reaction mixture was stirred at room temperature with a H_2 balloon until the reaction was complete. After filtration, the filtrate was evaporated to give diol **13** (116 mg, 80%). The product was purified by bulb-to-bulb distillation (56–57 °C (0.1 Torr)): $[\alpha]_D$ +10.5° (*c* 1.1, $CHCl_3$) (lit.[14] $[\alpha]_D$ +11.6° (*c* 2.12, $CHCl_3$); ^1H NMR δ 1.31 (t, *J* = 7.2 Hz, 2 H, $-OCH_2CH_3$), 1.35 (s, 3 H, $-CH_3$), 3.58 and 3.81 (ABq, *J* = 11.2 Hz, 2 H, $-CH_2OH$), 4.28 (q, *J* = 7.2 Hz, 2 H, $-OCH_2CH_3$); IR (NaCl, neat) ν 3444, 1732 (CO) cm^{-1}.

(*R*)-2,2,4-Trimethyl-1,3-dioxolane-4-carboxylic Acid Ethyl Ester (14).[14] To a solution of the diol **13** (40 mg, 0.27 mmol) in freshly distilled 2,2-dimethoxypropane (5 mL) was added *p*-toluenesulfonic acid (4 mg). The reaction mixture was stirred at room temperature under Ar overnight. Excess 2,2-dimethoxypropane was removed by distillation at ~40 °C (12 Torr), and the residue was treated with 2 mL of $NaHCO_3$(aq), CH_2Cl_2 (15 mL), and H_2O (10 mL). The organic phase was extracted, washed with H_2O, and dried over $MgSO_4$. Careful evaporation of the solvent resulted in the almost pure 1,3-dioxolane **14** (46 mg 90.5%) which was purified by bulb-to-bulb distillation (81 °C (15 Torr)): ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 1.40 (s, 3 H, C(2)CH_3), 1.42 (s, 3 H, C(2)CH_3), 1.49 (s, 3 H, C(4)CH_3), 3.75 ($^1/_2$ABq, *J* = 8.8 Hz, 1 H, OCH_2–), 4.20 (q, *J* = 7.3 Hz, 2 H, $-OCH_2CH_3$), 4.36 ($^1/_2$ABq, *J* = 8.8 Hz, 1 H, OCH_2); IR ν (CO) 1732 cm^{-1}.

(*S*)-2,2,4-Trimethyl-4-(hydroxymethyl)-1,3-dioxolane (15).[16] To a solution of LAH (40 mg) in 7 mL of THF was added a solution of ester **14** (46 mg, 0.24 mmol) in THF (3 mL) slowly at room temperature, and the reaction mixture was heated at reflux for 3 h under Ar. After being cooled to 0 °C it was quenched with 0.04 mL of H_2O, followed by 0.04 mL of 15% NaOH(aq) followed by 0.12 mL of H_2O followed by heating at reflux for 30 min. The mixture was filtered, and the filtrate was dried over $MgSO_4$. The solvent was evaporated carefully, and the residue was purified by careful bulb-to-bulb distillation to give 22 mg (62%) of **15**: $[\alpha]_D$ –5.4° (*c* 1.1, CH_2Cl_2) (lit.[16] $[\alpha]_D$ –5.33° (*c* 0.3, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3 H, C(4)CH_3), 1.39 (s, 3 H, C(2)CH_3), 1.41 (s, 3 H, C(2)CH_3), 2.50 (bs, 1 H, $-OCH_2OH$), 3.47 (ABq, *J* = 11.7 Hz, 2 H, $-OCH_2OH$), 3.70 ($^1/_2$ABq, *J* = 8.5 Hz, 1 H, $-OCH_2$), 3.96 ($^1/_2$ABq, *J* = 8.5 Hz, 1 H, $-OCH_2$–); IR ν 3391, 2986, 2936, 1875 cm^{-1}.

(*R*)-2,2,4-Trimethyl-4-(dimethoxymethyl)-1,3-dioxolane (16). To a solution of 1,3-dioxolane ester **14** (68 mg, 0.36 mmol) in Et_2O (3 mL) was added DIBAH (0.72 mL, 0.72 mmol) at –78 °C under Ar. The reaction mixture was stirred at –78 °C under Ar for 5 h. A solution of MeOH (0.5 mL) and H_2O (0.5 mL) was added, the cooling bath was removed, and the temperature was raised to rt and recooled to 0 °C. Saturated $NaHCO_3$(aq) (1 mL) was added, and the mixture was stirred at 0 °C for 30 min. The organic phase was extracted, washed with brine, and dried over $MgSO_4$.

$[Pd(H_2O)_2(diphos)](CF_3SO_3)_2$[22] (34 mg) and freshly distilled 2,2-dimethoxypropane (2 mL) in CH_2Cl_2 (8 mL) were added to the mixture which then was stirred at room temperature for 5 days under Ar. After careful evaporation of solvent (20 mmHg, 0 °C), the residue was dissolved in Et_2O (5 mL) and filtered to remove the Pd catalyst. After careful evaporation of solvent, the product was purified by bulb-to-bulb distillation (0.3 mmHg, room temperature). The yield was 16 mg (23%) as colorless oil with mesityl oxide as an impurity. Found $[\alpha]_D$ +1.6°; estimated $[\alpha]_D$ by ^1H NMR integration +3.4° (*c* 0.10, CH_2Cl_2). The amount of **16** in the sample was estimated by the careful comparison of integration of multiple peaks of **16** via the contaminant mesityl oxide, and the rotation was estimated on that amount of material: ^1H NMR δ 1.25 (s, 3 H, C(4)CH_3), 1.38 (s, 3 H, C(2)CH_3), 1.39 (s, 3 H, C(2)CH_3), 3.47 (s, 3 H, $-CH(OCH_3)_2$), 3.53 (s, 3 H, $-CH(OCH_3)_2$), 3.66 and 4.01 (ABq, *J* = 8.8 Hz, 2 H, $-OCH_2$–), 4.08 (s, 1 H, $-CH(OMe)_2$); IR (NaCl, neat) ν 2963, 2360, 1644, 1457, 1261, 1091 cm^{-1}.

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Rapid, High-Yield Synthesis of the Marine Sesquiterpenes Debromoaplysin and Aplysin via the Acid-Catalyzed Rearrangement of a Cyclobutachromanol†

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A short, stereocontrolled, high-yield synthesis of debromoaplysin (**1**) and aplysin (**2**) from the chromone **13** is described. The cycloaddition of ethylene to **13**, followed by the addition of methylmagnesium iodide to the cycloadduct, furnished the cyclobutachromanol **15**. Treatment of **15** in benzene with BF_3·Et_2O furnished a mixture of the alkenes **16** and **17**, which can be visualized as arising by way of the initial 1,2-migration of the external and internal bonds, respectively, of the cyclobutane ring of **15**. Similar rearrangement of **18**, an ethyl analogue of **15**, yielded **19** and **20**. Rearrangement of **15** on treatment with sulfuric acid in petroleum ether at –78 °C furnished, almost exclusively, **17**. In contrast, when performed in nitroethane at –78 °C, the same reaction afforded **16** exclusively. Thus, the solvent exerted a remarkable effect on the outcome of the rearrangement. Since alkene **16** had previously been converted to **1** and **2**, this work represents an improved synthesis of the two sesquiterpenes.

Introduction

The novel structures of the marine sesquiterpenes debromoaplysin (**1**) and aplysin (**2**)[1] have attracted the attention of synthetic organic chemists.[2] Recently, we described[3] a short, stereocontrolled synthesis of **1** and **2** and the related compounds debromoaplysinol (**3**), aplysinol (**4**), and isoaplysin (**5**). Therein an intramolecular ketene-to-alkene cycloaddition was the key step. Here we describe an alternate route to **1** and **2**, one that represents a rapid and improved synthesis of these compounds.

The method described here relies on the acid-catalyzed rearrangement of fused-ring cyclobutyl carbinols to gen-

† This paper is respectfully dedicated to Prof. U. R. Ghatak on his 60th birthday.

(1) Yamamura, S.; Hirata, Y. *Tetrahedron* **1963**, *19*, 1485.

(2) (a) Yamada, K.; Yazawa, H.; Uemura, D.; Toda, M.; Hirata, Y. *Tetrahedron* **1969**, *25*, 3509. (b) Ronald, R. C. *Tetrahedron Lett.* **1976**, *49*, 4413. (c) Ronadl, R. C.; Gewali, M. B.; Ronald, B. P. *J. Org. Chem.* **1980**, *45*, 2224. (d) Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R., III. *Ibid.* **1980**, *45*, 3989. (e) Laronze, J.-Y.; Boukili, R. E.; Cartier, D.; Laronze, J.; Levy, J. *Tetrahedron Lett.* **1989**, *30*, 2229.

(3) Biswas, S.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1990**, *55*, 3498.

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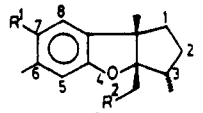
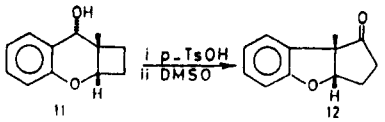


1: $R^1 = R^2 = H$
2: $R^1 = Br$; $R^2 = H$
3: $R^1 = H$; $R^2 = OH$
4: $R^1 = Br$; $R^2 = OH$
5: $R^1 = H$; $R^2 = Br$

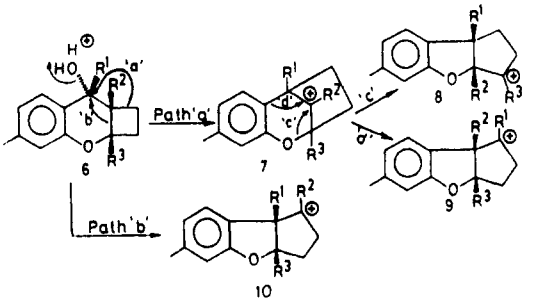
erate the tricarbocyclic frameworks of 1 and 2. Such Wagner–Meerwein rearrangements of cyclobutylcarbinyl systems have been elegantly employed in recent years to construct the complex polycyclic skeletons of various natural products.[4] In the incipient cyclobutylcarbinyl cation, "bridge" migration involving the external bond should be preferred based on the principle of maximum continuous overlap. Nevertheless, "fused" migrations involving the internal bond have also been frequently observed in the rearrangement of bicyclo[4.2.0]octane systems.[4b,d,j] In the cases of selective bond migration the product profile has been explained in terms of a concerted process.[4f,h,i] In adopting this protocol of rearrangement of a cyclobutylcarbinyl system to the synthesis of 1 and 2, we envisioned that a cyclobutachromanol like 6, readily obtainable from a suitable chromone by way of the cycloaddition of ethylene, could serve as a progenitor of the tricyclic skeleton of those compounds, by way of the rearrangement pathways indicated (Scheme I). It is interesting to note that when the substituents R^1 and R^2 are the same, the final product formed by way of paths a and d would be identical to that formed by way of path b. However, when R^1 and R^2 are different, the products will be isomers in which R^1 and R^2 are interchanged. It was difficult to predict which of the two routes would be preferentially followed by compound 6. Hence, an experiment with a model compound was performed, in the hope that the results would serve as a guide to the appropriate positioning of the required methyl groups in the starting material for the final synthesis of 1 and 2. In a previously reported model study,[5] it was shown that the cyclobutachromanol 11, on acid-catalyzed rearrangement and oxidation, afforded the tricyclic ketone 12 as the major



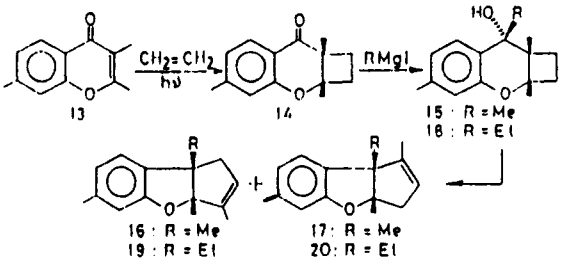
11 12

product. It was thus demonstrated that the rearrangement could lead to the tricyclic aplysin skeleton. Furthermore, the results suggested that the initial step in the rearrangement would be migration of the external bond, which would lead to a trichothecane-like cationic intermediate (path a). That species would then rearrange by way of migration of the aryl bond (path d) and produce the desired tricyclic skeleton.

Scheme I



Scheme II



Since it had been demonstrated that the rearrangement of a cyclobutachromanol could yield the tricyclic skeleton of aplysin, it remained to choose an appropriate methyl-susbstituted cyclobutachromanol and rearrange it to produce an advanced intermediate for the synthesis of the natural products. The cyclobutachromanol 15 seemed most suited to fulfill the requirements. However, before a program aimed at synthesizing 15 was pursued, a few additional points were considered. Because minor changes in the structure of the cyclobutylcarbinol markedly affect the structure(s) of the product(s) of rearrangement,[4g] the possibility existed that the rearrangement of 15 could yield undesired products. If the trichothecane-like cationic intermediate 7 ($R^1 = R^2 = R^3 = Me$) which would arise by the initial migration of the external bond of 15 followed the same pathway as did 11, then the product would be the isomer 9 ($R^1 = R^2 = R^3 = Me$), which would be useless for our purpose. However, support for our belief that 15 would be a suitable choice was available from the work of Goldsmith et al.[2d] on the synthesis of aplysin. Therein, the rearrangement of a structurally similar trichothecane-like intermediate did in fact yield the desired aplysin precursor.[6] Thus, we were sanguine that, in our case, the desired product would be obtained. The manner in which our goal was realized is delineated below.

Results and Discussion

The point of departure was 2,3,7-trimethylchromone (13).[7] This was prepared in better overall yield than was originally reported by employing a modification that involved treatment of the crude product with sulfuric acid to ensure complete dehydration. Irradiation of a benzene solution of 13 with UV light for 10 h while a continuous flow of ethylene was maintained through the solution furnished the cycloadduct 14 in 90% yield. That the ring juncture was cis was assumed by analogy with the results of earlier work.[5,8] The reaction of 14 with methyl-

(4) (a) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1964**, *86*, 1652. (b) Do Khac Manh, D.; Fetizon, M.; Kone, M. *Tetrahedron* **1978**, *34*, 3513. (c) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (d) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta*, **1981**, *64*, 1347. (e) White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376. (f) Ikeda, M.; Takahashi, M.; Uchino, T.; Ohno, K.; Tamura, Y. *Ibid.* **1983**, *48*, 4241. (g) Takeda, K.; Shimono, Y.; Yoshii, E. *J. Am. Chem. Soc.* **1983**, *105*, 563. (h) Smith, A. B., III.; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *Ibid.* **1985**, *107*, 1308. (i) Fetizon, M.; Do Khac, D.; Dinh Tho, N. *Tetrahedron Lett.* **1986**, *26*, 1777. (j) Paquette, L. A.; Lin, H.-S.; Gunn, B. P.; Coghlan, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 5818. (k) Ranu, B. C.; Sarkar, D. C.; Basu, M. K. *Tetrahedron*, **1989**, *45*, 3107.

(5) Sengupta, D.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1986**, 1638.

(6) An alternate pathway, which involves protonation of the pyranyl oxygen followed by ring opening to a diene and recyclization was proposed by the authors. However 1,2-oxygen shifts have, in fact, been postulated to occur during the rearrangement of trichothecene natural products. See: Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Ch. *Helv. Chim. Acta* **1964**, *47*, 2234. Godtfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1965**, *19*, 1088.

(7) Robertson, A.; Waters, R. B.; Jones, E. T. *J. Chem. Soc.* **1932**, 1681.

magnesium iodide delivered a single epimer of the cyclobutachromanol **15** in 92% yield. The assignment of stereochemistry to carbinol **15** is based on analogy with earlier observations[5] relating to formation of **11** from hydride reduction. The homogeneity of the product was demonstrated by its ^{1}H NMR spectrum. Now that the required chromanol was in hand, the stage was set for the pivotal rearrangement. Initially BF_3·Et_2O was employed as the acid catalyst. Treatment of **15** with a catalytic amount of BF_3·Et_2O in benzene at ambient temperature for 1 h furnished, in 88% yield, a 1.5:1.0 mixture of the alkenes **16** and **17** (Scheme II). The ratio of **16** to **17** was determined by GLC and ^{1}H NMR analysis. The two alkenes were isolated in pure form by preparative TLC. Because the two compounds are quite similar in polarity, complete resolution of the mixture could not be effected. The less polar component was identical (GLC, ^{1}H NMR) to a sample of **16** prepared earlier.[3] Since **16** had served as an advanced intermediate in the synthesis[3] of **1** and **2**, what is described here constitutes an extremely short, stereocontrolled, and economical synthesis of these two compounds. Alkene **16** may be visualized as arising by way of a formal 1,2-shift of the pyranyl oxygen (path c)[9] of the trichothecane-like intermediate **7** (R^1 = R^2 = R^3 = Me), which, in turn, was generated from **15** by way of path a. The structure of **17** was inferred from its ^{1}H NMR spectrum, which resembles that of **16**, albeit with minor variations in the chemical shifts of the signals. Compound **17** could have arisen either from **7** by way of an aryl group migration (path d) or from **15** by way of an internal bond migration (path b) (Scheme I). Although the results would not necessarily be relevant from a synthetic perspective, an experiment was performed to gain additional information about the operative rearrangement pathways. Thus, the reaction of chromanone **14** with ethylmagnesium iodide furnished the chromanol **18**. Treatment of **18** with BF_3·Et_2O in benzene under the conditions described earlier afforded a 1.5:1.0 mixture of the alkenes **19** and **20**, in 90% yield (Scheme II). The two were separated by preparative TLC. Their structures were assigned by analogy with the structures of **16** and **17**. In the ^{1}H NMR spectrum of **19**, the multiplet due to the C-1 methylene protons is compact like the corresponding signal in the spectrum of **16** and is located closer to the benzylic proton singlet. In the spectrum of isomer **20**, the position of the multiplet due to the C-3 methylene protons was comparable to that of the corresponding signal in the spectrum of **17**: both were well separated and well downfield from the benzylic proton singlet. Furthermore, it could be seen from molecular models that the conformation of **20** in which substituent interaction is minimized is that in which the angular ethyl group is situated so as to place the methyl protons within the magnetic shielding zone of the benzene ring. In the ^{1}H NMR spectrum of **20** an upfield shift of the signal due to the methyl protons was in fact discernible. The chromatographic behavior of the alkenes **19** and **20** also paralleled that of **16** and **17**: the polarity of isomer **20** is akin to that of **17**. These observations confirmed the tentative conclusion that **17** and **20** arose by way of an initial internal bond migration in **15** and **18**, respectively, which, in both cases, was followed by the loss of a proton (path b).

(8) Hanifin, J. W.; Cohen, E. *J. Am. Chem. Soc.* **1969**, *91*, 4494.
(9) In light of the postulated alternate mode of rearrangement,[2d] **16** may be visualized as arising from **15** as follows:

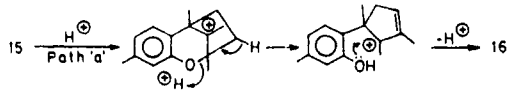
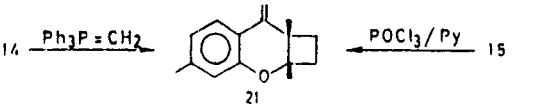


Table I. Effects of Solvent, Temperature, and Catalysts on the Rearrangements of 15[a]

entry	solvent	temp (°C)	catalyst	product ratio (16:17)[b]
1	benzene	rt	BF_3·Et_2O	1.5:1
2		6	BF_3·Et_2O	1:1
3			H_2SO_4	1:4
4	petroleum ether	−78	BF_3·Et_2O	1:1.5
5			H_2SO_4	1:19
6	nitromethane[c]	−25	BF_3·Et_2O	2:1
7			H_2SO_4	1.7:1
8	nitroethane	−78	BF_3·Et_2O	1:0
9			H_2SO_4	1:0

[a] Reaction time: 1 h with BF_3·Et_2O; 30 min with H_2SO_4. [b] The yields, in all cases, were between 80 and 85%. The ratio of **16** to **17** was determined by GLC and ^{1}H NMR analysis. [c] In $MeNO_2$ at rt a 1.0:1.0 mixture of **16** and **17** was produced. At 0 °C, the product ratio was between 1.3:1.0 and 1.5:1.0.

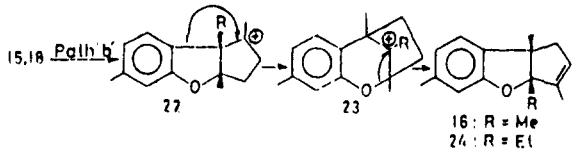
Although the facile rearrangement of **15** to **16** thus provided ready access to both **1** and **2**, the competing formation of **17** and the problems encountered in efficiently separating **16** and **17** affected the final yield of **16**. Hence, it became imperative to find a way whereby the yield of **16** could be maximized and that of the undesired alkene **17** minimized. It seemed reasonable to assume that path a involves a free carbonium ion and preferential migration of the external bond, whereas path b involves a stereoelectronically controlled concerted migration of the properly aligned internal bond. If this were so, then two possible ways for improving the yield of the desired alkene **16** suggested themselves. The first would involve finding conditions under which migration of the external bond (path a) of **15** would occur exclusively and thus eventually yield only **16**. The second possibility was to employ as the starting material an analogue of **15**; i.e., the isomer in which the configuration of the carbon bearing the geminal methyl and hydroxyl groups was inverted. Then, rearrangement by way of both the free carbonium ion and the concerted pathways should involve migration of the external bond. It was decided to attempt first to realize the seemingly more convenient second possibility. Thus, the methylene derivative **21** was prepared, in excellent yield, by both



Wittig olefination of the chromanone **14** and dehydration of the carbinol **15**. It was expected, by analogy with the results of the addition of Grignard reagents to **14**, that the epoxidation of **21** would occur preferentially from the exo face of the molecule and that reduction of the product epoxide would provide an analogue of **15** in which the configuration of the carbon bearing the geminal methyl and hydroxyl groups is inverted. However, attempted epoxidation of **21** with *m*-CPBA under various conditions yielded only chromanone **14** and varying amounts of **21**. Conceivably the epoxide ring, as soon as it is formed, opens under the action of *m*-CPBA and the product subsequently fragments to yield to chromanone **14**. Similar behavior has been observed during the epoxidation of enol ethers.[10] Because efforts to realize the second possibility had failed,

(10) (a) Borowitz, I. J.; Williams, G. J. *Tetrahedron Lett.* **1965**, 3813. (b) Borowitz, I. J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. J. *J. Org. Chem.* **1966**, *31*, 3032 and references cited therein.

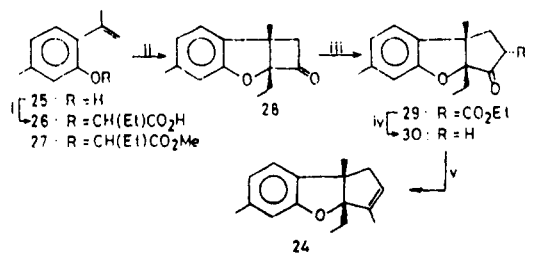
Scheme III



we turned our attention to realize the first possibility. A study was hence undertaken directed toward finding conditions under which the migration of either the external or the internal bond of a single stereodefined cyclobutylcarbinol could be selectively induced, thereby yielding only one of the two structurally variant carbocycles in high yield. Such a study was unprecedented. If the hypothesis that the rearrangement of **15** involves both a free carbonium ion and a concerted process was valid, then the use of a polar solvent should favor rearrangement by way of the former, whereas the use of a nonpolar solvent should favor rearrangement by way of the latter. Hence the effects of solvent and temperature on the outcome of the rearrangement were determined. BF_3·Et_2O and concentrated sulfuric acid served as the catalysts. The results are shown in Table I. It can be seen that the use of nonpolar solvents and low temperatures favored reaction by way of the concerted pathway. In contrast, the use of polar solvents favored reaction by way of path a. Nitroethane was employed at −78 °C (entries 8, 9) because nitromethane could not be employed at temperatures below −25 °C. Gratifyingly, when nitroethane was used, the desired alkene **16** was produced exclusively. The reactions were performed on a 100–200-mg scale. In all cases the yields were in the 80–85% range. The results, which fulfilled the hope that the proper choice of solvent would favorably affect the outcome of the rearrangement, also revealed (entries 8, 9) an extremely short, economical, and high-yield synthesis of **1** and **2**. It can also be seen that the outcome of the rearrangement can be better controlled by using sulfuric acid as the catalyst. Thus, by a proper choice of reaction conditions it proved possible to "finetune" the rearrangement of chromanol **15** so as to afford, selectively, either **16** or **17**, even though **17** could not be obtained to the total exclusion of its isomer. The chromanol **18** also responded favorably. Thus, treatment of **18** with sulfur acid in nitroethane at −78 °C afforded exclusively **19**. In contrast, when petroleum ether was the solvent, at −78 °C, a 1.0:2.3 mixture of **19** and **20** was produced. The full implications of this highly exhilarating observation that the outcome of the acid-catalyzed rearrangement of cyclobutylcarbinols can be controlled are being evaluated by applying the methodology described here to a variety of substrates. The results are expected to provide useful guidelines for future synthetic applications of such rearrangements.

Besides the postulated pathway, an alternate route from **15** to **16** appeared to be feasible. This presumed that rearrangement of **15** involving only a concerted process (path b, Scheme I) would first lead to the intermediate **22** (R = Me), which by loss of a proton would afford **17**. Furthermore, the migration of the aryl group of **22** could lead to a trichothecane-like cationic intermediate **23** (R = Me), rearrangement of which would eventually provide alkene **16** (Scheme III). When R = Me, the product arising in this manner would be indistinguishable from that which would arise by path a. However, if R = Et, rearrangement would give rise to alkene **24**, an isomer of **19** and **20**. To determine if this could be the case, a synthesis of the alkene **24** from the styrenol **25** was carried out. In the manner described earlier,[3] **25** was O-alkylated by

Scheme IV[a]



[a] Reagents: (i) NaH, $EtCH(Br)CO_2H$, THF; (ii) *p*-TSCl, Et_3N, benzene, reflux; (iii) BF_3·Et_2O. N_2CHCO_2Et; (iv) LiCl, DMSO, H_2O, 160 °C; (v) MeMgI, Et_2O, then $POCl_3$, pyridine.

treatment with α-bromobutanoic acid to yield **26**. Compound **26** was then transformed into the cyclobutanone **28** through an intramolecular ketene-to-alkene cycloaddition. Regioselective ring enlargement of **28** gave the β-keto ester **29**, deethoxycarbonylation of which furnished the cyclopentanone **30**. The reaction of **30** with methylmagnesium iodide and dehydration of the ensuing carbinol afforded the alkene **24** (Scheme IV). Alkene **24** differed spectroscopically from both **19** and **20**, which supported the earlier hypothesis that only two mechanisms are operative in the rearrangements of **15** and **18** and that alkenes **16** and **19** are in fact generated by way of an initial external bond migration.

Thus, an extremely short synthesis of the marine sesquiterpenes **1** and **2** has been developed. The acid-catalyzed rearrangement of a cyclobutyl carbinol provides the key intermediate. The most attractive features of the synthesis are that readily available, inexpensive reagents are used and only easily attainable experimental conditions are required. The synthesis is therefore economical. A significant result of the efforts described here is the observation that the proper choice of solvent and reaction temperature dramatically controls the inital step of the rearrangement. The methodology described here provides aplysin in five high-yield steps, starting from the chromone **13**.

Experimental Section

General. All the compounds described herein which possess asymmetric carbons are racemates. All reactions were performed under N_2. Melting point is uncorrected. Liquid products were purified by bulb-to-bulb distillations to obtain analytical samples and the oven temperature is designated as ot. Solvents and reagents were reagent-grade materials and were further purified by conventional methods. The petroleum ether that was used is that fraction of bp 60–80 °C. The purity of the products was routinely monitored by TLC. Preparative TLC was performed with silica gel 60 HF_{254} (E. Merck) plates of 1-mm thickness. Na_2SO_4 was used to dry organic extracts.

^1H NMR spectra of $CDCl_3$ solutions were recorded at 200 MHz. The IR spectra are of $CHCl_3$ solutions. GLC analyses were performed with 2-m OV-17 (column-I) or SE-30 (column-II) columns. N_2 was the carrier gas.

2,3,7-Trimethylchromone (13). A mixture of 2-hydroxy-4-methylpropiophenone (10 g, 61 mmol), Ac_2O (80 mL), and anhydrous NaOAc (12 g) was allowed to react as described earlier.[7] The crude product was stirred with 50% H_2SO_4 (50 mL) at 50 °C for 2 h. The mixture was then cooled, diluted with cold water (100 mL), and extracted with Et_2O. The extract was washed (water, cold 2% aq NaOH, and water), dried, and concentrated to afford the chromone **13** as a solid (5.90 g, 61%, based on the propiophenone): mp 88–89 °C (benzene) (lit.[7] mp 86 °C); IR 1630 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H), 2.42 (s, 3 H), 2.48 (s, 3 H), 7.21 (m, 2 H), 8.11 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.74; H, 6.50.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8a-trimethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-one (14).** A solution of chromone **13** (1.07

g) in dry thiophene-free benzene (450 mL) was irradiated through a Pyrex filter with a Hanovia 450-W mercury lamp for 10 h, during which time ethylene was bubbled through the solution. Then the solvent was evaporated under reduced pressure. Bulb-to-bulb distillation [110–115 °C (0.15 mmHg)] of the residual oil afforded the cyclobutachromanone **14** (1.10 g, 90%): IR 1665 cm^{-1}; ^1H NMR δ 1.32 (s, 3 H), 1.58 (s, 3 H), 1.64–1.92 (m, 2 H), 2.16–2.28 (m, 1 H), 2.36 (s, 3 H), 2.48–2.66 (m, 1 H), 6.72 (br s, 1 H), 6.84 (br d, J = 8 Hz, 1 H), 7.82 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.76; H, 7.39.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8,8a-tetramethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-ol (15).** To a magnetically stirred solution of MeMgI [prepared from Mg(60 mg, 0.0025 g-atom), MeI (355 mg, 2.5 mmol), and dry Et_2O (15 mL)] at 0 °C was added a solution of **14** (490 mg, 2.26 mmol) in dry Et_2O (5 mL). The mixture was brought to rt and was stirred there for 15 min. Then it was refluxed for 30 min. The mixture was cooled to 0 °C and was decomposed by adding saturated aqueous NH_4Cl. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated to afford **15** as a colorless oil (485 mg, 92%): ^1H NMR δ 1.28 (s, 3 H), 1.32 (s, 3 H), 1.43 (s, 3 H), 1.48–1.66 (m, 2 H), 1.68 (s, D_2O-exchangeable, 1 H), 1.82–2.20 (m, 2 H), 2.32 (s, 3 H), 6.78 (br s, 1 H), 6.88 (br d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H). This material was used in the next step without further purification.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8a-trimethyl-8-ethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-ol (18).** Similarly, the reaction of EtMgI [prepared from Mg (49 mg, 0.002 g-atom) and EtI (312 mg, 2 mmol)] and chromone **14** (350 mg, 1.62 mmol) afforded the chromanol **18** (370 mg, 93%): ^1H NMR δ 0.62 (t, J = 7.4 Hz, 3 H), 1.18–2.18 (m, 7 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 2.32 (s, 3 H), 6.77 (br s, 1 H), 6.87 (m, 1 H), 7.38 (d, J = 8 Hz, 1 H). This material was used in the next step without further purification.

Rearrangement of Cyclobutachromanol 15. Method A (Entry 1, Table I). To a magnetically stirred solution of chromanol **15** (110 mg) in dry benzene (10 mL) at rt was added a drop of freshly distilled BF_3·Et_2O by means of a syringe. The mixture was stirred for 1 h, and then it was decomposed by adding saturated aqueous $NaHCO_3$. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed (saturated brine and water) and dried. Evaporation of the solvent and preparative TLC [petroleum ether/EtOAc (99:1)] of the residual oil afforded a colorless oil (90 mg, 88%). GLC analysis (column-I) showed this to be a 1.5:1.0 mixture of two compounds, t_R = 1.9 min (major component) and 2.07 min (minor component), at a column temperature of 180 °C. This result was confirmed by recording the ^1H NMR spectrum of the mixture and determining the ratio of the integrals of the signals due to the olefinic protons (δ = 5.4 and 5.28 ppm, respectively) of the two compounds. The mixture was again subjected to preparative TLC, as above. The less polar component, an oil, was identified as **16**. Its ^1H NMR spectrum was identical to that of an authentic sample.[3]

The more polar component was alkene **17**: ot 65–70 °C (0.15 mmHg); ^1H NMR δ 1.29 (s, 3 H), 1.38 (s, 3 H), 1.62 (ddd, J = 1.8, 0.9, 0.7 Hz, 3 H), 2.29 (s, 3 H), 2.69 (m, 2 H), 5.28 (br s, 1 H), 6.58 (br s, 1 H), 6.67 (m, 1 H), 7.02 (d, J = 7.6 Hz, 1 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.01; H, 8.75.

Similar rearrangement of the chromanol **18** (210 mg) furnished a 1.5:1.0 mixture of the alkenes **19** and **20** (175 mg, 90%), as GLC analysis (column-II) showed, t_R = 2.24 min (major component) and 2.48 min (minor component), at a column temperature of 180 °C. The two could also be separated as in the case of **16** and **17**, by preparative TLC [petroleum ether/EtOAc (99:1)]. Isomer **19**: ot 100–105 °C (0.05 mmHg); ^1H NMR δ 0.93 (t, J = 7.4 Hz, 3 H), 1.45 (s, 3 H), 1.58–1.66 (m, 2 H), 1.68 (ddd, J = 1.6, 1.0, 0.6 Hz, 3 H), 2.29 (s, 3 H), 2.52 (m, 2 H), 5.41 (br s, 1 H), 6.59 (br s, 1 H), 6.67 (m, 1 H), 7.07 (d, J = 7.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.05; H, 9.06.

Isomer **20**: ot 102–108 °C (0.1 mmHg); ^1H NMR δ 0.81 (t, J = 7.4 Hz, 3 H), 1.41 (s, 3 H), 1.54 (ddd, J = 1.4, 0.9, 0.8 Hz, 3 H), 1.58–1.70 (m, 1 H), 1.97–2.12 (m, 1 H), 2.28 (s, 3 H), 2.63 (m, 2 H), 5.41 (br s, 1 H), 6.56 (br s, 1 H), 6.66 (br d, J = 7.5 Hz, 1 H), 7.0 (d, J = 7.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.42; H, 8.73.

Method B (Entry 5, Table I). To a magnetically stirred solution of chromanol **15** (140 mg) in dry petroleum ether (15 mL) at −78 °C was added a drop of concentrated H_2SO_4 by means of a syringe. The mixture was stirred at −78 °C for 30 min and then was allowed to warm to rt and was decomposed by adding saturated aqueous $NaHCO_3$. Et_2O was then added. The two liquid layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC [petroleum ether/EtOAc (99:1)]. GLC analysis (column-I) of the product (100 mg, 85%) showed it to be a 1:19 mixture of **16** and **17**.

Method C (Entries 8, 9, Table I). To a magnetically stirred solution of chromanol **15** (100 mg) in dry $EtNO_2$ (10 mL) at −78 °C was added, a drop of concentrated H_2SO_4 or BF_3·Et_2O by means of a syringe. After 30 min of stirring (1 h when BF_3·Et_2O was the catalyst), the reaction mixture was allowed to warm to 0 °C and then was decomposed by adding saturated aqueous $NaHCO_3$. Et_2O was added, and the two liquid layers that formed were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC [petroleum ether/EtOAc (99:1)] to afford alkene **16** (75 mg, 82%). This was identical (GLC, ^1H NMR) with a sample of **16** prepared by method A. GLC analysis showed **17** to be absent.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8a-trimethyl-8-methylenebenzo[*b*]cyclobuta[*e*]pyran (21). Method A.** To a magnetically stirred suspension of K^+t-BuO^- (112 mg, 1.0 mmol) in dry Et_2O (10 mL) was added $MePh_3P^+I^-$ (404 mg, 1.0 mmol). The mixture was then refluxed for 1 h. Most of the Et_2O was removed by distillation. A solution of chromanone **14** (130 mg, 0.6 mmol) in Et_2O (5 mL) was then added. Most of the Et_2O was again distilled from the mixture, which was then heated at 60–70 °C for 3 h. The mixture was cooled, diluted with water, and extracted with petroleum ether. The combined extracts were washed with water and saturated brine, dried, and concentrated. Preparative TLC (petroleum ether) of the residual oil afforded olefin **21** (110 mg, 85%): ot 75–80 °C (0.15 mmHg); ^1H NMR δ 1.28 (s, 3 H), 1.42 (s, 3 H), 1.68–2.28 (m, 4 H), 2.32 (s, 3 H), 5.08 (s, 1 H), 5.54 (s, 1 H), 6.68 (br s, 1 H), 6.78 (m, 1 H), 7.42 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.39.

Method B. To a stirred solution of carbinol **15** (490 mg, 2.11 mmol) in pyridine (6 mL) at 0 °C was added $POCl_3$ (690 mg, 4.5 mmol). The stirred mixture was allowed to warm to rt and was kept there for 24 h. It was then diluted with cold water and was extracted with Et_2O. The extract was washed with water and dried. The oil obtained after evaporation of Et_2O was purified by preparative TLC (petroleum ether) to afford olefin **21** (410 mg, 90%), which was identical to a sample prepared by method A.

For details of the preparation of **24** from **25**, see ref 3.

2-(2-Isopropenyl-5-methylphenoxy)butanoic acid (26): yield 2.95 g (60%) from 3.10 g of **25**; ^1H NMR δ 1.08 (t, J = 7.4 Hz, 3 H), 2.0–2.14 (m, 2 H), 2.16 (dd, J = 0.8, 0.6 Hz, 3 H), 2.31 (s, 3 H), 4.67 (t, J = 5.6 Hz, 1 H), 5.12 (m, 1 H), 5.22 (m, 1 H), 6.64 (br s, 1 H), 6.84 (br d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H). Analytical data were obtained for the corresponding methyl ester **27**, prepared by treating **26** with CH_2N_2: ot 105–110 °C (0.1 mmHg); ^1H NMR δ 1.05 (t, J = 7.4 Hz, 3 H), 1.92–2.06 (m, 2 H), 2.15 (dd, J = 0.9, 0.5 Hz, 3 H), 2.30 (s, 3 H), 3.74 (s, 3 H), 4.61 (t, J = 6.1 Hz, 1 H), 5.10 (m, 1 H), 5.14 (m, 1 H), 6.52 (br s, 1 H), 6.76 (br d, J = 8 Hz, 1 H), 7.12 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.25; H, 7.96.

***cis*-2a,7b-Dihydro-2a-ethyl-5,7b-dimethylcyclobuta[*b*]benzofuran-2(1*H*)-one (28):** yield 220 mg (79%) from 300 mg of **26**; ot 90–95 °C (0.05 mmHg); IR 1780 cm^{-1}; ^1H NMR δ 1.16 (t, J = 7.4 Hz, 3 H), 1.59 (s, 3 H), 1.84–2.08 (m, 2 H), 2.31 (s, 3 H), 3.12 and 3.22 (AB q, J = 17.7 Hz, 2 H), 6.69 (br s, 1 H), 6.76 (m, 1 H), 7.09 (d, J = 7.7 Hz, 1 H). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 78.07; H, 7.76.

***cis*-3-Oxo-1,2,3a,8b-tetrahydro-3a-ethyl-6,8b-dimethyl-3*H*-cyclopenta[*b*]benzofuran (30):** yield 150 mg (70%) from 200 mg of **28**; ot 125–130 °C (0.05 mmHg); IR 1745 cm^{-1}; ^1H NMR δ 1.05 (t, J = 7.5 Hz, 3 H), 1.38 (s, 3 H), 1.8–2.13 (m, 4 H), 2.28 (s, 3 H), 2.29–2.44 (m, 2 H), 6.63 (br s, 1 H), 6.74 (m, 1 H), 7.01

(d, J = 7.6 Hz, 1 H). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.51; H, 7.96.

***cis*-3a,8b-Dihydro-3,6,8b-trimethyl-3a-ethyl-1*H*-cyclopenta[*b*]benzofuran (24)**: yield 90 mg (91%) from 100 mg of **30**; ot 110–115 °C (0.06 mmHg); GLC (column II), t_R = 2.31 min at a column temperature of 180 °C; ^{1}H NMR δ 0.84 (t, J = 7.6 Hz, 3 H), 1.33 (s, 3 H), 1.68 (ddd, J = 1.6, 1.0, 0.6 Hz, 3 H), 1.06–2.12 (m, 2 H), 2.27 (s, 3 H), 2.36–2.74 (m, 2 H), 5.54 (br s, 1 H), 6.57 (br s, 1 H), 6.66 (br d, J = 7.5 Hz, 1 H), 7.0 (d, J = 7.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.50; H, 8.99.

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Registry No. (±)-**1**, 21019-65-8; (±)-**2**, 21019-64-7; **13**, 106949-32-0; (±)-**14**, 138629-60-4; (±)-**15**, 138629-61-5; (±)-**16**, 63023-41-6; (±)-**17**, 138629-62-6; (±)-**18**, 138629-63-7; (±)-**19**, 138629-64-8; (±)-**20**, 138629-65-9; (±)-**21**, 138629-66-0; (±)-**24**, 138629-67-1; **25**, 18612-99-2; (±)-**26**, 138629-68-2; (±)-**27**, 138629-69-3; (±)-**28**, 138629-70-6; (±)-**29**, 138629-71-7; (±)-**30**, 138629-72-8; 2-hydroxy-4-methylpropiophenone, 2886-52-4.

Macrocyclic Polylactones by Catalyzed Cyclooligomerization. Tetra[(*S*)-β-butyrolactone][1]

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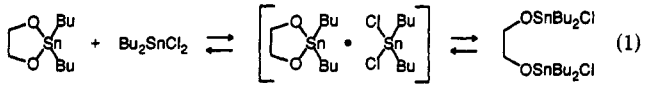
The synthesis of the elusive macrotetrolide **2** of 3-hydroxybutyric acid has been approached by cyclooligomerization of enantiomerically pure (*S*)-β-butyrolactone (**3**), promoted by the catalytic system 2,2-dibutyl-1,3,2-dioxastannolane/dibutyltin dichloride (DOS/DTC). The product has been isolated in 10% yield, demonstrating that it is not inaccessible, and its structure has been proven by X-ray crystal structure analysis. DOS/DTC afforded a thermodynamically controlled cyclooligomerization mixture, which was analyzed by means of a revised version of the Jacobson–Stockmayer theory, providing an evaluation of the effective molarity (EM) parameter for the formation of the tetrameric macrolide. The EM value was found to be five times lower than the corresponding value for tetra(β-propiolactone), its strainless unsubstituted analogue. The observed EM allowed a quantitative measure (1.1 kcal mol^{-1}) of the strain induced in the 16-membered macrotetrolide by the introduction of a methyl group into four homochiral stereocenters of the ring. Such relatively small strain is sufficient to depress to an appreciable extent the yield of **2** that can be expected from a thermodynamically controlled reaction. The possible origin of the observed strain is discussed.

In a previous communication,[1] it has been shown that the catalytic system 2,2-dibutyl-1,3,2-dioxastannolane/dibutyltin dichloride (DOS/DTC) can efficiently induce thermodynamically controlled cyclooligomerization of lactones under mild conditions. In connection with this



(1)

DOS DTC DOS/DTC

discovery, we have recently developed a revised version[2] of the Jacobson and Stockmayer theory[3] in which the product distribution of equilibrated polymeric mixtures is conveniently described in terms of effective molarity (EM) of cyclic compounds and an equilibrium constant (K_{inter}) for the intermolecular polymerization reaction.[4] In the revised presentation, given (or estimated) the EM_n and K_{inter} parameters, the application of the theory to practical cases is straightforward and provides the complete product distribution. Conversely, EM_n and K_{inter} can be evaluated for different systems by fitting the observed product distribution with the theoretical equations.

It appears that the combination of such mathematical treatment with the use of the above catalytic system might represent a powerful tool for achieving the synthesis of molecular targets that are cyclic oligomers of accessible

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(1) Group 14 Organometallic Reagents. 11. For part 10, see: Roelens, S. *J. Chem. Soc., Chem. Commun.* **1990**, 58.

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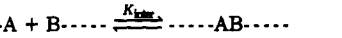
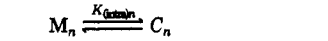
(3) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600.

(4) K_{inter} is defined as the equilibrium constant relative to the intermolecular reversible reaction between the A and B reactive chain-end of a growing polymer, giving rise to the AB functional group. The thermodynamic effective molarity EM_n relative to the reversible formation of the nth cyclic oligomer C_n from the open chain precursor M_n





is defined as

$$EM_n = K_{(intra)n}/K_{inter}$$

For a detailed discussion on the EM parameter and its relevance to cyclization processes, see: Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

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