Synthesis of (±)-Marasmic Acid via 1-Oxaspirohexane Rearrangement

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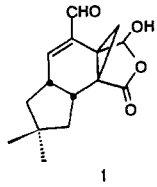
Abstract: A formal total synthesis of marasmic acid (**1**), an antimicrobial sesquiterpene, has been achieved in a stereoselective manner from known enone **9**. The initial key step involves stereo- and regioselective photocycloaddition of allene to enone **8**. The most important strategic transformation in this synthesis is the acid-catalyzed rearrangement of 1-oxaspirohexane **7** to lactone **6** having a norcarane skeleton with an appendage suitable for further manipulation. Finally, Sharpless allylic oxidation followed by Swern oxidation of hydroxy ester **24** provided a route to methyl marasmate (**5**).

Marasmic acid (**1**), a biologically active sesquiterpene, was first isolated from *Marasmius conigenus* by Kavanagh et al. in 1949,[1] and its structure was assigned by de Mayo et al. in 1965.[2] It showed marked activity against *Staphyloccocus aureus* and slight activity against *Esherichia coli*.[1] A closely related member of marasmane-type sesquiterpene, isovelleral (**2**), displayed anti-



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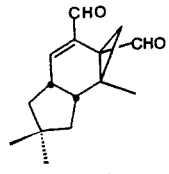

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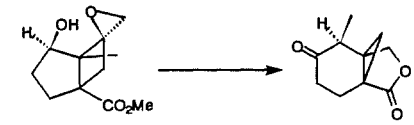
microbial and antifeedant activities and has been shown to be a key constituent of the chemical defence system of some fungi.[3] Moreover, both **1** and **2** were found recently to possess strong mutagenic activity in the *Salmonella*/microsome assay.[4] The α,β-unsaturated dialdehyde functionality masked as the lactol form in the case of **1** is presumed to be responsible for these activities. These marasmane sesquiterpenes have unique tricyclic carbon frameworks composed of fused 5-6-3-membered rings. The central feature of the structure of **1** is the norcarane (bicyclo-[4.1.0]heptane) skeleton with three contiguous oxygen-containing appendages. In view of its biological activities and unique structure, it has been the target of synthetic studies,[5,6] and two total syntheses have been accomplished by the groups of Woodward[6a,b] and Boeckman.[6c] Both of these syntheses took advantage of an intermolecular Diels-Alder reaction or its intramolecular version as the key synthetic strategy by which the central six-membered ring was constructed.[6] Herein we disclose our own approach to the formal synthesis of this target, **1**, based on the acid-catalyzed rearrangement of 1-oxaspirohexane derivatives developed in our laboratory.

As part of studies on natural product synthesis by 1-oxaspirohexane rearrangement, we reported that acid-catalyzed rearrangement of endo,endo hydroxy epoxides such as **3** gave through cyclobutyl-cyclopropylcarbinyl transformation norcarane derivative **4** with functional groups suitable for further manipulation.[7]



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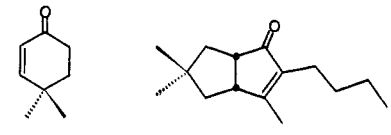
We envisaged that this technique could be applicable to the efficient synthesis of marasmane-type sesquiterpenes including marasmic acid (**1**) as shown in Scheme I. Thus, lactone **6**, which would be obtained from oxirane **7** by the above-mentioned rearrangement, could be transformed to methyl marasmate (**5**),[2,6c] a synthetic precursor of marasmic acid (**1**), by oxidation of a methyl group and the lactone ring. Oxirane **7** would be derived stereoselectively from enone **8** via a [2 + 2] photocycloaddition protocol.

Results and Discussion

The synthesis of **5** begins with the preparation of enone **8**. Toward this end, known β-methyl-substituted enone **9**, readily obtained from 4,4-dimethylcyclohexenone **13**[8] according to Fro-



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borg et al.,[9] was converted to α,β-dimethyl-substituted enone **11** through the protocol described by Smith[10] (Scheme II).[11] Thus, bromination-dehydrobromination of **9** followed by ketalization gave bromoketal **10** in 91% yield. Bromoketal **10** was treated with *sec*-butyllithium followed by methyl iodide, and the subsequent hydrolytic workup gave enone **11** in 90% isolated yield. The use of *sec*-butyllithium instead of *n*-butyllithium for the halogen-metal exchange process is essential to perform this conversion efficiently

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(2) Dugan, J. J.; de Mayo, P.; Nisbet, M.; Anchel, M. *J. Am. Chem. Soc.* **1965**, *87*, 2768.
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(4) Sterner, O.; Carter, R. E.; Nilsson, L. M. *Mutat. Res.* **1987**, *188*, 169.
(5) (a) Helmlinger, D.; de Mayo, P.; Nye, M.; Westfelt, L.; Yeats, R. B. *Tetrahedron Lett.* **1970**, 349. (b) Wilson, S. R.; Turner, R. B. *J. Org. Chem.* **1973**, *38*, 2870. (c) Morisaki, N.; Furukawa, J.; Nozoe, S.; Itai, A.; Iitaka, Y. *Chem. Pharm. Bull.* **1980**, *28*, 500.
(6) (a) Woodward, R. B.; Greenlee, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 6075. (b) Woodward, R. B.; Greenlee, W. J. *Tetrahedron* **1980**, *36*, 3367. (c) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.
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(8) (a) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399. (b) Paquette, L. A.; Farkas, E.; Galemmo, R. *J. Org. Chem.* **1981**, *46*, 5434.
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(10) (a) Smith, A. B., III; Branca, S. J.; Pitla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (b) Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth.* **1983**, *61*, 65.
(11) We also tried several other methods to prepare **11**; however, the procedure described in the text turned out to be best with regard to overall yield and suitability for large-scale preparations. For example, treatment of **9** with [(dimethylphenyl)silyl]lithium in the presence of copper(I) iodide[12] followed by addition of methyl iodide and the subsequent elimination with copper(II) bromide[12] afforded **11** in 45% overall yield. Although this procedure can be done in two steps, it is more laborious on large scale than Smith's method.
(12) (a) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520. (b) Engel, W.; Fleming, I.; Smithers, R. H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1637.

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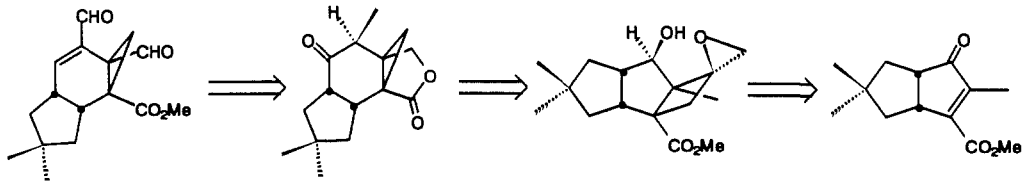
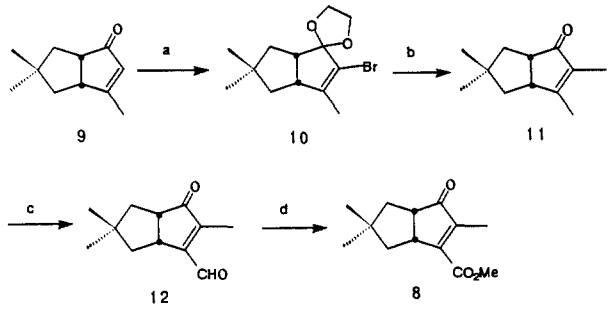
Scheme I



5 6 7 8

Scheme II[a]



9 10 11 12 8

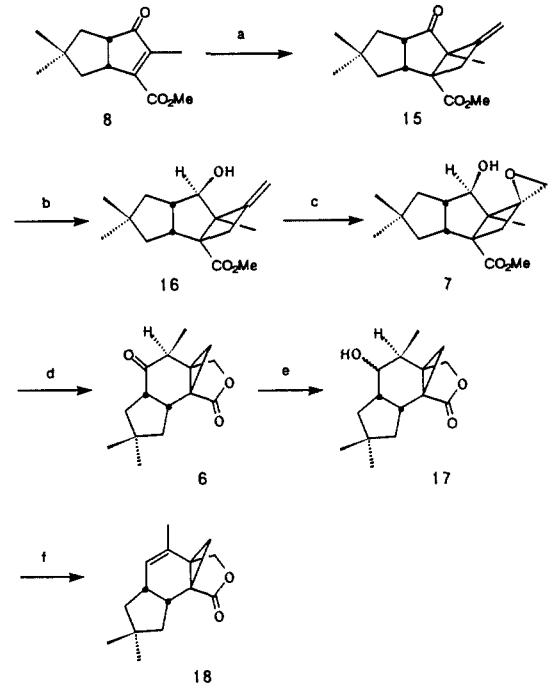
[a] (a) (i) Br_2, CCl_4, then Et_3N; (ii) $HOCH_2CH_2OH$, TsOH, C_6H_6. (b) *s*-BuLi, MeI, HMPA, THF, then HCl. (c) SeO_2, bromobenzene. (d) (i) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, *t*-BuOH; (ii) MeOH, H_2SO_4, $ClCH_2CH_2Cl$.

since *n*-butyl-substituted enone **14** was formed along with **11** in the latter case. Selective oxidation of the β-methyl group was achieved with selenium dioxide in refluxing bromobenzene to give aldehyde **12** in 68% yield. Oxidation of **12** with sodium chlorite[13] followed by esterification provided enone **8** in 86% yield.

With enone **8** in hand, we carried out the [2 + 2] photocycloaddition. Irradiation of **8** with a large excess of allene in dichloromethane at −78 °C gave head to head photoadduct **15** as the major product (91% selectivity) in 73% yield (Scheme III). The stereochemistry of **15** was assumed on the basis of the approach of allene from the less hindered side of **8** and was finally established by completion of the synthesis of **5** from **15**. Whether the minor product differs in stereo- or regiochemistry from **15** is not confirmed. Transformation of **15** to epoxide **7**, the substrate for the acid-catalyzed rearrangement, was carried out without difficulty in a highly stereoselective manner. Sodium borohydride reduction of **15** afforded alcohol **16** as the single product in 98% yield. The stereochemistry of the hydroxyl group was assumed to be endo with respect to the bicyclo[3.2.0] subunit on the basis of the vicinal coupling constant[14] (^3J = 9.8 Hz) and the stereoselectivity observed in the subsequent epoxidation. Treatment of **16** with *m*-chloroperbenzoic acid buffered with disodium hydrogen phosphate yielded endo,endo hydroxy epoxide **7** as the sole product in 89% yield. The stereochemical assignment of the epoxide group was done by the chemical shift difference of the epoxy methylene protons[15] ($\Delta\delta$ = 0.15 ppm).

Now the stage was set for acid-catalyzed rearrangement of **7**, the key transformation in this synthesis. As expected, when **7** was treated with concentrated sulfuric acid in dichloromethane at room temperature, the rearrangement proceeded smoothly to give lactone **6** in good yield (80%).[16] The stereochemistry of the key methyl group of **6** was assumed to be endo with respect to the norcarane skeleton on the basis of mechanistic considerations. Reduction of the carbonyl with sodium borohydride gave a mixture of alcohols **17** (9:1 ratio) which was dehydrated with methanesulfonyl chloride in pyridine–dimethylformamide to afford olefin

Scheme III[a]

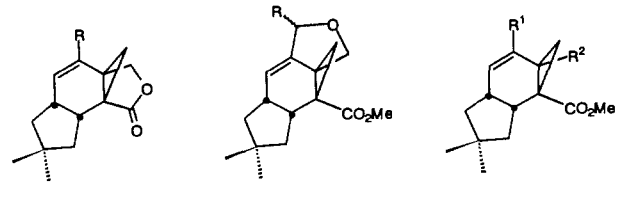


8 15 16 7 6 17 18

[a] (a) *hν*, allene, CH_2Cl_2, −78 °C. (b) $NaBH_4$, MeOH. (c) MCPBA, Na_2HPO_4, CH_2Cl_2. (d) H_2SO_4, CH_2Cl_2. (e) $NaBH_4$, MeOH. (f) MsCl, pyridine, DMF.

18 as the major product in 87% yield for the two steps.

Completion of the synthesis of methyl marasmate (**5**) required an allylic oxidation as well as oxidation of the lactone methylene of **18** to generate the three contiguous oxygenated functionalities of **5**. We planned to pursue this transformation through two routes: oxidation of the methyl followed by lactone cleavage or lactone hydrolysis followed by methyl oxidation. Previous syntheses of **1**[6a,b] as well as the related molecules[17] suggested that the introduction of an α,β-unsaturated dialdehyde functionality would meet with difficulty because of a pronounced tendency towards ring formation between these positions during oxidative functional group transformations. In any event, although we focused our attention to avoid such cyclization, we were successful only in the latter route. First, allylic oxidation of **18** was carried out with selenium dioxide in refluxing ethanol to give aldehyde **19** in 50% yield. For the purpose of protecting the formyl group



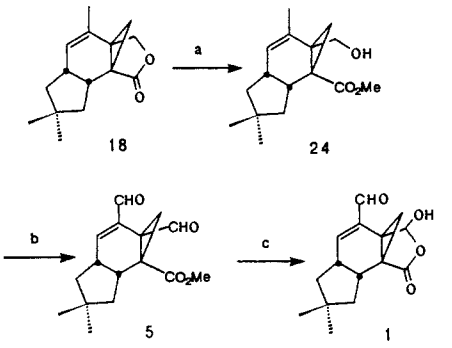
19 R=CHO
20 R=CH_2OH
21 R=$CH(OMe)_2$

22 R=H
23 R=OMe

25 R^1=Me, R^2=CHO
26 R^1=R^2=CH_2OH

(13) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(14) Tobe, Y.; Doi, A.; Kimura, K.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 639.
(15) Tobe, Y.; Kishida, T.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 1437.
(16) A small amount (<5%) of an isomer of **6** with opposite stereochemistry of the methyl group was also obtained.
(17) (a) Nakata, T.; Akita, H.; Naito, T.; Oishi, T. *J. Am. Chem. Soc.* **1979**, *101*, 4400. (b) Kimura, A.; Isoe, S. *Abstracts of Papers*, 22nd Symposium on the Chemistry of Natural Products, Japan; 1979; p 198.

Scheme IV[a]



[a](a) NaOH, H_2O, MeOH. (b) (i) TBHP, SeO_2, CH_2Cl_2; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −60 °C, then Et_3N. (c) Reference 6c.

from cyclization, **19** was converted to either allylic alcohol **20** ($NaBH_4$, $CeCl_3 \cdot 7H_2O$,[18] 94%) or acetal **21** [$(MeO)_3CH$, $YbCl_3 \cdot 6H_2O$,[19] 95%).[20] To our dismay, hydrolysis of **20** and **21** with methanolic aqueous sodium hydroxide followed by esterification with diazomethane gave cyclized products, ether **22** (71%) and acetal **23** (94%), respectively, as the major products. Since this route was thus hampered by cyclization during hydrolysis of the lactone ring, our effort was now concentrated on the second route (Scheme IV). Hydrolysis of **18** gave hydroxy ester **24** (90%), and subsequent Swern oxidation[21] afforded aldehyde **25** in 93% yield. However, all attempts to oxidize the methyl group resulted in the formation of complex mixtures which did not contain the desired methyl marasmate (**5**). This observation combined with successful oxidation of lactone **18** to aldehyde **19** suggested that the allylic oxidation is sensitive to the oxidation level of the neighboring angular substituent. In order to solve the final obstacle, we chose conditions under which allyl alcohol rather than allylic aldehyde would be produced. Thus, oxidation of **24** under the conditions reported by Sharpless et al.[22] gave a mixture of products containing diol **26**, which was not isolated because of its lability. Swern oxidation[21] of the crude products of the above reaction provided methyl marasmate (**5**) in 19% isolated yield for the two steps, which was spectroscopically identical with the authentic sample provided by Professors de Mayo and Boeckman. Since demethylation of **5** has been reported to give marasmic acid (**1**) in 50% yield,[6c] a formal total synthesis of **1** has thus been achieved.

In summary, the total synthesis of methyl marasmate (**5**) has been accomplished with excellent stereoselectivity in 15 steps from known enone **9**. It is worth noting that the acid-catalyzed rearrangement of the 1-oxaspirohexane derivative played the crucial role in the construction of the marasmane skeleton and demonstrated the utility of skeletal transformations in natural product synthesis.

Experimental Section[23]

3-Bromo-2,2-(ethylenedioxy)-4,7,7-trimethylbicyclo[3.3.0]oct-3-ene (10). To a solution of 2.90 g (18.0 mmol) of enone **9**[9] in 10 mL of CCl_4 at 0 °C was added 3.1 g (20 mmol) of bromine in 10 mL of CCl_4. The mixture was stirred for 4 h at 0 °C, treated with 2.70 g (27 mmol) of triethylamine, allowed to warm to room temperature, stirred for 2 h, and then filtered. The filtrate was diluted with CCl_4, washed with 10% HCl, saturated $NaHCO_3$, and brine, dried with $MgSO_4$, and evaporated. Chromatography on silica gel (elution with petroleum ether/ether, 9:1) gave 4.30 g (98%) of 3-bromo-4,7,7-trimethylbicyclo[3.3.0]oct-3-en-2-one: ^1H NMR ($CDCl_3$) δ 3.32 (dd, J = 7.8, 15.6 Hz, 1 H), 3.04 (ddd, J = 7.3, 7.3, 9.7 Hz, 1 H), 2.12 (s, 3 H), 1.89–1.80 (m, 2 H), 1.45 (dd, J = 7.8, 12.2 Hz, 1 H), 1.24 (dd, J = 7.3, 12.2 Hz, 1 H), 1.03 (s, 3 H), 1.00 (s, 3 H); IR (neat) 1700, 1600, 950 cm^{-1}; MS m/e (rel intensity) 244, 242 (M^+, 87), 198 (88), 196 (90), 95 (100). Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.66; H, 6.31; Br, 32.65.

A mixture of 12.9 g (53.1 mmol) of the above enone, 14 mL of ethylene glycol, and 1.02 g (5.3 mmol) of *p*-toluenesulfonic acid monohydrate in 110 mL of benzene was heated at reflux with continuous removal of water with a Dean-Stark trap for 3 days. The mixture was diluted with water, and the organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (elution with petroleum ether/ether, 97:3) to give 8.67 g (93% based on recovered starting material) of enone **10** and 5.07 g (elution with petroleum ether/ether, 9:1) of recovered starting material. **10**: mp 65–66 °C (recrystallized from petroleum ether); ^1H NMR ($CDCl_3$) δ 4.18–4.09 (m, 2 H), 3.93–3.80 (m, 2 H), 3.08 (dd, J = 8.8, 17.1 Hz, 1 H), 2.77 (dd, J = 8.8, 17.1 Hz, 1 H), 1.73 (d, J = 1.0 Hz, 3 H), 1.66 (ddd, J = 1.9, 8.8, 12.2 Hz, 1 H), 1.58 (dd, J = 9.8, 12.7 Hz, 1 H), 1.46 (ddd, J = 2.0, 8.8, 12.7 Hz, 1 H), 1.12 (dd, J = 8.8, 12.2 Hz, 1 H), 1.05 (s, 3 H), 0.94 (s, 3 H); IR (KBr) 1200, 1060 cm^{-1}; MS m/e (rel intensity) 288, 286 (M^+, 33), 207 (100). Anal. Calcd for $C_{13}H_{19}O_2Br$: C, 54.36; H, 6.67; Br, 27.83. Found: C, 54.34; H, 6.64; Br, 27.61.

3,4,7,7-Tetramethylbicyclo[3.3.0]oct-3-en-2-one (11). To a solution of 7.90 g (27.5 mmol) of **10** in 160 mL of THF at −78 °C was added dropwise 36 mL of 1.3 M *sec*-butyllithium (47 mmol) in hexane during 15 min. The mixture was stirred for 10 min; a mixture of 46.7 g (0.33 mol) of methyl iodide and 13.5 mL (80 mmol) of HMPA was added during 10 min and stirred for 1.5 h before 50 mL of 10% HCl was added. The mixture was warmed to room temperature and extracted with ether. The extract was dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on silica gel (elution with petroleum ether/ether, 9:1) to give 4.36 g (90%) of **11** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.17 (br t, J = ca. 12 Hz, 1 H), 2.88 (ddd, J = 6.8, 7.3, 9.8 Hz, 1 H), 1.97 (s, 3 H), 1.82–1.72 (m, 2 H), 1.63 (d, J = 1.0 Hz, 3 H), 1.38 (dd, J = 7.3, 12.7 Hz, 1 H), 1.16 (dd, J = 7.3, 12.7 Hz, 1 H), 1.01 (s, 3 H), 0.95 (s, 3 H); IR (neat) 1695, 1640, 1320 cm^{-1}; MS m/e (rel intensity) 178 (M^+, 100), 164 (53), 123 (79). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.20.

A similar reaction with *n*-butyllithium gave **11** (30%) along with enone **14** (12%): ^1H NMR ($CDCl_3$) δ 3.17 (q, J = 7.3 Hz, 1 H), 2.89 (ddd, J = 6.6, 7.3, 13.9 Hz, 1 H), 2.11 (t, J = 6.6 Hz, 2 H), 1.97 (s, 3 H), 1.97–1.73 (m, 2 H), 1.40 (dd, J = 5.9, 12.5 Hz, 1 H), 1.35–1.24 (m, 4 H), 1.16 (dd, J = 7.3, 12.5 Hz, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.89 (t, J = 7.3 Hz, 3 H); IR (neat) 1700, 1640, 1385 cm^{-1}; MS m/e (rel intensity) 220 (M^+, 45). 205 (51), 178 (100), 122 (49).

4-Formyl-3,7,7-trimethylbicyclo[3.3.0]oct-3-en-2-one (12). A mixture of 6.00 g (33.7 mmol) of **11** and 6.0 g (54 mmol) of SeO_2 in 300 mL of bromobenzene was heated at reflux for 6 h. The mixture was diluted with water, filtered through Celite, and extracted with ether. The extract was dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by chromatography on silica gel (elution with petroleum ether/ether, 85:15) to give 4.40 g (68%) of **12**: ^1H NMR ($CDCl_3$) δ 10.38 (s, 1 H), 3.58–3.53 (m, 1 H), 3.03 (ddd, J = 7.1, 7.1, 9.9 Hz, 1 H), 2.09 (d, J = 2.2 Hz, 3 H), 1.98 (ddd, J = 1.6, 8.8, 13.2 Hz, 1 H), 1.86 (ddd, J = 2.2, 9.9, 13.2 Hz, 1 H), 1.43 (dd, J = 7.7, 13.2 Hz, 1 H), 1.12 (dd, J = 7.7, 13.2 Hz, 1 H), 1.02 (s, 3 H), 0.95 (s, 3 H); IR (neat) 1695, 1670, 1160 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 42), 178 (44), 163 (28), 122 (100).

4-(Methoxycarbonyl)-3,7,7-trimethylbicyclo[3.3.0]oct-3-en-2-one (8). To a solution of 5.70 g (29.7 mmol) of **12** and 165 mL of 2-methyl-2-butene in 620 mL of *tert*-butyl alcohol was added a mixture of 24.7 g (0.27 mol) of sodium chlorite and 32.1 g (0.21 mol) of $NaH_2PO_4 \cdot 2H_2O$ in 250 mL of water during 50 min, and the solution was stirred for 1.5 h. Most of the *tert*-butyl alcohol was evaporated, and the residue was diluted with water and washed with ether. The aqueous layer was acidified with HCl and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to give 4-carboxy-3,7,7-trimethylbicyclo[3.3.0]oct-3-en-2-one as a white solid. A small quantity of this material was recrystallized for analysis from acetone: mp 169–171 °C; IR (KBr) 3600–2400, 1715, 1675, 1630, 1220 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.71.

A mixture of the above crude acid, 3.7 mL of methanol, and 0.1 mL of H_2SO_4 in 65 mL of 1,2-dichloroethane was heated at reflux for 22 h. The mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography of the crude product on silica gel (elution with petroleum ether/ether,

(18) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(19) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.
(20) Acetalization of **19** was only successful under $YbCl_3$ catalysis. Other catalysts (NH_4NO_3, *p*-toluenesulfonic acid, $CeCl_3 \cdot 7H_2O$) were not effective.
(21) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
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(23) ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL JNM-GX-400 spectrometer, and mass spectra were taken on a JEOL JMS-DX303 or Hitachi RMU-6E spectrometer; the instruments belong to the Faculty of Engineering, Osaka University. IR spectra were recorded on a Hitachi 260-10 spectrometer. Column chromatography was performed with Wako C-200 silica gel and flash chromatography with Merck silica gel 60 (7729).

9:1) gave 5.68 g (86% from **12**) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.56–3.45 (m, 1 H), 3.02–2.95 (m, 1 H), 1.99 (d, J = 1.5 Hz, 3 H), 1.92 (dd, J = 9.3, 13.2 Hz, 1 H), 1.84 (t, J = 12.7 Hz, 1 H), 1.44 (dd, J = 7.3, 12.7 Hz, 1 H), 1.21 (dd, J = 7.8, 13.2 Hz, 1 H), 1.03 (s, 3 H), 0.97 (s, 3 H); IR (neat) 1705, 1620, 1210 cm^{-1}; MS m/e (rel intensity) 222 (M$^+$, 100), 217 (33), 163 (36), 134 (36). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.93; H, 8.18.

Photocycloaddition of Enone 8. A solution of 2.52 g (11.4 mmol) of **8** and 28 mL of allene in 50 mL of CH_2Cl_2 at −78 °C was irradiated in a Pyrex vessel with a 500-W high-pressure mercury lamp for 3 h. Allene and the solvent were evaporated, and the residue was chromatographed on silica gel (elution with petroleum ether/ether, 97:3) to give 2.38 g (80%) of a difficulty separable mixture (10:1) of **15** and its isomer. An analytical sample of **15** was obtained by preparative GLC: ^{1}H NMR ($CDCl_3$) δ 4.95 (ddd, J = 1.0, 3.0, 3.0 Hz, 1 H), 4.85 (ddd, J = 1.0, 2.9, 2.9 Hz, 1 H), 3.73 (s, 3 H), 3.38 (dd, J = 2.5, 2.9, 17.1 Hz, 1 H), 3.24–3.18 (m, 1 H), 2.97–2.92 (m, 1 H), 2.88 (ddd, J = 2.4, 2.4, 17.1 Hz, 1 H), 1.82 (dd, J = 4.4, 13.7 Hz, 1 H), 1.75 (ddd, J = 1.5, 9.3, 13.7 Hz, 1 H), 1.49 (dd, J = 6.4, 13.2 Hz, 1 H), 1.37 (s, 3 H), 1.02 (s, 3 H), 0.98 (t, J = 13.2 Hz, 1 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 216.7 (s), 173.1 (s), 145.2 (s), 167.6 (t), 63.0 (s), 51.2 (q), 50.8 (s), 50.6 (d), 48.9 (d), 44.5 (t), 40.9 (t), 39.7 (t), 39.2 (s), 29.5 (q), 28.7 (q), 16.8 (q); IR (neat) 1720, 1650, 880 cm^{-1}; MS m/e (rel intensity) 262 (M$^+$, 74), 203 (60), 175 (100). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.01; H, 8.47.

Hydride Reduction of 15. To a solution of 7.70 g (29.4 mmol) of a mixture of **15** and its isomer (10:1) in 380 mL of methanol was added 3.37 g (91.3 mmol) of sodium borohydride in portions. The mixture was stirred for 4 h before 3% HCl was added. Most of methanol was evaporated, and the residue was diluted with water, extracted with ether, dried ($MgSO_4$), and evaporated. Chromatography of the crude product on silica gel (elution with petroleum ether/ether, 9:1) gave 6.84 g (98% from **15** contained in the starting material) of **16** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.96 (t, J = 2.9 Hz, 1 H), 4.94 (t, J = 2.9 Hz, 1 H), 3.70 (s, 3 H), 3.62 (d, J = 9.8 Hz, 1 H), 3.27 (ddd, J = 2.4, 2.9, 17.1 Hz, 1 H), 2.54 (ddd, J = 2.4, 2.9, 17.1 Hz, 1 H), 2.51 (dd, J = 7.8, 11.7 Hz, 1 H), 2.36–2.29 (m, 1 H), 1.75 (dd, J = 7.8, 13.6 Hz, 1 H), 1.67 (dd, J = 2.3, 13.6 Hz, 1 H), 1.56 (br s, 1 H), 1.41 (t, J = 12.7 Hz, 1 H), 1.39 (dd, J = 6.3, 12.7 Hz, 1 H), 1.34 (s, 3 H), 1.12 (s, 3 H), 0.96 (s, 3 H); IR (neat) 3450, 1720, 1680, 880 cm^{-1}; MS m/e (rel intensity) 264 (M$^+$, 16), 232 (49), 205 (80), 187 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.63; H, 9.03.

Epoxidation of 16. To a solution of 330 mg (1.25 mmol) of **16** and 530 mg (3.7 mmol) of Na_2HPO_4 in 15 mL of CH_2Cl_2 at 0 °C was added 460 mg (1.9 mmol) of 70% *m*-chloroperbenzoic acid. The mixture was allowed to warm to room temperature and stirred for 2 h before water was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extract was washed with saturated Na_2SO_3, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel (elution with petroleum ether/ether, 85:15) to give 310 mg (89%) of **7** as white solid: mp 37–39 °C; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3 H), 3.61 (dd, J = 10.3, 11.2 Hz, 1 H), 3.15 (d, J = 14.2 Hz, 1 H), 2.94 (d, J = 11.7 Hz, 1 H), 2.88–2.84 (m, 1 H), 2.81 (d, J = 4.4 Hz, 1 H), 2.66 (d, J = 4.4 Hz, 1 H), 2.64–2.60 (m, 1 H), 2.25 (d, J = 14.2 Hz, 1 H), 1.83 (dd, J = 7.8, 13.7 Hz, 1 H), 1.72 (dd, J = 2.0, 13.7 Hz, 1 H), 1.43 (t, J = 12.7 Hz, 1 H), 1.38 (dd, J = 7.8, 12.7 Hz, 1 H), 1.30 (s, 3 H), 1.12 (s, 3 H), 0.99 (s, 3 H); IR (KBr) 3500, 1730, 1050 cm^{-1}; MS m/e (rel intensity) 280 (M$^+$, 1), 221 (62), 183 (58), 165 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.64.

Acid-Catalyzed Rearrangement of 7. To a solution of 2.25 g (8.09 mmol) of **7** in 120 mL of CH_2Cl_2 was added 0.11 mL of H_2SO_4, and the solution was stirred for 1 h before dilute $NaHCO_3$ was added. The aqueous phase was extracted with ether, and the CH_2Cl_2 layer and the ether extract were combined, dried ($MgSO_4$), and evaporated. Chromatography of the crude product on silica gel (elution with petroleum ether/ether, 7:3) gave 1.60 g (80%) of **6** as white solid: mp 173–173.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.26 (d, J = 9.3 Hz, 1 H), 4.25 (d, J = 9.3 Hz, 1 H), 3.20–3.11 (m, 2 H), 2.81 (dd, J = 9.3, 19.0 Hz, 1 H), 2.27 (ddd, J = 2.4, 7.3, 12.7 Hz, 1 H), 1.84 (ddd, J = 2.4, 9.3, 13.2 Hz, 1 H), 1.41 (dd, J = 13.2, 9.3 Hz, 1 H), 1.35 (t, J = 12.2 Hz, 1 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.10 (s, 3 H), 1.06 (dd, J = 2.0, 5.9 Hz, 1 H), 0.98 (s, 3 H), 0.96 (d, J = 5.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 211.0 (s), 175.9 (s), 71.6 (t), 48.2 (t), 48.0 (d), 45.8 (t), 40.7 (s), 40.0 (d), 37.0 (d), 34.6 (s), 29.0 (s), 28.8 (q), 26.2 (q), 18.9 (t), 12.43 (q); IR (KBr) 1770, 1700, 1070, 1030 cm^{-1}; MS m/e (rel intensity) 248 (M$^+$, 100), 152 (55), 125 (76). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.10.

Conversion of 6 to 18. To a solution of 520 mg (2.10 mmol) of **6** in 15 mL of THF and 30 mL of methanol was added 120 mg (3.16 mmol) of sodium borohydride, and the mixture was stirred overnight before it was treated with 10% HCl. Most of the solvent was evaporated, and the residue was extracted with ether, dried ($MgSO_4$), and evaporated to give crude alcohol **17**. The ^{1}H NMR spectrum of the crude product indicates the presence of two isomers in a ratio of 9:1. A small quantity of this material was recrystallized from ether–CH_2Cl_2 to give the major isomer **17**: mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 4.26 (d, J = 8.8 Hz, 1 H), 4.01 (d, J = 8.8 Hz, 1 H), 3.60 (dd, J = 4.4, 8.8 Hz, 1 H), 2.79 (ddd, J = 7.8, 7.8, 9.3 Hz, 1 H), 2.30–2.22 (m, 2 H), 2.17 (ddd, J = 2.0, 7.3, 11.2 Hz, 1 H), 1.73 (d, J = 4.9 Hz, 1 H), 1.59 (ddd, J = 2.0, 7.8, 12.7 Hz, 1 H), 1.55 (d, J = 3.9 Hz, 1 H), 1.38 (dd, J = 10.7, 13.2 Hz, 1 H), 1.23 (dd, J = 9.8, 12.7 Hz, 1 H), 1.12 (d, J = 7.3 Hz, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H), 0.89 (dd, J = 1.0, 4.9 Hz, 1 H); IR (KBr) 3450, 1770, 1080, 1035, 1005 cm^{-1}; MS m/e (rel intensity) 250 (M$^+$, 21), 126 (100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86: H, 8.80.

To a mixture of 170 mg of the above crude product in 0.60 mL of pyridine and 1.5 mL of DMF was added 0.26 mL (3.4 mmol) of methanesulfonyl chloride. The mixture was heated at 80 °C for 1 h before water was added. The mixture was extracted with CH_2Cl_2, washed with 10% HCl, saturated $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with petroleum ether/ether, 7:3) gave 138 mg (87% from **6**) of olefin **18**: ^{1}H NMR ($CDCl_3$) δ 4.99 (t, J = 1.5 Hz, 1 H), 4.34 (d, J = 8.8 Hz, 1 H), 4.22 (d, J = 8.8 Hz, 1 H), 2.85 (ddd, J = 6.4, 8.8, 12.7 Hz, 1 H), 2.52 (m, 1 H), 1.96 (dd, J = 6.8, 12.2 Hz, 1 H), 1.82 (dd, J = 1.5, 2.4 Hz, 3 H), 1.81 (dd, J = 8.8, 13.1 Hz, 1 H), 1.31 (dd, J = 3.4, 12.7 Hz, 1 H), 1.29 (d, J = 4.4 Hz, 1 H), 1.20 (d, J = 4.4 Hz, 1 H), 1.10 (t, J = 12.2 Hz, 1 H), 1.02 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1765, 1015, 1000 cm^{-1}; MS m/e (rel intensity) 232 (M$^+$, 100), 173 (51), 217 (40), 118 (55). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.46; H, 8.72.

Allylic Oxidation of 18. A mixture of 62 mg (0.26 mmol) of **18** and 289 mg (2.6 mmol) of SeO_2 in 1.2 mL of ethanol was heated at reflux for 3 h. The mixture was filtered through Celite, diluted with water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with petroleum ether/ether, 3:2) of the crude product gave 32 mg (50%) of **19** as a white solid: mp 106–108 °C (recrystallized from petroleum ether–ether); ^{1}H NMR ($CDCl_3$) δ 9.47 (s, 1 H), 6.42 (d, J = 2.9 Hz, 1 H), 4.74 (d, J = 9.7 Hz, 1 H), 4.31 (d, J = 9.7 Hz, 1 H), 3.03 (ddd, J = 7.0, 9.2, 12.8 Hz, 1 H), 2.84 (m, 1 H), 2.09 (dd, J = 7.0, 12.8 Hz, 1 H), 2.03 (dd, J = 10.2, 13.4 Hz, 1 H), 1.49 (dd, J = 4.3, 13.4 Hz, 1 H), 1.39 (d, J = 5.8 Hz, 1 H), 1.23 (d, J = 5.8 Hz, 1 H), 1.08 (s, 3 H), 1.05 (t, J = 12.8 Hz, 1 H), 1.03 (s, 3 H); IR (KBr) 1760, 1700, 1090, 1030 cm^{-1} MS m/e (rel intensity) 246 (M$^+$, 100), 231 (34), 201 (40).

Protection Followed by Hydrolysis of 19. To a mixture of 41 mg (0.17 mmol) of **19** and 63 mg (0.17 mmol) of $CeCl_3 \cdot 7H_2O$ in 0.4 mL of methanol was added 6 mg (0.16 mmol) of sodium borohydride, and the mixture was stirred for 30 min before water was added. The mixture was extracted with ether, dried ($MgSO_4$), and evaporated to give 39 mg (94%) of almost pure **20** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 1 H), 4.46 (d, J = 8.8 Hz, 1 H), 4.39 (d, J = 8.8 Hz, 1 H), 4.25 (br AB q, J = 7.3 Hz, 2 H), 2.91 (ddd, J = 7.3, 8.1, 11.2 Hz, 1 H), 2.60 (br m, 1 H), 2.00 (dd, J = 6.6, 12.4 Hz, 1 H), 1.87 (dd, J = 8.1, 13.2 Hz, 1 H), 1.60 (br s, 1 H), 1.34 (d, J = 2.9 Hz, 1 H), 1.30 (d, J = 2.9 Hz, 1 H), 1.29 (dd, J = 4.4, 13.2 Hz, 1 H), 1.11 (t, J = 12.4 Hz, 1 H), 1.03 (s, 3 H), 1.01 (s, 3 H); IR (neat) 3450, 1770, 1080, 1020 cm^{-1}; MS m/e (rel intensity) 248 (M$^+$, 100) 173 (57), 159 (66), 149 (54).

A mixture of the above product (38 mg, 0.15 mmol), 0.10 g of NaOH, and 0.1 mL of water in 2 mL of methanol was heated at reflux overnight. The mixture was diluted with water and washed with ether. The aqueous layer was acidified with cold 5% HCl and extracted quickly with ether, and the extract was treated with ethereal diazomethane and dried over K_2CO_3. Evaporation of the solvent followed by flash chromatography (elution with petroleum ether/ether, 4:1) gave 28 mg (71%) of ether **22** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.01 (br d, J = 1.5 Hz, 1 H), 4.54 (ddd, J = 2.0, 3.4, 12.7 Hz, 1 H), 4.35 (ddd, J = 2.0, 3.4, 12.7 Hz, 1 H), 4.17 (d, J = 9.3 Hz, 1 H), 4.05 (d, J = 9.3 Hz, 1 H), 3.67 (s, 3 H), 2.83 (ddd, J = 6.8, 6.8, 12.2 Hz, 1 H), 2.52 (br s, 1 H), 1.92 (dd, J = 6.8, 12.2 Hz, 1 H), 1.78 (dd, J = 7.8, 13.2 Hz, 1 H), 1.41 (dd, J = 1.0, 13.2 Hz, 1 H), 1.40 (d, J = 3.9 Hz, 1 H), 1.38 (d, J = 3.9 Hz, 1 H), 1.19 (t, J = 12.2 Hz, 1 H), 1.06 (s, 3 H), 0.98 (s, 3 H); IR (neat) 1720, 1290, 1240, 1150, 1130, 1040 cm^{-1}; MS m/e (rel intensity) 262 (M$^+$, 96) 203 (85), 173 (100). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.98; H, 8.44.

To a solution of 50 mg (0.20 mmol) of **19** in 0.4 mL of methanol was added 161 mg (0.42 mmol) of $YbCl_3 \cdot 6H_2O$ followed by 0.80 mL (7.7 mmol) of trimethyl orthoformate. The mixture was stirred for 3 h before saturated $NaHCO_3$ was added, filtered, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give 55 mg (95%) of almost pure **21** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ

5.40 (d, J = 1.5 Hz, 1 H), 4.70 (br s, 1 H), 4.40 (d, J = 9.5 Hz, 1 H), 4.37 (d, J = 9.5 Hz, 1 H), 3.36 (s, 3 H), 3.32 (s, 3 H), 2.91 (ddd, J = 7.3, 8.8, 12.5 Hz, 1 H), 2.61 (br t, J = 8.8 Hz, 1 H), 2.01 (dd, J = 6.6, 12.5 Hz, 1 H), 1.88 (dd, J = 8.8, 13.2 Hz, 1 H), 1.37 (dd, J = 3.7, 13.2 Hz, 1 H), 1.27 (s, 2 H), 1.12 (t, J = 12.5 Hz, 1 H), 1.04 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1765, 1355, 1080, 1060 cm^{-1}; MS m/e (rel intensity) 292 (M^+, 41), 261 (70), 260 (56), 75 (100).

The above crude **21** was treated with methanolic NaOH as described for **20** to give 44 mg (94%) of **23**: ^1H NMR ($CDCl_3$) δ 5.43 (dd, J = 1.5, 2.5 Hz, 1 H), 5.32 (br s, 1 H), 4.23 (d, J = 9.3 Hz, 1 H), 4.11 (d, J = 9.3 Hz, 1 H), 3.68 (s, 3 H), 3.40 (s, 3 H), 2.86 (ddd, J = 6.8, 6.8, 12.2 Hz, 1 H), 2.57 (br t, J = ca. 7 Hz, 1 H), 1.91 (dd, J = 6.4, 12.2 Hz, 1 H), 1.80 (dd, J = 7.8, 13.2 Hz, 1 H), 1.45 (dd, J = 1.0, 13.2 Hz, 1 H), 1.40 (d, J = 3.9 Hz, 1 H), 1.35 (d, J = 3.4 Hz, 1 H), 1.25 (t, J = 12.2 Hz, 1 H), 1.06 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1720, 1290, 1240, 1155, 1140, 1015, 1005 cm^{-1}; MS m/e (rel intensity) 292 (M^+, 12), 260 (72), 201 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.08; H, 8.28.

Hydrolysis of 18. Hydrolysis of 364 mg (1.6 mmol) of **18** was carried out as described for **20** to give 380 mg (92%) of hydroxy ester **24** after flash chromatography (elution with petroleum ether/ether, 7:3) as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.98 (br s, 1 H), 4.26 (t, J = 12.1 Hz, 1 H), 3.75 (s, 3 H), 3.09 (dd, J = 3.4, 12.7 Hz, 1 H), 2.90 (dd, J = 2.9, 11.2 Hz, 1 H), 2.76 (ddd, J = 7.8, 7.8, 11.2 Hz, 1 H), 2.45 (m, 1 H), 1.96 (dd, J = 1.5, 3.1 Hz, 3 H), 1.74 (dd, J = 8.3, 13.2 Hz, 1 H), 1.49 (dd, J = 7.8, 11.9 Hz, 1 H), 1.33 (dd, J = 2.4, 13.2 Hz, 1 H), 1.11 (d, J = 4.4 Hz, 1 H), 1.08 (d, J = 4.4 Hz, 1 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.98 (t, J = 11.9 Hz, 1 H); IR (neat) 3500, 1720, 1270, 1140, 1020 cm^{-1}; MS m/e (rel intensity) 264 (M^+, 13), 232 (26), 187 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 9.17.

Swern Oxidation of 24. To a solution of 0.1 mL (0.78 mmol) of oxalyl chloride in 1.0 mL of CH_2Cl_2 at -60 °C was added 0.12 mL (1.7 mmol) of DMSO in 0.4 mL of CH_2Cl_2, and the mixture was stirred for 10 min. To this suspension was added 186 mg (0.76 mmol) of **24** in 0.8 mL of CH_2Cl_2, and the mixture was stirred for 15 min before 0.5 mL (3.6 mmol) of triethylamine was added. The mixture was allowed to warm to room temperature, diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with petroleum ether/ether, 4:1) of the crude product gave 172 mg (93%) of aldehyde **25** as a colorless oil: ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 5.06 (br s, 1 H), 3.68 (s, 3 H), 2.83 (dt, J = 12.2, 7.3 Hz, 1 H), 2.50 (m, 1 H), 2.12 (d, J = 4.4 Hz, 1 H), 1.96 (dd, J = 1.5, 2.4 Hz, 3 H), 1.76 (dd, J = 8.3, 13.2 Hz, 1 H), 1.61 (dd, J = 6.3, 12.2 Hz, 1 H), 1.49 (t, J = 12.2 Hz, 1 H), 1.42 (d, J = 4.4 Hz, 1 H), 1.37 (dd, J = 2.0, 13.2 Hz, 1 H), 1.03 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1730, 1720, 1260, 1140 cm^{-1}; MS m/e (rel intensity) 262 (M^+, 32), 247 (69), 203 (75), 202 (100), 187 (86), 173 (90). All attempts to convert **25** to methyl marasmate (**5**) were unsuccessful.

Methyl Marasmate (5). To a solution of *tert*-butyl hydroperoxide (79 mg, 0.7 mmol) in 0.1 mL of CH_2Cl_2 was added 19 mg (0.17 mmol) of SeO_2, and the mixture was stirred for 10 min. Then 87 mg (0.33 mmol) of **24** in 0.15 mL of CH_2Cl_2 was added, and the mixture was stirred overnight. The mixture was diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Since an attempt to isolate diol **26** by chromatography was not successful, the crude product was subjected directly to Swern oxidation as described for **24**. Methyl marasmate (**5**) (18 mg, 19%) was isolated by flash chromatography (elution with petroleum ether/ether, 7:3), which was spectroscopically (IR, ^1H NMR, and ^{13}C NMR) identical with an authentic sample: ^1H NMR ($CDCl_3$) δ 9.85 (s, 1 H), 9.47 (s, 1 H), 6.50 (d, J = 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.00 (ddd, J = 7.0, 8.0, 12.4 Hz, 1 H), 2.78 (br t, J = 8.6 Hz, 1 H), 2.35 (d, J = 4.8 Hz, 1 H), 2.00 (dd, J = 9.1, 13.4 Hz, 1 H), 1.69 (dd, J = 7.0, 12.9 Hz, 1 H), 1.58 (dd, J = 3.2, 13.4 Hz, 1 H), 1.44 (t, J = 12.9 Hz, 1 H), 1.17 (d, J = 4.8 Hz, 1 H), 1.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 197.0, 191.5, 170.9, 152.7, 139.2, 52.5, 46.7, 45.4, 40.9, 39.3, 37.9, 37.0, 33.4, 31.2, 30.6, 24.4.

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Registry No. (±)-**1**, 61216-74-8; (±)-**5**, 75918-37-5; (±)-**6**, 123675-62-7; (±)-**6** methyl epimer, 123750-17-4; (±)-**7**, 123675-63-8; (±)-**8**, 123675-64-9; (±)-**8** acid, 123675-80-9; (±)-**9**, 60064-71-3; (±)-**10**, 123675-65-0; (±)-**10** ketone, 123675-81-0; (±)-**11**, 123675-66-1; (±)-**12**, 123675-67-2; **13**, 1073-13-8; (±)-**14**, 123675-68-3; (±)-**15**, 123675-69-4; (±)-**16**, 123675-70-7; (±)-**17** isomer 1, 123675-71-8; (±)-**17** isomer 2, 123750-16-3; (±)-**18**, 123675-72-9; (±)-**19**, 123675-73-0; (±)-**20**, 123750-15-2; (±)-**21**, 123675-74-1; (±)-**22**, 123675-75-2; **23**, 123675-76-3; (±)-**24**, 123675-77-4; (±)-**25**, 123675-78-5; (±)-**26**, 123675-79-6.

A Systematic Entropy Relationship for the General-Base Catalysis of the Deprotonation of a Carbon Acid. A Quantitative Probe of Transition-State Solvation

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Abstract: The general-base-catalyzed deprotonation of a carbon acid, the 1-methyl-4-(phenylacetyl)pyridinium cation (pK_a = 9.02 at 25 °C), has been investigated for 32 general-base catalysts (25 amines and seven phenoxide ions) in aqueous solution. Amines give a generally scattered Brønsted plot; ring-substituted benzylamines have β = 0.52, and ring-substituted phenoxides have β = 0.60, with the phenoxides being more reactive than amines of similar basicity. The temperature dependences of the general-base-catalyzed deprotonation of this carbon acid have been measured over the range 15-45 °C for 12 base catalysts (eight primary, secondary, and tertiary amines; 4-(dimethylamino)pyridine; two phenoxide ions; hydroxide ion). The entropies of activation for these deprotonations show a clean curvilinear dependence upon the entropies of protonation of these base species, with the hydroxide ion being the only significant deviant from this relationship. This observation quantitatively establishes the importance of solvation effects as the major source of deviations that are commonly observed in Brønsted relationships for general-base-catalyzed processes.

The Brønsted relationship is commonly used to describe the efficiency of general-base catalysis in a wide range of reactions in organic chemistry.[1-4] However, it is also recognized that this relationship is less general than one might expect for a relatively simple free energy relationship that relates rate and equilibrium constants. Even for the general-base-catalyzed deprotonation of carbon acids (eq 1), in which proton transfer is not coupled to

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