(10 800), 533 (10 400), 601 (8950), 659 (51 800). Anal. Calcd for $C_{34}H_{38}N_4O_4$: C, 72.06; H, 6.76; N, 9.89. Found: C, 72.20; H, 6.73; N, 10.13.

Acknowledgment. We thank the National Science Foundation for support of this research through Grant CHE-78-25557, the Research Corporation for a grant to purchase the high-performance LC system, and the UC Davis NMR Facility for a grant. This paper is dedicated (by K.M.S.) to the memory of Professor R. B. Woodward.

Registry No. (*R*)-**2**, 59924-02-6; (*S*)-**2**, 73365-61-4; **4**, 55721-87-4; **7**, 73347-54-3; **7**, copper complex, 72415-74-8; **9**, 72415-75-9; **10**, 72415-77-1; **11**, 73347-55-4; **11**, 2-(2-acetoxyethyl) derivative, 73347-56-5; **11**, 2-(2-hydroxyethyl) derivative, 73347-57-6; **13**, 73333-65-0; **14**, 73333-66-1; **15**, 68528-79-0; (*R*)-**16**, 59954-18-6; (*S*)-**16**, 61665-26-7; **17**, 6453-67-4; **19**, 66230-00-0; **20**, 73347-58-7; δ-methylpurpurin-18 methyl ester, 73333-67-2; δ-methyl-2-(2-chloroethyl)-2-devinylpurpurin-18 methyl ester, 73347-59-8.

Total Synthesis of (-)-Aplysin and (-)-Debromoaplysin

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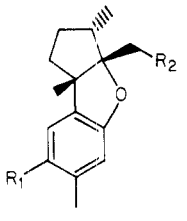
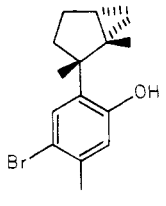
Received September 25, 1979

The total synthesis of optically active (-)-aplysin (**1**) and (-)-debromoaplysin (**2**) employing novel (isopinocampheyloxy)methyl ethers for phenolic hydroxyl protection and diastereomeric resolution is described. A key transformation is the unusual cyclization of the diastereomeric chlorohydrins **12** and **13** in methanolic base to form the enantiomeric tricyclic alcohols (-)-**16** and (+)-**16** with cleavage of the acetal-linked (isopinocampheyloxy)methyl resolving/protecting group. This transformation was followed by substitution of the tertiary hydroxyl via the derived chloride with a methyl group by Grignard coupling with methylmagnesium bromide. The methyl insertion occurred with retention of configuration and resulted in formation of the natural aplysin system from **12** in just three steps. The conversion of the methylated tricyclic ether **20** to (-)-debromoaplysin (**2**) was accomplished in two steps by double bond isomerization and selective reduction. Bromination of (-)-**2** afforded (-)-aplysin (**1**).

One of the first halogenated sesquiterpenes to be isolated from marine sources was (-)-aplysin (**1**) which occurs in



1, R_1 = Br; R_2 = H
2, R_1 = R_2 = H
4, R_1 = Br; R_2 = OH



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the sea hare, *Aplysia kurodai*, that inhabits the eastern Pacific.[2,3] It is also found in opisthobranchs which inhabit the coasts of North America.[3] These mollusks tend to accumulate aplysin and related substances in the gut along with the presumptive aplysin precursor debromoaplysin (**2**). These compounds appear to function as antifeedants which make these slow-moving, shelless creatures unpalatable to predators.[4] They may also function as antioxidants to scavenge reactive halogen which would explain the frequent co-occurrence of the unhalogenated forms.

The sesquiterpenes in *Aplysia* appear to be derived from the red algae which constitute their principal dietary component.[3] These algae, especially of the genus *Laurencia*, have been shown to be a rich source of unusual terpenoids containing both bromine and chlorine. Aplysin (**1**) appears to be a metabolite derived from the algal constituent laurinterol (**3**); bioconversion of **3** to **1** is supported by the facile acid-catalyzed cyclization of **1** observed in vitro.[5] The absolute configurations of **1** and the related alcohol aplysinol (**4**) have been determined and are as shown.[6]

These compounds, as representatives of the first class of halogenated sesquiterpenes to be discovered in marine sources, have been of synthetic interest for several years.[7] This work describes the first reported total synthesis of (-)-**1** and (-)-**2** and was developed from our interest in mixed acetals as directing and stabilizing groups for aromatic metalation reactions and from our preliminary work on the synthesis of racemic **1** and **2**.[8] This approach, that of using an optically active alcohol for the preparation of a chiral alkoxymethyl ether protecting group, is potentially applicable to the synthesis of a wide variety of optically active natural products.

Results and Discussion

The selectivity and reactivity of aromatic methoxymethyl ethers in metalation reactions support the hypothesis that the ether oxygens coordinate with the organometallic center forming a relatively stable chelate.[9]

(1) On leave from Tribhuvan University, Katmandu, Nepal.
(2) S. Yamaur and Y. Hirata, *Tetrahedron*, **19**, 1485-96 (1963).
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(4) W. Fenical, Abstracts, 177th National Meeting of the American Chemical Society, Honolulu, HI, Apr 1979, No. ORGN 335.
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(7) K. Yamada, M. Toda, and Y. Hirata, *Chem. Commun.*, 1432 (1968); K. Yamada, D. Uemura, M. Toda, and Y. Hirata, *Tetrahedron*, **25**, 3509-20 (1969); G. I. Feutrill, R. Mirrington, and R. Nichols, *Aust. J. Chem.*, **26**, 345-55 (1973); J. E. McMurray and L. Von Beroldingen, *Tetrahedron*, **30**, 2027-32 (1974).
(8) R. C. Ronald, *Tetrahedron Lett.*, 4413-16 (1976); 3973-4 (1975).
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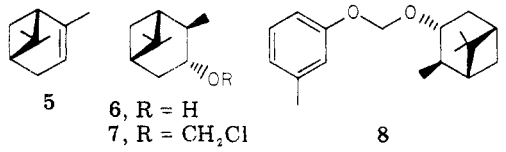
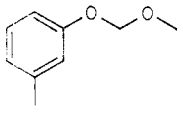
Therefore, it occurred to us that by incorporating a chiral moiety into the acetal, advantage could be taken of the relatively rigid chelate structure, so that these organometallic reagents might be capable of asymmetric inductions in carbonyl reactions (or at the least be a convenient and practical method of diastereomeric resolution). Thus, in the context of aromatic metalation reactions, these chiral derivatives could provide the multiple functions of hydroxyl protection, ring activation toward metalation, and diastereomeric resolution.

Most formaldehyde mixed acetals, including the methoxymethyl ethers, are conveniently prepared by O-alkylation using a chloromethyl ether. These chloromethyl ethers are usually prepared by chloromethylation of the desired alcohol with formaldehyde and hydrogen chloride, a method which generally works well as long as the alcohol substrates are stable to the strongly acidic conditions of chloromethylation. A readily available class of optically active alcohols are the terpenols; however, since it was imperative to avoid acid-catalyzed eliminations and rearrangements, tertiary alcohols and those belonging to the bicyclo[2.2.1]heptane series were excluded from consideration. Several other terpenes such as *l*-menthol were considered, but the most promising candidate appeared to be isopinocampheol, which is readily available by hydroboration of α-pinene.[10] Secondary alcohols were expected to be stable to the chloromethylation conditions; and isopinocampheol had the added advantage that both enantiomeric α-pinene precursors are commercially available in acceptable optical purity.

Hydroboration of (+)-α-pinene[11] **5** afforded (-)-isopinocampheol **6** which was used in the work described below. Treatment of **6** under conditions similar to those



5 **6**, R = H; **7**, R = CH_2Cl **8**

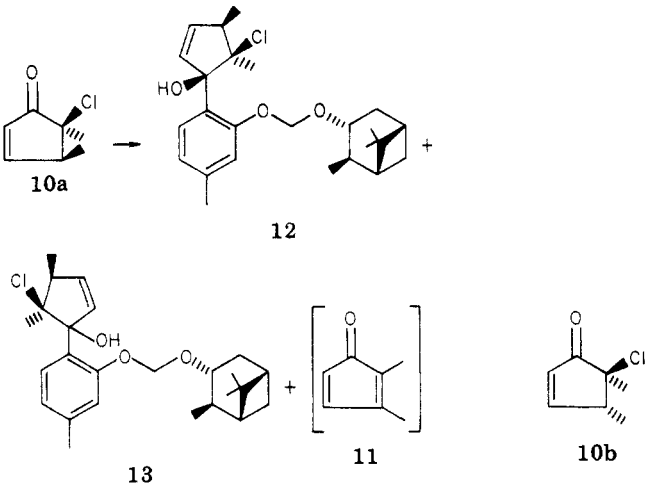


9

described by Corey for the preparation of methoxyethoxymethyl chloride (MEM chloride)[12] did not afford the desired chloromethylation reaction until it was realized that insolubility of HCl in the reaction mixture was the cause of the lack of reactivity. Addition of a small amount of ether resulted in smooth uptake of HCl and the slow separation of an aqueous phase. The chloromethyl ether **7** is highly reactive but could readily be isolated by extraction into petroleum ether followed by a rapid aqueous wash to remove acids. Distillation at reduced pressure afforded the ether **7** in good yield. This material hydrolyzes rapidly on contact with silica gel or other hydroxylic materials.

Reaction of **7** with the sodium salt of *m*-cresol in ether–dimethylformamide (DMF) afforded the acetal (-)-**8** in excellent yield. Since the aromatic ring of **8** was to eventually become the aromatic ring of aplysin, our intention was to metalate it in a manner similar to that of the simple

Scheme I



10a **12** **13** **11** **10b**

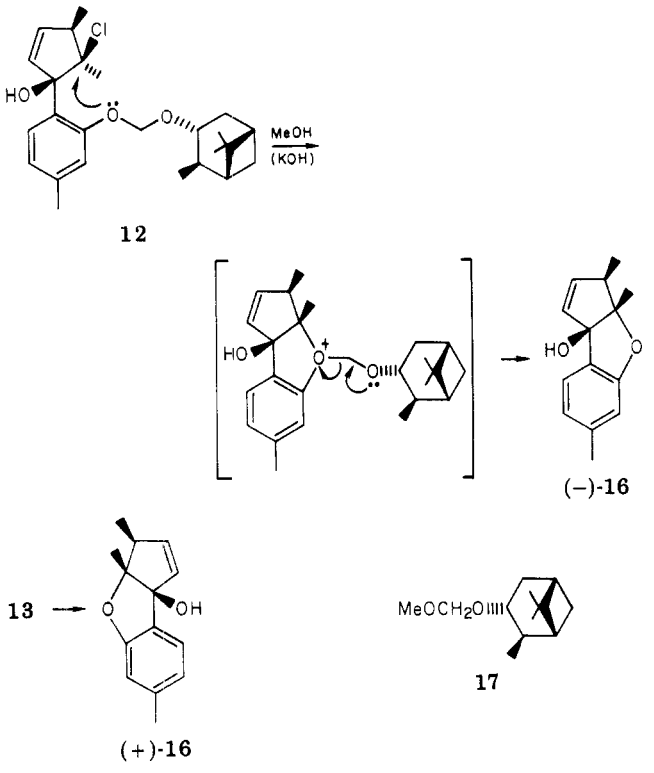
methoxymethyl analogue **9**.[8] Treatment of **8** with butyllithium solutions proved to be complicated. When these reaction mixtures were quenched with D_2O or acetaldehyde, the same regioselectivity of aromatic metalation at the ortho position para to the methyl group observed for **9** also occurred; however, the amount of this anion obtained from **8** appeared to be quite small. The bulky (isopinocampheyloxy)methyl group seemed to inhibit formation of the desired metalated product, and even with a large excess of butyllithium reagent the metalation could not be forced to more than 50% conversion. Various solvents and added electron donors produced no significant beneficial effects.

An even more serious problem was encountered when these anion solutions were allowed to react with the chlorocyclopentenone **10a** which contained the other half of the aplysin structure. This enone was readily prepared by the condensation of acetylene with tigoyl chloride in the presence of $AlCl_3$[11] to afford a mixture of *trans*-**10a** and *cis*-**10b** isomers which were readily separable by chromatography on silica gel. Upon reaction with organometallic reagents these ketones produced *cis*- and *trans*-chlorohydrin isomers, respectively.[8] These enones are, however, very sensitive to base and upon deprotonation afford an orange polymer, presumably through elimination to the cyclopentadienone **11** which subsequently polymerizes. When solutions of the anion prepared from **8** with butyllithium reagents were added to **10a**, only a small amount of carbonyl adduct was observed; the bulk of the material was orange polymeric material. Preparative thin-layer chromatography enabled isolation of the adducts and afforded two similar but closely migrating bands, which contained the two desired diastereomeric *cis*-chlorohydrins **12** and **13** (Scheme I).

The formation of **12** and **13** in about 25% combined yield from **8** indicated that the aromatic anion, if formed, adds as expected but that some basic side product, presumably generated in the reaction with the butyllithium, is responsible for the deprotonation and ultimate polymerization of **10a**. This was confirmed by the generation of the same anion by lithium–bromide exchange and the isolation of the adducts **12** and **13** in excellent yield. Bromophenol (**14**) was required for the preparation of the necessary bromide for this metalation. Direct bromination of *m*-cresol is reported to produce fair amounts of **14**;[14] however, in our hands only inseparable mixtures of the two

(10) G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, **86**, 393–7 (1964).
(11) Aldrich Chemical Co., Milwaukee, WI.
(12) E. J. Corey, J.-L. Gras, and P. Ullrich, *Tetrahedron Lett.*, 809–12 (1976).
(13) G. J. Martin and G. Daviaud, *Bull. Soc. Chim. Fr.*, 3098–102 (1970).
(14) R. C. Huston and J. Hutchinson, *J. Am. Chem. Soc.*, **54**, 1504–6 (1932).

Scheme II



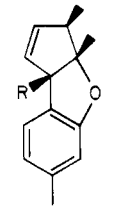
o-bromo isomers were obtained. However, since metalation of **9** occurs regioselectively in high yield, **14** was conveniently prepared from **9** by using ethylene dibromide as a halogenating agent. Hydrolysis of the crude bromination mixture with acid afforded **14** in about 50% yield contaminated with *m*-cresol. Separation was facilitated by the hydrogen bonding of the *o*-bromo substituent, which rendered **14** much more mobile on silica gel with dichloromethane as an eluant. Bromophenol (**14**) was converted to the isopenocampheyl derivative with **7** in the same manner as for the preparation of **8**.

On a preparative scale, addition of metalated bromo ether **15** to chloro enone **10a** showed a slight preference for the more polar diastereoisomer **13**. Since at this stage of the synthesis it was not clear which of the two chlorohydrins would be the precursor to (−)-aplysin, conditions were selected to maximize the production of chlorohydrins from **15** and **10a**. When equimolar quantities were employed at room temperature, a 37% yield of the more mobile chlorohydrin **12**, $[\alpha]^{21}_D$ −89°, and a 38% yield of the less mobile diastereoisomer **13**, $[\alpha]^{21}_D$ −22°, were obtained. As it will be seen below, the more mobile isomer **12** eventually led to (−)-aplysin. Since the diastereoisomers were not produced in exactly equal quantities, it is possible that even greater diastereoselection would occur if a large excess of **10a** were used at low temperature. However, since **13** appears to be the preferred isomer, such a kinetic resolution would require **15** to be made from the antipodal (−)-α-pinene.

The chlorohydrins **12** and **13** are extremely sensitive to acid and in polar solvents such as methanol undergo rapid solvolysis with liberation of acid which causes extensive decomposition. By keeping the methanol solutions basic, the chlorohydrins could be induced to cyclize with concomitant loss of the (isopinocampheyloxy)methyl protecting group to form the tricyclic alcohols (−)-**16** and (+)-**16**, which have an aplysin-like structure. From **12** a 52% yield of (−)-**16**, $[\alpha]^{22}_D$ −212°, was obtained after prolonged refluxing in methanol containing a slight excess of KOH. Similarly, **13** afforded (+)-**16**, $[\alpha]^{22}_D$ +215° (see Scheme II).

This transformation is presumably a solvolytic reaction in which the phenolic oxygen interacts with the incipient cation formed at the tertiary chloride center. Loss of chloride results in the formation of an oxonium ion which fragments to **16** and an O-alkylated formyl cation that is trapped by methanol to form **17**. The principal function of KOH in this solvolysis is to keep the solution basic.

Although alcohol **16** is tertiary, allylic, benzylic, and highly reactive toward substitution, it is remarkably stable toward acid-catalyzed dehydration. This must in part be due to the strain introduced when the benzylic carbon is constrained to become planar. Initial experiments demonstrated that **16** could be converted to the labile bromo compound **18** by treatment with either HBr or PBr_3. This



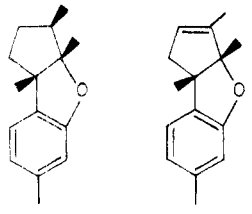
18, R = Br
19, R = Cl
20, R = Me

material was extremely difficult to handle, as any contact with water or hydroxylic material, e.g., silica gel, resulted in immediate hydrolysis back to **16**. Substitutions on **16** and its derivatives apparently take place with retention of configurations since there was a remarkable similarity in the IR and NMR spectra of **16** and **18**, with the exception of those spectral features due to the obvious changes in functionality. The bromide also appears to be resistant to elimination. Treatment of **16** with PCl_3 in a manner analogous to that for preparation of **18** afforded chloride **19** which is somewhat more stable.

The high reactivity of the halides **18** and **19** toward substitution, coupled with their reluctance to undergo elimination, made it possible to introduce the quarternary benzylic methyl group by an unusual organometallic coupling reaction. With methyllithium or methyl Grignard, **18** afforded modest yields (20%) of the quarternary methylation product **20**. The Grignard reagent appeared to be somewhat superior; however, a significant improvement was realized with the chloride **19** instead of the bromide, and thus, with methylmagnesium bromide a 96% yield of **20** from **19** was realized. These results seem to suggest that this substitutiton occurs by an ion-pair process in which the basicity of the chloride and the acidity of the magnesium are important factors. The introduction of the methyl group appears to take place with retention of configuration; examination of molecular models indicates that significant strain is introduced upon inversion of the benzylic center, and the folded shape of the tricyclic system does not make backside attack appear particularly attractive. From (−)-**16** the only methylated material appears to be (−)-**20**, $[\alpha]^{22}_D$ −244°, and thus in just three steps from **8** or **15** and **10a** the entire carbon skeleton of aplysin had been assembled in optically active form. Analogously, (+)-**16** afforded (+)-**20**, $[\alpha]^{21}_D$ +244°.

For the final conversion of (−)-**20** to (−)-aplysin all that remained was epimerization of the secondary methyl group, saturation of the cyclopentene ring, and introduction of the aromatic bromine substituent. Previous work had shown that catalytic reduction of a trisubstituted double bond in the carbocyclic five-membered ring occurs

with selective delivery of hydrogen to the face syn to the methyl groups.[7] Thus, by moving the double bond of **20** into the trisubstituted position, one could then accomplish the epimerization and saturation in a single operation. Attempts to isomerize the double bond with palladium or platinum catalysts were unsuccessful. In the absence of hydrogen these catalysts were inactive, and after activation with hydrogen there was a significant amount of reduction without bond migration, resulting in the undesired epimeric methyl isomer **21**, isodebromoaplysin. Acidic reagents



21 **22**

also were ineffective, as was $RhCl_3$ in ethanol which has been reported to afford excellent yields of double bond migration products.[15] The less acidic Wilkinson's catalyst $[(PPh_3)_3RhCl]$ in refluxing toluene–isobutyl alcohol afforded clean conversion of **20** to **22** when refluxed for several days in contact with air.[16] In the lower boiling ethanol–benzene mixture the isomerization was too slow, and in solvents boiling higher than toluene–isobutyl alcohol catalyst decomposition became significant. Primary alcohols were far superior to secondary or tertiary alcohols in promoting the isomerization even though under the prolonged reaction times required some polymerization seemed to occur. The nature of this polymeric material was not determined, but it was easily removed by distillation. A small amount of triphenylphosphine was very beneficial in preserving the catalytic activity of the rhodium species. Even under the best conditions, the isomerization was very slow, and about 4 days was required for a 97% conversion of (-)-**20** to (-)-**22**, $[\alpha]^{21}_D$ -132°.

Reduction of (-)-**22** with hydrogen over platinum (Adam's catalyst) in ethanol resulted in smooth uptake of hydrogen and formation of debromoaplysin (**2**). By GC the selectivity was at least 94.5% for the formation of **2**, and only a minor amount of the undesired epimer **21** was obtained. Fortunately, these isomers were readily separated by preparative TLC to afford pure **2** (>98%) in 69% yield after bulb to bulb distillation. Synthetic (-)-**2**, $[\alpha]^{21}_D$ -68°, was identical in all respects with an authentic sample of natural debromoaplysin.[17]

Previously, we reported that debromoaplysin could be selectively brominated to afford aplysin if a base was present to scavenge HBr.[8] Treatment of (-)-**2** with 1 equiv of Br_2 in hexane containing suspended Na_2CO_3 resulted in rapid (~2 min) disappearance of bromine color. After filtration of the crude material through silica gel and recrystallization from methanol, pure synthetic (-)-aplysin **1** (mp 82–83 °C, $[\alpha]^{21}_D$ -84.2°) was obtained. Synthetic (-)-**1** was identical in all respects with an authentic sample of natural (-)-aplysin and had an undepressed melting point admixture.

The total synthesis of (-)-**1** and (-)-**2** affords material identical with natural material in an overall 3.7% yield. This synthesis is an example of the use of chiral protecting groups to achieve optical resolution at a convenient stage in the synthesis of a complex natural material without resorting to a separate series of steps to construct resolvable diastereoisomers. The method conceivably could be applied to a wide variety of natural product syntheses.

Experimental Section

General Methods. Melting point determinations were made in sealed evacuated capillaries by using a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a Beckman Model IR 18 or on an Acculab 1 spectrophotometer. Spectra of liquid samples were obtained as films and of solid samples as KBr mulls unless otherwise noted. Nuclear magnetic resonance spectra were obtained in CCl_4 or $CDCl_3$ solution containing tetramethylsilane as an internal standard on either a Varian Associates Model EM-360 spectrophotometer or on a Bruker WH 90 spectrophotometer. Gas chromatograms were obtained on a Packard-Becker Model 417 gas chromatograph using a 3 mm × 2.6 m glass column packed with 3% OV-17 on 80/100 Chromosorb W HP. Optical rotations were obtained on a Rudolph polarimeter in a 1-dm cuvette. Analytical thin-layer chromatograms were run on Merck precoated silica plates with 250-μm layers. Preparative thin-layer chromatograms were run on 20 × 20 cm plates coated with a 1.6-mm layer of Merck silica gel PF 254. Column chromatography was performed in a pumped system with Merck 0.040–0.063-mm (230–400 mesh) silica gel 60 which was slurry packed into commercial glass columns. Combustion analyses were performed by Galbraith Laboratories.

(-)-Isopinocampheyl Chloromethyl Ether (7). The method of Corey[12] was modified. Isopinocampheol[10] (**6**; 14 g, 0.091 mol) and *s*-trioxane (4.67 g) in ether (20 mL) were placed in a 250-mL round-bottomed flask that was closed with a plug of glass wool. Dry hydrogen chloride was introduced slowly over a 5-h period by using a 25-mL volumetric pipet as a bubbler. The bulge in the pipet prevents the solution from backing up into the cylinder. An induction period of about 0.5 h was observed before the uptake of HCl began and the mixture became cloudy.

When the uptake of HCl ceased, the mixture was diluted with petroleum ether, rapidly washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated at reduced pressure. The residue was distilled at 82–83 °C (2 mm) to afford a 15-g (60%) yield of product: $[\alpha]^{21}_D$ -66° (*c* 4.04, $CHCl_3$); IR 2920 (s), 1540 and 1500 (m), 1125 (s), 640 (s) cm^{-1}; NMR δ 5.6 (2 H, s), 4.0–4.3 (1 H, m), 1.6–2.6 (br m), 1.25 and 0.95 (CH_3, s), 1.15 (CH_3, d). Anal. Calcd for $C_{11}H_{19}ClO$: C, 65.35; H, 9.41. Found: C, 65.12; H, 9.46.

(-)-3-Methylphenyl (Isopinocampheyloxy)methyl Ether (8). Sodium hydride dispersion (0.59 g, 57% NaH in oil) was washed free of the oil with hexane and suspended in 10 mL of dry ether in a nitrogen atmosphere. A solution of *m*-cresol (1.08 g, 10 mmol) in 2 mL of dimethylformamide (DMF) was added dropwise. After the evolution of H_2 ceased, a solution of isopinocampheyl chloromethyl ether (**7**; 2.02 g, 10 mmol) in 5 mL of ether was added in one portion. After 10 min the reaction mixture was poured into H_2O overlaid with petroleum ether and extracted three times with petroleum ether. The combined extracts were washed with 10% aqueous NaOH, H_2O, and brine, dried with anhydrous magnesium sulfate, and concentrated to afford an oil. Bulb to bulb distillation [112–116 °C (0.05 mm)] yielded 2.52 g (92%) of ether **8**: $[\alpha]^{21}_D$ -67° (*c* 1.12, $CHCl_3$); IR 2920 (s), 1590–1620, 1490, 1250, 1085 (s), 1030 (s), 780 cm^{-1}; NMR δ 7.4–6.6 (4 H, m), 5.35 (2 H, s), 3.9–4.3 (1 H, m), 2.4 (CH_3, s), 1.6–2.6 (br m), 1.25 and 1.0 (CH_3, s), 1.2 (CH_3, d). Anal. Calcd for $C_{18}H_{25}O_2$: C, 78.83; H, 9.49. Found: C, 78.63; H, 9.55.

2-Bromo-5-methylphenol (14). A solution of *tert*-butyllithium in pentane (50 mL is equivalent to 32 mmol) was transferred to a 100-mL round-bottomed flask sealed with a rubber septum and maintained under a N_2 atmosphere with cooling to 0 °C. A solution of *m*-cresol methoxymethyl ether (**9**;[8] 4.9 g, 32 mmol) in 10 mL of pentane was added with stirring. After 1 h the stirring was stopped and the anion allowed to settle for 6 h. The supernatant was decanted and the precipitate washed with a 20-mL portion of pentane.

The anion was suspended in 50 mL of dry tetrahydrofuran

(15) P. A. Grieco, N. Nishizawa, N. Marinovic, and W. Ehmann, *J. Am. Chem. Soc.*, **98**, 7102–4 (1976).
(16) R. L. Augustine and J. F. Van Peppen, *Chem. Commun.*, 495–6, 497–8, 571–2 (1970).
(17) We are indebted to Dr. W. Fenical of the Scripps Oceanographic Institute, La Jolla, CA, for authentic samples of debromoaplysin and aplysin.

(THF) and the thick suspension cooled to −78 °C. A solution of ethylene dibromide (6.2 g, 33 mmol) in 10 mL of THF was added slowly. After 2 h at −78 °C the mixture was allowed to warm to ambient temperature overnight.

The reaction mixture was poured into H_2O overlaid with ether and extracted three times with ether. The combined extracts were washed with H_2O and brine, dried with anhydrous magnesium sulfate, and concentrated.

The crude product was dissolved in methanol (15 mL) containing toluenesulfonic acid (20 mg) in a flask fitted for distillation with a short-path still head. The mixture was heated to boiling and the methanol slowly distilled over a 2-h period. The residue, a mixture of *m*-cresol and 6-bromo-*m*-cresol, was chromatographed on a 4.3 cm × 33 cm column of silica gel eluted with dichloromethane. The bromocresol eluted with the solvent front and amounted to 2.50 g (42%); bp 216–218 °C.[14]

(−)-2-Bromo-5-methylphenyl (Isopinocampheyloxy)methyl Ether (15). Sodium hydride dispersion (0.75 g, 57% in mineral oil) was washed free of oil with hexane and then suspended in 20 mL of dry ether under a nitrogen atmosphere. A solution of 2-bromo-5-methylphenol (14; 2.50 g, 13.4 mmol) in ether (10 mL) and DMF (14 mL) was added slowly. When the evolution of hydrogen ceased, a solution of isopinocampheyl chloromethyl ether (2.9 g, 14.4 mmol) in ether (10 mL) was added slowly.

After 0.5 h the reaction mixture was poured into water overlaid with petroleum ether and extracted three times with petroleum ether. The combined extracts were washed with 10% aqueous NaOH, H_2O, and brine, dried with anhydrous magnesium sulfate, and concentrated to afford a yellow oil.

This was chromatographed on a 4.3 cm × 20 cm column of silica gel eluted with dichloromethane to afford a colorless oil. Bulb to bulb distillation at 139–142 °C (0.05 mm) yielded **15**: 4.28 g (90.5%); $[\alpha]^{21}$ −51° (*c* 1.04, $CHCl_3$); IR 2950 (s), 1590, 1580, 1480 (s), 1380, 1280, 1255, 1175, 1090, 1030 (s), 1005, 985, 800 cm^{-1}; NMR δ 7.50 (1 H, d), 7.10 (1 H, br s), 6.8 (1 H, d), 5.4 (2 H, s), 4.0 (OH, s), 2.4 (CH_3, s), 1.5–2.7 (br m), 1.3 and 0.95 (CH_3, s), 1.25 (CH_3, d). Anal. Calcd for $C_{18}H_{25}BrO_2$: C, 61.19; H, 7.08; Br, 22.66. Found: C, 61.35; H, 6.98; Br, 22.80.

***trans*-5-Chloro-4,5-dimethyl-2-cyclopentenone (10a).** The method of Martin and Daviaud was used.[13] A solution of tigoyl chloride (11 g) in 1,2-dichloroethane (20 mL) was added rapidly to a suspension of $AlCl_3$ (12.5 g) in 1,2-dichloroethane (50 mL). The mixture was heated to 40–42 °C, and acetylene was bubbled into the mixture for 24 h. The black mixture was poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated. The crude mixture was distilled at 80–90 °C (13 mm) [lit.[13] bp 97 °C (25 mm)] to afford a mixture of *trans*-**10a** and *cis*-**10b** isomers.

The ketone mixture was chromatographed on a 5 cm × 50 cm column containing 500 g of silica gel. The ketones were eluted with a mixture of 25% ether in petroleum ether. The cis isomer **10b** (2.1 g) eluted first and was distinguishable from the trans isomer **10a** (3.4 g) by the resonances of the C-4 proton at δ 3.45 for **10b** (cis to chlorine) and at δ 3.05 for **10a** (cis to methyl).

Chlorohydrins 12 and 13. Method A. From Metalation of 3-Methylphenyl (Isopinocampheyloxy)methyl Ether (8). A solution of **8** (137 mg, 0.5 mmol) in pentane was treated with *tert*-butyllithium (0.5 mL, equivalent to 0.8 mmol). Metalation was very slow at room temperature until the addition of TMEDA (70 μL, 0.5 mmol); metalation was then evidenced by the formation of a yellowish solid. After 0.5 h ether (2 mL) was added and the resulting solution cooled to 0 °C. A solution of racemic *trans*-5-chloro-4,5-dimethyl-2-cyclopentenone (**10a**; 100 mg, 0.7 mmol) in ether (1 mL) was added slowly.

After 15 min the mixture was poured into H_2O and extracted with three portions of ether. The combined extracts were washed with H_2O and brine, dried with anhydrous magnesium sulfate, and concentrated at reduced pressure to afford a yellow oil.

The crude product was chromatographed on a 12.5 mm × 50 cm column of silica gel eluted with a mixture of 7% ether in petroleum ether to afford 23 mg of **12** and 22 mg of **13** as slightly yellow oils. The combined yield of chlorohydrins by this method was 24%.

Method B. From Metalation of 2-Bromo-5-methylphenyl (Isopinocampheyloxy)methyl Ether (15). A solution of **15** (3.19 g, 9.03 mmol) in ether (20 mL) was treated with 1.8 M *n*-butyllithium (5.0 mL, 9 mmol) at 0 °C. After 15 min the solution of the anion was transferred to a flask containing a rapidly stirred solution of chloro enone **10a** (1.30 g, 9.03 mmol) in ether (50 mL). After 10 min the reaction was quenched by the addition of 5 mL of H_2O, poured into water, and extracted with ether three times. The combined extracts were washed with H_2O and brine, dried with anhydrous magnesium sulfate, and concentrated to afford a pale yellow oil.

This was chromatographed on a 5 cm × 50 cm column containing 450 g of silica gel eluted with 7.5% ether in petroleum ether to afford three fractions: 0.44 g [shown by GC to be 95% **8** (retention time 1.9 min at 260 °C) and 5% **15** (retention time 3.64 min at 260 °C], 1.39 g of **12** (37% yield), and 1.44 g of **13** (38% yield).

Diastereoisomer **12** had the following: $[\alpha]^{21}_D$ −89° (*c* 1.42, $CHCl_3$); NMR δ 6.7–7.3 (3 H, m), 5.9–6.3 (2 H, m), 5.4 (CH_2, s), 4.9 (OH, s), 4.0–4.4 (CH–O, m), 2.4 (CH_3, s), 1.6–2.8 (br m), 1.25 and 0.95 (CH_3, s), 1.2 and 1.1 (CH_3, d); IR 3500 (OH, m), 3020–2860 (CH, s), 1651, 1415, 1380, 1365, 1240, 1080, 1010, 985 cm^{-1}.

Diastereoisomer **13**, $[\alpha]^{21}_D$ −21° (*c* 1.61, $CHCl_3$), had spectral properties almost identical with those of **12**. Both diastereoisomers were extremely labile and were not purified further but were immediately converted to the tricyclic alcohols.

(−)-8b-Hydroxy-3a,8b-dihydro-3,3a,6-trimethyl-3*H*-cyclopenta[*b*]benzofuran ((−)-16). The *cis*-chlorohydrin **12**, obtained from column chromatography (1.29 g, 3.10 mmol), was dissolved in a solution of methanol (20 mL) containing KOH (358 mg). It is important that the KOH be dissolved in the methanol before addition of the chlorohydrin. The mixture was heated to reflux for 3.5 days, during which time the slow disappearance of the chlorohydrin could be observed by TLC.

The reaction mixture was poured into water overlaid with petroleum ether and extracted with petroleum ether three times. The combined extracts were washed with water, aqueous sodium hydroxide, water, and brine, dried with anhydrous magnesium sulfate, and concentrated to afford a yellow oil.

The crude product was chromatographed on a 2.5 cm × 100 cm column of silica gel eluted with a mixture of 25% ether in petroleum ether to yield 324 mg of crystalline (−)-**16** (52%): IR 3350 (OH, s), 3050, 3000–2850 (CH, s), 1620, 1590, 1490, 1260, 1105 (s), 1020, 960, 890, 800 (s), 765 (s); NMR δ 6.6–7.4 (3 H, m), 5.9 (2 H, s), 3.0 (1 H, q, J = 7 Hz), 2.4 (CH_3, s), 1.9 (OH, s), 1.3 (CH_3, s), 1.2 (CH_3, d, J = 7 Hz). An analytical sample was obtained by recrystallization from pentane: mp 84–85 °C; $[\alpha]^{22}_D$ −212° (*c* 0.91, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.78; H, 7.41. Found: C, 77.79; H, 7.50.

(+)-8b-Hydroxy-3a,8b-dihydro-3,3a,6-trimethyl-3*H*-cyclopenta[*b*]benzofuran ((+)-16). The procedure was identical with that used for the tricyclic alcohol (−)-**16**. From **13** (1.08 g, 2.60 mmol) in MeOH (20 mL) containing KOH (275 mg) was obtained after chromatography 276 mg of (+)-**16** (53%). An analytical sample was obtained by recrystallization from pentane (mp 84–85 °C; $[\alpha]^{22}_D$ +215° (*c* 1.03, $CHCl_3$)) and except for the sign of the optical rotation appeared to be identical with (−)-**16**.

(−)-3,3a,8b-Trihydro-3,3a,6,8b-tetramethylcyclopenta[*b*]benzofuran ((−)-20). Method A. From the Chloride 19. The tricyclic alcohol (−)-**16** (127 mg, 0.59 mmol) in ether (14 mL) was treated with PCl_3 (36 μL, 0.41 mmol) under a nitrogen atmosphere. The alcohol reacted completely within 10 min (as determined by the disappearance of the alcohol peak, retention time 3.35 min at 200 °C, in the gas chromatogram) to produce a cloudy suspension. A solution of CH_3MgBr in ether (0.6 mL, equivalent to 1.8 mmol) was added slowly. At the end of the addition solid material collected as a gummy ball, leaving a nearly clear colorless solution. Analysis by GC at this point showed complete conversion to **20** (retention time 2.2 min at 200 °C).

The reaction mixture was carefully poured into water overlaid with petroleum ether and extracted three times with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated to afford a yellow oil. This was chromatographed on a 12.5 mm × 1 m column of silica gel eluted with 2.5% ether in petroleum ether to afford colorless **20**. Bulb to bulb distillation at 75 °C (0.05 mm) yielded 121 mg of pure **20**: $[\alpha]^{21}_D$ −244° (*c* 0.088, $CHCl_3$); IR 3050, 2980 (s), 2920, 2870, 1610, 1590, 1490 (s), 1380, 1260, 1100 (s), 1040,

945 (s), 860, 800, 765 cm^{-1}; NMR δ 6.4–7.0 (3 H, m), 5.4–5.8 (olefinic, ABX, J = 8 and 2 Hz), 3.0 (1 H, br q), 2.25 (CH_3, s), 1.2 (CH_3, s), 1.0 (CH_3, d, J = 8 Hz). Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 83.95; H, 8.29.

Method B. From the Bromide 18. The tricyclic alcohol (−)-**16** (205 mg, 0.95 mmol) in ether (24 mL) was treated with a portion of PBr_3 (100 μL) and then a second portion after 20 min (100 μL). After 1 h the mixture was poured into concentrated HBr and extracted four times with ether. The combined extracts were dried with anhydrous magnesium sulfate and then added to excess 3 M methylmagnesium bromide in ether. After 1 h the mixture was quenched with water and extracted into ether. The ether extract was washed with H_2O and brine, dried with magnesium sulfate, and concentrated. The residue was chromatographed on a silica gel plate developed with 16% ether–petroleum ether to afford 49 mg (24%) of **20**.

(−)-3a,8b-Dihydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran (22). A solution of **20** (80 mg, 0.37 mmol) in 1:1 toluene–isobutyl alcohol (2 mL) containing Wilkinson's catalyst [$(Ph_3P)_3RhCl$, 10 mg] and triphenylphosphine (16 mg) was heated to reflux in an open flask for 5 days. At this time the isomerization was 97% complete as determined by GC (**20**, retention time 2.4 min at 190 °C; **22**, retention time 2.25 min at 190 °C).

The mixture was poured into water overlaid with petroleum ether and extracted three times with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure.

The crude material was chromatographed on a silica gel preparative plate developed with 2% ether in petroleum ether. The material in the major band was extracted with ether and purified by bulb to bulb distillation at 80 °C (0.05 mm) to yield 33 mg (41%) of **22**: $[\alpha]^{21}_D$ −132° (c 0.66, $CHCl_3$); IR 3040, 2960, 2920, 2840, 1615, 1585, 1490 (s), 1440, 1260, 1085, 1060, 940, 850, 795 cm^{-1}; NMR δ 6.4–7.1 (3 H, m), 5.4 (1 H, m), 2.5 (2 H, m), 2.35 (CH_3, s), 1.75 (CH_3, br), 1.4 (CH_3, s), 1.25 (CH_3, s). Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 84.31; H, 8.40.

(−)-Debromoaplysin (2). A solution of **22** (32 mg, 0.15 mmol) in ethanol (1.5 mL) with 5.6 mg of Adam's catalyst was placed in a small flask. The flask was sealed with a septum, and H_2 gas was introduced with a needle connected to a small balloon. After being flushed with H_2, the mixture was stirred rapidly for 2 h. Analysis by GC showed that **22** had all reacted and that the volatile product was 94.5% debromoaplysin (**2**, retention time 2.45 min at 180 °C) and 5.5% **21** (retention time 3.10 min at 180 °C).

The mixture was poured into water and extracted three times with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated to afford 33 mg of crude debromoaplysin.

The crude material was chromatographed on a silica gel preparative plate developed with 1% ether in petroleum ether. Extraction of the major band followed by bulb to bulb distillation at 70 °C (0.05 mm) yielded 22 mg (69%) of pure **2**, $[\alpha]^{21}_D$ −68°. Anal. Calcd for $C_{15}H_{20}O$: C, 83.33; H, 9.26. Found: C, 83.13; H, 9.49. This material was identical in all respects (GC, IR, NMR, TLC, analysis, optical rotation) with an authentic sample of natural debromoaplysin.[17]

(−)-Aplysin (1). Debromoaplysin (**2**; 22 mg, 0.10 mmol) was dissolved in hexane (1 mL) containing suspended anhydrous sodium carbonate (16 mg). Bromine (7 μL) was added slowly. Within 2 min after addition of the bromine, GC indicated that less than 2% of the starting material remained. The reaction mixture was filtered through a short (3 cm) column of silica gel with 10% ether in petroleum ether as an eluant to afford 30 mg of crude aplysin. Recrystallization from methanol yielded 21 mg of white needles: mp 82–83 °C; $[\alpha]^{21}_D$ −84.2° (c 0.31, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.02; H, 6.44; Br, 27.12. Found: C, 61.10; H, 6.46; Br, 27.04. This material was identical in all respects with an authentic sample of aplysin[17] (GC, IR, NMR, TLC, analysis, optical rotation) and gave an undepressed melting point admixture.

Acknowledgment. The authors wish to thank the Research Corp., the Washington State University Research Fund, and the National Institutes of Health for their support of this work. The generous support of Tribhuvan University, Katmandu, Nepal, and the International Institute of Education for a fellowship for M.B.G. is gratefully acknowledged.

Registry No. (−)-**1**, 6790-63-2; (−)-**2**, 23444-68-0; **6**, 1196-00-5; (−)-**7**, 73286-59-6; (−)-**8**, 73286-60-9; **9**, 57234-27-2; (±)-*trans*-**10a**, 63023-42-7; (±)-*cis*-**10b**, 63023-32-5; **12**, 73286-61-0; **13**, 73346-52-8; **14**, 14847-51-9; (−)-**15**, 73286-62-1; (−)-**16**, 73307-73-0; (+)-**16**, 73307-74-1; **18**, 73286-63-2; **19**, 73286-64-3; (−)-**20**, 73307-75-2; (+)-**20**, 73307-76-3; **21**, 73307-77-4; (−)-**22**, 73307-78-5; *m*-cresol, 108-39-4; isopinocampheyl chloromethyl ether, 73286-59-6.

Synthesis of the Optical Isomers of 3-Methyl-6-isopropenyl-9-decen-1-yl Acetate, a Component of the California Red Scale Pheromone[1]

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Received October 22, 1979

The synthesis of the optical isomers of 3-methyl-6-isopropenyl-9-decen-1-yl acetate (**1**), a component of the California red scale pheromone, and the determination of their biological activity were completed. Initially, (±)-citronellol was converted in four steps to a mixture of all four diastereomers of **1**, the key step being the reaction of lithium di(3-butenyl)cuprate with 6,7-epoxycitronellyl acetate (**4**). This mixture strongly attracted male California red scale. To determine which of the four diastereomers of **1** were biologically active, (3*R*,6*RS*)- and (3*S*,6*RS*)-**1** were then prepared from (*R*)-(+)-citronellol and (*S*)-(−)-citronellol, respectively. Since the 3*S*,6*RS* diastereomeric mixture was found to be a powerful attractant whereas the 3*R*,6*RS* diastereomeric mixture was devoid of attractancy, the 3*S*,6*R* and 3*S*,6*S* diastereomers of **1** were then prepared. The key to the synthesis of each of these two diastereomers of **1** was the high-performance LC separation of the diastereomeric MTP esters **12a** and **12b**. Lithium aluminum hydride reduction of **12a** and **12b** gave the corresponding diols **11a** and **11b**, which were intermediates in the synthesis of (3*S*,6*R*)- and (3*S*,6*S*)-**1**, respectively. The assignment of absolute configuration at C-6 in diols **11a** and **11b** (and therefore of the diastereomers of **1**) was made on the basis of induced CD spectra of each diol and of the closely related diol of (10*S*)-JH III (**13**). The 3*S*,6*R* diastereomer of **1** was found to be more attractive to male California red scale than was the 3*S*,6*S* diastereomer. The naturally occurring pheromone component **1**, upon examination by capillary GLC under conditions which gave separation of the 3*S*,6*R* and 3*S*,6*S* diastereomers, eluted with the synthetic 3*S*,6*R* diastereomer.

The sex pheromone of the California red scale, *Aonidiella aurantii*, was recently isolated and identified as a mixture of 3-methyl-6-isopropenyl-9-decen-1-yl acetate (**1**) and the closely related (*Z*)-3-methyl-6-isopropenyl-3,9-

0022-3263/80/1945-2229$01.00/0