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Synthesis of 2,8-Dioxabicyclo[3.3.1]nonane Derivatives via a Sequential Knoevenagel Condensation and Hetero-Diels–Alder Reaction in an Aqueous Medium

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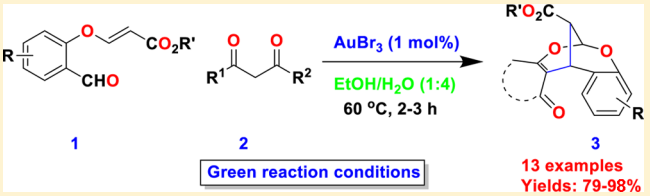
Supporting Information

ABSTRACT: Utilizing aldehyde-substituted vinylogous carbonates and 1,3-diketones, a simple protocol is presented for the synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives via Knoevenagel condensation followed by a hetero-Diels–Alder reaction under green reaction conditions. The structure of a key product is unequivocally confirmed by X-ray crystallography.



Tandem/domino reactions are a powerful tool in organic synthetic chemistry that allows for efficient and stereoselective construction of a plethora of complex molecules from simple starting materials and combines a variety of transformations in a single reaction vessel.[1] These reactions have been studied in detail by Tietze and co-workers.[2] The domino Knoevenagel and hetero-Diels–Alder reactions of alkene-substituted aromatic and aliphatic aldehydes with different 1,3-dicarbonyl compounds have been described previously.[3] An important way to reduce human effort, the amount of chemical waste, and cost is to use tandem reactions, as they involve multiple sequences of reactions in a single step or one-pot process.[4]

The 2,8-dioxabicyclo[3.3.1]nonane motifs have been identified as attractive synthetic targets because of their prevalence in many naturally occurring products and due to their medicinally interesting bioactivities (Chart 1).[5] In accordance, a great deal of effort has been devoted to the synthesis of similar types of molecular frameworks in recent years.[5,6] Recently, this type of motifs have been synthesized via a silver triflate catalyzed reaction of 2-hydroxychalcones with naphthols/substituted phenols[6a] and an iodine-catalyzed reaction of 2-hydroxychalcones with 4-hydroxycoumarines as starting precursors under environmentally benign conditions.[6b] A proline-catalyzed reaction toward these derivatives has also been described; however, the reaction time was longer (24 h), and more importantly, the use of acetylacetone and 1,3-cyclopentadione failed to give the 2,8-dioxabicyclo[3.3.1]nonane derivatives even at elevated temperatures.[6c]

Organic reactions in aqueous media have attracted much attention because (i) water induces unique reactivity and selectivity that are not observed for reactions in organic media and (ii) water as solvent reduces the use of harmful organic solvents and may lead to the development of environmentally friendly chemical processes.[7] It is also important to note that the Diels–Alder reactions can be accelerated in water medium.[8]

Vinylogous carbonates have been extensively used in organic synthesis for the construction of many heterocycles and polycyclics having pharmaceutical and biological significance. For example, Gharpure and co-workers have been working extensively on these substrates to achieve the benzoxepines, oxa-/aza-angular triquinanes, 2,3-disubstituted dihydrobenzofurans, oxazino[4,3-*a*]indoles, unsymmetrical dioxa-cage compounds, 2,3,3,5-tetrasubstituted tetrahydrofurans, and (+)-Hagen's gland lactones.[9,10] On the basis of previous results and keeping the importance of these vinylogous carbonates in mind, herein we report a method for the construction of the 2,8-dioxabicyclo[3.3.1]nonane derivatives by using a gold(III)-catalyzed reaction of aldehyde-substituted vinylogous carbonates and 1,3-diketones via a domino KC/HDA sequence in an aqueous medium. Gold catalysts have become a well-established synthetic tool for the construction of several heterocycles and polycyclics because simple hydrocarbons such as alkenes, alkynes, or allenes can be selectively activated toward the attack of a plethora of carbon- and heteroatom-based nucleophiles under very mild conditions.[11]

The required compounds are aldehyde-based vinylogous carbonates **1a–e** that are prepared from the commercially available substituted salicyladehydes and ethyl propiolate or methyl propiolate (Scheme 1).[12]

At the outset, vinylogous carbonate **1a** and the acetylacetone **2a** were selected as the model substrates for the $AuBr_3$-catalyzed Knoevenagel condensation/hetero-Diels–Alder (KC/HDA) reaction. The diketone **2a** was found to be less reactive when compared to the diketones **2c–d**.[6c] Thus, we chose this diketone (**2a**) for the optimization reactions and improvement of the product yields (Table 1). The reaction of vinylogous carbonate **1a** with diketone **2a** in dichloroethane (DCE) as the solvent at 80 °C in the absence of any catalyst did not produce the expected product (Table 1, entry 1), and the use of

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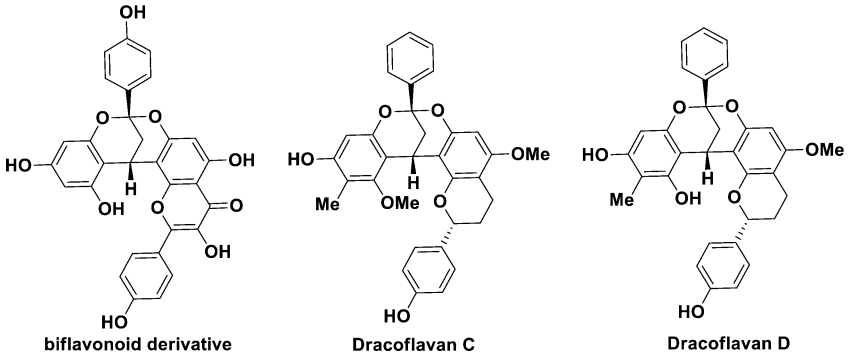
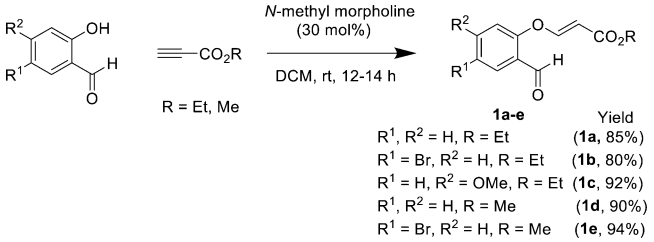
Chart 1. Natural Products Containing 2,8-Dioxabicyclo[3.3.1]nonane Skeleton

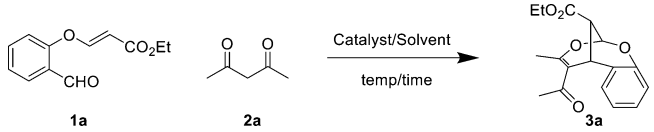


Scheme 1. Synthesis of Aldehyde-Substituted Vinylogous Carbonates 1a–e



organocatalyst D-proline in EtOAc as the solvent produced only 5% of the isolated product **3a** (Table 1, entry 2). Therefore, we changed our attention to the metal catalysts. The use of $ZnBr_2$ (20 mol %) in dichloroethane (DCE) at 80 °C failed to give the product (Table 1, entry 3). With $Zn(OTf)_2$ (10 mol %) as catalyst in DCE or toluene, product **3a** was formed in moderate yields (Table 1, entries 4 and 5). The use of metal salts like AgOTf (10 mol %) or $FeCl_3$(10 mol %) in DCE at 60 °C gave the product **3a** in moderate yield (Table 1, entries 6 and 7). Fortunately, when the reaction was performed with $AuBr_3$ (5 mol %) in DCE, product **3a** was produced in an excellent yield (Table 1, entry 8). To our surprise, decreasing the catalyst loading to 1.0 mol % also afforded the product in an excellent yield (Table 1, entry 9). In our recent studies, we have reported the propargylamine synthesis by using gold(III) salt as catalyst in a water medium.[11h] Therefore, we performed the Knoevenagel condensation/hetero-Diels–Alder (KC/HDA) reactions in the aqueous medium, but the yield was very low (Table 1, entry 10). To our surprise, however, when vinylogous carbonate **1a** was treated with the diketone **2a** using catalytic $AuBr_3$ (1 mol %) in ethanol/water (1:1), compound **3a** was produced in excellent yield (Table 1, entry 11). Changing the ratio of ethanol/water to 1:4 also provided an excellent yield (Table 1, entry 12). The reaction time was longer (4 h) when we used 1.0 molar equiv of the 1,3-diketone, and the yield of the compound **3a** did not change (92%) by decreasing the 1,3-

Table 1. Optimization Studies for the Synthesis of 2,8-Dioxabicyclo[3.3.1]nonane Derivative 3a



entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%) (**3a**)
1		DCE	80	24	NR[a]
2	D-proline	EtOAc	50	24	5
3	$ZnBr_2$ (20)	DCE	80	18	NR[a]
4	$Zn(OTf)_2$ (10)	DCE	60	18	58
5	$Zn(OTf)_2$ (10)	toluene	100	20	43
6	AgOTf (10)	DCE	60	7	62
7	$FeCl_3$ (10)	DCE	80	6	36
8	$AuBr_3$ (5)	DCE	50	8	89
9	$AuBr_3$ (1)	DCE	50	8	85
10	$AuBr_3$ (1)	H_2O	60	10	10
11	$AuBr_3$ (1)	EtOH/H_2O (1:1)	60	4	95
12	$AuBr_3$ (1)	EtOH/H_2O (1:4)	60	2	92
13	$Zn(OTf)_2$ (10)	EtOH/H_2O (1:1)	80	16	43
14	$FeCl_3$ (10)	EtOH/H_2O (1:1)	80	18	NR[a]
15	CuI (10)	EtOH/H_2O (1:1)	80	20	NR[a]
16	$AuBr_3$ (5)	DMF	100	18	50
17	$AuBr_3$ (5)	toluene	100	14	64
18	$AuBr_3$ (5)	THF	60	20	42
19	$AuBr_3$ (5)	acetonitrile	80	16	54

[a]NR = no reaction.

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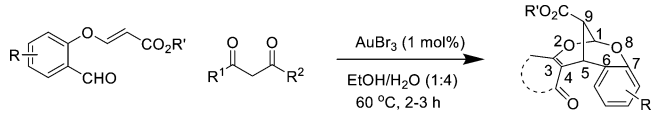
Table 2. Substrate Scope of the Synthesis of 2,8-Dioxabicyclo[3.3.1]nonane Derivatives 3a−m



entry	vinylogous carbonate (**1**)	1,3-diketone (**2**)	product (**3**)	yield (%)[a]
1	**1a**	**2a**	**3a**	92
2	**1b**	**2a**	**3b** (X-ray)	88
3	**1b**	**2b**	**3c**	79
4	**1a**	**2c**	**3d**	98
5	**1b**	**2c**	**3e**	96
6	**1c**	**2c**	**3f**	90
7	**1a**	**2d**	**3g**	95
8	**1b**	**2d**	**3h**	98
9	**1c**	**2d**	**3i**	92
10	**1d**	**2a**	**3j**	95
11	**1e**	**2b**	**3k**	86
12	**1e**	**2c**	**3l**	96
13	**1e**	**2d**	**3m**	90

[a]Reaction conditions: compound **1** (0.23 mmol) and compound **2** (0.46 mmol) in ethanol/water (1:4, 4 mL) and $AuBr_3$ (1.0 mg, 0.0023 mmol) at 60 °C for 2−3 h.

diketone molar equivalents. Thus, we believe that the reaction can be performed by using green conditions that can reduce the chemical waste. However, except for $Zn(OTf)_2$, the use of other metal salts like $FeCl_3$ and CuI did not produce the KC/HDA product (Table 1, entries 13−15). We have also studied the solvent effect by using $AuBr_3$ (5 mol %) as the catalyst. When the reaction was carried out by changing the solvents, such as DMF, toluene, THF, and acetonitrile, the product **3a** was obtained in moderate yields (Table 1, entries 16−19).

With the optimal reaction conditions in hand, we then examined the KC/HDA reaction of various aldehyde-based vinylogous carbonates **1a−e** and 1,3-diketones **2a−d** in aqueous medium to afford the bicyclic compounds (**3**) in good yields (Table 2). The incorporation of the gold(III) catalyst increased the yield, and the reaction was completed in a short reaction time (2−3 h) when compared to the proline-catalyzed conditions. By using the optimized conditions, the vinylogous carbonates **1a,b** were treated with acetylacetone (**2a**) to yield the products **3a,b** in excellent yields (92% and 88%, entries 1 and 2, Table 2). These compounds are characterized by their $^1H/^{13}C$ NMR spectra. The product **3b** was further confirmed by single-crystal X-ray crystallography (see the Supporting Information, Figure S1). It is interesting to note that the reaction of bromine-substituted vinylogous carbonate **1b** with the less reactive 1,3-cyclopantadione **2b** also afforded the product **3c** in good yield (79%, Table 2). The bromine-substituted and methoxy-substituted vinylogous carbonates **1b,c** also reacted smoothly with the diketones **2c,d** to yield the final products **3d−i**. The reaction mixture contained exclusively the final product, and it could be easily passed through a short silica gel column to afford the expected product in excellent isolated yields (90−98%, entries 4−9, Table 2). The different types of vinylogous carbonates **1d−e** were also employed as the starting materials to establish the generality of the present transformation. When compound **1d** was treated with acetylacetone (**2a**), it was interesting to note that the reaction successfully yielded the expected product **3j** in high yield (95%, entry 10, Table 2). In a similar manner, the reaction

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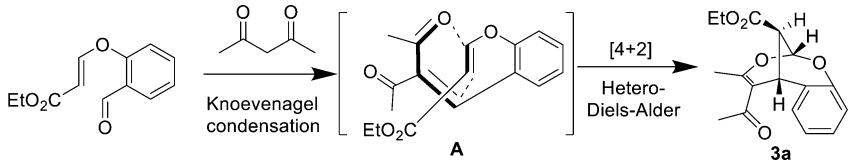
Scheme 2. Possible Pathway for the Formation of Compound 3a via KC/HDA Reaction



of bromine-substituted compound **1e** with 1,3-cyclopentadione (**2b**) also furnished the product **3k** in excellent yields (86%, entry 11, Table 2). Finally, reaction of the compound **1e** with 1,3-diketones **2c**,**d** was also gave the expected products **3l**,**m** in very good yields (96% and 90%, entries 12 and 13, Table 2). Overall, these results highlight the great potential and versatility of the method, which provides a direct and practical access to highly valuable 2,8-dioxabicyclo[3.3.1]nonane derivatives from readily accessible starting materials.

On the basis of a previous report,[13] the present Au(III)-catalyzed domino process can be rationalized as depicted in Scheme 2. Initially, the intermediate **A** was formed via Knoevenagel condensation, and then this intermediate **A** underwent hetero-Diels–Alder reaction in [4 + 2] fashion to form only one diastereomer (**3a**). It may be due to the restricted conformation of intermediate **A**, as revealed from the X-ray crystal structure of final product **3b** (Figure S1, Supporting Information).

In summary, we have described an effective $AuBr_3$-catalyzed protocol for the synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives via the domino Knoevenagel condensation/hetero-Diels–Alder reaction in an aqueous reaction medium. The precursors used are aldehyde-based vinylogous carbonates and 1,3-diketones. We have also shown that the less reactive 1,3-diketones such as acetylacetone and 1,3-dicyclopentadione are effective under the reaction conditions to provide 2,8-dioxabicyclo[3.3.1]nonane derivatives. The products are important motifs in many natural products and pharmaceuticals, and this atom-economical and mild approach delivers an attractive alternative to the classical protocols.

EXPERIMENTAL SECTION

General Remarks. All materials were obtained and used as received from commercial sources unless otherwise noted. Melting points were recorded on a micromelting point apparatus. Infrared (IR) spectra were recorded on a FT/IR (Fourier transform infrared spectrometer) in $CHCl_3$. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were determined at rt on a 400 MHz spectrometer in $CDCl_3$ solution. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane for ^1H spectra and are referenced to $CDCl_3$ for ^{13}C (δ_C 77.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet and m = multiplet), coupling constants (Hz), and integration. The mass spectra (MS) were measured on a mass spectrometer (EI). Analytical thin-layer chromatography (TLC) was performed on a silica gel glass plate. Silica gel 60N (spherical, neutral) was received by local manufacturer and used for flash column chromatography, and the column was usually eluted with ethyl acetate–hexane mixture. The starting materials **1a**–**e** are prepared by following the reported procedures, and the $^1H/^{13}C$ NMR data are consistent with the reported compounds.[12]

General Procedure for the Synthesis of 2,8-Dioxabicyclo-[3.3.1]nonane Derivative (3a). To a solution of **1a** (0.23 mmol) and **2a** (0.46 mmol) in ethanol/water (1:4, 4 mL) was added $AuBr_3$ (1.0 mg, 0.0023 mmol) and the mixture stirred at 60 °C for 2–3 h. When there was no starting material remaining (TLC or ^1H NMR), the reaction mixture was concentrated in vacuo. Then the mixture was diluted with ethyl acetate (10 mL), and an excess of water (5 mL) and extracted. The aqueous layer was washed again with ethyl acetate (10 mL). The combined organic layer was washed with water (10 mL) and saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4. Subsequent evaporation of organic solvent by using a rotary evaporator afforded a brown gummy material. The residue was purified by silica gel column chromatography [hexanes/ethyl acetate (1:4)] to give the final compound **3a**.

The remaining products (**3b**–**m**) were also prepared by following the general procedure using the same molar quantities of **1a**–**e** and **2a**–**d**.

*Compound **3a**:* yield 0.066 g (92%); gummy liquid; IR ($CHCl_3$, cm^{-1}) 2951, 1739, 1631, 1472, 1386, 1229; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.3 Hz, 3H), 2.21 (s, 3H), 2.39 (s, 3H), 3.07 (dd→t, J = 1.3 Hz, 1H), 4.13–4.26 (m, 2H), 4.60 (br, 1H), 6.24 (t, J = 1.8 Hz, 1H), 6.88–6.95 (m, 2H), 7.11–7.16 (m, 1H), 7.30–7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.5, 28.9, 30.9, 40.1, 61.5, 91.5, 116.5, 121.9, 125.4, 128.2, 128.3, 150.1, 162.2, 168.4, 196.0; MS (EI) m/z 302 $[M]^+$. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.41; H, 5.73.

*Compound **3b**:* yield 0.076 g (88%); mp 152–154 °C; IR ($CHCl_3$, cm^{-1}) 2952, 1740, 1632, 1472, 1386, 1228; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.39 (s, 3H), 3.03 (dd→t, J = 1.4 Hz, 1H), 4.12–4.26 (m, 2H), 4.59 (br, 1H), 6.24 (t, J = 1.8 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 8.7, 2.2 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.6, 28.5, 31.0, 39.8, 61.6, 91.4, 114.2, 116.4, 118.3, 127.6, 130.9, 131.2, 149.4, 162.4, 168.0, 195.5; MS (EI) m/z 380 $[M]^+$. Anal. Calcd for $C_{17}H_{17}BrO_5$: C, 53.56; H, 4.50. Found: C, 53.23; H, 4.64. This compound was crystallized from ethyl acetate/hexane (1:9, 2 mL) mixture at 20 °C. The X-ray structure was determined for this sample (Figure S1, Supporting Information).

*Compound **3c**:* yield 0.068 g (79%); mp 157–159 °C; IR ($CHCl_3$, cm^{-1}) 2952, 1741, 1634, 1472, 1385, 1286; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.4 Hz, 3H), 2.40–2.45 (m, 2H), 2.53–2.57 (m, 2H), 3.13 (dd→t, J = 2.3 Hz, 1H), 4.16–4.24 (m, 3H), 6.42 (t, J = 1.8 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 7.22–7.26 (m, 1H), 7.43 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.8, 26.3, 34.3, 40.3, 61.9, 94.2, 114.6, 118.3, 118.7, 126.9, 130.6, 131.4, 149.8, 167.4, 181.2, 200.5; MS (EI) m/z 378 $[M]^+$. Anal. Calcd for $C_{17}H_{15}BrO_5$: C, 53.85; H, 3.99. Found: C, 53.85; H, 4.17.

*Compound **3d**:* yield 0.077 g (98%); mp 163–165 °C; IR ($CHCl_3$, cm^{-1}) 2966, 1734, 1631, 1462, 1387, 1234; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 0.99 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.16–2.32 (m, 4H), 3.11 (dd→t, J = 2.8 Hz, 1H), 4.12–4.24 (m, 2H), 4.54 (br, 1H), 6.30 (t, J = 4.1 Hz, 1H), 6.86–6.92 (m, 2H), 7.09–7.13 (m, 1H), 7.34 (dd, J = 7.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.4, 27.1, 29.3, 32.5, 40.2, 41.2, 50.3, 61.6, 92.3, 114.0, 116.1, 122.0, 125.5, 128.0, 128.4, 150.2, 166.8, 168.3, 195.4; MS (EI) m/z 342 $[M]^+$. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.48; H, 6.14.

*Compound **3e**:* yield 0.092 g (96%); mp 122–124 °C; IR ($CHCl_3$, cm^{-1}) 2960, 1736, 1636, 1471, 1385, 1233; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.19–2.34 (m, 4H), 3.07 (dd→t, J = 2.7 Hz, 1H), 4.11–4.22 (m, 2H), 4.50 (br, 1H), 6.30 (t, J = 2.3 Hz, 1H), 6.80 (d, J = 9.2 Hz, 1H), 7.21 (dd, J = 9.2, 2.3 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.2, 27.1, 29.4, 32.6, 40.0, 41.2, 50.3, 61.7, 92.3, 113.5, 114.2, 118.0, 127.5, 130.9, 131.0, 149.5, 166.9, 167.9, 195.2; MS (EI) m/z 420 $[M]^+$. Anal. Calcd for $C_{20}H_{21}BrO_5$: C, 57.02; H, 5.02. Found: C, 57.02; H, 5.33.

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Compound ***3f****:* yield 0.077 g (90%); gummy liquid; IR ($CHCl_3$, cm^{-1}) 2958, 1735, 1632, 1383, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 0.98 (s, 3H), 1.24 (t, J = 7.3 Hz, 3H), 2.16−2.29 (m, 4H), 3.09 (dd→t, J = 1.8 Hz, 1H), 3.73 (s, 3H), 4.17 (q, J = 7.3 Hz, 2H), 4.48 (br, 1H), 6.28 (t, J = 1.8 Hz, 1H), 6.44−6.47 (m, 2H), 7.22 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.7, 27.0, 29.2, 32.5, 40.5, 41.1, 50.3, 55.4, 61.5, 92.3, 101.7, 108.0, 114.4, 117.9, 128.8, 151.0, 159.5, 166.5, 168.3, 195.4; MS (EI) m/z 372 $[M]^+$. Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.82; H, 6.45.

Compound ***3g****:* yield 0.068 g (95%); gummy liquid; IR ($CHCl_3$, cm^{-1}) 2928, 1735, 1630, 1459, 1385, 1234; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, 3H), 1.86−1.92 (m, 2H), 2.24−2.34 (m, 2H), 2.39−2.42 (m, 2H), 3.10 (dd→t, J = 3.2 Hz, 1H), 4.10−4.27 (m, 2H), 4.55 (br, 1H), 6.30 (t, J = 2.3 Hz, 1H), 6.89−6.93 (m, 2H), 7.10−7.15 (m, 1H), 7.36 (dd, J = 8.3, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.7, 25.5, 27.5, 36.4, 40.3, 61.5, 92.2, 115.1, 116.2, 122.0, 125.5, 128.1, 128.6, 150.2, 168.3, 168.6, 195.7; MS (EI) m/z 314 $[M]^+$. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.45; H, 5.52.

Compound ***3h****:* yield 0.088 g (98%); mp 136−138 °C; IR ($CHCl_3$, cm^{-1}) 2948, 1736, 1632, 1472, 1385, 1230, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, 3H), 1.87−1.94 (m, 2H), 2.30−2.35 (m, 2H), 2.40−2.43 (m, 2H), 3.07 (dd→t, J = 2.8 Hz, 1H), 4.11−4.26 (m, 2H), 4.51 (br, 1H), 6.28 (t, J = 1.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 8.7, 2.7 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.6, 25.3, 27.4, 36.3, 40.0, 61.6, 92.0, 114.2, 114.5, 118.0, 127.5, 131.0_0, 131.0_5, 149.4, 167.8, 168.6, 195.4; MS (EI) m/z 392 $[M]^+$. Anal. Calcd for $C_{18}H_{17}BrO_5$: C, 54.98; H, 4.36. Found: C, 54.62; H, 4.44.

Compound ***3i****:* yield 0.072g (92%); mp 182−184 °C; IR ($CHCl_3$, cm^{-1}) 2948, 1736, 1632, 1472, 1385, 1230, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, 3H), 1.86−1.94 (m, 2H), 2.28−2.42 (m, 4H), 3.07 (dd→t, J = 2.3 Hz, 1H), 3.74 (s, 3H), 4.12−4.24 (m, 2H), 4.48 (br, 1H), 6.28 (t, J = 1.8 Hz, 1H), 6.46−6.48 (m, 2H), 7.22−7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.7, 24.9, 27.4, 36.4, 40.6, 55.5, 61.4, 92.1, 101.7, 108.1, 115.5, 117.9, 128.9, 151.0, 159.6, 168.3$_0$, 168.3$_2$, 195.7; MS (EI) m/z 344 $[M]^+$. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.19; H, 5.86.

Compound ***3j****:* yield 0.063 g (95%); mp 150−152 °C; IR ($CHCl_3$, cm^{-1}) 2951, 1739, 1631, 1472, 1386, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.39 (s, 3H), 3.09 (dd→t, J = 3.2 Hz, 1H), 3.73 (s, 3H), 4.61 (t, J = 2.4 Hz, 1H), 6.24 (t, J = 1.8 Hz, 1H), 6.89−6.93 (m, 2H), 7.11−7.16 (m, 1H), 7.32 (dd, J = 6.7, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 28.8, 30.9, 40.0, 52.6, 91.4, 116.5, 116.6, 121.9, 125.5, 128.2, 128.3, 150.1, 162.2, 168.9, 196.0; MS (EI) m/z 288 $[M]^+$. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.42; H, 5.62.

Compound ***3k****:* yield 0.071 g (86%); mp 170−172 °C; IR ($CHCl_3$, cm^{-1}) 3068, 2926, 1729, 1670, 1470, 1580, 1467, 1222; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41−2.44 (m, 2H), 2.54−2.58 (m, 2H), 3.14 (dd→t, J = 3.2 Hz, 1H), 3.75 (s, 3H), 4.20 (br, 1H), 6.42 (t, J = 1.8 Hz, 1H), 6.81 (dd, J = 8.4, 1.8 Hz, 1H), 7.23−7.26 (m, 1H), 7.42 (t, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.4, 34.3, 40.2, 52.9, 94.1, 114.6, 118.3, 118.7, 126.9, 130.5, 131.5, 149.8, 167.9, 181.3, 200.6; MS (EI) m/z 364 $[M]^+$. Anal. Calcd for $C_{16}H_{13}BrO_5$: C, 52.63; H, 3.59. Found: C, 52.54; H, 3.78.

Compound ***3l****:* yield 0.089 g (96%); mp 146−148 °C; IR ($CHCl_3$, cm^{-1}) 2950, 1731, 1635, 1469, 1228; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 0.98 (s, 3H), 2.19−2.30 (m, 4H), 3.08 (dd→t, J = 2.8 Hz, 1H), 3.71 (s, 3H), 4.50 (br, 1H), 6.30 (t, J = 1.8 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 26.9, 29.5, 32.6, 39.9, 41.2, 50.3, 52.7, 92.2, 113.6, 114.3, 118.0, 127.5, 131.0, 131.1, 149.5, 166.9, 168.4, 195.2; MS (EI) m/z 406 $[M]^+$. Anal. Calcd for $C_{19}H_{19}BrO_5$: C, 56.04; H, 4.70. Found: C, 56.12; H, 4.68.

Compound ***3m****:* yield 0.077 g (90%); mp 134−136 °C; IR ($CHCl_3$, cm^{-1}) 2952, 1739, 1632, 1472, 1386, 1228; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87−1.94 (m, 2H), 2.26−2.44 (m, 4H), 3.07 (dd→t, J = 2.3 Hz, 1H), 3.72 (s, 3H), 4.50 (br, 1H), 6.28 (t, J = 1.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 8.8, 2.8 Hz, 1H), 7.50 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 25.4, 27.5, 36.4, 40.0, 52.7, 92.0, 114.3, 114.5, 118.0, 127.6, 131.1, 149.5, 168.4, 168.6, 195.5; MS (EI) m/z 378 $[M]^+$. Anal. Calcd for $C_{17}H_{15}BrO_5$: C, 53.85; H, 3.99. Found: C, 53.62; H, 3.78.

X-ray Data. Single-crystal X-ray diffraction data for compound **3b** were collected on a X-ray diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The structure was solved and refined by standard methods.

Crystal data for compound ***3b****:* colorless plate, $C_{17}H_{17}BrO_5$, M = 381.21, monoclinic, space group $C2/c$, a = 23.335(6) Å, b = 6.2952(15) Å, c = 23.129(6) Å, β = 107.557(3)°, V = 3239.3(14) Å^3, Z = 8, μ = 2.561 mm^{-1}, data/restraints/parameters: 3724/0/211, R indices ($I > 2\sigma(I)$): R1 = 0.0346, wR2 (all data) = 0.1242. The data (CCDC no. 957790) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

Materials including the ORTEP diagram of the compound **3b**, copies of $^1H/^{13}C$ NMR spectra of all new products, and X-ray data of compound **3b** (CIF). 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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■ REFERENCES

(1) (a) Tietze, L. F.; Gordon, B.; Kersten, G. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (e) Hussian, M. M.; Patrick, J. W. *Acc. Chem. Res.* **2008**, *41*, 883. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (g) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem.* **2010**, *2*, 167. (h) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (i) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (j) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278.

(2) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; p 160.

(3) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (c) Tietze, L. F. In *Selectivity−A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag-Chemie: Weinheim, 1984; p 299.

(4) (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Gharpure, S. J.; Reddy, S. R. B. *Eur. J. Org. Chem.* **2013**, 2981.

(5) Yin, G.; Ren, T.; Rao, Y.; Zhou, Y.; Li, Z.; Shu, W.; Wu, A. *J. Org. Chem.* **2013**, *78*, 3132.

(6) (a) Rao, Y.; Yin, G. *Org. Biomol. Chem.* **2013**, *11*, 6029. (b) Ganguly, N. C.; Mondal, P.; Roy, S. *Tetrahedron Lett.* **2013**, *54*, 2386. (c) Kim, I.; Kim, S. G.; Choi, J.; Lee, G. H. *Tetrahedron* **2008**, *64*, 664.

(7) (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (b) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (c) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563. (d) Minakata, S.; Komatsu,

M. *Chem. Rev.* **2009**, *109*, 711. (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725. (f) Sajna, K. V.; Srinivas, V.; Kumara Swamy, K. C. *Adv. Synth. Catal.* **2010**, *352*, 3069.
(8) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809.
(9) (a) Gharpure, S. J.; Reddy, S. R. B. *Org. Lett.* **2009**, *11*, 2519. (b) Gharpure, S. J.; Shukla, M. K.; Vijayasree, U. *Org. Lett.* **2009**, *11*, 5466. (c) Gharpure, S. J.; Sathiyanarayanan, A. M. *Chem. Commun.* **2011**, *47*, 3625. (d) Gharpure, S. J.; Porwal, S. K. *Tetrahedron* **2011**, *67*, 1216. (e) Gharpure, S. J.; Niranjana, P.; Porwal, S. K. *Org. Lett.* **2012**, *14*, 5476. (f) Bennett, C. E.; Figueroa, R.; Hart, D. J.; Yang, D. *Heterocycles* **2006**, *70*, 119.
(10) Gharpure, S. J.; Nanda, L. M.; Shukla, M. K. *Eur. J. Org. Chem.* **2011**, 6632.
(11) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Furstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (e) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, *2*, 2417. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (g) Kotikalapudi, R.; Kumara Swamy, K. C. *Tetrahedron* **2013**, *69*, 8002. (h) Srinivas, V.; Koketsu, M. *Tetrahedron* **2013**, *69*, 8025. (i) Qiu, Y.; Ma, D.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2013**, *11*, 1666.
(12) (a) Cui, S.-L.; Wang, J.; Lin, X.-F.; Wang, Y.-G. *J. Org. Chem.* **2007**, *72*, 7779. (b) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542.
(13) Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, *53*, 810.