The Synthesis of (±)-Norketoagarofuran

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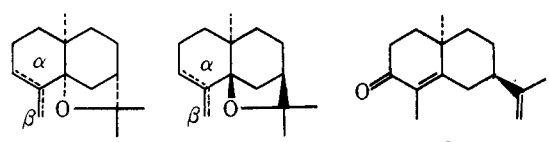
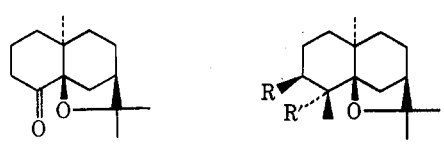
(±)-Norketoagarofuran (**4**) has been synthesized by a short, highly stereoselective route from **10**. Formic acid–hydrogen peroxide hydroxylation of **10** gives **18**, which is oxidized to **36**. Treatment of **36** with ethylene glycol and acid gives **37**, which is transesterified to **35**. The crucial epimerization–lactonization **35** → **41** → **38** is effected by lithium methoxide in dioxane but only if the reaction is driven to completion by continually removing the methanol as it is formed in the closure **41** → **38**. Without isolation **38** is treated successively with methyllithium and aqueous acid to afford **4**, presumably *via* **42**. A discussion of the factors affecting the conversion of **35** to **38** and related reactions is presented.

In 1963 Bhattacharyya and coworkers reported[2] the isolation and characterization of six closely related decalinic sequiterpenes found in agar-wood oil isolated from fungus-infected *Aquillaria agallocha* Roxb. Most of the degradative work was carried out on α- and β-agarofuran, which were assigned the structures and stereochemistry depicted by **1**. On the basis of both chemical and biogenetic considerations Barrett and Büchi deduced[3] that the geometric disposition of the tetrahydrofuran ring was more likely that shown in **2** and supported their conclusion by synthesizing α-agarofuran from (−)-epi-α-cyperone (**3**). Because



1 **2** **3**

of correlations carried out by Bhattacharyya, *et al.*,[2] the revised structures of the other naturally occurring agarofurans are norketoagarofuran (**4**), dihydroagarofuran (**5**),[4] 4-hydroxydihydroagarofuran (**6**), and 3,4-dihydroxydihydroagarofuran (**7**). In addition to the

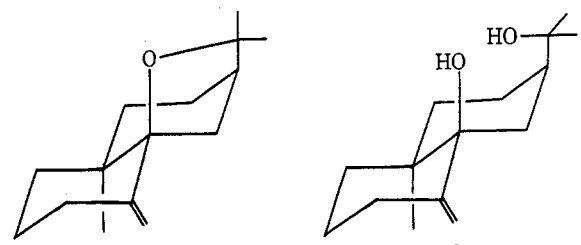


4

5, R = R′ = H
6, R = H; R′ = OH
7, R = R′ = OH

work of Barrett and Büchi[3] and the synthesis reported herein,[5] syntheses of various agarofurans have also been described by Marshall and Pike[6] and Asselin, Mongrain, and Deslongchamps.[4]

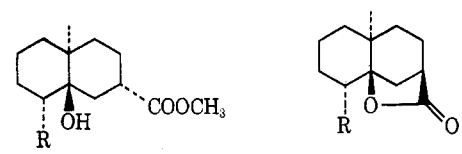
In considering approaches to the synthesis of the agarofurans the primary difficulty would appear to involve construction of the tetrahydrofuran ring. All successful syntheses have postponed forming the ether ring until the decalin framework has been fashioned. Since geometrical restrictions demand that the ether ring be diaxially fused to the decalin skeleton (*cf.* **8**), the isopropyl moiety (*cf.* **9**) must be located in the unstable axial position for ring closure (*i.e.*, **9** → **8**)



8 **9**

to occur. In all of the other syntheses[3,4,6] this problem was solved by using as starting material the readily available (−)-epi-α-cyperone (**3**) or its equivalent in which the β orientation of the isopropenyl grouping is already fixed.

Since earlier work[7,8] in these laboratories had shown that hydroxy esters **10** and **11** are converted into lactones **12** and **13** upon treatment with methanolic sodium methoxide, it was felt that such an epimerization–lactonization approach might provide an alternative route to the agarofurans.[9] Diol ester **14**, which is readily available from unsaturated acid **15**,[10] was selected as starting material.



10, R = H
11, R = CH_3
14, R = OH

12, R = H
13, R = CH_3

Treatment of **15** with performic acid[11] gives a mixture of diol acid monoformates **16** from which **17** can be isolated. Saponification of mixture **16** affords diol acid **18**, identical with material of known[7] stereochem-

(1) (a) Address correspondence to Department of Chemistry, Boston College, Chestnut Hill, Mass. 02167. (b) National Science Foundation Trainee, 1965–1968.

(2) (a) M. L. Maheshwari, K. R. Varma, and S. K. Bhattacharyya, *Tetrahedron*, **19**, 1519 (1963). (b) M. L. Maheshwari, T. C. Jain, R. B. Bates, and S. C. Bhattacharyya, *ibid.*, **19**, 1079 (1963). (c) Recently the structures of a number of sesquiterpene alkaloids which contain the tricyclic agarofuran ring system have been reported: S. M. Kupchan, R. M. Smith, and R. F. Bryan, *J. Amer. Chem. Soc.*, **92**, 6667 (1970); A. Klasek, Z. Samek, and F. Santavy, *Tetrahedron Lett.*, 941 (1972), and references cited therein.

(3) H. C. Barrett and G. Büchi, *J. Amer. Chem. Soc.*, **89**, 5665 (1967).

(4) The assignment of β stereochemistry to the C-4 methyl of **5** is due to A. Asselin, M. Mongrain, and P. DesLongchamps, *Can. J. Chem.*, **46**, 2817 (1968).

(5) A preliminary account describing some of this work has appeared: C. H. Heathcock and T. R. Kelly, *Chem. Commun.*, 267 (1968).

(6) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 434 (1968).

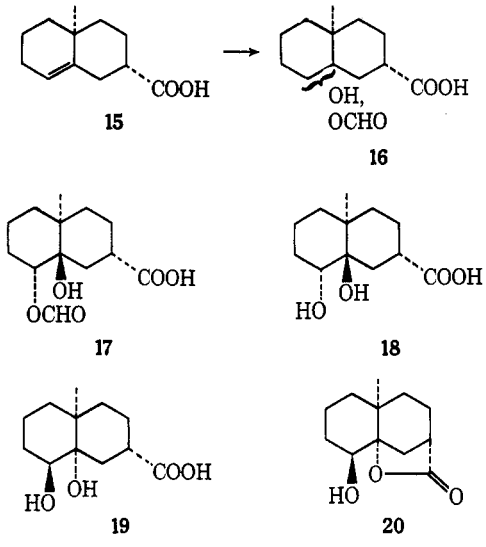
(7) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 3753 (1968). A second synthesis of lactone **12** has recently been reported: D. J. Dunham and R. G. Lawton, *J. Amer. Chem. Soc.*, **93**, 2075 (1971).

(8) C. H. Heathcock and Y. Amano, *Tetrahedron*, **24**, 4917 (1968).

(9) Although all compounds whose synthesis is reported herein are racemic, only that enantiomer corresponding to the natural configuration of the agarofurans is depicted. In previous papers[7,8,10] some of these racemic compounds were represented by the structure of the enantiomer.

(10) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968).

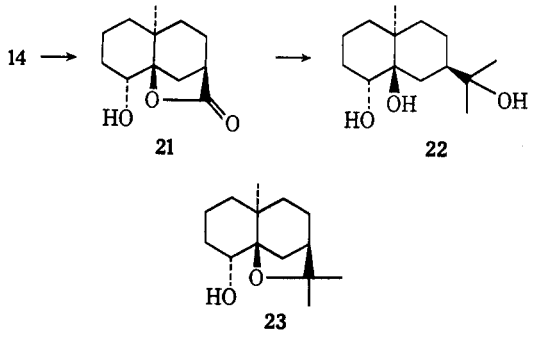
(11) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **71**, 3938 (1949).



15 16 17 18 19 20

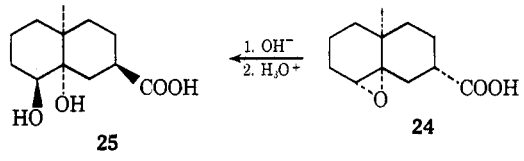
istry. In one run a small amount of another diol acid was obtained. This compound was assigned structure **19** on the basis of mechanistic considerations and the fact that upon heating it forms a γ-lactone ($\nu_{C=O}$ 1775 cm^{-1}), presumably **20**. Diol acid **18** reacts with ethereal diazomethane to give the desired diol ester **14**.

Treatment of **14** with methanolic sodium methoxide did not afford lactone **21**, but, when dioxane was substituted for methanol, epimerization and lactonization did take place, giving the desired hydroxy lactone **21**. The crude lactone, when treated successively



21 22 23

with methyllithium and Jones reagent,[12] was transformed into norketoagarofuran (**4**), presumably *via* **22** and **23**, with the acidic nature of the oxidant serving to catalyze ether formation. Unfortunately, numerous attempts to repeat the conversion of **14** to **21** were unsuccessful. An examination of the products from unsuccessful attempts at lactonization of **14** with sodium methoxide indicated the presence of a diol acid which we had previously prepared[7] from epoxy acid **24** and assigned structure **25**. A possible mech-

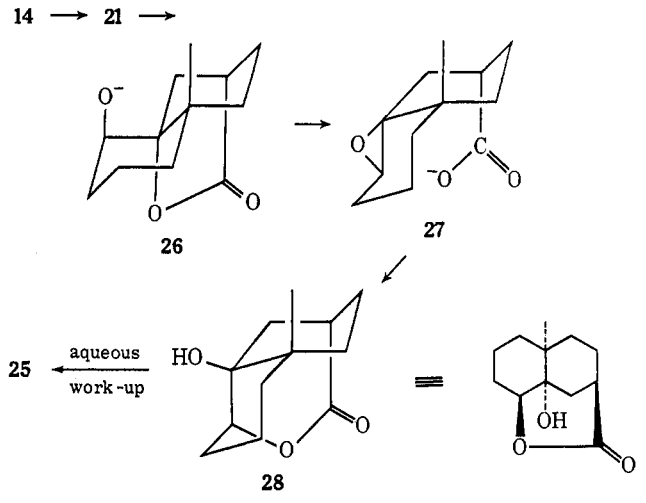


25 24

anism for the conversion of **14** into **25** is outlined in Scheme I.

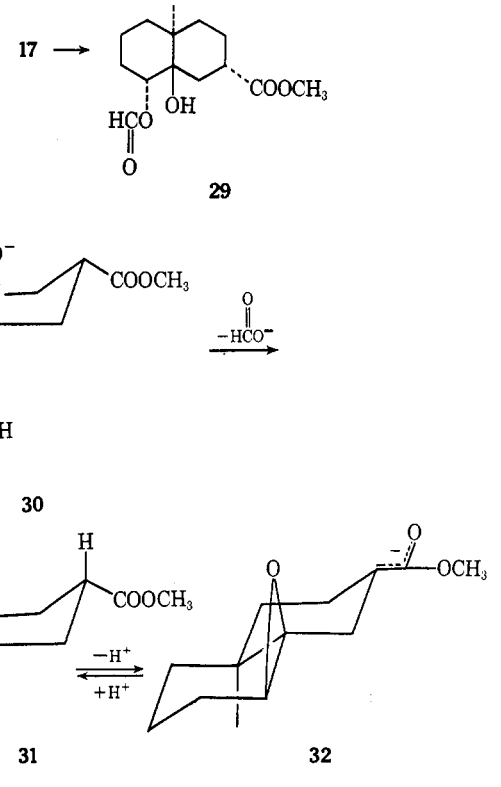
(12) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

SCHEME I



26 27 28

Support for the intramolecular displacement of carboxylate (**26** → **27**) is found in the observation that diol ester monoformate **29**, prepared from **17** by esterification with diazomethane, affords the known[7] epoxy ester **31** in 70% yield under similar conditions. Epoxide formation almost certainly results from an intramolecular displacement of formate (**30** → **31**), although it is surprising that such a reaction is preferred over transesterification of the formate to give **14**. Under the reaction conditions epoxy ester **31** is apparently converted to anion **32**, as carbonyl absorption in the



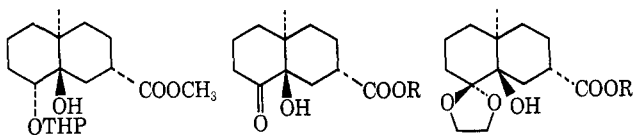
29 30 31 32

ir spectrum gradually disappears with the simultaneous appearance of absorption attributed[13] to enolate anions. Upon work-up, anion **32** suffers axial protonation, giving back **31**.

These considerations suggested that the secondary hydroxyl group in diol ester **14** should be replaced with

(13) H. Lenormant, *Ann. Chim. (Paris)*, **5**, 516 (1950).

some function incapable of participating in displacement reactions such as **26** → **27**. The tetrahydropyranyl ether **33** could not be synthesized and ketol ester **34**, prepared by Jones oxidation[12] of diol ester **14**, appeared to be essentially inert to sodium methoxide in dioxane. Since the potential[14] for rearrangement inherent in the α-ketol moiety argues against subjecting **34** to forcing conditions, the corresponding ketal **35** was prepared. Jones oxidation[12] of diol acid **18**



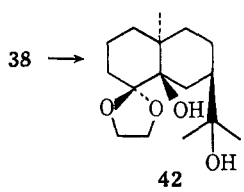
33 **34**, R = CH_3 **35**, R = CH_3
36, R = H **37**, R = CH_2CH_2OH

affords ketol acid **36**. Treatment of the latter with ethylene glycol and *p*-toluenesulfonic acid gives **37**, which is converted into the desired hydroxy ketal ester **35** upon transesterification with methanolic sodium methoxide.

When **35** is treated with lithium methoxide in refluxing dioxane, no reaction occurs. However, when methanol is removed by causing the condensed vapor to pass through a modified Soxhlet extractor[15] equipped with a thimble containing calcium hydride during its return to the reaction flask, lactone formation occurs. The simplest explanation of this result is that lactone **38** is less stable than hydroxy ester **35** and that the position of the equilibrium (**35** ⇄ **38** + CH_3OH) is driven to the right as methanol is removed.

Alternatively, **38** could be more stable than **35** but lithium methoxide may not be a sufficiently strong base to catalyze the conversion at an appreciable rate. In this event removal of methanol could result in the formation of greater amounts of tertiary alkoxide **39**, which should be sufficiently basic to promote the formation of enolate **40** (Scheme II). Enolate **40** could then suffer intermolecular protonation to give **41**, which would lactonize to give **38**.

Since it was anticipated that ketal lactone **38** would be sensitive to hydrolysis, no attempt was made to isolate it but rather the crude material was treated directly with methyllithium to give ketal diol **42**.



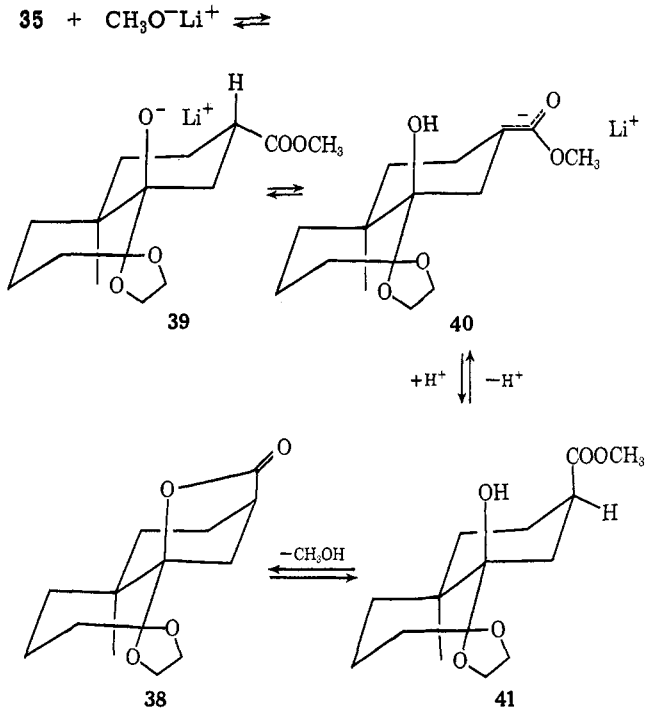
42

Without isolation, this compound was treated with aqueous acid to effect both deketalization and cyclization to racemic norketoagarofuran (**4**). The synthetic material exhibited nmr and ir spectra identical with those reported[2a] for the optically active material.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 237 infrared spectrometer. Nmr spectra were determined on a Varian A-60 instrument. Chemical shifts are given in parts per million downfield from internal tetramethylsilane. Vpc analyses were performed with an Aerograph A-90-P instrument. Melting points (Pyrex capillary) and boiling points are uncorrected. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

SCHEME II



39 **40** **38** **41**

4aβ-Methyl-8β,8aα-dihydroxydecahydronaphth-2β-oic Acid (18) and 4aβ-Methyl-8α,8aβ-dihydroxydecahydronaphth-2β-oic Acid (19).—To 20.00 g of 4aβ-methyl-1,2,3,4,4a,5,6,7-octahydronaphth-2β-oic acid (**15**), partially dissolved in 500 ml of 88% formic acid, was added 40 ml of 30% hydrogen peroxide.[11] After the reaction mixture was stirred at room temperature for 17 hr, volatile material was removed at or below 25° on a rotary evaporator connected to a vacuum pump. The residual crude diol acid monoformate (**16**, 32 g) was dissolved in 275 ml of 0.9 *M* sodium hydroxide. The resulting solution was heated on a steam bath for 2.5 hr and then allowed to cool. The alkaline solution was layered with methylene chloride (200 ml) and acidified. The voluminous precipitate was collected by filtration and the filtrate was set aside (*vide infra*).

The solid was taken up in methanol and dried over sodium sulfate. Removal of the methanol afforded 15.30 g of white solid, mp 200–220°. Recrystallization from acetone gave 11.75 g (50%) of diol acid **18** in several crops, mp 208–212, which was shown to be identical by mixture melting point and spectral comparison with a sample of **18** prepared by an independent route.[7]

The above-mentioned two-phase filtrate was separated and the aqueous layer was extracted several times with methylene chloride. After drying over $MgSO_4$ the combined methylene chloride layers were evaporated to afford 1.7 g of semisolid, which was triturated with methylene chloride. Filtration yielded 500 mg (2%) of analytically pure diol acid **19**: mp 143.5–146.5° (gas evolution); nmr (methanol) δ 1.03 (angular methyl); ir (KBr) 3570, 3490, 3300–2400, 1695 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 62.89; H, 8.90.

4aβ-Methyl-8β-formyloxy-8aα-hydroxydecahydronaphth-2β-oic Acid (17).—In one run a portion of the semisolid mixture of diol acid monoformates **16** was crystallized from water to afford crude diol acid monoformate **17**, mp 110–140°. Recrystallization from benzene afforded material with mp 143.5–147.5°. The overall yield from unsaturated acid **15** is on the order of 25%. Further recrystallization from benzene afforded analytically pure material: mp 145.8–147.0°; ir (KBr) 3490, 3200–2500, 1710 (broad), and 1205 cm^{-1}; nmr (methanol) δ 1.20 (angular methyl), 8.02 (HCO_2^-).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.28; H, 8.09.

(14) Y. Mazur and M. Nassim, *Tetrahedron Lett.*, 817 (1961).
(15) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, revised, D. C. Heath, Boston, Mass., 1955, p 50, Figure 7-2.

4aβ-Methyl-8α,8aβ-dihydroxydecahydronaphth-2β-oic Acid Lactone (20).—Diol acid **19** (66 mg) was heated at 150–160° for 15 min, at which point gas evolution had ceased. After partial cooling 0.5 ml of benzene was added and the solid material was removed by filtration and washed with 0.5 ml of hexane. The combined filtrate and wash were diluted with 10 ml of hexane. Cooling of this solution gave 32 mg (52%) of lactone **20**, mp 101–105°. Analytically pure material (mp 101.3–103.4°) was obtained upon recrystallization from hexane: ir ($CHCl_3$) 3600, 3450, and 1775 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (angular methyl), 4.25 (very broad, axial[16] C_8 proton).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.47.

Methyl 4aβ-Methyl-8β,8aα-dihydroxydecahydronaphth-2β-oate (14).—A solution of 1.025 g of diol acid **18** in 25 ml of methanol was esterified at 5° with ethereal diazomethane. The solvent was evaporated on a steam bath and the residue was taken up in ether and dried over $MgSO_4$. Removal of solvent afforded 1.00 g (92%) of ester **14**, mp 106–110°. Recrystallization from benzene–hexane afforded analytically pure material: mp 108.2–109.9; nmr ($CDCl_3$) δ 1.23 (angular methyl), 3.65 (OCH_3); ir ($CHCl_3$) 3600, 3490, and 1725 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.53; H, 9.20.

Conversion of Diol Ester 14 to (±)-Norketoagarofuran (4).—A solution of 500 mg of diol ester **14** in 20 ml of dry dioxane was refluxed for several hours under nitrogen through a modified Soxhlet extractor[15] equipped with a thimble containing calcium hydride. After the dioxane solution was cooled to room temperature, approximately 1 equiv of sodium methoxide was added and the resulting suspension was refluxed. The reaction was monitored by ir. After 20 hr the reaction appeared to have stopped. An ir spectrum of the reaction mixture showed peaks at 1780 and 1730 cm^{-1} in a ratio of 3:1. The reaction mixture was allowed to cool to room temperature and 25 ml of dry ether was added followed by 5 ml of 1.5 *M* methyllithium in ether. After the mixture was stirred at room temperature for 3 hr, residual methyllithium was destroyed by the dropwise addition of brine. The organic phase was washed once with brine, dried over $MgSO_4$, and evaporated to give 500 mg of oil.

The crude oil was dissolved in acetone and oxidized with Jones reagent. After the usual work-up the crude product was chromatographed on activity III neutral alumina. Elution with benzene afforded approximately 30 mg of (±)-norketoagarofuran (**4**) whose ir and nmr spectra were identical with those previously reported.[2]

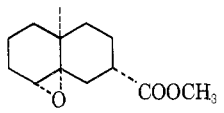
Attempts to repeat the conversion of diol ester **14** into lactone **21** were unsuccessful. In one run diol acid **25** was isolated from the reaction.

A solution of 600 mg of diol ester **14** in 30 ml of dry dioxane was refluxed through the calcium hydride equipped Soxhlet extraction as above. Then a suspension of 200 mg of sodium methoxide in 7 ml of dioxane containing 100 μl of ethyl benzoate (water scavenger) which had been heated at 60° for 12 hr was added to the solution of diol ester **14**. The resulting suspension was refluxed for 1 hr, at which time an ir spectrum of the reaction mixture showed no absorption in the carbonyl region. The reaction was allowed to cool and the dioxane was removed under vacuum. Water was added to the residue and the resulting solution was acidified with dilute sulfuric acid and extracted twice with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to give 700 mg of semisolid which was triturated with benzene. Filtration gave 110 mg (19%) of solid, mp 175–180°, with gas evolution. This material was shown to be identical with diol acid **25** which had been prepared in another manner[7] by comparison of spectra of both it and the derived lactone **28**.

Methyl 4aβ-Methyl-8β-formyloxy-8aα-hydroxydecahydronaphth-2β-oate (29).—A solution of 1.50 g of acid **17** in 50 ml of ether was esterified with ethereal diazomethane. After the ether was evaporated on a steam bath the crude ester was dissolved in ether and dried over magnesium sulfate. Removal of the ether afforded 1.53 g of oil which crystallized. One recrystallization from hexane gave 1.41 g (89%) of ester **29**, mp 88.0–90.2°. The analytical sample (mp 88.8–90.4°) was obtained upon one additional recrystallization from hexane: ir ($CHCl_3$) 3600, 3500, 1730, 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (angular methyl), 3.63 (CH_3O–), 4.82 ($W_{1/2}$ = 8 cps, equatorial[16] C_8 proton), 8.05 (HCO_2–).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.92; H, 7.92.

Reaction of Diol Ester Monoformate 29 with Lithium Methoxide.—To 20 ml of dry dioxane under a dry nitrogen atmosphere was added 1.5 ml of 1.5 *M* methyllithium in ether. Then a slight molar excess (90 μl) of methanol was added dropwise. After gas evolution had ceased (15 min), approximately 450 mg of formate ester **29** was added and the resulting cloudy solution was refluxed. The reaction was monitored by observing the infrared spectrum in the carbonyl region. After 4 hr, the ir spectrum showed essentially no absorption in the carbonyl region, but a broad band centered at *ca.* 1500 cm^{-1} was evident. The latter absorption is characteristic[13] of enolate anions. Heating was ceased and the reaction was allowed to cool overnight. The cooled solution was evaporated and 20 ml of water was added. The resulting two-phase mixture was thrice extracted with ether. The combined extracts were dried over $MgSO_4$ and evaporated, giving 260 mg (70%) of essentially pure epoxy ester **31**. The structure assignment was based on comparison of nmr and ir spectra of this material and those of a previously prepared 3:1 mixture of epoxy ester **31** and its epimer **43**. The analytical sample was



43

obtained by distillation at 0.1 mm (bath temperature 95°): nmr (CCl_4) δ 1.10 (angular methyl), 3.48 (OCH_3); ir (CCl_4) 1735 and 1025 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.28; H, 9.03.

Attempted Formation of the Tetrahydropyranol Ether of Diol Acid 18.—To a solution of 5.0 g of dihydropyran in 50 ml of dry ether was added 700 mg of diol acid[18] (mp 204–210°) and 5 drops of concentrated HCl. The diol acid did not appear to be soluble. After it had been stirred at room temperature for 18 hr the reaction mixture appeared unchanged and 20 ml of dry glyme was added which caused most of the suspended solid to dissolve. After 2.5 days the reaction was worked up in the usual manner. An nmr spectrum of the product (920 mg) showed several resonances attributable to angular methyl groups. No other attempts to prepare the THP ether were made.

Methyl 4aβ-Methyl-8-oxo-8aα-hydroxydecahydronaphth-2β-oate (34).—A solution of 300 mg of diol ester **14** in 15 ml of acetone was oxidized at 5° with 0.5 ml of Jones reagent.[12] The two-phase reaction mixture was added to 50 ml of saturated NaCl containing 1 ml of 10% aqueous $NaHSO_3$. The resulting two-phase mixture was thrice extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give 290 mg of oil which crystallized. Recrystallization from hexane afforded 220 mg of keto ester **34** in two crops, mp 84–88°. One additional recrystallization from hexane gave analytically pure material: mp 87.0–88.7°; nmr ($CHCl_3$) δ 0.85 (angular methyl), 3.66 ($-OCH_3$); ir (CCl_4) 3590, 3490, 1735, 1715 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.03; H, 8.71.

Attempted Lactonization of Ketol Ester 34.—To 20 ml of dioxane under dry nitrogen was added 0.75 ml of 1.5 *M* CH_3Li in ether and 50 μl of methanol. After the resulting solution was stirred for 30 min, 50 μl of ethyl benzoate (water scavenger) was added and the solution was heated at 70° for 5 hr. The solution was cooled to room temperature, 110 mg of dry ketol ester **34** was added, and the reaction mixture was refluxed. An ir spectrum of the reaction mixture after 7 hr of reflux showed no absorption characteristic of a γ-lactone. The reaction was worked up in the usual manner to give material whose nmr spectrum indicated that it was mainly unreacted **34**.

4aβ-Methyl-8-oxo-8aα-hydroxydecahydronaphth-2β-oic Acid (36).—A solution of 400 mg of analytically pure diol acid **18** in 25 ml of acetone was oxidized at 0° with 0.6 ml of Jones reagent.[12] The reaction mixture was poured into 50 ml of saturated NaCl containing 1 ml of 10% aqueous $NaHSO_3$. The resulting two-phase solution was extracted once with ether and four times with methylene chloride. The extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to give 370 mg (93%)

(16) A. Hassner and C. H. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

of a slightly green solid, mp 151–154°. The analytical sample (mp 159.8–161.8°) was obtained after one recrystallization from benzene, sublimation at 115° (20 μ), one additional recrystallization from $CHCl_3$ (0.75% ethanol), and drying at 55° (20 μ). When impure diol acid **18** was used, ketol acid **36** with a satisfactory melting point could not be obtained: nmr (pyridine) δ 0.92 (angular methyl); ir (KBr) 3480, 3300–2500, 1720, and 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.97; H, 7.69.

2′-Hydroxyethyl 4aβ-Methyl-8,8-ethylenedioxy-8aα-hydroxydecahydronaphth-2β-oate (37).—A rapidly stirred mixture of 2.00 g of ketol acid **36** (mp 149–158° with previous softening), 34 mg of *p*-toluenesulfonic acid monohydrate, 50 ml of benzene, and 10 ml of ethylene glycol was refluxed through a calcium hydride water separator[15] for exactly 2 hr under dry nitrogen. Heating was discontinued and the two-phase reaction mixture was poured into an aqueous solution composed of 5 ml of 10% KOH, 95 ml of H_2O, and 25 ml of saturated NaCl (to break emulsion). The resulting two-phase mixture was extracted thrice with ether and the combined extracts were dried ($MgSO_4$) and evaporated to give 2.07 g of solid material. Two recrystallizations from benzene–hexane gave 1.12 g (42%) of hydroxy ketal ester **37**, mp 108–112°. Several additional recrystallizations from the same solvent gave analytically pure material: mp 110.8–113.2°; nmr ($CDCl_3$ containing approximately 5% benzene) δ 1.10 (angular methyl), 3.6–4.3 (eight-proton multiplet, $-CH_2O-$); ir ($CHCl_3$) 3600, 3575, 3450, and 1725 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_5$: C, 61.13; H, 8.34. Found: C, 61.12; H, 8.32.

If the ketalization is carried out under more vigorous conditions the sole product of the reaction is a compound whose nmr spectrum suggests the presence of three ethylene glycol moieties.

Methyl 4aβ-Methyl-8,8-ethylenedioxy-8aα-hydroxydecahydronaphth-2β-oate (35).—To 20 ml of "anhydrous" (0.017% H_2O) methanol was carefully added 5 ml of 1.5 *M* methyllithium in ether, followed by 300 μl of ethyl benzoate (water scavenger). After refluxing under nitrogen for 2 hr, the methanol solution was cooled and to it was added 910 mg of **37**. The reaction mixture was refluxed for 0.5 hr and partially neutralized with solid $NaHCO_3$. The resulting methanol solution was poured into brine and the resulting mixture was thrice extracted with ether. The combined ether extracts were thrice washed with brine, dried over $MgSO_4$, and evaporated to give 930 mg of methyl ester **35** containing approximately 30% methyl benzoate as estimated by nmr. An analytical sample was obtained by vpc (6 ft × 0.25 in. 15% SF-96 on Chromosorb W at 220°): nmr ($CDCl_3$) δ 1.11 (angular methyl), 3.63, and 3.81 (OCH_3, $-CH_2O-$); ir ($CHCl_3$) 3650, 3580, and 1725 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.38; H, 8.45. Found: C, 63.55; H, 8.50.

Conversion of Hydroxy Ketal Ester 35 into (±)-Norketoagarofuran (4).—To 20 ml of dry dioxane, under nitrogen, was added 4 ml of 1.5 *M* methyllithium in ether, followed by a slight excess (250 μl) of dry methanol. To remove any hydroxide ion present, 150 μl of ethyl benzoate was added, and the reaction mixture was refluxed for 3 hr, at which time the ir spectrum still showed carbonyl absorption. To this solution was added 680 mg of 70% pure (*vide supra*) hydroxy ketal methyl ester **35**. The reaction mixture was refluxed and the progress of the reaction was followed by ir. After 18 hr, no reaction appeared to have taken place and no lactone absorption was visible in the ir spectrum. The reaction was cooled and a small modified Soxhlet extractor[15] with a thimble containing calcium hydride was added to the system. The reaction mixture was then refluxed with the condensate passing through the CaH_2 on its return to the reaction flask. After 29 hr of reflux, the reaction had apparently stopped. An ir spectrum of the reaction mixture showed two carbonyl absorptions of similar intensity at 1780 and 1730 cm^{-1}.

The reaction mixture was allowed to cool overnight and 9 ml of 1.5 *M* methyllithium in ether was added. After the reaction mixture was stirred at room temperature for 1.75 hr, 25 ml of saturated NaCl was carefully added. The two-phase mixture was separated and the aqueous phase was extracted with ether (two 25-ml portions). The initial dioxane layer and the ether extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to give 750 mg of oil.

This oil was dissolved in 40 ml of acetone containing 4 ml of H_2O, and 8 drops of concentrated HCl was added. The acetone solution was stored at 0°. After 2.5 days, 0.5 g of solid K_2CO_3 was added and the acetone was removed below 25°. The residue was extracted into ether and this ether extract was dried over $MgSO_4$ and evaporated to give 540 mg of oil. An ir spectrum of this oil indicated that complete hydrolysis of the ketal had not occurred. The oil was dissolved in 30 ml of acetone containing 3 ml of H_2O, and 20 drops of concentrated HCl was added. The resulting solution was refluxed on a steam bath for 1.75 hr. After cooling, solid K_2CO_3 was added and the reaction mixture was poured into saturated NaCl. The resulting two-phase mixture was thrice extracted with ether. The ether extracts were combined, washed with saturated NaCl, dried over $MgSO_4$, and evaporated to give 330 mg of oil. This oil was chromatographed on 10 g of Merck alumina packed with benzene. Elution with 60 ml of benzene afforded 140 mg of oil. A vpc of this oil showed it to be a readily separable mixture of (±)-norketoagarofuran (**4**) (65%) and isopropenylbenzene (30%). An analytical sample of **4**, obtained by preparative vpc (6 ft × 0.25 in. 15% SF-96 on Chromosorb W at 170°) gave nmr and ir spectra identical with those published for the levorotatory antipode of **4**:[2] nmr (CCl_4) three singlets at δ 0.83, 1.07, and 1.35; ir (CCl_4) 1718, 1380, 1360, 1110, 1010, and 888 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.66; H, 10.02.

Registry No.—**4**, 35666-91-2; **14**, 35666-92-3; **17**, 35666-93-4; **18**, 35666-94-5; **19**, 35666-95-6; **20**, 35666-96-7; **25**, 35666-97-8; **29**, 35666-98-9; **31**, 35666-99-0; **34**, 35667-00-6; **35**, 35667-01-7; **36**, 35667-02-8; **37**, 35666-03-9; **43**, 35667-04-0.

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