Tetrahedron Vol. 36, pp. 3361 to 3366
Pergamon Press Ltd., 1980. Printed in Great Britain

MARASMIC ACID—I

TOTAL SYNTHESIS OF (±)-ISOMARASMIC ACID

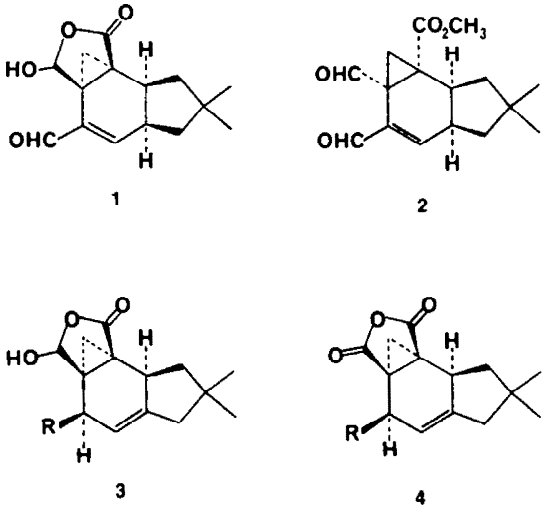
W. J. GREENLEE* and R. B. WOODWARD ✠
Department of Chemistry, Harvard University, Cambridge, MA 02138, U.S.A.

(*Received in U.S.A. 22 October* 1979)

Marasmic acid was first reported by Kavanaugh, *et al.* during a general survey of the constituents of *Basidiomycetes* (true mushrooms) having antibacterial activity.[1] This substance, isolated as a crystalline solid from *Marasmius conigenus*, showed marked activity against *Staphyloccocus aureus* and slight activity against *Escherichia coli.* Marasmic acid was partially characterized, but because its antibacterial activity diminished rapidly in blood, and due to its high toxicity, was not further investigated. In 1965, de Mayo *et al.* reported the re-isolation of marasmic acid and established the correct empirical formula, $C_{15}H_{18}O_4$.[2] On the basis of spectral data and several chemical transformations and correlations, the structure **1** was assigned. A final point of uncertainty, the stereochemistry of the ring fusion, was established by Chadwick and Sim by an X-ray crystal structure of a derivative of the natural product.[3]

Although marasmic acid has been the object of two synthetic studies, no total synthesis had been reported at the beginning of our work.[4] In their work, de Mayo *et al.* obtained methyl isomarasmate (**2**), which differs from the natural product in the stereochemistry of the polycyclic ring system.[5] During the course of our work, Wilson and Turner reported studies in which a Diels–Alder reaction was utilized for construction of the hydrindane ring system, and described an intermediate thought to possess the skeleton of marasmic acid.[6] Our own, independently conceived, work on the Diels–Alder approach to marasmic acid has led to the first total systhesis of the molecule (see accompanying paper), as well as to synthesis of methyl isomarasmate (**2**), previously obtained by de Mayo.[5] This latter work is described here.

In devising a synthetic route to marasmic acid, we first focused our attention on the cyclohexene ring, about which four chiral centers of the molecule are arranged. Such a grouping of four adjacent *cis*-oriented substituents about a cyclohexene ring is often constructed by Diels–Alder reaction of an (*E,E*)-1,4-dissubstituted diene with an appropriate dienophile. Such a reaction appeared applicable to preparation of a hypothetical synthetic precursor **3** (R = protected aldehyde) of marasmic acid.† The similarity of the lactol function of marasmic acid to a cyclic anhydride suggested a selective reduction of anhydride **4** as a simple approach to **3**. An efficient route to **4** using dimethyl acetylenedicarboxylate as a dienophile was envisioned (Fig. 1). The expected adduct **5** might be cyclopropanated by addition of diazomethane followed by photolysis of the resulting pyrazoline(s). Saponification of **6**, followed by dehydration, would then provide anhydride **4**.



With this synthetic route in mind, our first task was synthesis of the diene component, namely diene aldehyde **9** or a protected derivative thereof. A logical precursor of **9** was aldehyde **7**, a facile synthesis of which has been reported by Magnusson and Thoren.[7] Treatment of **7** with triethylorthoformate and a catalytic amount of *p*-toluene-sulfonic acid in ethanol (24 hr) afforded the diethyl acetal **8** in 95% yield. The acetal was allowed to react with ethyl vinyl ether and anhydrous zinc chloride in ethyl acetate[8] (24 hr, room temp) and the resulting ethoxy acetal, without isolation, was subjected to the action of sodium acetate in aqueous acetic acid (90°, 4 hr), affording diene aldehyde **9** in 93% yield. Treatment of **9** with trimethyl orthoformate in methanol containing a catalytic amount of ammonium nitrate furnished dimethyl acetal **10** in 86% yield.

Diels–Alder reaction of **10** with dimethyl acetylenedicarboxylate was quite slow (110°, 8 days), but adduct **11** was formed in high yield. Support for the structure assigned was provided by the UV spectrum (95% C_2H_5OH) showing $\lambda_{max} = 278$ ($\epsilon = 860$) and by conversion of **11** to aromatic derivative **12** upon treatment with dichlorodicyanobenzoquinone in refluxing benzene (60% yield).

The 1,3-dipolar addition of diazomethane to unsaturated esters has been extensively investigated and

*NSF Predoctoral Fellow, 1972–1975. Present Address, Merck Sharp and Dohme Research Laboratories, Merck and Co., Inc., Rahway, NJ 07065, U.S.A.

✠Deceased, July 8, 1979.

†The assumption that the *cis* ring fusion would be produced upon migration of the double bond of **3** into conjugation with the aldehyde was supported by the observed hydrolysis of diacetate **i** (prepared from the natural product) to marasmic acid.[2]

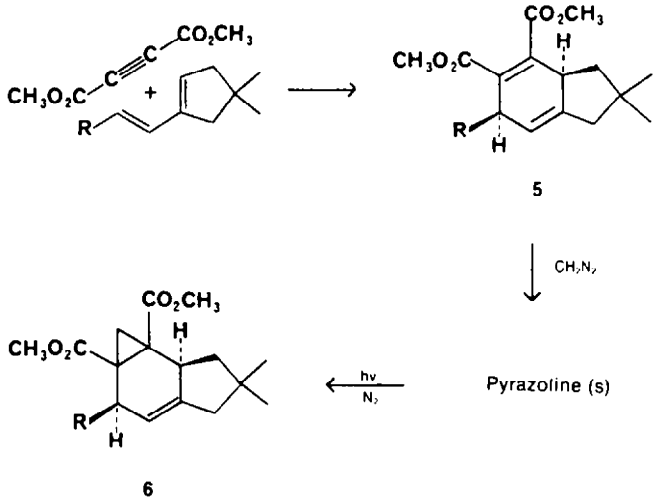
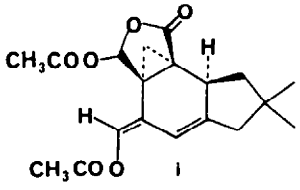
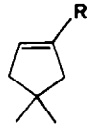
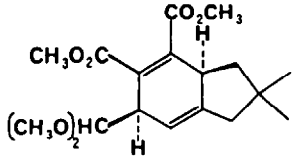


Fig. 1.



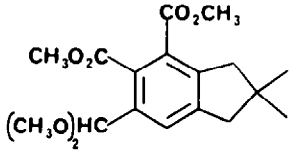


7: CHO
8: $CH(OCH_2CH_3)_2$
9: CH=CHCHO
10: $CH=CHCH(OCH_3)_2$



found quite sensitive to steric effects.[9] Examination of a model of **11** led us to conclude that approach of diazomethane to the activated olefin should occur predominantly from the side opposite the substituents at the adjacent C atoms, and thus lead mainly to pyrazolines **13** and **14** (although formation of pyrazolines **15** and **16** in detectable amounts seemed probable). Since pyrazolines produce cyclopropanes stereospecifically on photolysis,[10] **13** and **14** would furnish **17**, possessing the desired *cis* relationship of the cyclopropane ring relative to the adjacent hydrogen at the ring fusion.

When adduct **11** was placed in contact with a sixfold excess of ethereal diazomethane, a 4:1 mixture of two pyrazolines formed during 14 days. These two produced the identical cyclopropane in high yield when photolyzed in ether solution through a Pyrex filter, demonstrating that they were derived from exclusive addition of diazomethane to one side of **11**. Based on our steric arguments, we supposed the cyclopropane to have the stereochemistry represented by structure **17**, and our subsequent work was based on this belief. However, further chemical transformations established that our cyclopropane possessed the stereochemistry depicted by structure **18**. Although an explanation for the exclusive addition to what appears to be the more-hindered side of **11** is not readily available, our results place in doubt the assignment of the marasmic acid skeleton to the similar cyclopropane obtained by Wilson and Turner,[6] also *via* a pyrazoline.†‡



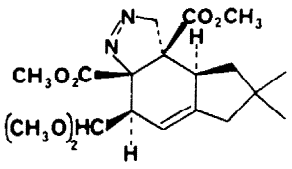
Saponification of **18** with sodium hydroxide in aqueous methanol (90°, 48 hr) provided diacid **19** as a white foam in 97% yield. The diacid, without purification, was warmed with acetic anhydride (55°, 30 min) affording anhydride **20** in 96% yield.

Believing that we had in hand the proposed anhydride precursor **4** ($R=-CH(OMe)_2$) of marasmic acid, we sought an efficient method for its conversion to lactol **21**. Among the reported methods for reduction of cyclic anhydrides to lactols,[12] only that using disodium tetracarbonylferrate (Collman's reagent) as reductant[13] produced lactols from anhydride **20**. It was hoped that the acetal moiety might serve as a directing group,§ leading to predominant formation of the desired lactol **21**. Instead, a 1:1 mixture of lactols **21** and **22** was

†The stereochemical deductions of Wilson and Turner were in the main based upon steric arguments which paralleled our own during the planning stages of our work, and which we regard as reasonable even now. Consequently, the fact that the pertinent reactions follow the opposite course from that independently predicted by both groups poses a theoretical problem of much interest.

‡Wilson and Turner obtained a single pyrazoline which they believed should have the structure **ii**; some support for this structure was subsequently put forward on the basis of NMR studies with an lanthanide shift reagent;[11] it now appears that the assumptions underlying these arguments should be re-examined.

§Disodium tetracarbonylferrate forms a stable complex with dioxane (available from Alfa Inorganics).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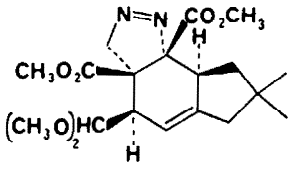
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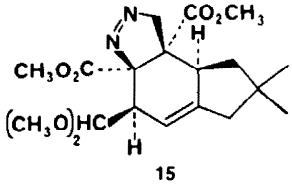
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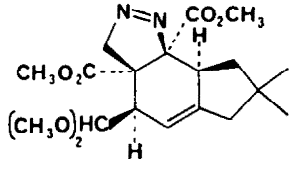
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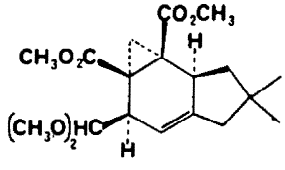
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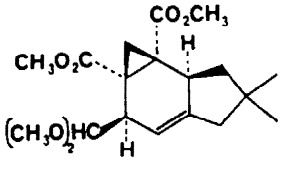
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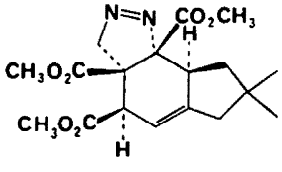

ii

produced, accompanied by a small amount of lactone **23**. Although **23** could be isolated from the mixture by chromatography on silica gel, the lactols were more conveniently separated after conversion to lactol acetates **24** and **25** by treatment of the crude mixture with acetic anhydride (90°, 2 hr). Separation by chromatography on silica gel provided **24** and **25** in 35% overall yield. Pure lactol **21** was obtained by saponification of **24** with potassium carbonate in wet methanol (95% yield).

The structures of the lactols, their acetates and of lactone **23** were assigned by inspection of the NMR spectra. For each of the reduction products listed in Table 1 except for lactol **21** and its acetate **24**, the appearance of the acetal function resembles that of the starting anhydride **20**. The larger coupling constant for **21** and **24**, as well as the upfield shift, suggested that reduction had occurred at the near side of the anhydride.

Although hydrolysis of the acetal moiety of **21** proved troublesome, exposure of **21** to THF—10% aqueous HCl (1:1) for 3 hr afforded an α,β-unsaturated aldehyde in 35–40% yield. Similarities of this substance to the natural product were seen in the UV spectrum (95% EtOH) which showed $\lambda_{max} = 237$ ($\epsilon = 10{,}100$), the IR spectrum which confirmed the presence of lactol (3400, 1700 cm^{-1}) and unsaturated aldehyde (2720, 1670, 1630 cm^{-1})

Table 1. NMR spectra ($CDCl_3$)

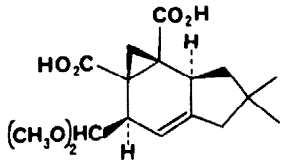
	$-CH(OCH_3)_2$	J	$-CH(OCH_3)_2$	
20	4.67 δ	3 Hz	3.45, 3.47	δ
22	4.65	3	3.46	3.46
23	4.87	2	3.51	3.51
25	4.86	2	3.54	3.56
21	4.14	7	3.40	3.44
24	4.11	8	3.40	3.44

moieties, and the combustion analysis. However, the synthetic material was clearly *not* marasmic acid. The IR and proton NMR spectra of the synthetic material and that of marasmic acid from natural sources† showed obvious differences, the most striking being in the chemical shifts of the respective vinyl protons; 6.85δ (J = 4. Hz) for the synthetic material contrasted to 6.57δ (J = 2.5 Hz) for the natural product. Structure **26**, that of isomarasmic acid, was thus assigned to the synthetic material. Finally, treatment of **26** with ethereal diazomethane afforded methyl isomarasmate (**2**) identical by IR, proton NMR, and UV spectra† to that prepared by de Mayo, *et al.* by a different route.[5]

EXPERIMENTAL

M.ps unless otherwise stated were taken on a Kofler hot-stage apparatus and are uncorrected as are all b.ps. Mass spectra were recorded on an AEI MS-9 double-focusing instrument at 70 eV. NMR spectra were obtained using Varian HA-100 and XL-100 instruments. IR spectra were measured on Perkin–Elmer 137 and 457A instruments. UV spectra were taken on a Cary model 14 spectrophotometer. Elemental analysis were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark, or by Midwest Microlabs, Indianapolis, Indiana. Ac_2O was distilled from NaOAc, and $ZnCl_2$ was fused three times at 330° (0.1 mm) before use.

†We wish to thank Dr. P. de Mayo for a sample of marasmic acid from natural sources and for copies of his IR and proton NMR spectra of methyl isomarasmate.



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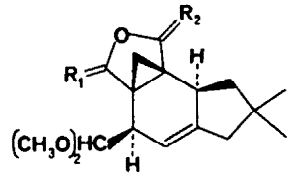
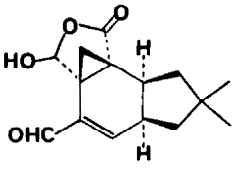


	R_1	$=R_2$
20:	$=O$	$=O$
21:	H, OH	$=O$
22:	$=O$	H, OH
23:	O	H, H
24:	H, OAc	$=O$
25:	$=O$	H, OAc



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4,4-Dimethylcyclopentene-1-carboxaldehyde diethyl acetal (**8**). To aldehyde **7**[7] (34.8 g, 0.280 mol) were added triethyl orthoformate (52.3 g, 0.353 mol), abs EtOH (20 ml) and a few crystals of *p*-toluenesulfonic acid monohydrate. The mixture was allowed to stand for 19 hr, then diluted with ether (250 ml), washed twice with sat $NaHCO_3$ aq and once with brine and dried (Na_2CO_3). Evaporation, and distillation of the residue gave 44.7 g (0.201 mol, 72%) of **8**, b.p. 74.5–75.5°. (Found: C, 72.40; H, 11.40. Calc. for $C_{12}H_{22}O_2$: C, 72.68, H, 11.18). IR (film) 1650, 1200–1000 cm^{-1}. NMR ($CDCl_3$) 1.08 (6H, s), 1.20 (6H, t, J = 7), 2.14 (4H, s), 3.2–3.8 (4H, m), 4.84 (1H, broad s), 5.58 (1H, broad s). MS *m/e* 198 (M^+).

(E)-3-(4,4-Dimethylcyclopentenyl) propenal (**9**). To acetal **8** (17.0 g, 76.5 mmol) was added 0.40 ml of a 10% soln of anhyd $ZnCl_2$ in dry EtOAc. The soln was stirred briefly, and then 6.0 ml of the $ZnCl_2$ soln and 7.70 ml (5.82 g, 80.6 mmol) of ethyl vinyl ether were added simultaneously over 30 min. Stirring was continued for 20 hr and then a mixture consisting of NaOAc (6.1 g), AcOH (61 ml) and water (4.3 ml) was added. The resulting soln was heated at 90° for 4 hr. The cooled mixture was diluted with water (200 ml) and extracted with petroleum ether (b.p. 30–60°, 4 × 100 ml). The combined organic portions were washed twice with water, twice with sat $NaHCO_3$ aq and once with brine, then dried (Na_2SO_4) and concentrated. Distillation gave 9.96 g (66.3 mmol, 87%) of **9**, b.p. 68–69° (1 mm). IR (film) 2680, 1670, 1620, 1580 cm^{-1}. UV (95% C_2H_5OH) 283 nm (18,100). NMR ($CDCl_3$) 1.14 (6H, s), 2.30 (4H, s), 5.81 (1H, d of d, J = 7, 15), 7.09 (1H, d, J = 15), 6.08 (1H, broad s), 9.39 (1H, d, J = 7). (Found: C, 63.77; H, 8.05; N, 20.23. Calc. as semicarbazone, m.p. 191.5–192°, $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27). MS *m/e* 150 (M^+).

(E)-3-(4,4-Dimethylcyclopentenyl) propenal dimethyl acetal (**10**). Aldehyde **9** (8.02 g, 53.2 mmol), trimethylorthoformate (7.36 g, 69.4 mmol), MeOH (2.8 ml), and ammonium nitrate (100 mg) were combined and stirred under N_2 for 24 hr. The mixture was diluted with ether (125 ml), washed with sat $NaHCO_3$ aq and brine, dried (Na_2CO_3), and concentrated. Distillation gave 8.99 g (46.0 mmol, 86%) of **10**, b.p. 75–75.5° (0.8 mm). (Found: C, 73.15; H, 10.51. Calc. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27). IR (film) 3010, 1660, 1610 cm^{-1}. UV (95% C_2H_5OH) 235 nm (23,600). NMR ($CDCl_3$) 1.10 (6H, s), 2.20 (4H, broad s), 3.17 (6H, s), 4.71 (1H, d, J = 5), 5.12 (1H, d of d, J = 5, 15), 6.34 (1H, d, J = 15), 5.52 (1H, broad s). MS *m/e* 196 (M^+).

2,3-Dicarbomethoxy-8,8-dimethylbicyclo[4,3,0]nona-2,5-diene-4-carboxaldehyde dimethyl acetal (**11**). Acetal **10** (13.0 g, 66.3 mmol) and freshly-distilled dimethyl acetylenedicarboxylate (9.42 g, 66.3 mmol) were combined and sealed under vacuum in two thick-walled glass tubes. The tubes were heated for 8 days at 110°, then cooled and opened. Tlc of the viscous yellow syrup (silica gel, 1:1 hexane: ether) showed adduct (R_f 0.5) and a very small impurity spot (R_f 0.9). IR (film) 1730, 1630 cm^{-1}. UV (95% C_2H_5OH) 278 nm (850). NMR ($CDCl_3$) 1.00 (3H, s), 1.11 (3H, s), 3.32 (3H, s), 3.35 (3H, s), 3.72 (3H, s), 3.75 (3H, s), 4.31 (1H, d, J = 5), 5.4 (1H, broad s).

4,5-Dicarbomethoxy-2,2-dimethyl-2,3-dihydroindene-6-carboxaldehyde dimethyl acetal (**12**). Adduct **11** (66.3 mg, 0.196 mmol) was treated with dichlorodicyanobenzoquinone (56.7 mg, 0.250 mmol) in refluxing benzene (4.0 ml) for 3 hr. The mixture was diluted with CH_2Cl_2 (25 ml) and passed through a short column (1 × 5 cm) of basic alumina (Woelm, activity I). Evaporation gave a milky-white oil (46.7 mg) which was purified by preparative tlc on silica gel (65:35 hexane:ether) affording 39.3 mg (0.117 mmol, 59%) of **12**, m.p. 60–63°. Four recrystallizations from hexane gave the analytical sample, m.p. 65.5–67°. (Found: C, 63.99; H, 7.27. Calc. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19). IR (KBr) 1740, 1730 cm^{-1}. UV (95% C_2H_5OH) 289 nm (2420). NMR (CCl_4) 1.14 (6H, s), 2.70 (2H, broad s), 2.86 (2H, broad s), 3.14 (6H, s), 3.71 (3H, s), 3.74 (3H, s), 5.48 (1H, s), 7.40 (1H, s). MS *m/e* 336 (M^+).

2,6-Dicarbomethoxy-11,11-dimethyl-4,5-diazatricyclo[7,3,0,0^{2,6}]dodeca-4,8-diene-7-carboxaldehyde dimethyl acetal (**15**) *and 2,6-dicarbomethoxy-11,11-dimethyl-3,4-diazatricyclo[7,3,0,0^{2,6}]dodeca-3,8-diene-7-carboxaldehyde dimethyl acetal* (**16**). The viscous adduct **11** (22.4 g; from above) was dissolved in ether (250 ml) and 0.53 mol freshly-distilled ethereal diazomethane (0.50 M; dried over KOH pellets) was added. The soln was allowed to stand in the dark for 7 days. Then the remaining diazomethane was removed in a stream of N_2, and the soln was evaporated to a thick, yellow syrup. After re-treatment with 0.26 mol of ethereal diazomethane (0.51 M), excess reagent and ether were removed as before, giving a viscous yellow syrup (25.8 g). A portion of the crude mixture (4.02 g) was placed onto a column (2.7 × 90 cm) of silica gel (Woelm, activity I, 200 g) slurry-packed in 3:1 hexane:ether. Elution with the same solvent gave **15** (1.80 g, 4.75 mmol) as a colorless oil. Elution was continued with 1:1 hexane:ether, giving **16** (0.575 g, 1.51 mmol) as a light-yellow solid, m.p. 112.5–117.5°. Pyrazoline **15** was purified for analysis by preparative tlc on silica gel (1:1 hexane:ether), then dried at 55° (0.05 mm) for 24 hr (Found: C, 60.01; H, 7.42; N, 7.00. Calc. for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36). IR (film) 1750, 1570 cm^{-1}. UV (95% C_2H_5OH) 323 nm (422). NMR (CCl_4) 1.00 (3H, s), 1.13 (3H, s), 3.20 (3H, s), 3.23 (3H, s), 3.54 (3H, s), 3.57 (3H, s), 4.12 (1H, d, J = 7), 4.72 (2H, AB, J_{AB} = 20, δ_{AB} = 62), 5.3 (1H, broad s). Pyrazoline **16** was recrystallized twice from hexane–acetone, giving a sample, m.p. 117–118°. Found: C, 60.06; H, 7.41; N, 7.48. IR (KBr) 1740, 1570 cm^{-1}. UV (95% C_2H_5OH) 320 nm (288). NMR ($CDCl_3$) 0.93 (3H, s), 1.10 (3H, s), 3.38 (3H, s), 3.54 (3H, s), 3.63 (3H, s), 3.74 (3H, s), 4.51 (2H, AB, J_{AB} = 18, δ_{AB} = 92), 4.90 (1H, d, J = 8), 5.4 (1H, m).

1,9-Dicarbomethoxy-4,4-dimethylbicyclo[7,1,0,0^{2,6}]dec-6-ene-8-carboxaldehyde dimethyl acetal (**18**). The remaining crude pyrazoline mixture (21.7 g) from above was divided into three equal portions, each of which was dissolved in anhyd ether (4.3 l), degassed with dry N_2, and photolyzed with a Hanovia 450-watt lamp (Pyrex filter) for 10 hr. The three portions were combined and evaporated, giving 19.8 g of crude cyclopropane as

a thick, yellow syrup. This was placed onto a column (4.5 × 100 cm) of silica gel (Woelm, activity 1, 350 g) slurry-packed in 3:1 hexane:ether. Elution with hexane–ether mixtures gave 11.8 g (33.4 mmol) of **18** as a white solid (60% yield from **10**, based on pyrazolines not set aside). Recrystallization from hexane gave 8.02 g of white flakes, m.p. 77–79°, which was used in the next step. Five recrystallizations from hexane gave the analytical sample, m.p. 78.5–79.5°. (Found: C, 64.78; H, 7.96. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01). IR (KBr) 1740, 1730 cm^{-1}. NMR ($CDCl_3$) 1.03 (3H, s), 1.06 (3H, s), 3.40 (3H, s), 3.41 (3H, s), 3.71 (6H, s), 4.17 (1H, d, J = 6), 5.3 (1H, broad s). MS *m/e* 352 (M^+).

1,9 - *Dicarboxy* - 4,4 - *dimethyltricyclo*[7,1,0,$0^{2,6}$]*dec* - 6 - *ene* - 8 - *carboxaldehyde dimethyl acetal* (**19**). The soln formed by combining cyclopropane **18** (2.46 g, 7.00 mmol) with 70 ml of 3N NaOH and 70 ml MeOH was heated under N_2 at 90° for 47 hr. The mixture was diluted with water (150 ml), and ether (250 ml) was layered over the aqueous soln. The mixture was cooled (ice bath) and acidified with 1N HCl (210 ml). The layers were separated, and the aqueous layer was extracted with ether (2 × 100 ml). The combined ether portions were washed immediately with brine, dried (Na_2SO_4) and concentrated, giving 2.20 g (6.80 mmol, 97%) of **19** as a white foam. IR (KBr) 3500–2500, 1720 cm^{-1}. NMR ($CDCl_3$) 1.04 (3H, s), 1.08 (3H, s), 3.42 (3H, s), 3.44 (3H, s), 4.23 (1H, d, J = 6), 5.35 (1H, m), 8.5–8.9 (2H, broad). MS *m/e* 324 (M^+).

4,4-*Dimethyl*-10,12-*dioxo*-11-*oxatetracyclo*[7,3,1,0,$0^{2,6}$]*tridec*-6-*ene*-8-*carboxaldehyde dimethyl acetal* (**20**). A soln of **19** (2.20 g, 6.80 mmol) in Ac_2O (60 ml) was stirred at 55° for 30 min. Solvent was removed under reduced pressure, giving 2.00 g (6.53 mmol, 96%) of **20**, m.p. 101.5–104.5°. Four recrystallizations from hexane gave the analytical sample, m.p. 106.5–107.5°. (Found: C, 66.39; H, 7.26. Calc. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24). IR (KBr) 1860, 1780 cm^{-1}. NMR ($CDCl_3$) 1.03 (3H, s), 1.07 (3H, s), 1.70 (2H, AB, J_{AB} = 5, δ_{AB} = 16), 3.45 (3H, s), 3.47 (3H, s), 4.67 (1H, d, J = 3), 5.3 (1H, m). MS *m/e* 306 (M^+).

4,4 - *Dimethyl* - 10 - *hydroxy* - 12 - *oxo* - 11 - *oxatetracyclo*[7,3,1,0,$0^{2,6}$]*tridec* - 6 - *ene* - 8 - *carboxaldehyde dimethyl acetal* (**21**), 4,4 - *dimethyl* - 12 - *hydroxy* - 10 - *oxo* - 11 - *oxatetracyclo*[7,3,1,0,$0^{2,6}$]*tridec* - 6 - *ene* - 8 - *carboxaldehyde dimethyl acetal* (**22**), and 4,4 - *dimethyl* - 10 - *oxo* - 11 - *oxatetracyclo*[7,3,1,0,$0^{2,6}$]*tridec* - 6 - *ene* - 8 - *carboxaldehyde dimethyl acetal* (**23**). Disodium tetracarbonylferrate dioxanate (6.50 g, 18.8 mmol) was transferred under N_2 to a flask to which were added dry THF (55 ml) and then a soln of **20** (2.53 g, 8.27 mmol) in dry THF (50 ml). The mixture was stirred for 5 hr, then quenched with glacial AcOH (2 ml). After concentration and dilution with 2N HCl (100 ml), the mixture was extracted with ether (5 × 60 ml). The combined ether portions were then extracted with 5% $NaHCO_3$ aq (10 × 25 ml). Ether (250 ml) was layered over the combined bicarbonate portions, and 2N HCl (100 ml) was added with ice cooling. The layers were separated, and the aqueous layer extracted with ether (5 × 50 ml). The combined ether portions were washed with brine, dried (Na_2SO_4), and concentrated, giving 1.78 g of a light brown foam. This was placed onto a column (2.5 × 48 cm) of silica gel (Woelm, activity 1, 120 g), slurry-packed in 3:2 hexane:ether. Elution with the same solvent gave 121 mg (0.415 mmol, 5.0%) of **23** as a white solid. Further elution with 1:1 hexane:ether gave 1.01 g (3.28 mmol, 40%) of **21** and **22** (1:1 mixture). Two recrystallizations of **23** from hexane gave a sample, m.p. 103.5–104.5°. (Found: C, 69.91; H, 8.22. Calc. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27). IR (KBr) 1775 cm^{-1}. NMR ($CDCl_3$) 0.92 (1H, 1/2 of AB, J_{AB} = 5), 1.03 (6H, s), 3.51 (6H, s), 4.26 (2H, ABX, J_{AB} = 9, δ_{AB} = 22, J_{AX} = 1, J_{BX} = 0), 4.87 (1H, d, J = 2), 5.4 (1H, m).

Lactol acetate **24** and *lactol acetate* **25**. Anhydride **20** (1.00 g, 3.24 mmol) was treated as described above with disodium tetracarbonylferrate dioxanate (2.53 g, 7.32 mmol) in dry THF (55 ml). The mixture was worked up as before, and the resulting white foam (0.887 g) was warmed with Ac_2O (50 ml) at 90° for 2 hr. Removal of solvent under reduced pressure gave a white foam (0.866 g). Tlc on silica gel (1:1 hexane:ether) showed lactol acetates **24** and **25** (R_f 0.3 and 0.4) and lactone **23** (R_f 0.15). The mixture was placed onto a column (2.5 × 50 cm) of silica gel (Woelm, activity 1, 100 g), slurry-packed in 10:1 hexane:ether. Elution with the same solvent gave 178 mg of **25** (white solid). Elution with 5:1 hexane:ether gave 181 mg of **24** (white solid). The combined yield was thus 359 mg (1.03 mmol, 31% overall yield from **20**). Lactone **23** (still on the column) was not isolated in this case. Four recrystallizations of **24** from hexane gave the analytical sample, m.p. 115–116.5°. (Found: C, 65.18; H, 7.58. Calc. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48). IR (KBr) 1780, 1760 cm^{-1}. NMR ($CDCl_3$) 1.08 (2H, AB, J_{AB} = 6, δ_{AB} = 28), 1.06 (3H, s), 1.10 (3H, s), 2.16 (3H, s), 3.40 (3H, s), 3.44 (3H, s), 4.11 (1H, d, J = 8), 5.2 (1H, m), 6.52 (1H, s). Four recrystallizations of **25** from hexane gave a sample, m.p. 125–128.5°. Found: C, 65.08; H, 7.54. IR (KBr) 1775, 1760 cm^{-1}. NMR ($CDCl_3$) 1.04 (3H, s), 1.06 (3H, s), 2.10 (3H, s), 3.54 (3H, s), 3.56 (3H, s), 4.86 (1H, d, J = 2), 5.4 (1H, m), 6.48 (1H, s).

Lactol **21** *by saponification of lactol acetate* **24**. A soln of **24** (143 mg, 0.409 mmol) and K_2CO_3 (270 mg, 6 equiv) in MeOH (12 ml) was stirred under N_2 for 5 hr. The mixture was concentrated under reduced pressure, diluted with 1N H_2SO_4 (15 ml), and extracted with ether (3 × 10 ml). The combined ether portions were dried (Na_2SO_4) and concentrated, giving 119 mg (0.386 mmol, 95%) of **21**, m.p. 88.5–91°. Two recrystallizations from hexane-methyl acetate gave a sample, m.p. 96–99°. IR (film) 3350, 1770 cm^{-1}. NMR ($CDCl_3$) 1.01 (3H, s), 1.07 (3H, s), 3.40 (3H, s), 3.44 (3H, s), 4.14 (1H, d, J = 7), 4.7–5.1 (1H, broad), 5.2 (1H, m), 5.6–6.0 (1H, broad). MS *m/e* 308 (M^+).

Isomarasmic acid (**26**). Lactol **21** (404 mg, 1.31 mmol) was combined with THF (12.5 ml) and 10% HCl (12.5 ml), and the resulting soln was stirred under argon for 3 hr. The mixture was diluted with brine (50 ml) and extracted with ether (3 × 50 ml). The combined ether portions were washed once with brine, dried ($MgSO_4$) and concentrated, giving 330 mg of crude isomarasmic acid as a light-yellow oil. Purification on a column (1 × 35 cm) of silica gel (Woelm, activity 1, 35 g) with 1:1 hexane:ether as eluant provided 113.5 mg (0.434 mmol, 33%) of isomarasmic acid as a white solid. Two recrystallizations from hexane-methyl acetate gave the analytical sample, m.p. 140–144°. (Found: C, 68.36; H, 6.85. Calc. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92). IR (KBr) 3400, 2720, 1770, 1670, 1630 cm^{-1}. UV (95% C_2H_5OH) 237 nm (10,100). NMR ($CDCl_3$) 1.07 (3H, s), 1.10 (3H, s), 4.0–4.5 (1H, broad), 6.12 (1H, s), 6.85 (1H, d, J = 4), 9.53 (1H, s). MS Calc. for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1236.

Methyl isomarasmate (**2**). To a soln of isomarasmic acid (3.0 mg, 0.012 mmol) in CH_2Cl_2 (1 ml) was added an excess of ethereal diazomethane. After 2 min, solvent was removed and the light yellow oil was purified by preparative tlc on silica gel (1:3 hexane:ether), giving 2.7 mg methyl isomarasmate as a colorless oil. IR (CCl_4) 1740 (shoulder), 1718, 1690, 1640 cm^{-1}. UV (CH_3OH) 236 nm (5, 650). NMR ($CDCl_3$) 1.06 (3H, s), 1.08 (3H, s), 1.70 (2H, AB, J_{AB} = 5, δ_{AB} = 82), 3.68 (3H, s), 6.85 (1H, d, J = 2), 9.47 (1H, s), 9.62 (1H, s).

Acknowledgement—This work was generously supported by the National Institutes of Health through grant 5R01 GM 04229-22.

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