

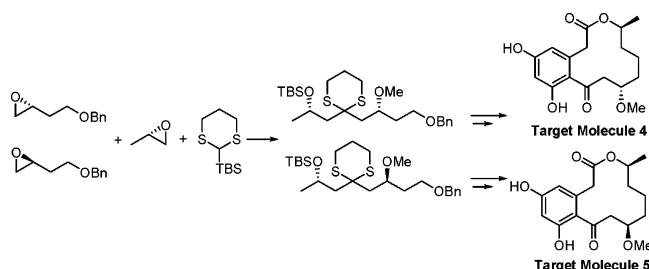
First Total Syntheses and Spectral Data Corrections of 11- α -Methoxycurvarin and 11- β -Methoxycurvarin

Qiren Liang,[†] Yongquan Sun,[†] Binxun Yu,[†]
Xuegong She,^{*,†,‡} and Xinfu Pan^{*,†}

Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, People's Republic of China, State Key Laboratory for Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China

shexg@lzu.edu.cn

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Concise and efficient total syntheses of 11- α -methoxycurvarin and 11- β -methoxycurvarin were accomplished for the first time. The three-component linchpin coupling and intramolecular acylation reactions were key steps, in which we found the spectral data of 11- α -methoxycurvarin and 11- β -methoxycurvarin, reported in the literature, were reversed with each other.

11- α -Methoxycurvarin and 11- β -methoxycurvarin are members of the curvarin family isolated from the mycelium of the hybrid strain ME 005 derived from *penicillium citreoviride* 4692 and 6200 (Figure 1).¹ They were discovered to have considerable cytotoxicity toward a panel of four human cancer cell lines [NCI-H460, MCF-7, SF-268, MIA. Pa Ca-2].² Also, they have been reported to inhibit sea urchin embryogenesis by acting on components of the mitotic apparatus,³ 90 (HSP90),⁴ a promising target for anticancer drug discovery.⁵ Structurally,

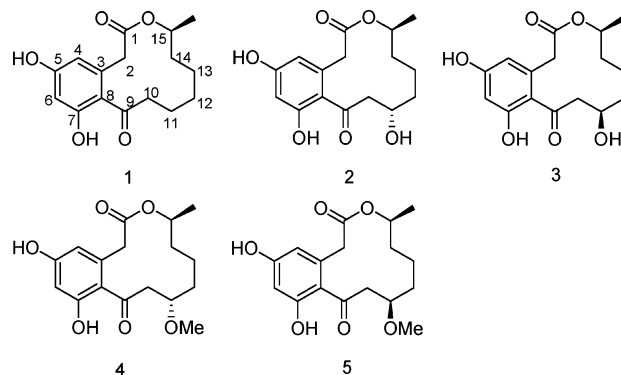


FIGURE 1. Curvarin (1), 11- α -hydroxycurvarin (2), 11- β -hydroxycurvarin (3), 11- α -methoxycurvarin (4), and 11- β -methoxycurvarin (5).

compounds 4 and 5 feature a 12-membered macrolide lactone containing a fused 1,3-dihydroxybenzene ring. The absolute configurations of 11- α -methoxycurvarin and 11- β -methoxycurvarin were assigned as (11*S*,15*S*) and (11*R*,15*S*) by comparing the ¹H NMR data with those of 11- α -hydroxycurvarin 2 and 11- β -hydroxycurvarin 3, respectively.¹ Their favorable bioactivities as well as interesting structures inspired our syntheses of 4 and 5 using a process that would be flexible enough to provide suitable derivatives for later SAR experiments. Herein, we wish to report the concise total syntheses of 4 and 5 together with revisions of the spectral data of the natural products, 11- α -methoxycurvarin and 11- β -methoxycurvarin.

Retrosynthetic analysis of macrolide 4 is depicted in Scheme 1. We envisioned that macrolide 4 could be available from acid 15a by the intramolecular acylation. In turn acid 15a might be prepared from 10a and 3,5-dimethoxyphenylacetic acid 12 through several transformations. As the key strategic step, a one-flask three-component linchpin coupling reaction of (*S*)-(-)-methyloxirane 8, benzyl ether of (*R*)-1,2-epoxy-4-butanol 7a, and dithianes 9 would provide the desired adduct 10a.

A three-component, one-flask linchpin coupling employing 2-*tert*-(butyldimethylsilyl)-1,3-dithiane with two different epoxide electrophiles to construct unsymmetrical adducts exploited a solvent-controlled Brook rearrangement (Scheme 2).⁶ This route leads to the rapid, efficient, and stereocontrolled assembly of highly functionalized intermediates for complex molecule synthesis.⁷ In this note, we report the application of this tactic for the efficient construction of the target molecule 4.

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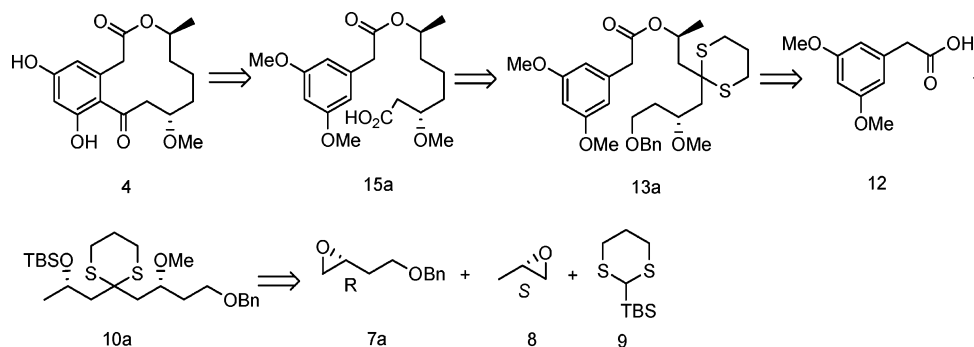
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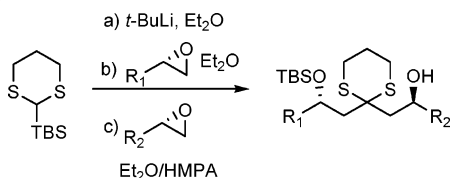
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SCHEME 1. Retrosynthetic Analysis of Compound 4



SCHEME 2. Three-Component, One-Flask Linchpin Coupling



The synthesis of target molecule **4** commenced from (*R*)-1,2-epoxy-4-butanol **6**, which was prepared from (*S*)-(-)-malic acid according to the route made by Kenji Mori and its NMR data and optical rotation were identical with those reported in the literature.⁸ As shown in Scheme 3, the multicomponent linchpin coupling was employed with commercially available (*S*)-(-)-methyloxirane **8** and epoxide **7a**, and the latter is readily prepared from (*R*)-**6** with BnBr and NaH.⁹ Pleasingly, with lithiation of dithiane **9** in THF *n*-BuLi (−78 to −10 °C) was used, followed by the addition of epoxide (*S*)-**8** (−78 °C), warming to −40 °C, and stirring for an additional 1 h at −40 °C, and then adding HMPA (3 equiv) and epoxide **7a** in THF, letting it warm to 0 °C for 1 h. Last MeI (3 equiv) was added and the mixture was stirred for 0.5 h at 0 °C, furnishing **10a** in 74% isolated yield. The structure of **10a** was secured by careful ¹H and ¹³C NMR and HRMS experiments. However, in this transformation when we used the TBDPS ether of (*R*)-**6** as the substrate, the products of linchpin coupling were complex and no desired product was obtained.

With compound **10a** in hand, deprotection of the TBS group produced **11a** in 99% yield.¹⁰ Esterification of **11a** with 3,5-dimethoxyphenylacetic acid **12**^{11,12} using DCC and DMAP gave the ester **13a** in 98% yield.¹² The dithiane and benzyl groups of **13a** were removed with Raney Ni under reflux for 6 h, affording **14a** in 75.4% yield.¹³ Oxidation of the hydroxy group of **14a** with Jones reagent (5 equiv) in acetone at 0 °C for 15 min gave the acid **15a** in 86% yield.^{7h} The macrolide **16a** was obtained by intramolecular Friedel–Crafts reaction of the

carboxylic acid **15a** in a mixture of TFA and TFAA.¹⁴ Deprotection of the methoxy groups at C5 and C7 of macrolide **16a** with freshly prepared AlI₃ completed the synthesis of (11*S*, 15*S*)-**4** (i.e., 11- α -methoxycurvarin).¹⁵ However, the ¹H NMR (400 MHz, CDCl₃) and optical rotation of the synthetic **4** were in disagreement with that of the reported natural product 11- α -methoxycurvarin, though identical with the reported 11- β -methoxycurvarin epimer.¹ To further confirm the experimental results, (11*R*,15*S*)-**5** (i.e., 11- β -methoxycurvarin) was synthesized by using the same strategy as the synthesis of **4** from (*S*)-1,2-epoxy-4-butanol **6** (prepared from (*S*)-(-)-malic acid according to Kenji Mori)⁸ and (*S*)-**8** (see the Supporting Information). As expected the spectral data of **5** (¹H NMR and optical rotation) were identical with those previously reported for 11- α -methoxycurvarin.¹ Thus, we concluded that the corresponding spectral data for the absolute configuration of 11- α -methoxycurvarin are the data reported for the natural product 11- β -methoxycurvarin and the corresponding spectral data for the structure of 11- β -methoxycurvarin are the data reported for the natural product 11- α -methoxycurvarin—both are just opposite what is reported in the literature.

In summary a concise and efficient total synthesis of 11- α -methoxycurvarin and 11- β -methoxycurvarin has been accomplished for the first time in 8 steps with an overall yield of 10.0% and 13.3%, respectively. The hydroxy groups at C11 and C15 were efficiently constructed by using a one-flask three-component linchpin coupling. The ring closure was achieved by using an intramolecular Friedel–Crafts reaction.

Experimental Section

Syntheses of Compounds 10a and 10b. *n*-Butyllithium (2.8 mL, 2.1 M in hexanes) was added to a solution of 2-*tert*-(butyldimethylsilyl)-1,3-dithiane **9** (1.404 g, 6 mmol) in 25 mL of THF at −78 °C under Ar. The mixture was warmed to −10 °C then stirred for 1 h, followed by cooling to −78 °C and the addition of the (*S*)-(-)-methyloxirane **8** (348 mg, 6 mmol) in 2 mL of THF. Completion of the first alkylation was achieved in 1 h at −40 °C. The mixture was cooled to −78 °C and HMPA (3.2 g, 18 mmol) was added, warming the mixture to −40 °C and stirring for 10 min. The mixture was recooled to −78 °C and the second epoxide **7a** (1.28 g, 7.2 mmol) in 10 mL of THF was added. The mixture was stirred at 0 °C for 1 h, then MeI (2.56 g, 18 mmol) was added and the mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with saturated NH₄Cl and extracted with ether (3 × 60

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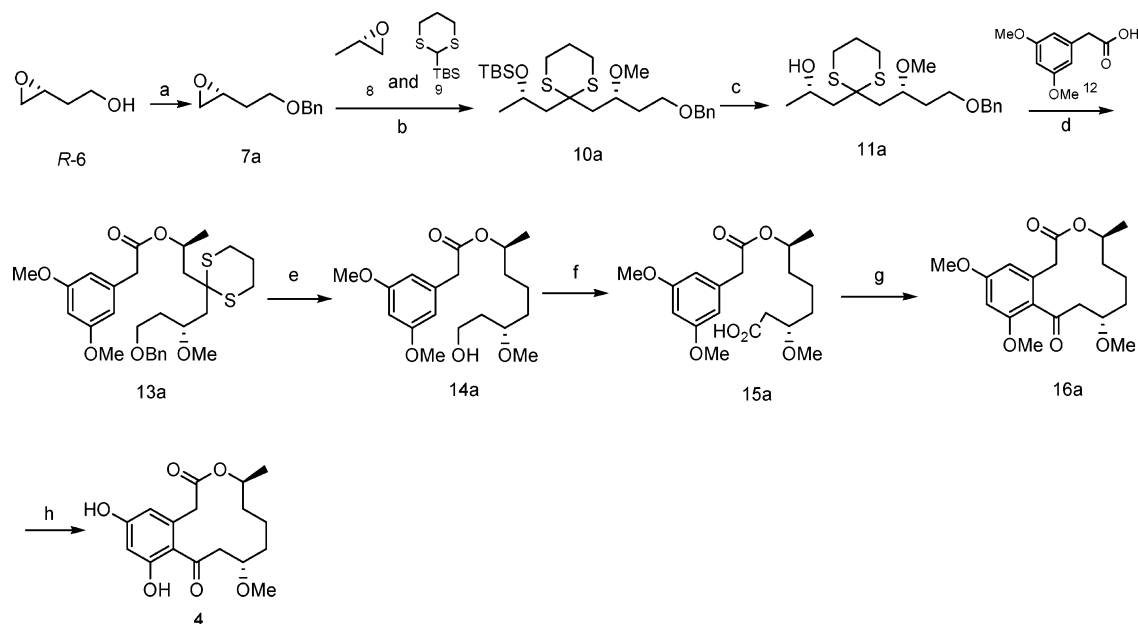
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SCHEME 3^a

^a Reagents and conditions: (a) NaH, BnBr, Bu₄N⁺I[−], THF, rt, 99%; (b) *n*-BuLi, HMPA, MeI, THF, −78 °C to 0 °C, 74%; (c) HCl (1% solution in MeOH), rt, 99%; (d) DCC, DMAP, Et₂O, rt, 4 h, 98%; (e) Raney Ni, H₂, EtOH, 80 °C, 8 h, 75%; (f) Jones reagent, 0 °C, 15 min, 86%; (g) TFA, TFAA, rt, 8 h, 42%; (h) AlI₃, Bu₄N⁺I[−], Ph, 10 °C, 15 min, 68%.

mL), and the combined organic solutions were washed with brine (3 × 15 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 50:1) to give compound **10a** (2.15 g, 74%) as a colorless oil: [α]_D²⁵ −5 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.26–7.37 (m, 5H), 4.51 (dd, *J* = 14.1 Hz, 11.7 Hz, 2H), 4.18 (dd, *J* = 9.9 Hz, 5.7 Hz, 1H), 3.67 (dd, *J* = 9.9 Hz, 5.7 Hz, 1H), 3.58 (dd, *J* = 6.9 Hz, 5.7 Hz, 2H), 3.31 (s, 3H), 3.27–3.80 (m, 4H), 2.13–2.22 (m, 3H), 2.05 (dd, *J* = 15.0 Hz, 3.6 Hz, 1H), 1.87–1.94 (m, 4H), 1.22 (dd, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 5.1 Hz, 9H), 0.09 (d, *J* = 5.1 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 128.3, 127.7, 127.5, 76.0, 73.0, 66.9, 66.3, 56.3, 51.9, 49.2, 44.6, 34.6, 26.4, 26.1, 26.0, 25.0, 18.0, −4.0, −4.1; IR (KBr) 3388, 2929, 2855, 1457, 1366, 1252, 1095, 1002, 833, 755 cm^{−1}; HRMS *m/z* calcd for C₂₅H₄₄S₂O₃Si [M + Na]⁺ 507.2393, found 507.2387.

The title compound **10b** (7.53 g, 76%) was obtained from (S)-(-)-methyloxirane **8** (1.16 g, 20 mmol), (R)-2-(2-(benzyloxy)ethyl)-oxirane **7b** (4.272 g, 24 mmol), 2-*tert*-(butyldimethylsilyl)-1,3-dithiane **9** (4.68 g, 20 mmol), HMPA (10.74 g, 60 mmol), and MeI (8.52 g, 60 mmol) by the same operation as the synthesis of **10a**: [α]_D²⁵ −10 (c 1.7, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.26–7.37 (m, 5H), 4.51 (dd, *J* = 14.1 Hz, 11.7 Hz, 2H), 4.19 (dd, *J* = 11.7 Hz, 5.4 Hz, 1H), 3.69 (t, *J* = 6.0 Hz, 1H), 3.58 (td, *J* = 6.0 Hz, 2.4 Hz, 2H), 3.32 (s, 3H), 2.71–2.80 (m, 4H), 2.07–2.23 (m, 4H), 1.84–1.94 (m, 4H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 3.0 Hz, 9H), 0.08 (t, *J* = 3.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 138.4, 128.3, 127.7, 127.5, 76.0, 73.0, 67.0, 66.4, 56.2, 52.0, 49.9, 45.4, 35.0, 26.3, 26.1, 25.9, 24.9, 17.9, −4.0, −4.2; IR (KBr) 3392, 2929, 2856, 1457, 1252, 1093, 1002, 834, 775 cm^{−1}; HRMS *m/z* calcd for C₂₅H₄₄S₂O₃Si [M + Na]⁺ 507.2393 found 507.2388.

Syntheses of Macrolides 16a and 16b. The acid **15a** (80 mg, 0.22 mmol) was dissolved in a mixture of trifluoroacetic acid (6 mL) and trifluoroacetic acid anhydride (1 mL) under Ar. The solution was stirred over night at rt, poured into an excess of sodium hydrogen carbonate, extracted with ether (3 × 5 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 5:1) to give the metabolite **16a** (32 mg, 42%) as a colorless oil: [α]_D²⁵ −5 (c 1.1, CHCl₃);

¹H NMR (300 MHz, CDCl₃) δ 6.49 (d, *J* = 1.8 Hz, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 6.27 (d, *J* = 15.9 Hz, 1H), 4.89 (t, *J* = 6.3 Hz, 1H), 3.86 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.37 (d, *J* = 4.2 Hz, 3H), 2.35 (dd, *J* = 12.9 Hz, 6.3 Hz, 1H), 2.19 (dd, *J* = 15.9 Hz, 8.4 Hz, 1H), 1.41–1.58 (m, 4H), 1.16 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.4, 170.5, 161.7, 158.9, 156.3, 133.3, 132.9, 122.5, 106.6, 97.7, 72.9, 55.9, 55.6, 55.4, 39.6, 34.3, 34.1, 24.4, 20.3; IR (KBr) 3380, 2929, 1725, 1655, 1602, 1458, 1312, 1156, 1085 cm^{−1}; HRMS *m/z* calcd for C₁₉H₂₆O₆ [M + Na]⁺ 373.1627, found 373.1622.

15b (200 mg, 0.54 mmol) was treated with 10 mL of TFA and 2 mL of TFAA as described for the synthesis of **16a** to give **16b** (39 mg, 20%) as a colorless oil: [α]_D²⁵ −36 (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 6.48 (s, 1H), 6.40 (s, 1H), 6.25 (d, *J* = 15.6 Hz, 1H), 4.88 (t, *J* = 6.3 Hz, 1H), 3.83 (s, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.33 (d, *J* = 18.6 Hz, 3H), 2.32 (t, *J* = 6.9 Hz, 1H), 2.18 (t, *J* = 6.9 Hz, 1H), 1.75–1.90 (m, 2H), 1.37–1.53 (m, 4H), 1.15 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.5, 170.5, 160.9, 157.5, 156.5, 133.2, 132.8, 122.5, 106.5, 97.8, 72.9, 55.8, 55.6, 55.4, 39.5, 34.2, 34.1, 24.4, 20.3; IR (KBr) 3380, 2929, 1724, 1655, 1603, 1458, 1312, 1157, 1084 cm^{−1}; HRMS *m/z* calcd for C₁₉H₂₆O₆ [M + H]⁺ 351.1808, found 351.1801.

Syntheses of Target Molecules 4 and 5. Iodine (564 mg, 2.22 mmol) was added to a mixture of aluminum (80 mg, 3 mmol) in anhydrous benzene (4 mL). The mixture was refluxed for 0.5 h and cooled to 10 °C, then *n*-Bu₄N⁺I[−] (2 mg) and **16a** (26 mg, 0.07 mmol) in benzene (2 mL) were added. The mixture were stirred for 15 min at 10 °C and quenched with 2 M HCl at 0 °C. The mixture were then extracted with EtOAc (3 × 20 mL). The organic phase was washed with NaHCO₃ solution and brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 2:1) to afford the target molecule **4** (16 mg, 68%) as a colorless oil: [α]_D²⁵ −17 (c 1.0, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 6.29 (d, *J* = 2.0 Hz, 1H), 6.22 (d, *J* = 1.6 Hz, 1H), 4.92 (t, *J* = 6.8 Hz, 1H), 3.89 (d, *J* = 15.6 Hz, 1H), 3.81 (d, *J* = 3.6 Hz, 1H), 3.70 (dd, *J* = 15.6 Hz, 6.8 Hz, 1H), 3.39 (d, *J* = 12.0 Hz, 1H), 3.36 (s, 3H), 3.01 (dd, *J* = 14.8 Hz, 8.8 Hz, 1H), 1.53–1.62 (m, 6H), 1.19 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 205.1, 172.2, 159.3, 158.3,

135.6, 119.6, 112.4, 102.7, 77.0, 73.9, 55.9, 48.8, 39.9, 32.6, 31.9, 20.9; IR (KBr) 3402, 2924, 1959, 1713, 1654, 1614, 1460, 1403, 1268, 1152, 1083, 1026, 848 cm^{-1} ; HRMS m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_6$ $[\text{M} + \text{H}]^+$ 323.1489, found 323.1493.

Target molecule **5** (19 mg, 70%) was obtained as a colorless oil from **16b** (30 mg, 0.086 mmol), iodine (326 mg, 1.28 mmol), and aluminum (100 mg, 3.7 mmol) by the same operation for the synthesis of **4**: $[\alpha]_D^{25} -4$ (c 0.3, EtOH); ^1H NMR (300 MHz, CDCl_3) δ 8.98 (s, 1H), 6.94 (s, 1H), 6.34 (d, $J = 2.4$ Hz, 1H), 5.97 (d, $J = 2.4$ Hz, 1H), 5.13 (t, $J = 6.0$ Hz, 1H), 3.95 (d, $J = 15.9$ Hz, 1H), 3.78 (d, $J = 14.1$ Hz, 1H), 3.59 (d, $J = 16.5$ Hz, 1H), 3.33 (d, $J = 5.2$ Hz, 1H), 3.25 (s, 3H), 3.13 (dd, $J = 14.1$ Hz, 8.1 Hz, 1H), 1.55–1.87 (m, 6H), 1.25 (d, $J = 5.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.3, 172.0, 159.5, 159.4, 135.6, 118.3, 113.2, 102.7, 75.7, 72.3, 54.1, 49.2, 40.2, 31.2, 30.5, 18.8, 17.7; IR (KBr) 3402, 2923, 1959, 1712, 1655, 1614, 1461, 1403, 1269, 1153, 1083,

1026, 846 cm^{-1} ; HRMS m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_6$ $[\text{M} + \text{Na}]^+$ 345.1309, found 345.1312.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7a** and **7b**, **10a/10b–16a/16b**, **4**, and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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