlc, elemental analysis) with the natural material[9].

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References and Notes

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8. Satisfactory spectral and analytical data were obtained for all compounds reported.
9. The author is indebted to Dr. W. Fenical of the Scripps Oceanographic Institute, La Jolla, California, for authentic samples of debromoaplysin and aplysin.
10. R. L. Augustine and J. F. Van Peppen, Chem. Comm., 495 (1970); ibid, 571 (1970).