A Concise and Stereospecific One-Shot Synthesis of Bicyclo[3.3.1]nonenols from Dimethyl 1,3-Acetonedicarboxylate and Enals via the Sequential Michael Addition−Intramolecular Aldolization

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The reactions of dimethyl 1,3-acetonedicarboxylate **1** with enals **2** proceeded very smoothly in the presence of a catalytic amount of tetrabutylammonium fluoride or piperidine in THF at room temperature, giving the corresponding bicyclo[3.3.1]nonane derivatives **3** in high yields. Both of the two fused rings of **3** are newly constructed from the starting two acyclic substrates via the sequential Michael addition−intramolecular aldolization in one shot.

Introduction

The structural framework of bicyclo[3.3.1]nonane is often found in biologically active natural products, and therefore the development of highly stereocontrolled synthetic methods for bicyclo[3.3.1]nonane derivatives is of keen interest to synthetic chemists.[1] The syntheses of bicyclic compounds from *cyclic ketones* were reported: (1) tandem Michael addition−intramolecular aldolization of ketones with α,β-unsaturated aldehydes[2,3] or ketones (eq 1),[4] (2) palladium-catalyzed reaction of cyclic β-keto esters with methallyl diacetate (eq 2),[5] and (3) the annulation of β-keto thiolesters[6] or β-keto sulfones (eq 3).[7] In the previous cases, one of the two fused rings of bicyclic compounds comes from the ring system of the starting cyclic ketones. We previously found that *o*-carborane $C_2B_{10}H_{12}$ underwent [3 + 2]annulation reaction with enals and enones in the presence of tetrabutylammonium fluoride (TBAF) to give the corresponding five-membered carbocyclic compounds (eq 4).[8] It occurred to us that if we can switch the uncommon dicarbanion of *o*-carborane, which is produced from *o*-carborane upon treatment with TBAF, to more popular dicarbanions of ordinary carbonyl
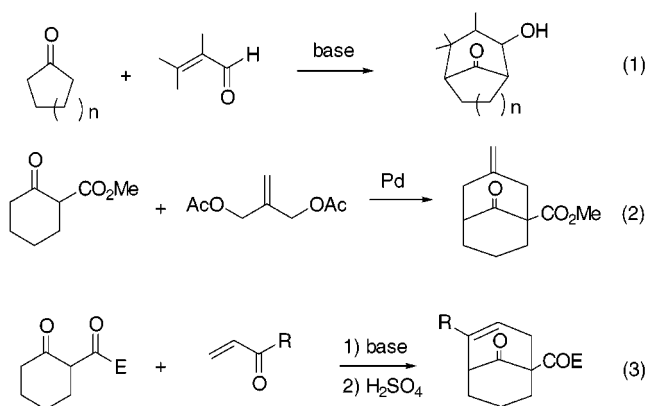
compounds, a [3 + *n*]annulation may take place which is more synthetically important than the *o*-carborane-based [3 + 2]annulation (eq 5). We first examined the TBAF-mediated reaction of dimethyl 1,3-acetonedicarboxylate **1** with crotonaldehyde **2a**, but quite unexpectedly the three-component coupling product **3a** was obtained instead of the two-component coupling [3 + 3] product (eq 6).[9] Herein we report a concise and stereospecific one-shot synthesis of bicyclo[3.3.1]nonane derivatives **3** from *acyclic substrates*, such as dimethyl 1,3-acetonedicarboxylate **1** and enals **2**, via the sequential Michael addition−intramolecular aldolization (eq 6).[10]

Results and Discussion

The condensation reactions between 2 equiv of dimethyl 1,3-acetonedicarboxylate **1** and 1 equiv of enals **2** were carried out in the presence of TBAF or piperidine in THF at room temperature. The results are summarized in Table 1. The reaction of **1** with crotonaldehyde **2a** proceeded very smoothly in the presence of a stoichio-

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(9) Quite recently, a one-pot synthesis of tetrasubstituted phenols from **1** and ynals via a Michael addition−intramolecular aldolization sequence was reported: Covarrubias-Zúñiga, A.; Ríos-Barrios, E. *J. Org. Chem.* **1997,** *62,* 5688.

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**Table 1. Base-Catalyzed Sequential Michael Addition–Intramolecular Aldolization of Dimethyl
1,3-Acetonedicarboxylate 1 to Enals 2**

| entry	enals **2**	base (equiv)	time [a]	product **3**	yield [b] (%)
1	**2a**	TBAF (1.0)	1 h	**3a**	79
2	**2a**	TBAF (0.1)	5 d	**3a**	86
3	**2a**	piperidine (0.1)	6 d	**3a**	99
4	**2a**	pyrrolidine (0.1)	5 d	**3a**	56
5	**2b**	piperidine (0.1)	6 d	**3b**	90
6	**2c**	piperidine (0.1)	5 d	**3c** [c]	90
7	**2d**	TBAF (0.1)	5 d	**3d**	99
8	**2e**	TBAF (0.1)	5 d	**3e** [c]	53
9	**2f**	TBAF (1.0)	1 h	**3f**	64 (83 : 17) [d]

[a] The reaction progress was monitored by TLC. When 1,3-acetonedicarboxylate **1** was consumed completely (time is indicated), the reaction was quenched with an aqueous HCl (1 N) solution. [b] Isolated yield. [c] The detailed assignment of ^{1}H and ^{13}C NMR chemical shifts is indicated in Experimental Section. [d] Diastereomer ratio is shown in the parentheses.

$$(4)$$

$$(5)$$

$$(6)$$

E = CO$_2$Me
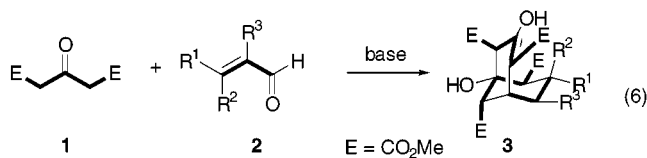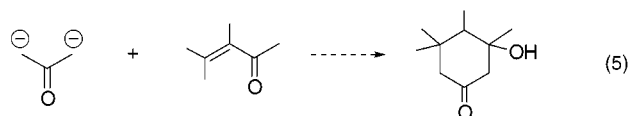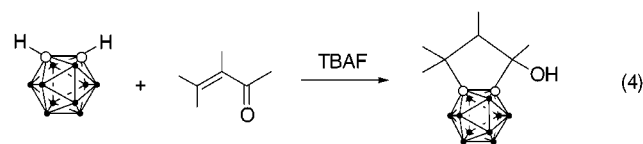
metric amount of TBAF (1.0 equiv), giving the corresponding bicyclic compound **3a** in 79% yield (entry 1). The condensation between **1** and **2a** proceeded even in the presence of a catalytic amount of TBAF (0.1 equiv), and the product **3a** was obtained in 86% yield (entry 2). When a catalytic amount (0.1 equiv) of piperidine was used as a base, **3a** was produced in 99% yield (entry 3). The use of pyrrolidine (0.1 equiv) gave **3a** in lower yield (56%, entry 4). Other β-substituted enals, such as 1-octenal (**2b**) and cinnamaldehyde (**2c**), gave the corresponding bicyclic compounds **3b** and **3c**, respectively, in high yields (entries 5 and 6). The reactions of acrolein (**2d**) and senecialdehyde (**2e**) proceeded more smoothly with catalytic amounts of TBAF (0.1 equiv) than with piperidine, giving **3d** in 99% yield and **3e** in 53% yield, respectively (entries 7 and 8). However, methacrolein (**2f**) needed a stoichiometric amount of TBAF to give **3f** in 64% yield with an 83:17 mixture of diastereomers (entry 9); the major isomer, which is shown as **3f** in the Table 1, has equatorial orientation of the Me group at the C6 position, whereas the minor isomer has axial orientation of the Me group.

Although the structures of **3a**–**f** were determined by their spectroscopic and analytical data, particularly the structure of **3c** was confirmed unambiguously by X-ray analysis (Figure 1). Compound **3c** was stable as its enol form. The ester group substituted at the C32 carbon took axial orientation. The distance between the enol (O12) proton and the conjugated ester oxygen (O15) was 1.86 Å, indicating that a strong hydrogen bonding exists between these two atoms. A weak hydrogen bonding may exists between the hydroxyl (O11) proton and the ester oxygen (O20), since the distance between these two atoms was 2.10 Å, which was significantly shorter than the ordinary van der Waals distance (2.60 Å). However, in the case of enal **2e** (Table 1, entry 8), the corresponding product **3e** was obtained as a ketone form, whose structure was determined by ^{1}H and ^{13}C NMR spectros-
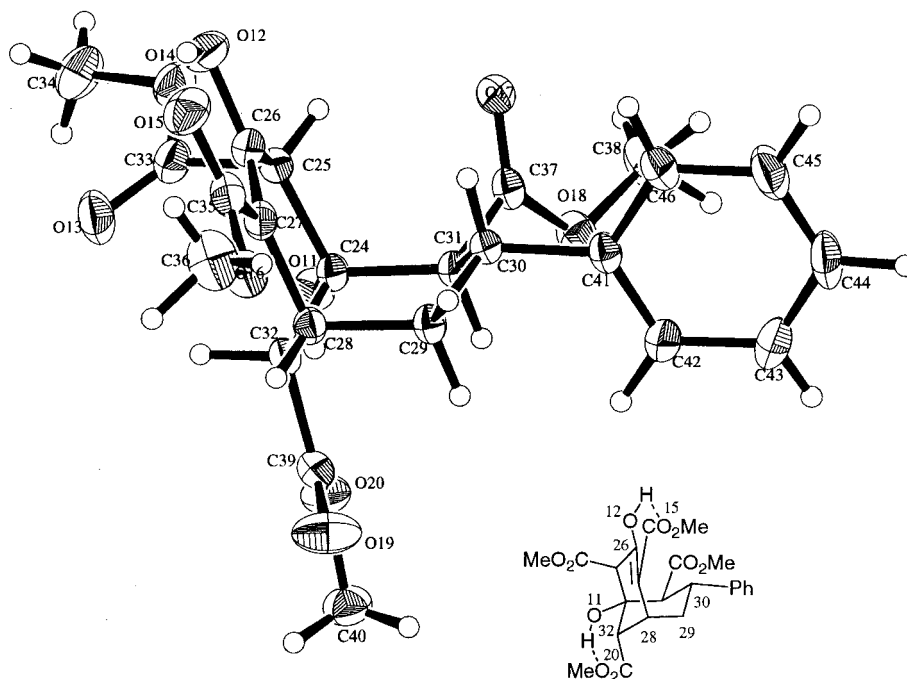
Figure 1. X-ray structure of **3c**.

copy. The ^{1}H NMR signals of enol protons of the bicyclo-[3.3.1]nonenols (**3a**–**d** and **3f**) appeared around δ 12.0, whereas the signal of the proton at the C4 carbon of the nonenone **3e** appeared at δ 4.84. Further, the ^{13}C NMR signals of the C3 carbon of the nonenols (**3a**–**d** and **3f**) appeared around δ 170, whereas the signal of the nonanone **3e** appeared at δ 197.75 (see Experimental Section). These results clearly indicate that **3e** takes a keto form, perhaps because the axial methyl group at C7 forces the ester group at C4 to keep away from it, hampering it from taking an enol form.
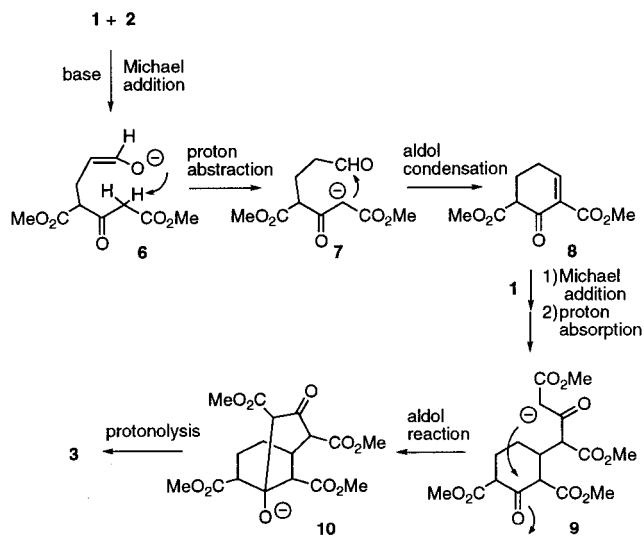
Next, the reaction of **1** with enones **4**, instead of enals **2**, was examined. However, the desired bicyclo[3.3.1]-nonenols were not obtained but the corresponding two-component coupling products, cyclohexenones **5**, were obtained in high yields (eq 7).[11] This result clearly
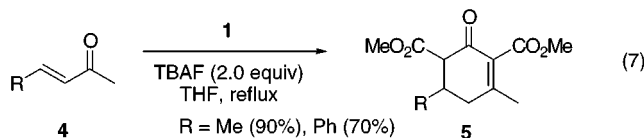
indicated that the second condensation step leading to the formation of bicyclo[3.3.1]nonenol did not take place from **5**. However, the TBAF-mediated reaction of **1** with 2-cyclohexenone occurred very smoothly, giving the corresponding bicyclo[3.3.1]nonenol in essentially quantitative yield. The TBAF-mediated reaction of **1** with 3-methyl-2-cyclohexenone did not take place under the same reaction conditions. Accordingly, it is clear that the Me group at the C3 position of **5** hampered the second condensation step.

On the basis of these observations, a plausible mechanism for the three-component coupling reaction is shown in Scheme 1. The first Michael addition of **1** to **2** would

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Scheme 1

give **6**, which would be converted to **7** on intramolecular hydrogen abstraction. The intramolecular aldol condensation of **7** would give the corresponding conjugated cyclohexenone **8**. The second Michael addition of **1** to **8**, followed by the intramolecular proton exchange, would give **9**. Further intramolecular aldol reaction of **9** would give the desired bicyclo[3.3.1]nonenols **3**. The second aldol step is presumably faster than the first step, because the double bond of the generated enone **8** is highly activated by two carbonyl groups whereas the starting enals **2** have only one carbonyl group. Actually, when the TBAF-catalyzed reaction was carried out with 1 equiv of **1** and 1 equiv of **2a**, the three-component coupling product **3a** was produced without formation of the two-component coupling product **8**. As mentioned above, when the C3 carbon of 2-cyclohexenone derivatives was substituted with Me, the second condensation was halted completely.

Conclusion

We found a concise and stereospecific one-shot synthesis of bicyclo[3.3.1]nonane derivatives **3** from dimethyl 1,3-acetonedicarboxylate **1** and enals **2** via the sequential Michael addition−intramolecular aldolization. In this new synthetic method, both of the two fused rings of **3** are newly constructed from the starting *two acyclic substrates*. We are now in a position to synthesize fascinating structural framework, bicyclo[3.3.1]nonane derivatives, from two different types of acyclic substrates in a one-shot operation. This concise procedure may be applicable to the synthesis of certain natural products containing bicyclo[3.3.1] framework.

Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in CDCl$_3$. The chemical shifts are reported in δ units relative to internal tetramethylsilane. IR spectra were obtained in KBr on a FT spectrophotometer. All commercially supplied chemicals were used without further purification. Column chromatography was performed with silica gel 60 (70−230 mesh).

General Procedure for Synthesis of Bicyclo[3.3.1]-nonenols 3. To a solution of enal **2** (2.0 mmol) and dimethyl 1,3-acetonedicarboxylate **1** (4.0 mmol) in THF (20 mL) was added TBAF (1.0 M in THF, 0.2 mL), and the mixture was stirred at room temperature for 5−6 days. The reaction was quenched by a diluted aqueous HCl (1 N), and the mixture was extracted with ether. The organic layer was neutralized with aqueous NaHCO$_3$ solution, washed with a saturated aqueous NaCl, dried over anhydrous MgSO$_4$, and then concentrated. Purification by silica gel column chromatography (hexane:ethyl acetate = 4:1) gave the bicyclic product **3** as a pure form. The structure of **3c** was confirmed unambiguously by X-ray analysis.

7-Methyl-2,4,8,9-tetramethoxycarbonylbicyclo[3.3.1]-3-nonene-1,3-diol (3a): colorless crystal; IR (KBr) 3500, 1759, 1728, 1668, 1624, 1271, 1215 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 11.98 (s, 1H), 4.52 (s, 1H), 4.47 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 173.45, 172.97, 170.77, 170.12, 167.62, 101.93, 71.95, 57.96, 52.34, 52.09, 51.95, 51.82, 46.48, 34.24, 31.89, 28.05, 19.39. HRMS (FAB) calcd for C$_{18}$H$_{24}$O$_{10}$: *m/z* 400.1370. Found: *m/z* 400.1381. Anal. Calcd for C$_{18}$H$_{24}$O$_{10}$: C, 54.00; H, 6.04. Found: C, 53.80; H, 5.95.

7-Pentyl-2,4,8,9-tetramethoxycarbonylbicyclo[3.3.1]-3-nonene-1,3-diol (3b): colorless crystal; IR (KBr) 3490, 1737, 1710, 1664, 1625, 1265, 1238 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 11.97 (s, 1H), 4.49 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.54 (m, 2H), 2.80 (d, *J* = 15.0 Hz, 1 H), 1.75 (m, 1H), 1.62 (d, *J* = 15.0 Hz, 1 H), 1.30−1.05 (m, 9H), 0.85 (t, *J* = 6.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 173.48, 173.13, 170.78, 170.23, 167.65, 101.89, 72.02, 56.81, 52.48, 52.31, 51.96, 51.81, 46.64, 34.00, 32.83, 31.98, 31.72, 31.24, 25.85, 22.46, 14.01. HRMS (FAB) calcd for C$_{22}$H$_{32}$O$_{10}$: *m/z* 456.1996. Found: *m/z* 456.2010. Anal. Calcd for C$_{22}$H$_{32}$O$_{10}$: C, 57.89; H, 7.07. Found: C, 57.86; H, 7.11.

7-Phenyl-2,4,8,9-tetramethoxycarbonylbicyclo[3.3.1]-3-nonene-1,3-diol (3c): colorless crystal; IR (KBr) 3546, 1724, 1668, 1622, 1440, 1271, 1238 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 12.09 (s, 1H, C4=C3(O*H*)−), 7.26−7.13 (m, 5H, Ar), 4.50 (s, 2H, C1-O*H* + C2-*H*), 3.86 (s, 3H, ester), 3.79 (s, 3H, ester), 3.76 (s, 3 H, ester), 3.67 (d, *J* = 3.1 Hz, 1 H, C9-*H*), 3.61 (dd, *J* = 9.0, 3.1 Hz, 1 H, C5-*H*), 3.44 (s, 3H, ester), 3.42 (s, 1H, C8-*H*), 2.99 (dt, *J* = 12.3, 3.1 Hz, 1 H), 1.76−1.67 (m, 2H, C6-*H*). ^{13}C NMR (CDCl$_3$) δ 173.47, 172.13, 170.85, 170.10, 167.77 (esters + C3), 141.24 (C4), 128.47 (Ar), 127.60 (Ar), 127.03 (Ar), 101.80 (C4), 72.07 (C1), 56.36 (C8), 52.57 (ester-Me), 52.43 (ester-Me), 52.20 (C2), 51.98 (ester-Me), 51.73 (ester-Me), 46.43 (C9), 39.68 (C7), 33.75 (C6), 32.03 (C5). HRMS (FAB) calcd for C$_{23}$H$_{26}$O$_{10}$: *m/z* 462.1526. Found: *m/z* 462.1531. Anal. Calcd for C$_{23}$H$_{26}$O$_{10}$: C, 59.74; H, 5.67. Found: C, 59.85; H, 5.76.

2,4,8,9-Tetramethoxycarbonylbicyclo[3.3.1]-3-nonene-1,3-diol (3d): colorless crystal; IR (KBr) 3487, 1660, 1631, 1440, 1265, 1230 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 12.00 (s, 1H), 4.66 (s, 1H), 4.19 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (s, 6 H), 3.52 (s, 1 H), 3.51 (s, 1H), 3.32 (m, 1H), 1.82 (m, 1 H), 1.59 (m, 3 H). ^{13}C NMR (CDCl$_3$) δ 173.80, 172.99, 170.75, 169.69, 167.38, 101.37, 71.26, 53.07, 52.45, 52.07, 52.04, 51.86, 48.73, 46.63, 52.09, 24.75, 21.46. HRMS (FAB) calcd for C$_{17}$H$_{22}$O$_{10}$: *m/z* = 386.1213. Found: *m/z* 386.1219. Anal. Calcd for C$_{17}$H$_{22}$O$_{10}$: C, 52.85; H, 5.74. Found: C, 52.83; H, 5.74.

7,7-Dimethtyl-1-hydroxy-2,4,8,9-tetramethoxycarbonylbicyclo[3.3.1]-3-nonanone (3e): colorless crystal; IR (KBr) 3508, 1749, 1730, 1203 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 4.84 (dt, *J* = 10.5, 1.5 Hz, 1 H, C4-*H*), 4.56 (d, *J* = 2.0 Hz, 1 H, C2-*H*), 4.37 (d, *J* = 0.8 Hz, 1 H, C1-O*H*), 3.95 (dt, *J* = 12.0, 10.5 Hz, 1 H, C5-*H*), 3.81 (s, 3 H, ester-Me), 3.72 (s, 3 H, ester-Me), 3.71 (s, 3 H, ester-Me), 3.68 (s, 3 H, ester-Me), 3.34 (dd, *J* = 12.0, 0.8 Hz, 1 H, C9-*H*), 3.12 (dd, *J* = 12.0, 2.0 Hz, 1 H, C8-*H*), 2.80 (d, *J* = 18.0 Hz, 1 H, C6-*H*), 2.64 (d, *J* = 18.0 Hz, 1 H, C6-*H*), 1.69 (d, *J* = 1.5 Hz, 3 H, C7-Me), 1.65 (d, *J* = 1.5 Hz, 3 H, C7-Me). ^{13}C NMR (CDCl$_3$) δ 197.75 (C3), 170.54 (ester), 170.44 (ester), 169.86 (ester), 167.67 (ester), 138.12 (C2), 122.10 (C4), 74.82 (C1), 61.93 (C8), 53.25 (C9), 52.71 (ester-Me), 52.12 (ester-Me), 51.92 (ester-Me), 51.85 (ester-Me), 42.48 (C5), 37.63 (C6), 25.91 (C7), 18.20 (Me), 16.76 (Me). HRMS (FAB) calcd for C$_{19}$H$_{26}$O$_{10}$: *m/z* 414.1526. Found: *m/z* 414.1511. Anal. Calcd for C$_{19}$H$_{26}$O$_{10}$: C, 55.07; H, 6.32. Found: C, 54.63; H, 6.34.

6-Methtyl-2,4,8,9-tetramethoxycarbonylbicyclo[3.3.1]-3-nonene-1,3-diol (3f). Two diastereoisomers at C6 carbon of **3f** were obtained with the ratio of 83/17. Colorless crystal. IR (KBr) 3502, 1753, 1737, 1660, 1627, 1251, 1228 cm^{-1}. Major diastereoisomer: ^{1}H NMR (CDCl$_3$) δ 12.28 (s, 1H), 4.63 (s, 1 H), 4.18 (s, 1 H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H), 3.50 (d, *J* = 2.7 Hz, 1 H), 3.40 (dd, *J* = 3.0, 2.7 Hz, 2 H), 1.70 (m, 1 H), 1.69 (dt, *J* = 14.5, 4.0 Hz, 1 H), 1.26 (dd, *J* = 14.5, 13.0 Hz, 1 H), 0.76 (d, *J* = 8.1 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 173.68, 173.06, 171.65, 169.70, 168.22, 98.88, 71.27, 53.28, 52.51, 51.94, 51.66, 48.63, 47.68, 36.52, 31.51, 29.25, 18.91. Minor diastereoisomer: ^{1}H NMR (CDCl$_3$) δ 12.04 (s, 1H), 4.58 (s, 1 H), 4.51 (s, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 6 H), 3.45 (m, 3H), 1.90 (m, 2 H), 1.54 (m, 1 H), 0.76 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$) δ 173.71, 173.09, 171.68, 169.73, 168.29, 98.92, 71.32, 52.17, 51.96, 51.86, 51.81, 44.93, 44.06, 38.21, 31.43, 28.59, 18.16. Anal. Calcd for C$_{18}$H$_{24}$O$_{10}$: C, 53.99; H, 6.04. Found: C, 53.76; H, 5.96.