tadienyl derivatives of the transition metals also opens for study many new systems in terms of metal-stabilized carbocations and related species.[26] Further investigations along these lines are in progress in our laboratory.

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(14) All organo transition metal compounds described in this communication have exhibited combustion analyses with ±0.3% of the calculated values.

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(18) Spectral data for **16**–**23** (^{1}H NMR, $CDCl_3$, and IR, $CDCl_3$, unless otherwise indicated): **16**, δ 5.84 (m, 4 H, C_5H_4), 8.90 ppm (s, 1 H, CHO), and ν_{CO} 2030, 1995, 1675 cm^{-1}; **17**, δ 2.34 (s, 3 H, CH_3), 5.69 (t, 2 H, $H_{3,4}$), 5.90 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2050, 1990, 1660 cm^{-1}; **18**, δ 3.78 (s, 3 H, CH_3), 5.63 (t, 2 H, $H_{3,4}$), 5.95 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2035, 1985, 1715 cm^{-1}; **19**, δ 5.40 (s, 4 H, C_5H_4), 9.40 ppm (s, 1 H, CHO), and ν_{CO} 2015, 1980, 1675 cm^{-1}; **20**, δ 2.38 (s, 3 H, CH_3), 5.39 ppm (m, 4 H, C_5H_4), and ν_{CO} 2020, 1980, 1660 cm^{-1}; **21**, δ 3.80 (s, 3 H, CH_3), 5.24 (t, 2 H, $H_{3,4}$), 5.45 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2020, 1990, 1715 cm^{-1}; **22**, δ 5.10 (t, 2 H, $H_{3,4}$), 5.25 (t, 2 H, $H_{2,5}$), 5.2–6.6 ppm (m, 2 H, vinyl), and ν_{CO} 2020, 1960 cm^{-1}; **23** (^{1}H NMR recorded in C_6D_6), δ 1.74 (s, 3 H, CH_3), 4.55 (t, 2 H, $H_{3,4}$), 4.84 (t, 2 H, $H_{2,5}$), 4.8–5.2 ppm (m, 2 H, CH_2), and ν_{CO} 2020, 1960 cm^{-1}.

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(21) Spectral data for **24**–**29** (^{1}H NMR, $CDCl_3$, and IR, KBr, unless otherwise noted): **24**, δ 3.81 (s, 3 H, CH_3), 5.14 (t, 2 H, $H_{3,4}$), 5.78 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2030, 1955 cm^{-1}, ν_{CO}, ν_{NO} 1710 cm^{-1} (IR recorded neat); **25**, δ 3.80 (s, 3 H, CH_3), 5.62 (t, 2 H, $H_{3,4}$), 6.23 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2025, 1945, 1720 cm^{-1}, ν_{NO} 1665 cm^{-1}; **26**, δ 3.82 (s, 3 H, CH_3), 5.70 (t, 2 H, $H_{3,4}$), 6.26 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2005, 1930, 1715 cm^{-1}, ν_{NO} 1655 cm^{-1}; **27**, δ 0.82 ppm (s, 3 H, M–CH_3), and ν_{CO} 2030, 1950, 1735 cm^{-1} (IR recorded in pentane); **28**, δ 0.45 (s, 3 H, M–CH_3), 3.83 (s, 3 H, OCH_3), 5.39 (t, 2 H, $H_{3,4}$), 5.78 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2010, 1915, 1710 cm^{-1}; **29**, δ 0.47 (s, 3 H, M–CH_3), 3.85 (s, 3 H, OCH_3), 5.49 (t, 2 H, $H_{3,4}$), 5.83 (t, 2 H, $H_{2,5}$), and ν_{CO} 2005, 1910, 1710 cm^{-1}.

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(23) Spectral data for **30**–**37** (^{1}H NMR, $CDCl_3$, and IR, KBr, unless otherwise noted): **30**, δ 0.45 (s, 3 H, M–CH_3), 5.52 (t, 2 H, $H_{3,4}$), 5.72 (t, 2 H, $H_{2,5}$), 9.58 ppm (s, 1 H, CHO), and ν_{CO} 2020, 1920, 1680 cm^{-1}; **31**, δ 0.47 (s, 3 H, M–CH_3), 5.62 (t, 2 H, $H_{3,4}$), 5.74 (t, 2 H, $H_{2,5}$), 9.57 ppm (s, 1 H, CHO), and ν_{CO} 2000, 1915, 1675 cm^{-1}; **32**, δ 0.44 (s, 3 H, M–CH_3), 2.35 (s, 3 H, $COCH_3$), 5.47 (t, 2 H, $H_{3,4}$), 5.73 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2020, 1920, 1665 cm^{-1}; **33**, δ 0.45 (s, 3 H, M–CH_3), 2.34 (s, 3 H, $COCH_3$), 5.52 (t, 2 H, $H_{3,4}$), 5.72 ppm (t, 2 H, $H_{2,5}$), and ν_{CO} 2010, 1920, 1670 cm^{-1}; **34**, δ 0.32 (s, 3 H, M–CH_3), 5.1–5.5 (m, 6 H, C_5H_4 + $=CH_2$), 5.9–6.5 ppm (m, 1 H, =CH), and ν_{CO} 2005, 1920 cm^{-1}; **35**, δ 0.40 (s, 3 H, M–CH_3), 5.1–5.5 (m, 6 H, C_5H_4 + $=CH_2$), 6.0–6.5 ppm (m, 1 H, =CH), and ν_{CO} 2000, 1915 cm^{-1}; **36**, δ 0.33 (s, 3 H, M–CH_3), 1.91 (d, 3 H, $C(CH_3)$), 5.0–5.2 (m, 2 H, $=CH_2$), 5.28 (m, 2 H, $H_{3,4}$), 5.38 ppm (m, 2 H, $H_{2,5}$), and ν_{CO} 2000, 1915 cm^{-1}; **37** δ 0.39 (s, 3 H, M–CH_3), 1.92 (d, 3 H, $C(CH_3)$), 5.0–5.2 (m, 2 H, $=CH_2$), 5.34 (m, 2 H, $H_{3,4}$), 5.44 ppm (m, 2 H, $H_{2,5}$), and ν_{CO} 2005, 1910 cm^{-1}.

(24) Macomber, D. W., unpublished studies.

(25) For example, a reaction between **11** and $(\eta^5\text{-}C_5H_5)TiCl_3$ (THF, 25 °C) has afforded $(\eta^5$-methoxycarbonylcyclopentadienyl$)(\eta^5$-cyclopentadienyl$)$-dichlorotitanium $[(\eta^5\text{-}C_5H_4CO_2CH_3)(\eta^5\text{-}C_5H_5)TiCl_2]$: mp 188–190 °C, ν_{CO} 1725 cm^{-1}, $M^+ = m/e$ 308.[19]

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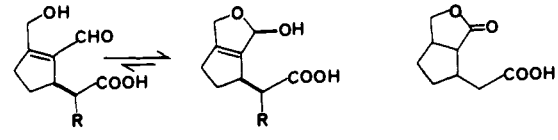
Synthesis of the Alleged Genipic Acid by Photoannelation[1]

Sir:

In 1964 Tallent proposed structures **1** and **2** for genipic acid and genepinic acid, respectively, two unstable antibiotics isolated from Puerto Rican jagua fruit.[2] We now present an unambiguous synthesis of structure **1** and its methyl ester which suggest beyond reasonable doubt that genipic acid cannot be as orginally formulated.



1; R=H

2; R=$COOCH_3$

3

Tallent's assignment of structure **1** to genipic acid rests primarily on three pieces of evidence. First, exposure of **1** to prereduced PtO_2 and H_2 afforded a 16% yield of lactone **3**, identical with an "authentic" sample,[3] suggesting the indicated carbon substitution pattern on a cyclopentane ring. Secondly, genipic acid undergoes mutarotation in basic solution, consistent with a hemiacetal structure. Finally, the NMR spectrum of genipic acid confirms the presence of the hemacetal with a signal at δ 5.8 (no CHO), while a two-proton signal at δ 4.30 with no absorptions for vinyl hydrogens located the tetrasubstituted double bond between C-1 and C-2 as indicated. It is somewhat curious that genipic acid should exist in the lactol form because of the anticipated strain, but it is possible that sufficient stabilization is gained by hydrogen bonding with the carboxylic acid group to make such a structure energetically plausible. Unfortunately, such an explanation is not possible for the methyl ester of genipic acid (CH_2N_2) which persists as a hemiacetal (δ 5.88 and 4.17, no CHO).

During the intervening years only a single publication dealing with synthetic efforts in the genipic acid area has appeared.[4] In 1978 Whitesell and Matthews reported an eminently rational approach to genipic acid, which, although unsuccessful, raised significant questions about the validity of the published structure. Problems seemed to rest primarily with the remarkable reluctance of a hydroxymethyl cyclopentene-

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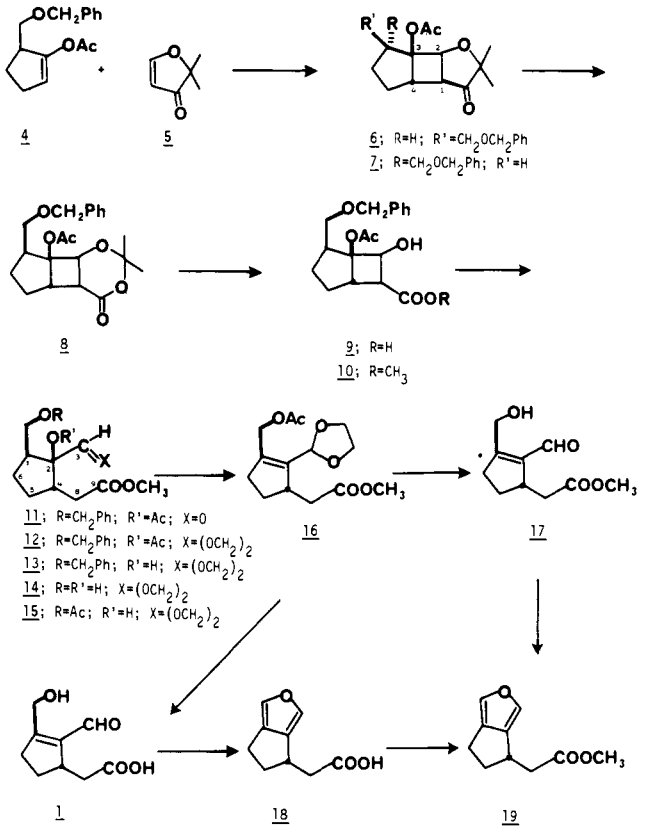
Scheme I



carboxaldehyde to exist as a hemiacetal, in complete accord with our findings.

The present synthesis of **1** relies on recent photochemical studies involving 2,2-dimethyl-3(2*H*)-furanone (**5**),[5] with our initial intention being the production of a derivative of **1** with three differentially protected functional groups (e.g., **16**). Thus irradiation of a hexane solution of cyclopentene **4**[6,7] with furanone **5**[8] led to a mixture of photoproducts **6** and **7** (70–80%) (Scheme I) which were quantitatively separated by chromatography on alumina (**6:7**, 1.8:1).[9] The major isomer **6** [mp 58.5–59.5 °C; NMR ($CDCl_3$) δ 1.22 and 1.36 (2s, 6 H, *gem*-CH_3), 2.01 (s, 3 H, $COCH_3$), 2.51 (t, J = 5.5 Hz, 1 H, H_4), 2.80 (m, 2 H, H_1 and methine), 3.28 (AB of ABX, 2 H, CH_2O), 4.46 (AB, $\Delta\nu$ = 10.6 Hz, J = 12 Hz, 2 H, CH_2Ar), 4.59 (d, J = 5 Hz, 1 H, H_2), 7.29 (s, 5 H, Ar)] was then oxidized (mcpba, CH_2Cl_2, HCO_3^-) to give the crystalline lactone **8** [mp 140–141 °C; NMR ($CDCl_3$) δ 1.59 (s, 6 H, *gem*-CH_3), 2.04 (s, 3 H, $COCH_3$), 2.59 (t, J = 6 Hz, 1 H, H_4), 2.87 (m, 1 H, methine), 3.17 (m, 1 H, H_1), 3.35 (AB of ABX, 2 H, CH_2O), 4.51 (AB, $\Delta\nu$ = 11.3 Hz, J = 14 Hz, CH_2Ar), 4.65 (d, J = 6 Hz, 1 H, H_2)] which on exposure to aqueous methanol followed by CH_2N_2 yielded methyl ester **10** (83% from **6**). The free aldehyde was obtained by retroaldol cyclobutanol fragmentation (NaH, ether) to give **11** as a viscous oil [NMR (CCl_4) δ 1.93 (s, 3 H, $COCH_3$), 3.58 (s, 3 H, OCH_3), 4.34 (AB, $\Delta\nu$ = 7 Hz, J_{AB} = 12 Hz, 2 H, OCH_2), 7.15 (s, 5 H, Ar), 9.27 (s, 1 H, CHO)]. Protection of the aldehyde as the 1,3-dioxolane, followed by successive removal of the tertiary acetate (K_2CO_3, CH_3OH) and benzyl ether groups (H_2, Pd/C, CH_3OH), gave diol **14** [NMR ($CDCl_3$) δ 3.69 (s, 3 H, OCH_3), 3.7–4.1 (m, 6 H, CH_2O), 4.71 (s, 1 H, $CH(OR)_2$)]. The free aldehyde from **14** showed no tendency to form an intramolecular hemiacetal in contrast to the free aldehyde derived from the diol epimeric at C-1 in a parallel series of experiments. These results are strongly suggestive of a trans arrangement of the protected aldehyde and hydroxymethyl groups in **14.** Selective acetylation of the primary alcohol then afforded **15** [60% from **10**; NMR ($CDCl_3$) δ 2.05 (s, 3 H, $COCH_3$), 3.68 (s, 3 H, OCH_3), 3.91 (m, 4 H, $(OCH_2)_2$), 4.21 (AB of ABX, 2 H, CH_2OAc), 4.70 (s, 1 H, $CH(OR)_2$)].

The final step in assembling a triprotected derivative of **1** was the regiospecific introduction of double bond of **16.** Although elimination of water from **15** can potentially occur in either of two directions, the trans disposition of the C-2 hydroxyl group and C-1 hydrogen compared with the cis relationship with the C-4 hydrogen provided the desired selectivity. Exposure of **15** to $SOCl_2$–pyridine[10] smoothly yielded **16** as the only product [99%; NMR (CCl_4) δ 2.02 (s, 3 H, $COCH_3$), 3.62 (s, 3 H, OCH_3), 3.90 (m, 4 H, $(OCH_2)_2$), 4.67 (s, 2 H, CH_2OAc), 5.44 (s, 1 H, $CH(OR)_2$].

At this point mild alkaline hydrolysis (1 N NaOH, CH_3OH, room temperature, 12 h) of the two ester groups of **16,** followed by brief agitation with 0.5% H_2SO_4 in an ether–water biphase, afforded **1** in good yield. That **1** exists as the free aldehyde rather than as the hemiacetal of authentic genipic acid was readily apparent from the NMR spectrum which exhibited a single aldehyde resonance at δ 9.98. In addition a two-proton peak for the allylic hydroxymethyl group at δ 4.57 was corroborative. In repeated experiments there was no indication of the δ 5.88 and 4.30 absorptions reported by Tallent for the hemiacetal of the natural material. Alternatively, selective hydrolysis (K_2CO_3, MeOH) of the acetate of **16,** followed by brief agitation in an acidic ether–water biphase as before, afforded methyl ester **18.** Again the free aldehydic nature of the product was apparent from the NMR spectrum with signals at δ 9.90 and 4.53 as well as 3.63. There was no indication of the δ 5.88 and 4.17 resonances reported for the hemiacetal of methyl genipate.

In several attempts to promote hemiacetal formation in **1** and **17** under a variety of mildly acidic conditions (40% HOAc, 2% H_2SO_4, 10% HCl), the isolated product was either unchanged starting material or complete conversion into furans **18** and **19.** Although **18** and **19** presumably form through the intermediacy of the desired hemiacetals,[11] the latter appear to be sufficiently unstable to resist detection, let alone isolation.

The above results are highly suggestive that **1** and genipic acid cannot be the same compound. Because repeated attempts to obtain either comparative samples or spectra were unsuccessful, a definitive statement is difficult. However, the total available body of knowledge leaves little room for doubt.

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(5) (a) Baldwin,, S. W.; Crimmins, M. T. *Tetrahedron Lett.* **1978,** 4197. (b) Baldwin, S. W.; Wilkinson, J. M. *Ibid.,* in press.
(6) Prepared in 50% yield from ethylene ketal of 2-hydroxymethylcyclopentanone. Takahashi, T.; Kato, A.; Matsuoka, S. *Yakugaku Zasshi* **1959,** *79,* 1087; *Chem. Abstr.* **1960,** *54,* 4543f. Reasons for the choice of this set of protecting groups will be discussed in a future publication dealing with mechanistic aspects of the photoaddition process.
(7) All new compounds reported in this work gave satisfactory spectral and analytical data (±0.3%) or correct high resolution mass spectral values for the molecular ion of chromatographically homogeneous samples. NMR measurements were determined at 100 MHz.
(8) Previous use of **5** as a photochemical addend has been reported. (a) Margaretha, P. *Chimia* **1975,** *29,* 203. (b) Margaretha, P. *Tetrahedron* **1973,** *29,* 1317. (c) Margaretha, P. *Ibid.* **1971,** *27,* 6209. (d) Margaretha, P. *Tetrahedron Lett.* **1971,** 4891.
(9) The head–tail regiochemistry of the photoaddition of **5** to enol derivatives was predicted on the basis of model work and was confirmed by the multiplicity of the aldehyde proton in 11 (singlet). The skeletal stereochemistry is assumed to be largely cis-anti-cis by analogy to the literature and is verified by spectral and chemical considerations throughout the synthetic path. The remaining point of stereochemical consequence, orientation of the benzyloxymethyl group, was profoundly affected by the nature of the alkene protecting groups and will be discussed subsequently.
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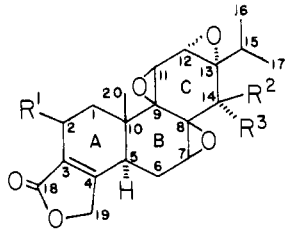
Total Synthesis of Triptolide and Triptonide

Sir:

The isolation of triptolide (**1**), tripdiolide (**2**), and triptonide (**3**) from extracts of *Tripterygium wilfordii* Hook F by Kupchan and co-workers provided the first recognized diterpenoid triepoxides[1] of which **1** and **2** are of special interest owing to their antileukemic activity.[2] Previously we have reported model studies for construction of the C-ring functionality of **3**.[3,4] A synthesis of the C-ring functionality of **1** in a model system has been reported by Koike and Tokoroyama[5] who also claim a synthesis of the A-ring butenolide moiety of **1** from dehydroabietic acid.[6]



1, $R^1 = R^3 = H$, $R^2 = OH$

2, $R^1 = R^2 = OH$, $R^3 = H$

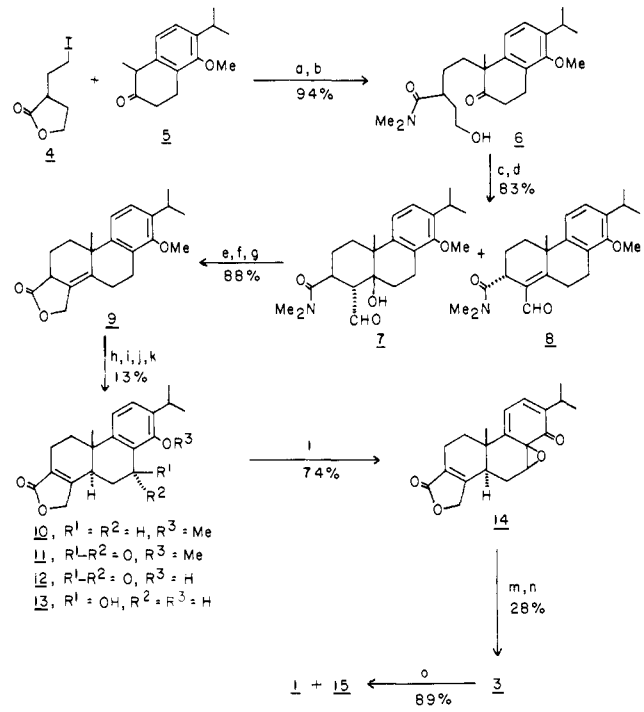
3, $R^1 = H$, R^2–$R^3 = O$

15, $R^1 = R^2 = H$, $R^3 = OH$

We report here the total synthesis of racemic **1** and **3** as outlined in Scheme I. Alkylation of the enolate of **5**[3] with **4** and subsequent cleavage of the lactone with Me_2NH afforded a 1:1 mixture of diastereomers **6**.[7] Oxidation of **6** with CrO_3·py complex gave the diastereomeric aldehydes that underwent Al_2O_3-catalyzed aldol condensation to afford a 1:1 mixture of **7** and **8**. Since cyclization of **6** occurs by approach from the α face of the ketone carbonyl, the stereochemistry of the C-5 hydroxyl group of **7** is β, and the amide and aldehyde groups are trans diequatorial ($J_{H_3\text{-}H_4}$ = 10 Hz). Amide **7** originates from one diastereomer of **6** and amide **8** from the other; therefore the amide group of **8** is α as indicated. Although **7** and **8** are readily separated, for further transformation the mixture is treated with acid to effect dehydration of **7**, followed by aldehyde reduction with $NaBH_4$ and acid-catalyzed lactonization during acidic workup, to afford a single isomer assigned structure **9**.[8] Methoxide-catalyzed isomerization of **9** afforded **10**.[8] Benzylic oxidation of **10** gave **11**[8,9] that was demethylated to afford phenol **12**. Reduction of **12** with $NaBH_4$ gave exclusively the C-7β alcohol (**13**),[8] the stereochemistry of which was established as described previously in model studies.[3]

Butenolide **13** was converted into **3** by a sequence similar to that developed previously for construction of the C-ring functionality.[4] Periodate oxidation of **13** afforded epoxy dienone **14**.[8] Epoxidation of **14** with *m*-CPBA gave the β oxide at C-9,11,[10] and subsequent epoxidation with basic H_2O_2 afforded the α oxide at C-12,13 to complete the total synthesis of racemic triptonide (**3**).[11] Borohydride reduction of **3**, as described by Kupchan,[2] afforded triptolide (**1**, 21%)[11] and 14-epitriptolide (**15**, 68%) which were separated by chromatography on silica gel. Although **1** is the minor product from the reduction of **3**, **15** can be reoxidized to **3** (CrO_3·py-CH_2Cl_2) in 77% yield.

Scheme I[a]



[a] (a) NaH, DMF, 25 °C, 12 h; (b) Me_2NH, 25 °C, 12 h; (c) CrO_3·py, CH_2Cl_2, 25 °C, 15 min; (d) grade 3 neutral alumina, EtOAc, 25 °C, 48 h; (e) *p*-TosOH (catalyst), C_6H_6, reflux, 2 h; (f) $NaBH_4$, EtOH, 25 °C, 2 h; (g) aqueous HCl (workup); (h) MeO^-, MeOH, 25 °C, 15 min; (i) CrO_3, HOAc–H_2O (9:1), 25 °C, 6 h; (j) BBr_3, CH_2Cl_2, 25 °C, 10 h; (k) $NaBH_4$, EtOH, 25 °C, 1 h; (l) $NaIO_4$, aqueous MeOH, 25 °C, 5 h; (m) *m*-CPBA (3 equiv), CH_2Cl_2, 35 °C, 20 h, to 25 °C, 18 h; (n) 30% H_2O_2 (1.75 equiv), 1 N aqueous NaOH (1.3 equiv), MeOH, 25 °C, 20 h; (o) $NaBH_4$, EtOH, 25 °C, 1 h.

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References and Notes

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(7) Satisfactory spectral data have been obtained for all new substances described. Satisfactory analytical data (combustion or high-resolution mass spectrum) have been obtained for all new substances except **13**. High-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (Principal Investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.
(8) **9**: mp 159–160 °C; IR ($CHCl_3$) 1786, 1770, (CCl_4) 1787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 6 H, J = 7 Hz, $-CHMe_2$), 1.38 (s, 3 H, $-CH_3$), 3.67 (s, 3 H, $-OCH_3$), 4.83 (m, 2 H, $-OCH_2-$), 7.01 (d, 1 H, J = 8 Hz, Ar H), 7.05 (d, 1 H, J = 8 Hz, Ar H). **10**: mp 162–162.5 °C; IR ($CHCl_3$) 1755, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, 6 H, $J \approx 7$ Hz, $-CHMe_2$), 1.30 (s, $-CH_3$), 3.64 (s, 3 H, $-OCH_3$), 4.75 (m, 2 H, $-OCH_2-$), 7.07 (s, 2 H, Ar H). **11**: mp 180–181 °C; IR ($CHCl_3$) 1752, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3 H, >C–CH_3), 1.24 (d, 3 H, J = 7 Hz, $-CHMe_2$), 1.26 (d, 3 H, J = 7 Hz, $-CHMe_2$), 1.6–3.2 (m, 7 H), 3.42 (septet, 1 H, J = 7 Hz, $-CHMe_2$), 3.86 (s, 3 H, $-OCH_3$), 4.80

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