Synthetic Proof for the Structures of Maturinone and Cacalol

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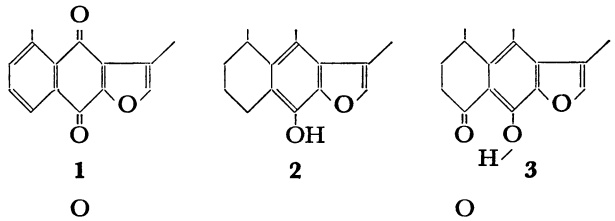
By unambiguous syntheses, the structures of maturinone and cacalol were shown to be 3,5-dimethylnaphtho-[2,3-*b*]furan-4,9-dione (**1**) and 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9-ol (**2**), respectively. 3,8-Dimethylnaphtho[2,3-*b*]furan-4,9-dione (**1a**), an isomer of maturione, was also synthesized.

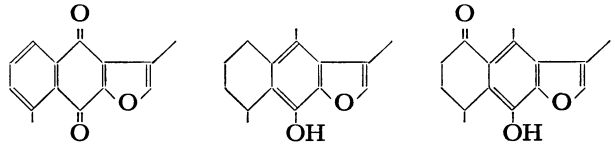
In 1964, Romo and Joseph-Nathan[1] isolated several components, now known as a rearranged eremophilanoid sesquiterpene, from the root of *Cacalia decomposita* A. Gray, a compositae widely distributed in the northern part of Mexico. Maturinone (**1**), cacalol (**2**), and cacalone are the major components. They were initially erroneously assigned as **1a**, **2a**, and **3a**, respectively, using their chemical and spectroscopic data.[2,3] The relations among these three compounds were shown as follows:

maturinone $\xleftarrow[\text{ii) } CrO_3]{\text{i) DDQ}}$ cacalol $\xleftarrow{LiAlH_4}$ cacalone

The alternative possibility of **1**, **2**, and **3** was abandoned chiefly because the characteristic absorption for the 8-hydroxy-1-tetralone moiety (see **3**) in the IR and NMR spectra of cacalone[1] was not recognized.



1 **2** **3**



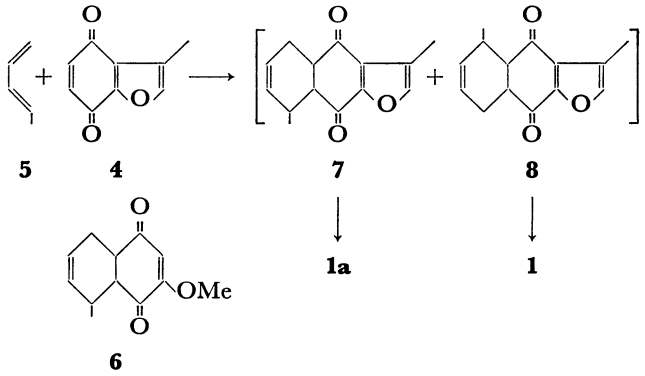
1a **2a** **3a**

In 1969, however, we synthesized both quinones, **1** and **1a**, and established the identity of **1** with maturinone.[4] At the same time, two other groups[5,6] reached the same conclusion by independent syntheses of the quinone **1**. These results required the structures of cacalol and cacalone to be revised as **2** and **3**, respectively, although the latter was pointed out[5] to be inconsistent with the reported spectroscopic data for cacalone. Joseph-Nathan referred to the structure of cacalone and explained the anomalous data by considering the presence of an inherently dissymmetric chromophore (ORD study).[7]

Since then, several Japanese workers[8-10] have reported the isolation of new compounds which belong to this class of sesquiterpene, from various *Cacalia* species. Although we, in collaboration with Romo, reported[4] the relation of cacalol with the known 6-epidecompostin derivative,[11] a recent synthesis of **2**[12] has finally established the structure of cacalol.

The present paper deals with the details of our synthetic works on maturinone (**1**) and cacalol (**2**).

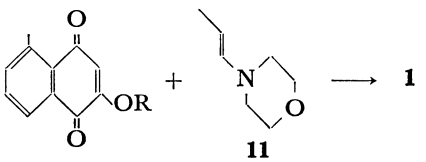
Synthesis of 3,8-Dimethylnaphtho[2,3-b]furan-4,9-dione (1a). In the course of our study on the Diels-Alder reaction of unsymmetrically substituted benzoquinones and dienes, both methoxybenzoquinone and 3-methylbenzofuran-4,7-dione (**4**) were found to exhibit high specificity to 6,6-dimethyl-1-vinylcyclohexene;[13] the orientation phenomena of both quinones were the same, with respect to the oxygen moiety, and were rationalized by considering the radical stabilities of the formal "biradical intermediates."[4,13] Based on the evidence that 1,3-pentadiene (**5**) reacted with methoxybenzoquinone to give mainly **6**,[14] we anticipated that the chief product in the Diels-Alder reaction of **4** and **5** would be **7**; the skeleton initially assumed was for maturinone.



5 **4** **7** **8** **1a** **1** **6**

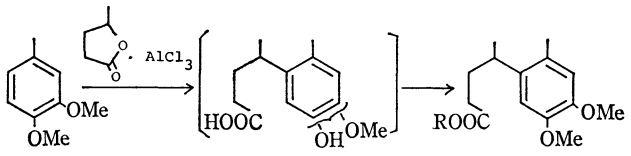
The reaction between **4** and **5** proceeded smoothly at room temperature and the *mixture* was oxidized by air in the presence of potassium hydroxide[15] to give the quinones **1a** and **1** (**1a**/**1**=7: 1) in 77% yield. Repeated recrystallization afforded the pure **1a**, mp 189—190 °C; its spectroscopic properties were very similar to those of maturinone, but distinct differences in the IR spectra were observed in the region of 1200—900 cm^{-1}.

Synthesis of 3,5-Dimethylnaphtho[2,3-b]furan-4,9-dione (1, Maturinone). Treatment[16] of 2-acetoxy-5-methyl-1,4-naphthoquinone (**10**), prepared from **9**[17] by acetylation with acetic anhydride and zinc chloride, with 1-morpholino-1-propene (**11**)[18] in the presence of a small amount of ethanol gave a quinone **1**, mp 164—166 °C, in 12% yield in a one-step reaction. The quinone **1** and maturinone were identical in every aspect.



9 R=H
10 R=Ac
11

Synthesis of 5,6,7,8-Tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-ol (2, Cacalol). The Friedel-Crafts reaction of 3,4-dimethoxytoluene (**12**) with γ-valerolactone in the presence of aluminium chloride gave a mixture **13** of two carboxylic acids, which without separation into each component was successively treated with diazomethane and dimethyl sulfate to afford a single ester **14** in 84% yield.



12 **13** **14** R=Me
15 R=H

The position of the new alkyl group was decided from the following facts. The two singlets which appear at 6.50 and 6.57 ppm in the NMR spectrum of **14** require the two hydrogens on the aromatic nucleus to be positioned para to each other and the pseudocontact shift with Eu-(fod)$_3$ clearly showed that the H_B proton present in **12** disappeared in **14** (Fig. 1). Furthermore, the corresponding acid **15** was converted into the 8-hydroxy-1-tetralone derivative **16**, as shown below.

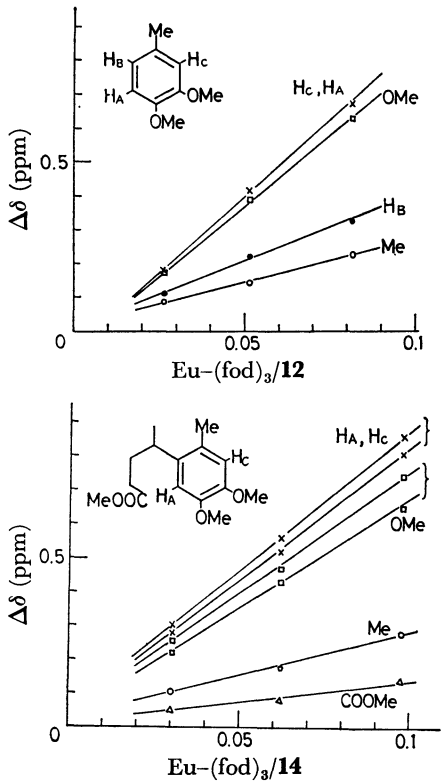
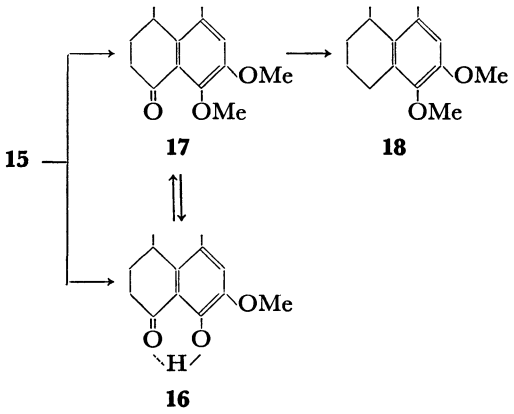


Fig. 1. Pseudocontact shifts of **12** (upper) and **14** (bottom) with Eu-(fod)$_3$ in CCl_4.

The acid **15** was cyclized with polyphosphoric acid at 160 °C to give 4,5-dimethyl-8-hydroxy-7-methoxy-1-tetralone (**16**); the carbonyl absorption at 1630 cm^{-1} in the IR spectrum and a singlet at 12.94 ppm in the NMR spectrum showed that the structure **16** has an 8-hydroxy-1-tetralone moiety. When diphosphorus pentoxide-methanesulfonic acid[19] was used, 7,8-dimethoxy-4,5-dimethyl-1-tetralone (**17**), $\nu_{C=O}$ at 1673 cm^{-1}, was obtained in 87% yield. Both tetralone **16** and **17** were convertible with each other. Catalytic hydrogenolysis of **17** over Pd–C in the presence of perchloric acid resulted in the removal of the carbonyl functional group to give 7,8-dimethoxy-4,5-dimethyltetraline (**18**).



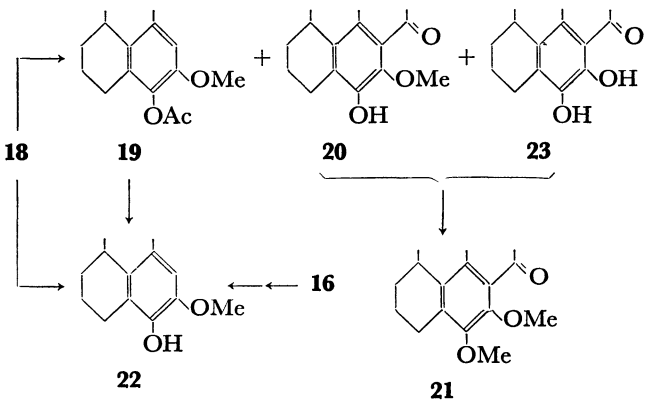
The next step is the introduction of the acetyl group at the remaining position on the aromatic nucleus. Friedel-Crafts acylations using two catalysts were investigated and the results are shown in Table 1.

Table 1. Friedel-Crafts acylation of **18**

Molar ratio **18**: Catalyst: AcCl			Temp (°C)	Time (h)	Yield (isolated %) **18**	**19**	**21**
	$AlCl_3$						
1	2	6	70—75	4		58	22
	$ZnCl_2$						
1	5	10	0—2	41	20	16[b]	55[a]
1	5	10	30	4	15	22[b]	51
1	5	10	70	1/4	11	43[b]	30

a) After methylation with dimethyl sulfate. b) After hydrolysis to **22**.

In the case of aluminium chloride, a complex mixture resulted, and by chromatographic separation the acetate **19** was obtained as the main product, in 58% yield. The residue contained a mixture of acetophenone derivatives **20** and **23**, and after methylation with dimethyl sulfate, the dimethoxyacetophenone **21** was isolated in 22% yield. No aromatic proton was observed in the NMR spectrum of **21**, but the new acetyl protons appeared at 2.07 ppm.



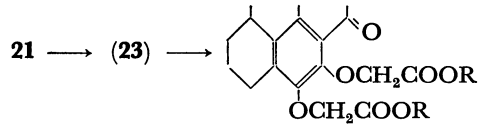
When the reaction was carried out without acetyl

chloride, only a monodemethylated compound **22** was obtained easily. **22** was also derived from the acetate **19** by lithium aluminium hydride reduction.

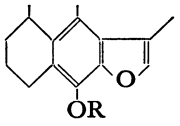
The position of the hydroxyl group in **22** was proved by deriving it from **16** with sodium borohydride reduction, followed by hydrogenolysis over Pd–C. The facile hydrolysis of the 8-methoxyl group in **18** would be explainable as due to a steric factor.[20]

On the other hand, the yield of **21** increased up to 55% when the reaction was done with zinc chloride, a fairly mild catalyst, at 0—2 °C. From Table 1, two points are worthy of notice in the case of zinc chloride. At low temperatures, introduction of the acetyl group on the aromatic nucleus was preferential but, at elevated temperatures, the hydrolysis increased drastically. Secondly, the reaction with zinc chloride differed from that with aluminium chloride in recovering some of the starting material in every case. These indicate that a complex reaction, including an equilibrium[21] between **18** and **21**, is involved in these conditions, but no further studies on these points were made in the present work.

The final step is the conversion of **21** into a furan derivative. As the ajacent methoxyl to the acetyl group was less reactive than the other to aluminium chloride or boron tribromide (see experimental), both methoxyl groups were cleaved with boron tribromide at room temperature to afford a dihydroxy compound **23**, which was subsequently converted into bis(methoxycarbonylmethyl) ether **24**, $\nu_{C=O}$ at 1760, 1740, and 1695 cm^{-1}. The corresponding carboxylic acid **25** was converted under the known process[22] into 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9-yl carboxymethyl ether **26** in good yield. The structure assignment was based on the presence of two signals coupled to each other at 2.38 (br. s, 3H) and 7.27 ppm (m, 1H) in the NMR spectrum, which correspond to the adjacent β-methyl and α-proton groups on a furan nucleus.



24 R=Me
25 R=H



26 R=CH_2COOH
27 R=CH_2CH_2OH
28 R=CH_2CH_2OTs
29 R=CH_2CH_2Br
30 R=Ac

After reduction of **26** with lithium aluminium hydride, removal of the hydroxyethyl group in **27** was achieved[23] by successive treatment with tosyl chloride in pyridine, sodium bromide in dimethyl sulfoxide, and butyllithium in ether to get 5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9-ol (**2**). The alcohol **2**, however, decomposed[24] gradually on storage and failed to crystallize even after purification by chromatography.

When the crude **2** was acetylated, the acetate **30** was obtained as a crystal, mp 119—120 °C, in 71% yield from **27**. The IR and NMR spectra of both **30** and cacalol acetate in carbon tetrachloride were identical in all respects.

On the Structure of Cacalone. Confirmation of the structures of maturinone (**1**) and cacalol (**2**) by unambiguous syntheses requires a reexamination of the structure of cacalone. The structure **3**[4] was only based on the report that cacalone was converted into cacalol (**2**) by lithium aluminium hydride.[1] Its spectroscopic properties, however, are inconsistent with the structure **3**, although Joseph-Nathan explained these anomalies by means of the presence of an inherently dissymmetric chromophore.[7]

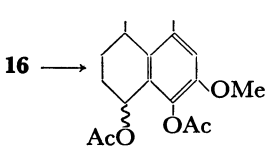
The tetralone **16** prepared in the present work is one of the model compounds for the structure **3**; the lack of the furan ring would cause little effect on the stereochemistry of cacalone. As shown before, the compound **16** showed normal spectroscopic properties for an 8-hydroxy-1-tetralone moiety: a strong chelation between the carbonyl and hydroxyl groups was observed in both IR and NMR spectra. Moreover, when **16** was subjected to react under the Romo's condition (lithium aluminium hydride reduction and subsequent acetylation),[1] no detectable amount of **19** was recognized, but two diacetates **31** and **32** were isolated in 88% yield (the ratio of **31**/**32** was *ca.* 2: 1; see experimental).

From these results, we can safely concluded that cacalone is neither **3** nor **3a** and abandon the former

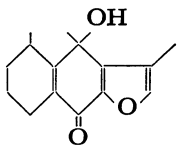
Table 2. Pseudocontact shift on the mixture of **31** and **32**

		δ (ppm) in CCl_4		
		31+**32**	Adn of 0.1 mol eq of Eu–$(fod)_3$	$\Delta\delta$
31	C_4-Me	1.26	1.45[a]	0.19
	C_1-OAc	1.99	3.03	1.04
	C_8-OAc	2.16	2.62	0.46
	C_5-Me	2.40	2.42	0.02
	C_7-OMe	3.83	3.90	0.07
	C_1-H	6.02(m)	7.56(m)	1.54
	C_6-H	6.69	6.88	0.19
32	C_4-Me	1.13	1.25[a]	0.12
	C_1-OAc	1.91	2.96	1.05
	C_8-OAc	2.16	2.56	0.40
	C_5-Me	2.40	2.42	0.02
	C_7-OMe	3.83	3.90	0.07
	C_1-H	6.02(m)	7.56(m)	1.54
	C_6-H	6.69	6.88	0.19

a) The relative intensities of these two signals are 2:1 (**31**:**32**).



31 cis
32 trans



33

proposal[4] for its structure. Recently, the *p*-quinol structure **33** was presented for the structure of cacalone.

Experimental

All melting points were uncorrected. IR and UV spectra were recorded on a Hitachi 215 grating spectrophotometer and a Hitachi EPS-3T spectrophotometer, respectively, and NMR spectra were obtained on a Hitachi H-60 spectrophotometer using TMS as an internal standard. Microanalyses were carried out at the Institute for Physical and Chemical Research.

Diels-Alder Reaction of 3-Methylbenzofuran-4,7-dione (4) and 1,3-Pentadiene (5). A mixture of 260 mg of 3-methylbenzofuran-4,7-dione (**4**)[13] and 350 mg of 1,3-pentadiene (**5**) in 4 ml of ethanol was left overnight. After evaporating the ethanol, the residue was oxidized in ethanol containing potassium hydroxide by bubbling air through the solution.[15] The ether extract, when evaporated, gave yellow solids (314 mg), form which 207 mg of 3,8-dimethylnaphtho[2,3-*b*]-furan-4,9-dione (**1a**) was obtained by recrystallization from chloroform–ethanol.

1a: mp 189—190 °C; IR (KBr): 1670, 1190, 1170, 1100, 1040, 995, and 950 cm^{-1}; UV (EtOH): 251 (log ε=4.34), 267 sh (3.91), 294 (3.56), and 357 nm (3.55); NMR ($CDCl_3$): 2.33 (d, 3H, J=1.5 Hz), 2.79 (s, 3H), 7.4—7.7 (m, 3H), 8.03 ppm (dd, 1H, J=3.5 and 6 Hz); NMR (C_6H_6): 2.03 (br. s, 3H) and 2.68 (s, 3H). Found: C, 74.61; H, 4.40%. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46%.

From the mother liquor, 73 mg more (total yield: 77%) of dimethylnaphtho[2,3-*b*]furan-4,9-diones, **1a** and **1**, were obtained; IR (KBr): 1670, 1190, 1170, 1150, 1100, 1040, 1030, 995, 965, and 950 cm^{-1}; NMR (C_6H_6): 2.03 (br. s, 3H), 2.63 (s, 1.5 H, **1**), and 2.68 ppm (s, 1.5 H, **1a**).

2-Acetoxy-5-methyl-1,4-naphthoquinone (10). A solution of 770 mg of 2-hydroxy-5-methyl-1,4-naphthoquinone (**9**),[17] mp 152—154 °C (dec), and a small amount of zinc chloride in 5 ml of acetic anhydride was left for 30 min at room temperature. The cloudy mixture was heated for several min until the solution became clear and then cooled to room temperature. After pouring the solution into ice–water, the precipitates which formed were collected on a filter paper to give 899 mg (96%) of 2-acetoxy-5-methyl-1,4-naphthoquinone (**10**). Recrystallization from ethanol afforded a pure **10**: mp 119—120 °C. Found: C, 68.09; H, 4.40%. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38%.

3,5-Dimethylnaphtho[2,3-b]furan-4,9-dione (1). A mixture of 100 mg of **10**, 72 mg of 1-morpholino-1-propene (**11**),[18] and 0.05 ml of ethanol was left overnight at room temperature.[16] The whole was chromatographed directly on silicic acid (10 g) and 12 mg (12%) of 3,5-dimethylnaphtho[2,3-*b*]-furan-4,9-dione (**1**) was obtained from the chloroform eluates. Recrystallization from ethanol gave a pure **1**: mp 164—166 °C; IR (KBr): 1670, 1170, 1150, 1110, 1090, 1030, 995, and 965 cm^{-1}; UV (EtOH): 251 (log ε=4.40), 267 sh (4.00), 294 (3.67), and 352 nm (3.67); NMR ($CDCl_3$): 2.35 (d, 3H, J=1.5 Hz), 2.77 (s, 3H), 7.4—7.7 (m, 3H), and 8.10 ppm (dd, 1H, J=3 and 5.5 Hz); NMR (C_6H_6): 2.01 (d, 3H, J=1.5 Hz) and 2.63 ppm (s, 3H). Found: C, 74.22; H, 4.35%. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46%.

The quinone **1** was identical with maturinone in every aspect and melted at 163—165 °C when mixed with maturinone.

From later fractions, 45 mg of orange crystals, mp 178—180 °C (ethanol), were obtained but no characterization was tried.

Friedel-Crafts Reaction of 3,4-Dimethoxytoluene (12) with γ-Valerolactone. To a cold solution of 15 g of 3,4-dimethoxytoluene (**12**) and 4.92 g of γ-valerolactone in 15 ml of tetrachloroethane (TCE), there was added in portions 26.4 g of freshly powdered aluminium chloride. After the addition was complete, the mixture was stirred mechanically at 70 °C for 4 h; 5 ml more of TCE was added and stirring was continued for another 4 h. After standing overnight, the whole was poured into 75 ml of concd hydrochloric acid and 200 g of ice, and was extracted with ether (140 ml×3). A mixture **13** of acidic materials was treated with an excess of ethereal diazomethane followed by dimethyl sulfate to obtain a red oil. Fractional distillation gave 11.03 g (84%) of the ester **14**: bp 157—159 °C/2 Torr; IR (CCl_4): 1730, 1250, 1200, and 1155 cm^{-1}; NMR (CCl_4): 1.17 (d, 3H, J=7 Hz), 2.19 (s, 3H), 3.53 (s, 3H), 3.74 (s with a shoulder at 3.72, 6H), 6.50 (s, 1H), and 6.57 ppm (s, 1H). Found: C, 67.73; H, 8.39%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

Cyclization of the Acid 15 with Polyphosphoric Acid. The ester **14** was hydrolyzed under refluxing in 1 M sodium hydroxide–methanol to give an acid, **15**.

The acid **15** (824 mg) was heated with polyphosphoric acid (prepared from 4 g of diphosphorus pentaoxide and 3.3 ml of phosphoric acid) at 160 °C for 20 min and the mixture was poured into ice–water. Products were taken in ether and the ether layer was washed with water and dried over Na_2SO_4. After removal of the ether, the residual oil was purified through a silica gel column and distilled to give 203 mg (28%) of a yellow 4,5-dimethyl-8-hydroxy-7-methoxy-1-tetralone (**16**): bp 134—136 °C/0.15 Torr. When left in a refrigerator, **16** crystallized and melted at 62—63 °C (pentane); IR ($CHCl_3$): 3540 w, 3320—2600 br, 1630, 1345, and 1265 cm^{-1}; NMR ($CDCl_3$): 1.26 (d, 3H, J=7 Hz), 2.29 (s, 3H), 3.86 (s, 3H), 6.87 (s, 1H), and 12.94 ppm (s, 1H). Found: C, 70.90; H, 7.33%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

Cyclization of the Acid 15 with Diphosphorus Pentaoxide–Methanesulfonic Acid. The acid **15** (1.5 g) was heated at 50—55 °C for 6 h with 25 g of diphosphorus pentaoxide–methanesulfonic acid (1: 10).[19] After cooling, the mixture was poured into ice–water and extracted with ether. The ether layer was washed with water, dil alkaline solution, water, and saline, and dried over Na_2SO_4. Evaporating the solvent gave 2.0 g (87%) of 7,8-dimethoxy-4,5-dimethyl-1-tetralone (**17**): mp 100—103 °C (methanol); IR (KBr): 1673 and 1585 cm^{-1}; NMR ($CDCl_3$): 1.21 (d, 3H, J=7 Hz), 2.33 (s, 3H), 3.85 (s, 3H), and 6.89 ppm (s, 1H). Found: C, 71.62; H, 7.81%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

Methylation of 16. A solution of 60 mg of **16** in 2 ml of acetone was refluxed for 5 h with 480 mg of anhydrous potassium carbonate and 240 mg of dimethyl sulfate. The mixture was poured into water and was extracted with ether. The ether layer was washed with dil sodium hydroxide solution, water, and saline, and was dried over Na_2SO_4. Evaporating off the ether and purifying through a silica gel column gave 47 mg (74%) of **17**.

Action of Aluminium Chloride on 17. To a solution of 500 mg of **17** in 5 ml of dry benzene, 570 mg of aluminium chloride was added at 0 °C and the mixture was stirred for for 3 h at room temperature. The whole was poured into ice–water, 4 ml of 6 M hydrochloric acid was added, and products were taken in ether. The ethereal extract was concentrated, purified through a silica gel column, and recrystallized from pentane to give 355 mg (76%) of **16**.

7,8-Dimethoxy-4,5-dimethyltetralin (18). The tetralone **17** (2.00 g) in 40 ml of acetic acid was hydrogenated over 280 mg of 10% Pd–C in the presence of 0.3 ml of 60% perchloric acid. After 8 h (468 ml of hydrogen consumed), 1 g of anhydrous potassium acetate was added and the catalyst

was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was dissolved in ether, which was washed with water, dil sodium hydroxide, water, and saline, and dried over Na_2SO_4. Evaporating off the solvent and fractional distillation gave 1.65 g (87%) of **18**; bp 145—146 °C/6 Torr; IR ($CHCl_3$): 1590, 1310, and 1120 cm^{-1}; NMR ($CDCl_3$): 1.11 (d, 3H, J=7 Hz), 2.20 (s, 3H), 3.66 (s, 3H), 3.73 (s, 3H), and 6.42 ppm (s, 1H). Found: C, 76.40; H, 9.14%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

Friedel-Crafts Acylation of ***18****.* *A) With Aluminium Chloride*: To a cooled (below −5 °C) solution of 962 mg of **18** and 2.06 g (6 eq) of acetyl chloride in 7 ml of TCE, there was added 1.16 g (2 eq) of aluminium chloride in portions, the mixture was stirred for one hour at room temperature, followed by heating at 70—75 °C for 4 h. The cooled mixture was poured into 200 ml of 6 M hydrochloric acid and 100 g of ice, and products were taken in ether. The ether layer was extracted with 1M sodium hydroxide to obtain acidic materials (mainly of **20** and **23**) and the neutral residue was chromatographed on silica acid. From the benzene eluates, 631 mg (58%) of **19** was obtained. Recrystallization from methanol gave a pure **19**: mp 68—69 °C; IR ($CHCl_3$): 1750, 1600, 1305, and 1115 cm^{-1}; NMR (CCl_4): 1.15 (d, 3H, J=7 Hz), 2.22 (s, 3H), 2.28 (s, 3H), 3.73 (s, 3H), and 6.53 ppm (s, 1H). Found: C, 72.56; H, 8.08%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

The acidic materials were refluxed in 30 ml of acetone with 0.5 ml of dimethyl sulfate in the presence of anhydrous potassium carbonate for 3 h. The mixture was poured into dil ammonia and a product was extracted with ether to give an oil. The oil was chromatographed on alumina (10 g) and 237 mg (22%) of **21** was collected from pentane to 10% benzene–pentane fractions: bp 100—115 °C (bath temp)/2 Torr; IR (CCl_4): 1700, 1320, and 1055 cm^{-1}; NMR (CCl_4): 1.15 (d, 3H, J=7 Hz), 2.07 (s, 3H), 2.38 (s, 3H), 3.75 (s, 3H), and 3.78 ppm (s, 3H). Found: C, 73.00; H, 8.13%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%.

When the acidic materials were directly subjected to chromatography (silicic acid, benzene–ethyl acetate (5: 1)), a monohydroxy compound **20** was obtained in 12% yield: mp 153—154 °C (ether–pentane); IR ($CHCl_3$): 3520, 1690, and 1620 cm^{-1}; NMR (CCl_4): 1.13 (d, 3H, J=7 Hz), 2.24 (s, 3H), 2.50 (s, 3H), 3.74 (s, 3H), and 8.24 ppm (s, 1H, exchangeable with D_2O). Found: C, 72.10; H, 8.08%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

B) With Zinc Chloride. To a cold solution of 220 mg (1 mmol) of **18** and 0.7 ml (10 mmol) of acetyl chloride in 2 ml of TCE, there was added 680 mg (5 mmol) of zinc chloride and the mixture was stirred at 0—2 °C for 41 h. The whole was treated with 4 ml of 6 M hydrochloric acid and was extracted with ether. The ether layer was washed with water, 1 M sodium hydroxide, water, and saline, and was dried over Na_2SO_4. Evaporating the solvent gave an oil, which was chromatographed on silicic acid (5 g). From 20% benzene–hexane eluates, 44 mg (20%) of **18** was recovered; from benzene to chloroform eluates, 193 mg of a mixture of **19** and **21** was obtained. The mixture was refluxed in 2 ml of methanol and 2 ml of 1 M sodium hydroxide for 30 min; 32 mg (16%) of **22** and 141 mg (54%) of **21** were separated from each other by a column chromatography on silicic acid (20% benzene–hexane).

By the same procedure, except for the temperature and time, several reaction were carried out; the results are shown in Table 1. In all cases, the optimal condition was not pursued.

*4,5-Dimethyl-8-hydroxy-7-methoxytetralin (****22****).* A) *From the Tetralone* ***16****.* To a solution of 86 mg of **16** in 2 ml of methanol, sodium borohydride was added until the yellow color disappeared. Dil hydrochloric acid was added, the solvent was evaporated, and the ether extract gave a colorless oil. The oil was hydrogenated under the same condition as **17** (9.5 ml of hydrogen consumed). By a chromatographic separation (silicic acid, benzene), 27 mg (33%) of **22** was obtained as a crystalline form. Recrystallization from pentane afforded a pure **22**: mp 46—48 °C; IR (CCl_4): 3540, 1610, 1480, 1295, and 1120 cm^{-1}; NMR (CCl_4): 1.14 (d, 3H, J=7 Hz), 2.22 (s, 3H), 3.80 (s, 3H), 5.32 (s, 1H, exchangeable with D_2O), and 6.42 ppm (s, 1H). Found: C, 75.58; H, 8.72%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.

B) From the Acetate ***19****:* The acetate **19** was reduced with lithium aluminium hydride under refluxing in dry ether to give **22** quantitatively.

C) From the Tetralin ***18****:* A mixture of 104 mg of **18** and 136 mg (2 eq) of aluminium chloride in 1 ml of TCE was heated at 66 °C for 2 h. About half of **18** was found to have been converted into **22** by VPC analysis (1.5% SE-30, 2.9 m, 170 °C).

Demethylation of ***21*** *and Preparation of the Bis(methoxycarbonylmethyl) Ether* ***24****.* To a solution of 230 mg of **21** in 10 ml of dichloromethane, *ca.* 800 mg of boron tribromide in 2 ml of dichloromethane was dropwise added at −70 °C and the mixture was stirred at room temperature for 2 h. The whole was poured into ether then the ether solution was washed with water and dried over Na_2SO_4. Evaporating the solvent afforded 197 mg of an oil, from which 157 mg (77%) of **23** was obtained by chromatography on silicic acid (15 g) with benzene. **23**; IR (CCl_4): 3540, 1625, and 1295 cm^{-1}; NMR ($CDCl_3$): 1.17 (d, 3H, J=7 Hz), 2.44 (s, 3H), 2.65 (s, 3H), 5.80 (s, 1H, exchangeable with D_2O), and 11.50 ppm (s, 1H, exchangeable with D_2O). This material was used directly in the subsequent reaction without further purification.

When the reaction was carried out with one equivalent of boron tribromide at room temperature for 50 min or with one equivalent of aluminium chloride at room temperature for several hours, the main product was recognized as the monodemethylated compound **20** by IR spectra.

A mixture of 125 mg of **23**, 400 mg of anhydrous-potassium carbonate, and 1 ml of methyl bromoacetate in 6 ml of acetone was refluxed for 2.5 h. Potassium carbonate was removed by filtration, and the filtrate was evaporated. The residue was chromatographed on silicic acid (5 g). From 20% chroform–benzene fractions, 130 mg (65%) of **24** was obtained; mp 89—90 °C (methanol); IR (CCl_4): 1760, 1740, 1695, 1200, and 1075 cm^{-1}; NMR ($CDCl_3$): 1.16 (d, 3H, J=7 Hz), 2.16 (s, 3H), 2.55 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.55 (s, 2H), and 4.63 ppm (s, 2H). Found: C, 63.38; H, 6.97%. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93%.

*5,6,7,8-Tetrahydro-3, 4, 5-trimethylnaphtho[2,3-b]furan-9-yl Carboxymethyl Ether (****26****).* A solution of 132 mg of **24** in 3 ml of methanol and 3 ml of 1 M sodium hydroxide was refluxed under nitrogen for one hour. The whole was acidified with dil hydrochlocic acid and was extracted with ether. After evaporating the ether, crystals (**25**: IR (CCl_4): 3300—2500 br, 1740, 1725, and 1700 cm^{-1}) were dried in a dessicator over diphosphorus pentaoxide and were heated under reflux with 300 mg of sodium acetate and 3 ml of acetic anhydride for 2 h.[22] The mixture was poured into ice–water and products were taken in ether. Evaporating the solvent gave a solid **26** (100 mg); the compound was difficult to recrystallize. **26**: mp 168—169 °C (acetone–hexane); NMR ($CDCl_3$): 1.18 (d, 3H, J=7 Hz), 2.38 (br. s, 3H), 2.54 (s, 3H), 4.96 (br. s, 2H), 7.27 (m, 1H), and 9.45 (br. s, 1H). Found: C, 70.28; H, 7.04%. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99%.

5,6,7,8-Tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-yl 2-Hydroxyethyl Ether (27). A solution of 110 mg of the acid **26** in 15 ml of dry ether was refluxed with lithium aluminium hydride for one hour. The excess lithium aluminium hydride was decomposed with the addition of ethyl acetate and the mixture was poured into dil hydrochloric acid. The ether extract was evaporated to give 105 mg of a crude alcohol, **27**. Recrystallization from pentane afforded a pure **27**: mp 78—79 °C; IR (CCl_4): 3580, 1335, and 1110 cm^{-1}; NMR (CCl_4): 1.16 (d, 3H, J=7 Hz), 2.18 (s, 1H, –OH), 2.38 (d, 3H, J=1.5 Hz), 2.52 (s, 3H), 3.80 (m, 2H), 4.30 (m, 2H), and 7.20 ppm (m, 1H). Found: C, 74.35; H, 8.17%. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

5,6,7,8-Tetrahydro-3,4,5-trimethylnaphtho[2,3-b]furan-9-yl Acetate (30). To a solution of 50 mg of **27** in 0.3 ml of pyridine, there was added 50 mg of tosyl chloride in 0.3 ml of pyridine at 0 °C; the mixture was left at −6 °C for 17 h. According to Johnson's procedure,[23b] a crude tosylate **28** was isolated as an oil (72 mg). Without purification, **28** was stirred for 94 h with 300 mg of sodium bromide in 2 ml of dimethyl sulfoxide. The product was taken in ether and 45 mg of a bromide **29** was obtained as an oil by chromatography on silicic acid (3 g). **29**: IR (CCl_4): 1605, 1333, and 1110 cm^{-1}; NMR (CCl_4): 1.16 (d, 3H, J=7 Hz), 2.38 (d, 3H, J=1.5 Hz), 2.51 (s, 3H), 3.58 (t, 2H, J=7 Hz), 4.56 (t, 2H, J=7 Hz), and 7.20 ppm (m, 1H).

To a cooled solution of 45 mg of **29** in 2 ml of dry ether, 0.6 ml of 15% butyllithium–hexane solution was added dropwise and the mixture was stirred at room temperature for 10 min.[23a] Aqueous ammonium chloride was added and the ether extract, when evaporated, gave an oily **2** (39 mg) which showed one spot on TLC.

The oily **2** was left overnight with 0.6 ml of acetic anhydride and 1 ml of pyridine. Working up as usual afforded crystals (36 mg, 71% from **27**). Recrystallization from acetone–hexane gave the acetate **30**: mp 119—120 °C; IR (CCl_4): 1760, 1200, 1190, and 1110 cm^{-1}; NMR (CCl_4): 1.18 (d, 3H, J=7 Hz), 2.30 (s, 3H), 2.35 (d, 3H, J=1.5 Hz), 2.53 (s, 3H), and 7.15 ppm (m, 1H). Found: C, 74.79; H, 7.40%. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%.

Lithium Aluminium Hydride Reduction of the Tetralone 16. According to the Romo's condition,[1] a solution of 53 mg of **16** in 5 ml of dry ether was treated with excess lithium aluminium hydride under reflux for one hour. Working up as usual gave an oil, which was acetylated with acetic anhydride in pyridine to give an oily mixture. The NMR spectrum of the mixture showed no detectable amount of **19** being formed. By a chromatographic separation on silicic acid (3 g), 65 mg (88%) of a mixture of *cis*-1,8-diacetoxy-4,5-dimethyl-7-methoxytetralin (**31**) and *trans*-1,8-diacetoxy-4,5-dimethyl-7-methoxytetralin (**32**) was obtained. The stereochemistry of both acetates was based on the pseudocontact shift with Eu-(fod)$_3$ (see Table 2). The ratio of **31**/**32** was *ca.* 2: 1.

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