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An Unusual Fragmentation of Oxetane-Embedded Tetracyclic Ketal Systems

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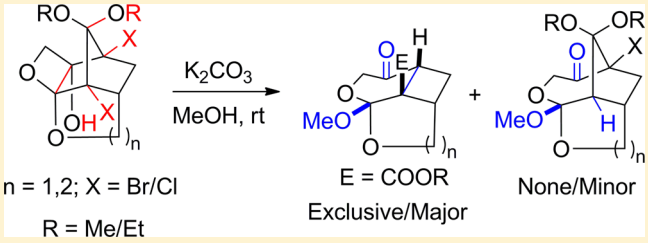
Supporting Information

ABSTRACT: An unusual route for the synthesis of functionalized cyclobutane derivatives starting from functionalized norbornane derivatives is reported. Base-induced fragmentation of an oxetanol-type moiety embedded in a tetracyclic norbornyl ketal leads to a cyclobutane-fused derivative as the major or exclusive product. The fragmentation reaction for bridgehead-bromine-substituted derivatives was much faster than for the corresponding chlorine-substituted substrates. The functionalized cyclobutane product was formed exclusively in high yield in the former case, while the latter furnished a minor uncyclized side product in varying yields.



Strained cyclic ethers are useful intermediates in organic synthesis because of their high reactivity and the variety of their reactions.[1] Moreover, epoxides, oxetanes, and tetrahydrofurans are of major interest in the field of polymer chemistry.[2] Oxetanes are receiving increased attention not only as reactive intermediates in various transformations but also as promising modules in drug discovery, leading to the development of new methods for their preparation.[3−5] There are a few synthetic methodologies of relevance to oxetane incorporation and subsequent elaboration in compounds of pharmacological interest, including taxol,[6] oxetanocin,[7] and oxetin.[8]

The ring opening of oxetane derivatives serves as a useful methodology in synthesis.[9] The oxetane ring is readily opened under acidic conditions,[10] basic conditions,[11] photolytic conditions,[12] etc. Rawal and co-workers reported the synthesis of di- and triquinanes by reductive fragmentation of Paterno−Büchi-derived oxetanes.[13a] With this strategy syntheses of (±)-5-oxosilphiperfol-6-ene and (±)-silphiperfol-6-ene have been accomplished in four and five steps, respectively.[13b] Grainger and co-workers synthesized 1,3-herbetenediol via a Paterno−Büchi photocyclization−oxetane fragmentation strategy.[14] Saurez and co-workers described a reductive opening of hydroxyoxetane upon treatment with imidazole, triphenylphosphine, and iodine.[15] Cohen and co-workers reported a chemoselective cleavage of the C−O bonds in oxetanes employing lithium di-*tert*-butyl biphenylide (LDBB) as the reductant.[16]

Our laboratory has reported diazomethane-mediated molecular rearrangements of easily accessible norbornyl α-keto hemiketals in which reasonable quantities of oxetane-embedded tetracyclic ketals were formed along with other products.[17] The intriguing assemblage of a reactive oxetanol-type moiety onto a norbornyl skeleton in these products prompted us to explore base-induced ring-opening reactions. It is noteworthy that while norbornyl derivatives have been extensively employed in organic synthesis to eventually unravel five- or six-membered carbocycles in a stereoselective manner,[18] their utility for constructing cyclobutanes is scarce. Martinez et al.[19] synthesized a cyclobutane derivative *trans*-fused with an eight membered cyclic ether from the camphor-derived di(spiroepoxide)-substituted 1-norbornyl triflate (obtained in five steps from camphor) in high yield. Tenaglia and Delphine[20] reported the formation of a cyclobutane-fused pyranose derivative by intramolecular [2 + 2] alkene−enone cycloaddition under photolytic conditions. We report herein a base-induced ring-opening study leading to an expeditious route for the synthesis of substituted cyclobutanes starting from functionalized norbornane derivatives.

We exposed methanolic solutions of substrates **1** to anhydrous K_2CO_3 and monitored the outcomes. The results obtained are depicted in Table 1. The chloro analogue **1a** underwent a smooth transformation at ambient temperature in the presence of anhydrous K_2CO_3 in MeOH to furnish a chromatographically separable mixture of two compounds. To our surprise, the major product was identified as cyclobutane-fused pyranose orthoester derivative **2a** on the basis of spectral evidence. The appearance of peaks at 206.8 ppm (C═O) and 170.0 ppm (−CO_2Me) in the ^{13}C NMR spectrum strongly pointed toward a major skeletal reorganization. Unequivocal proof for the structural assignment was established through single-crystal X-ray analysis of the related compound **2f** at a later stage. The second component was characterized as an eight-membered orthoester derivative, **3a**, which showed a peak at 3.07 ppm as a doublet in the ^{1}H NMR spectrum for the

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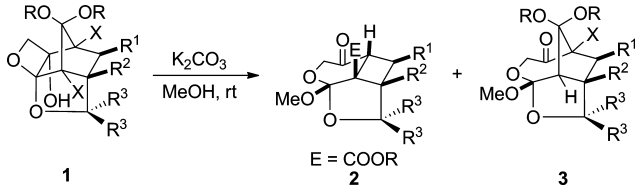
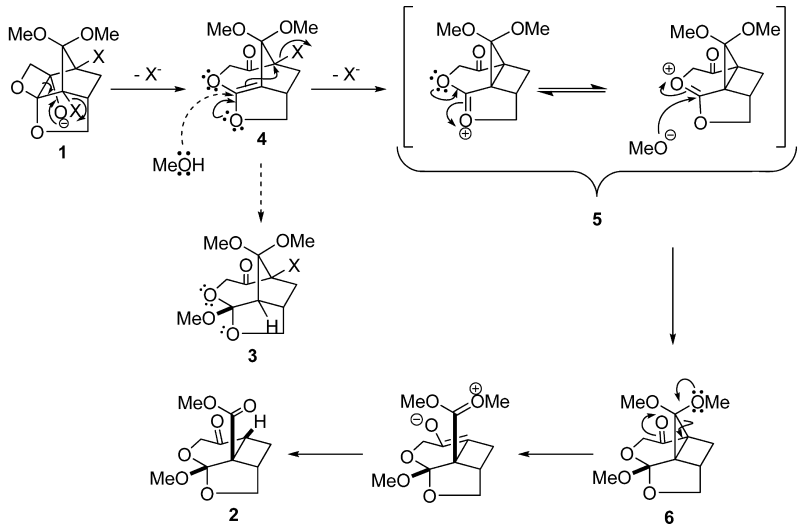
Table 1. Reaction of 1 with K_2CO_3



entry	substrate	R	X	R^1–R^3	time (h)	products, isolated yields (%) 2	3
1	**1a**	Me	Cl	R^1–R^3 = H	24	**2a**, 56	**3a**, 28
2	**1b**	Me	Br	R^1–R^3 = H	5	**2a**, 95	**3b**, –
3	**1c**	Me	Cl	R^1 = R^2 = H; R^3= Me	23	**2c**, 83	**3c**, –
4	**1d**	Me	Br	R^1 = R^2 = H; R^3 = Me	3	**2c**, 93	**3d**, –
5	**1e**	Me	Cl	R^2 = H; R^1 = R^3= Me	30	**2e**, 67	**3e**, 15
6	**1f**	Me	Cl	R^1 = H; R^2 = R^3 = Me	90	**2f**, 65	**3f**, 6
7	**1g**	Et	Cl	R^1–R^3 = H	24	**2g**, 51	**3g**, 26

Scheme 1. Proposed Mechanism for the Formation of 2 and 3



bridgehead hydrogen atom due to its coupling with the neighboring *exo* proton. Once again, the structural assignment was unambiguously confirmed through single-crystal X-ray analysis of the related compound **3g** in that series (vide infra). On the other hand, substrate **1b** under identical reaction conditions gave exclusively the cyclobutane-fused pyranose orthoester **2a** in excellent yield in a much shorter reaction time (Table 1, entry 2). Unlike in the case of chloro analogue **1a**, the eight-membered orthoester **3** was not detected.

Interestingly, the introduction of various methyl groups at R^1 to R^3 in **1** influenced the reaction outcome appreciably in the sense that the byproduct **3c** was not detected for the chloro analogue **1c**, in contrast to the result for **1a** under identical conditions, while for substrates **1e** and **1f** the corresponding byproducts **3e** and **3f** were formed in 15% and 6% yield, respectively. The bromo analogue **1d**, like **1b**, afforded **2c** in excellent yield in a short reaction time. The ^{1}H NMR spectral data revealed a diagnostic pair of signals at 4.41 and 4.14 ppm with a coupling constant of 17.3 Hz for the methylene group (−CO−C*H*$_2$−O), and in the ^{13}C NMR spectrum peaks appeared at 206.7 ppm (C═O), 170.3 ppm (−CO_2Me), and 117.7 ppm for the carbon attached to three oxygen atoms. These data strongly supported the assignments, which were consistent throughout the series.

A plausible mechanism for the formation of **2** and **3** is depicted in Scheme 1. Exposure of **1** to base would lead to abstraction of the proton from the hydroxyl group, triggering fragmentation of the susceptible C−C bond with the expulsion of the *β*-halogen leaving group to form reactive ketene acetal intermediate **4**. Intramolecular nucleophilic displacement of the bridgehead *α*-keto halogen would give a stabilized oxocarbenium intermediate **5**, which upon being quenched by the solvent MeOH would give donor−acceptor-substituted cyclopropane derivative **6**.[21] This intermediate represents an ideal push−pull system that is well-poised for the initial cleavage to give an enolate, which would then tautomerize to ketone **2**. The formation of byproduct **3** in the case of chloro analogues may be rationalized from the proposed highly reactive ketene acetal intermediate **4** through addition of solvent MeOH. The difference in the leaving-group abilities of bromine vs chlorine atoms in **1** during intramolecular nucleophilic displacement of the bridgehead *α*-keto halogen might be mainly responsible for the formation of byproduct of **3** in the case of chloro analogues.

In order to further support the mechanistic proposal described in Scheme 1, an experiment was set up with diethyl ketal analogue **1g**. In this case, an ethyl ester rather than a methyl ester derivative of cyclobutane was expected. Treatment of **1g** with K_2CO_3 under the usual conditions furnished

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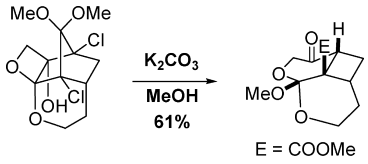
cyclobutane-fused pyranose orthoester **2g** and eight-membered tricyclic orthoester **3g** in 51% and 26% yield, respectively, as shown in Table 1, entry 7. Unambiguous structural proof for the eight-membered tricyclic orthoester **3g** was established by single-crystal X-ray analysis.

Altering the size of the ketal-forming rings connected to the oxetane moiety from five- to six-membered seemed to have no significant influence on the reaction outcome. Subjecting substrate **7** to the aforementioned fragmentation conditions furnished cyclobutane-fused pyranose derivative **8** in moderate yield, as shown in Scheme 2.

Scheme 2. Reaction of 7 with K_2CO_3



7 **8**

In conclusion, base-induced fragmentation of oxetane-embedded tetracyclic ketals leading to cyclobutane-fused pyranose derivatives and eight-membered orthoester side products is reported. The bromo analogues furnished a single fragmentation product in excellent yield, while the corresponding chloro analogues gave, in addition to the expected product, a byproduct resulting from the reaction of the proposed highly reactive ketene acetal intermediate with solvent MeOH. A plausible mechanism involving the formation of a transient donor–acceptor-substituted cyclopropane derivative is proposed.

EXPERIMENTAL SECTION

Starting Materials. For the preparation of the starting materials **1a–g** and **7**, see ref 17.

General Procedure for the Fragmentation of Norbornyl Hydroxy Oxetanes under Basic Conditions. To a solution of norbornyl oxetanol **1a** (300 mg, 1.01 mmol) in dry MeOH (2 mL) under argon was added anhydrous K_2CO_3 (280 mg, 2.02 mmol), and the mixture was stirred at room temperature until the disappearance of the starting material as monitored by TLC. The reaction mixture was diluted with water (8 mL), and the organic layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine solution (5 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated in vacuo to furnish a residue that was purified by silica gel column chromatography to afford cyclobutane-fused tricyclic orthoester **2a** and cyclic orthoester **3a**.

*4-Methoxy-9-methoxycarbonyl-3,5-dioxatricyclo[6.1.1.0^{4,9}]-decan-7-one (**2a**).* After silica gel column chromatography (13% EtOAc/hexane), compound **2a** was obtained as a colorless solid (160 mg, 56%); mp 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (d, 1H, J = 17.5 Hz), 4.26 (d, 1H, J = 17.5 Hz), 4.05 (dd, 1H, J = 9.2, 5.3 Hz), 3.93 (d, 1H, J = 9.2 Hz), 3.78 (s, 3H), 3.39 (s, 3H), 3.29–3.19 (m, 2H), 2.75–2.66 (m, 1H), 2.02–1.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 170.1, 118.1, 71.5, 70.0, 56.3, 52.6, 49.2, 41.4, 38.0, 27.1. IR (KBr): 2940, 1720 (CO_2Me), 1700 (C=O), 1260 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{11}H_{14}O_6$ $[M]^+$, 242.0790; found, 242.0792.

*8-Chloro-4,9,9-trimethoxy-3,5-dioxatricyclo[6.2.1.0^{4,10}]undecan-7-one (**3a**).* After silica gel column chromatography (8% EtOAc/hexane), compound **3a** was obtained as a colorless solid (85 mg, 28%); mp 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (d, 1H, J = 16.5 Hz), 4.47 (d, 1H, J = 16.5 Hz), 3.98 (dd, 1H, J = 9.0, 5.1 Hz), 3.83 (d, 1H, J = 9.0 Hz), 3.47 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.07 (d, 1H, J = 7.5 Hz), 3.01–2.95 (m, 1H), 2.72 (dd, 1H, J = 15.2, 10.5 Hz), 2.49 (dd, 1H, J = 15.2, 5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 120.6, 107.1, 83.6, 71.1, 68.8, 56.6, 52.0, 50.0, 49.7, 46.0, 38.1. IR (KBr): 2850, 1720 (C=O), 1320, 1220 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{12}H_{17}O_6Cl$ $[M]^+$, 292.0714; found, 292.0718.

*4-Methoxy-2,2-dimethyl-9-methoxycarbonyl-3,5-dioxatricyclo-[6.1.1.0^{4,9}]decan-7-one (**2c**).* After silica gel column chromatography (7% EtOAc/hexane), compound **2c** was obtained as a colorless solid (22 mg, 93%); mp 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (d, 1H, J = 17.3 Hz), 4.14 (d, 1H, J = 17.3 Hz), 3.74 (s, 3H), 3.35 (s, 3H), 3.14 (dd, 1H, J = 11.7, 6.8 Hz), 2.98 (dd, 1H, J = 9.0, 6.0 Hz), 2.40 (ddd, 1H, J = 12.9, 12.5, 9.0 Hz), 2.16 (ddd, 1H, J = 12.5, 10.5, 6.0 Hz), 1.40 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 170.3, 117.7, 83.2, 68.4, 59.4, 52.5, 49.7, 47.0, 41.2, 27.7, 23.6, 22.5. IR (KBr): 2850, 1700, 1420, 1300 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{13}H_{18}O_6$ $[M]^+$, 270.1103; found, 270.1105.

*4-Methoxy-1,2,2-trimethyl-9-methoxycarbonyl-3,5-dioxatricyclo-[6.1.1.0^{4,9}]decan-7-one (**2e**).* After silica gel column chromatography (7% EtOAc/hexane), compound **2e** was obtained as a colorless solid (19 mg, 67%); mp 94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (d, 1H, J = 17.0 Hz), 4.10 (d, 1H, J = 17.0 Hz), 3.72 (s, 3H), 3.34 (s, 3H), 2.65 (d, 1H, J = 7.0 Hz), 2.57–2.54 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.18 (d, 3H, J = 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 170.5, 118.1, 83.4, 68.0, 56.1, 55.5, 52.4, 49.7, 49.3, 31.9, 27.6, 23.1, 21.3. IR (KBr): 2900, 1730, 1700, 1420, 1260 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.91; H, 7.06.

*8-Chloro-4,9,9-trimethoxy-2,2,11-trimethyl-3,5-dioxatricyclo-[6.2.1.0^{4,10}]undecan-7-one (**3e**).* After silica gel column chromatography (7% EtOAc/hexane), compound **3e** was obtained as a colorless solid (5 mg, 15%); mp 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61 (d, 1H, J = 16.5 Hz), 4.34 (d, 1H, J = 16.5 Hz), 3.41 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 3.29 (d, 1H, J = 7.5 Hz), 2.59–2.55 (m, 1H), 2.15 (t, 1H, J = 7.0 Hz), 1.35 (s, 3H), 1.35 (s, 3H), 1.11 (d, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 119.6, 107.9, 89.8, 81.4, 67.7, 57.9, 56.7, 51.9, 50.0, 49.7, 40.5, 28.7, 23.0, 20.8. IR (KBr): 2900, 1720, 1440, 1260 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{15}H_{23}O_6Cl$ $[M]^+$, 334.1183; found, 334.1182.

*4-Methoxy-2,2,10-trimethyl-9-methoxycarbonyl-3,5-dioxatricyclo[6.1.1.0^{4,9}]decan-7-one (**2f**).* After silica gel column chromatography (8% EtOAc/hexane), compound **2f** was obtained as a viscous liquid (19 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (d, 1H, J = 16.3 Hz), 4.05 (d, 1H, J = 16.3 Hz), 3.64 (s, 3H), 3.30 (s, 3H), 3.08–3.03 (m, 1H), 2.52–2.47 (m, 1H), 1.81 (t, 1H, J = 11.4 Hz), 1.32 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 169.9, 118.8, 87.3, 68.2, 61.4, 53.7, 52.8, 50.4, 40.4, 31.9, 25.2, 22.4, 17.9. IR (neat): 2900, 1720, 1420, 1260 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{14}H_{20}O_6$ $[M]^+$, 284.1260; found, 284.1261.

*8-Chloro-4,9,9-trimethoxy-1,2,2-trimethyl-3,5-dioxatricyclo-[6.2.1.0^{4,10}]undecan-7-one (**3f**).* After silica gel column chromatography (7% EtOAc/hexane), compound **3f** was obtained as a viscous liquid (2 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (d, 1H, J = 16.5 Hz), 4.22 (d, 1H, J = 16.5 Hz), 3.39 (s, 3H), 3.29 (s, 3H), 3.27 (s, 3H), 2.89 (s, 1H), 2.79 (d, 1H, J = 16.1 Hz), 1.99 (d, 1H, J = 16.1 Hz), 1.23 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 118.9, 84.6, 83.9, 67.8, 61.9, 52.6, 51.5, 50.0, 49.3, 48.5, 29.6, 25.1, 22.5, 21.7. IR (neat): 2900, 1700, 1360, 1160 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{15}H_{23}O_6Cl[M]^+$, 334.1183; found, 334.1181.

*4-Methoxy-9-ethoxycarbonyl-3,5-dioxatricyclo[6.1.1.0^{4,9}]decan-7-one (**2g**).* After silica gel column chromatography (8–10% EtOAc/hexane), compound **2g** was obtained as a viscous liquid (26 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (d, 1H, J = 17.5 Hz), 4.23–4.13 (m, 3H), 3.98 (dd, 1H, J = 9.2, 5.3 Hz), 3.84 (d, 1H, J = 9.2 Hz), 3.31 (s, 3H), 3.21–3.11 (m, 2H), 2.67–2.58 (m, 1H), 1.94–1.88 (m, 1H), 1.21 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 169.6, 118.1, 71.4, 69.5, 61.3, 56.3, 49.0, 41.4, 38.0, 27.0, 14.0. IR (neat): 2900, 1720 (CO_2Et), 1700 (C=O), 1430, 1320 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{12}H_{16}O_6$ $[M]^+$, 256.0947; found, 256.0945.

*8-Chloro-9,9-diethoxy-4-methoxy-3,5-dioxatricyclo[6.2.1.0^{4,10}]-undecan-7-one (**3g**).* After silica gel column chromatography (4%

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EtOAc/hexane), compound **3g** was obtained as a colorless solid (17 mg, 26%); mp 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (d, 1H, J = 16.5 Hz), 4.39 (d, 1H, J = 16.5 Hz), 3.89−3.81 (m, 2H), 3.74−3.70 (m, 2H), 3.65−3.62 (m, 1H), 3.59−3.50 (m, 1H), 3.28 (s, 3H), 2.96 (d, 1H, J = 7.5 Hz), 2.94−2.87 (m, 1H), 2.64 (dd, 1H, J = 14.7, 11.1 Hz), 2.36 (dd, 1H, J = 14.7, 4.6 Hz), 1.17 (t, 3H, J = 7.0 Hz), 1.10 (t, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 120.0, 106.9, 83.7, 71.0, 69.3, 60.3, 57.9, 57.4, 49.5, 45.8, 38.9, 15.5, 14.9. IR (KBr): 2950, 1720, 1440, 1200 cm^{-1}. ESI-TOF-HRMS: m/z calcd for $C_{14}H_{21}O_6ClNa$ $[M + Na]^+$, 343.0924; found, 343.0920.

*5-Methoxy-10-methoxycarbonyl-4,6-dioxatricyclo[7.1.1.0^{5,10}]-undecane-2-one (**8**).* After silica gel column chromatography (14−16% EtOAc/hexane), compound **8** was obtained as a colorless solid (14 mg, 61%); mp 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31−4.27 (m, 1H), 4.26 (d, 1H, J = 18.0 Hz), 4.11 (d, 1H, J = 18.0 Hz), 4.01−3.97 (m, 1H), 3.69 (s, 3H), 3.31 (m, 1H), 3.31 (s, 3H), 3.0−2.94 (m, 1H), 2.41−2.33 (m, 1H), 2.19−2.12 (m, 1H), 2.07−1.97 (m, 1H), 1.4−1.36 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 171.8, 109.0, 68.6, 60.2, 52.2, 49.8, 48.5, 44.0, 34.1, 24.4, 22.7. IR (KBr): 2850, 1720 (CO_2Me), 1700 (C═O), 1420, 1240 cm^{-1}. EI-TOF-HRMS: m/z calcd for $C_{12}H_{16}O_6$ $[M]^+$, 256.0947; found, 256.0945.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds, ORTEP diagrams for compounds **2c** and **3g**, and their crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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