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Total Synthesis of (±)-Sacidumlignan D§

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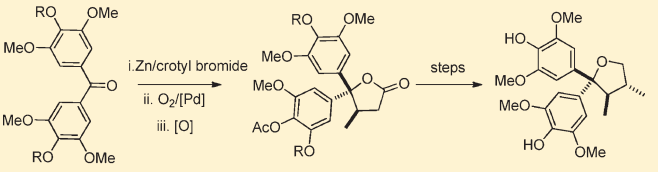
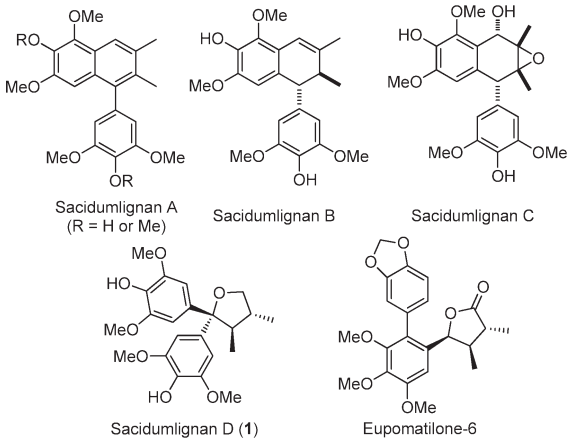
Supporting Information

ABSTRACT: The first total synthesis of (±)-sacidumlignan D featuring a Zn-mediated Barbier reaction and reverse Wacker oxidation to form the key γ-lactone, its diastereoselective α-methylation followed by reduction cyclization, was documented.



In 2005, four new lignans, namely sacidumlignans A−D, were isolated from the ethanolic extract of the whole plant of *Sarcostemma acidum* (Roxb.) collected from the Hainan Island of China.[1] The structure and the relative configuration of these four new compounds were elucidated by employing extensive 2D NMR spectroscopic techniques. Sacidumlignan D (**1**) was identified with a novel rearranged lignan skeleton and showed promising antimicrobial activities against Grampositive bacteria in vitro. Sacidumlignan D (**1**) is closely related to eupomatilones—another class of neolignans with unusual biaryl skeleton having a butyrolactone with C(2)−C(3)-dimethyl substituents.[2] We have recently documented the total synthesis of a putative structure and later the synthesis of the unnatural eupomatilone-6 enantiomer.[3,4]



Eupomatilone-6 also presents *trans*-C(2)−C(3)-dimethyl substituents on the lactone ring and this has been addressed by a diastereoselective α-methylation of a suitable lactone. Considering its unusual neolignan skeleton and its structural similarity with that of eupomatilone-6, the total synthesis of sacidumlignan D has been undertaken. Figure 1 provides the key retrosynthetic disconnections. The planned total synthesis of sacidumlignan D involves diastereoselective methylation of lactone **3** as a key step.

The resulting fully elaborated key lactone **2** can be transformed to sacidumlignan D (**1**) by carbonyl reduction and cyclization. On the other hand, it is anticipated that subjecting **2** to Friedel−Crafts conditions would lead to di- and tetrahydronaphthalenes which could be used for the synthesis of other sacidumlignans. The synthesis of lactone **3** was planned via crotylation of benzophenone derivatives **5** under Barbier conditions and subsequent hydroboration and oxidation. The synthesis of benzophenone **5** has been identified as the intermediate goal in the synthesis of sacidumlignan D.[5] Initially, allyl protection for the 4,4′-hydroxy groups of **5** has been opted, keeping in mind that it is stable under a variety of conditions. The synthesis of **5**-*diallyl* was intended from the addition of lithiated **6** to amide **7**.[6]

The synthesis of the coupling partner **6** started with the protection of the free −OH of known bromo-*o*-vanillin **8**[7] as its allyl ether by using allyl bromide and K_2CO_3 in the presence of phase transfer catalyst (TBAI) affording **9**. After examining various reagents and conditions, the Baeyer−Villiger oxidation of **9** was found to be facile with *m*-CPBA in dichloromethane and the desired phenol **10** was obtained in good yield.[8] Treatment of **10** with K_2CO_3 and MeI afforded the key bromo derivative **6**. Synthesis of the coupling partner **7** was begun from commercially available syringic acid. Initial allylation attempts with K_2CO_3 and allyl bromide in DMF resulted in the isolation of a *C*-allylated product **11** along with the desired *O*-allylated product **12**, in a 3:1 ratio.[9] When NaH was used as a base in the presence of phase transfer catalyst TBAI, the allylation proceeded smoothly to give **11** exclusively. Hydrolysis of **11** with aq KOH followed by coupling of the resulting acid **13** with morpholine gave the key amide partner **7** (Scheme 1).

Our next concern was the synthesis of **5**-*diallyl*. The treatment of **6** with ^{n}BuLi followed by addition of the amide **7** in excess (5 equiv) afforded the required benzophenone derivative **5**-*diallyl* and the triarylcarbinol **14** along with the dehalogenated compound. The deallylation of **5**-*diallyl* with use of *N*,*N*′-dimethylbarbituric acid in the presence of $Pd(OAc)_2$ and triphenylphosphine gave **5** in good yield.[10]

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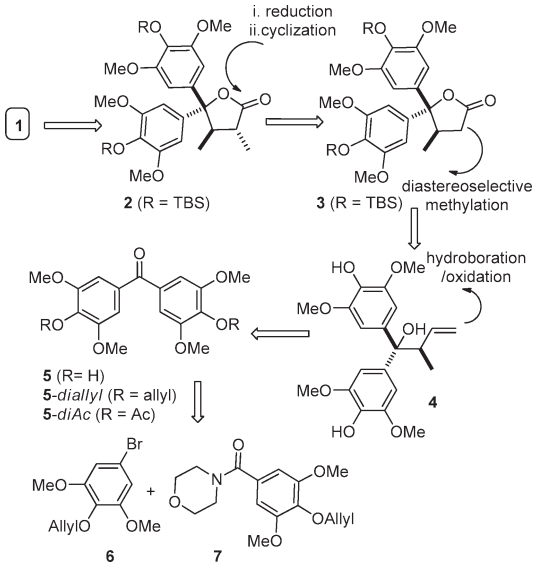
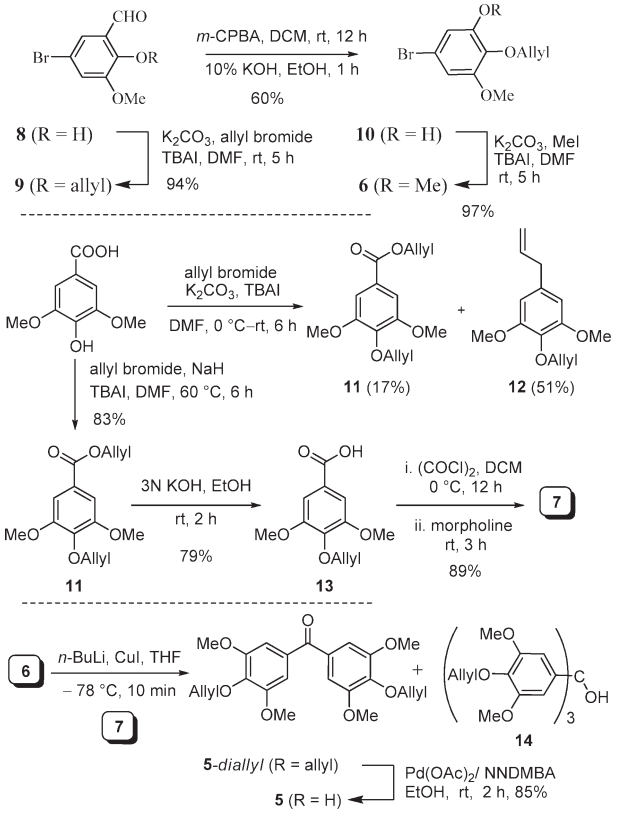


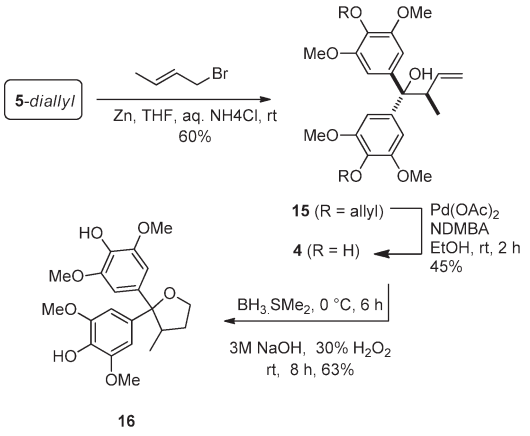
Figure 1. Key retrosynthetic disconnections.

Scheme 1. Synthesis and Coupling of 6 and 7



The crotylation of **5** was attempted in the next step. Under various Barbier conditions explored, the ketone **5** was found to be intact even after prolonged exposure.[11] However, with the diallyl derivative **5**-*diallyl*, the Barbier reaction proceeded smoothly and gave the requisite homoallylic alcohol **15** in respectable yields. The selective di-*O*-deallylation of **15** could be carried out employing $Pd(OAc)_2$ in the presence of *N*,*N*′-dimethylbarbituric acid; however, the yield was poor.

Scheme 2. Synthesis of *des*-Sacidumlignan



The next task was the hydroboration–oxidation of homoallylic alcohol **4** to obtain a diol. Surprisingly, the hydroboration–oxidation of **4** furnished the furan derivatve **16** (8-*desmethyl*-sacidumulignan D) exclusively (Scheme 2). Various other alternatives attempted in this regard met with failure. This undesired cyclization prior to the oxidation has prompted us to modify our synthetic strategy. A reverse Wacker oxidation of a suitably protected homoallylic alcohol was planned to secure a lactol that could be further oxidized to the requisite lactone.[12]

The revised synthetic strategy had as first step the crotylation of **5**-*diAc*. The Barbier reaction of **5**-*diAc* under standard conditions proceeded smoothly and homoallylic alcohol **17** was obtained in excellent yields. A comparison of Barbier reaction of **5** and its two derivatives indicates the influence of the protecting group of the 4-OH group on the outcome of the reaction. Next, after exploring various conditions,[12b] the reverse Wacker oxidation of **17** was found to be promising with $Pd(CH_3CN)_2(Cl)(NO_2)$, $CuCl_2$, and O_2.[13] However, the reaction gave a 1:1 mixure of lactols **18** and its *t*-Bu acetals **19**. The acetals **19** were hydrolyzed with TFA in CH_2Cl_2 to afford the lactols **18** in quantitative yield. The oxidation of lactols **18** was carried out by Celite supported silver carbonate to obtain the lactone **20**.[14] Compound **20** was converted to the key lactone **3** by deacetylation, using K_2CO_3 in methanol followed by reprotection of both the resulting phenolic-OH with TBSCl. After exploring different electrophiles, the diastereoselective methylation at C(3) of lactone **3** was successfully conducted by using MeOTf and LiHMDS as a base to afford **2**.[15] Our next task was the sequential reduction of the lactone, cyclization, and TBS deprotection. As expected, the initially formed diol after the reduction of lactone **2** with LAH, cyclized partially during the workup and treatment of the crude with cat. TFA in dichloromethane, provides exclusively the TBS-protected sacidumlignan **21**. Finally, the desilylation of **21** with TBAF in THF gave sacidumlignan D (**1**, Scheme 3). The spectral and the analytical data of **1** were in good agreement with data reported for natural sacidumlignan D.

To conclude, the first total synthesis of (±)-sacidumlignan D has been completed. The adopted approach features the crotylation of a benzophenone and the reverse Wacker oxidation to construct the central tetrahydrofuran framework and the diastereoselective C(2)-methylation of intermediate butyro-lactone to address the requisite *trans*-geometry of the C(2)- and C(3)-methyl substituents.

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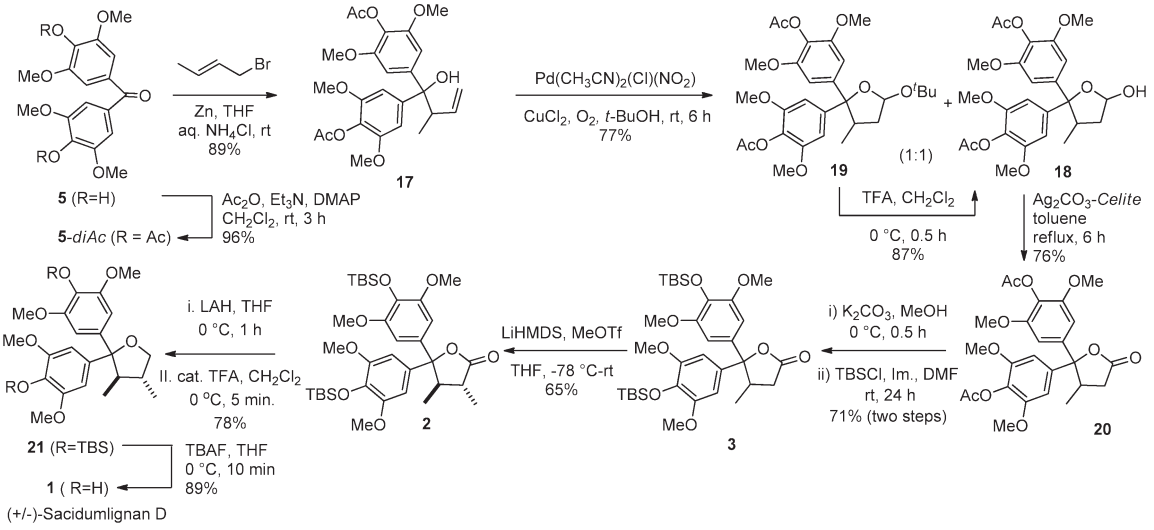
Scheme 3. Total Synthesis of (±)-Sacidumlignan D



EXPERIMENTAL SECTION

4,4′-(3-Methyl-5-oxotetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene) Diacetate (20). A suspension of lactols **18** (800 mg, 1.63 mmol) and Ag_2CO_3 impregnated on Celite (1.35 g, 4.89 mmol, contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent) in toluene (40 mL) was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite and the Celite pad was washed with ethyl acetate (3 × 30 mL). The combined filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (35% ethyl acetate in petroleum ether) to afford lactone **20** (600 mg, 76%) as a colorless crystalline solid.

Mp 211−212 °C; IR ($CHCl_3$) ν 3020, 2941, 2842, 1767, 1605, 1508, 1463, 1417, 1369, 1338, 1211, 1176, 1133, 759, 666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.77 (s, 2H), 6.55 (s, 2H), 3.82 (s, 6H), 3.77 (s, 6H), 3.39−3.30 (m, 1H), 2.77 (dd, J = 12.8, 3.5 Hz, 1H), 2.35 (m, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz) δ 17.1 (q), 20.3 (q, 2C), 37.5 (t), 38.3 (d), 56.1 (q, 2C), 56.2 (q, 2C), 91.8 (s), 102.2 (d, 2C), 103.0 (d, 2C), 127.8 (s), 128.5 (s), 138.3 (s), 140.6 (s), 151.8 (s, 2C), 152.0 (s, 2C), 168.4 (s), 168.4 (s), 175.3 (s); ESI-MS m/z 511.2 (100%, $[M + Na]^+$), 527 (14%, $[M + K]^+$), 506 (9%, $[M + H_2O]^+$), 469 (29%, $[M - H - H_2O]^+$). Anal. Calcd for $C_{25}H_{28}O_{10}$: C, 61.47; H, 5.78. Found: C, 61.53; H, 5.91.

(3*R*/3*S*,4*R*/3*S*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (2). At −78 °C, a solution of diTBS-derivative **3** (100 mg, 0.158 mmol) in anhydrous THF (1 mL) was treated with LiHMDS (1 M solution in THF, 1.55 mL), the contents were then stirred at the same temperature for 1 h and treated with MeOTf (18 μL, 0.158 mmol), and the stirring was continued for additional 2 h at −78 °C. The reaction mixture was warmed to rt and quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The crude was purified by silica gel chromatography (10% ethyl acetate in petroleum ether) to afford **2** (66 mg, 65%) as a colorless crystalline solid.

Mp 172−174 °C; IR ($CHCl_3$) ν 3023, 2930, 2850, 1760, 1590, 1515, 1465, 1412, 1334, 1248, 1126, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.61 (s, 2H), 6.20 (s, 2H), 3.76 (s, 6H), 3.67 (s, 6H), 2.86 (dq, J = 11.8, 6.7 Hz, 1H), 2.43 (dq, J = 11.8, 7.0 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), −0.13 (s, 6H), −0.11 (s, 6H); ^{13}C NMR (50 MHz) δ −4.7 (q, 4C), 13.2 (q), 16.2 (q), 18.7 (s, 2C), 25.7 (q, 6C), 41.1 (d), 46.2 (d), 55.7 (q, 2C), 56.0 (q, 2C), 91.0 (s), 104.1 (d, 2C), 104.8 (d, 2C), 132.7 (s), 133.7 (s), 134.5 (s), 135.5 (s), 150.9 (s, 2C), 151.2 (s, 2C), 178.8 (s); ESI-MS m/z 669.4 (100%, $[M + Na]^+$). Anal. Calcd for $C_{34}H_{54}O_8Si_2$: C, 63.12; H, 8.41. Found: C, 63.42; H, 8.29.

(3*R*/3*S*,4*R*/3*S*)-3,4-(Dimethyltetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene)bis(oxy)bis(*tert*-butyldimethylsilane) (21). To a solution of diTBS lactone **2** (50 mg, 154.6 μmol) in anhydrous THF (2 mL) at 0 °C was slowly added LAH (26 mg, 0.62 mmol). The reaction mixture was vigorously stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride and filtered through Celite and the filtrate was diluted by EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated. At 0 °C, a solution of the above crude product in dry CH_2Cl_2 (2 mL) was treated with TFA (20 μL) and the contents were stirred for 5 min. The reaction mixture was quenched with sat. $NaHCO_3$ and the organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by silica gel chromatography (10% ethyl acetate in petroleum ether) to give cyclized product **21** (30 mg, 78%) as a colorless solid.

Mp 114−117 °C; IR ($CHCl_3$) ν 3019, 2966, 2931, 2875, 1620, 1583, 1489, 1446, 1383, 1335, 1223, 1082, 1048, 1030, 928, 845, 757, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.32 (s, 2H), 4.30 (t, J = 7.8 Hz, 1H), 3.76 (s, 6H), 3.67 (s, 6H), 3.48 (dd, J = 10.5, 8.4 Hz, 1H), 2.37 (dq, J = 10.6, 6.8 Hz, 1H), 2.04 (ddq, J = 13.6, 10.6, 7.1 Hz, 1H), 1.02 (d, J = 7.0 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.83 (d, J = 6.7 Hz, 3H), −0.13 (s, 6H), −0.09 (s, 6H); ^{13}C NMR (50 MHz) δ −4.7 (q, 4C), 14.5 (q), 15.6 (q), 18.7 (s, 2C), 25.8 (q, 6C), 40.6 (d), 49.6 (d), 55.6 (q, 2C), 56.0 (q, 2C), 73.9 (t), 90.9 (s), 104.8 (d, 2C), 105.0 (d, 2C), 132.9 (s), 133.5 (s), 137.7 (s), 139.5 (s), 150.5 (s, 2C), 151.0 (s, 2C) ppm; ESI-MS m/z 655.3 (100%, $[M + Na]^+$). Anal. Calcd for $C_{34}H_{56}O_7Si_2$: C, 64.51; H, 8.92. Found: C, 64.60; H, 8.79.

(±)-Sacidumlignan D (1). Compound **21** (30 mg) was dissolved in dry THF (0.5 mL) and treated with TBAF (27 mg 0.66 mmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction mixture was quenched with saturated ammonium chloride, extracted with EtOAc (2 × 5 mL), washed with brine, and dried over Na_2SO_4 then solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography by eluting with light petroleum ether/ethyl acetate (40% ethyl acetate in petroleum ether) to procure sacidumlignan D (**1**) (15 mg, 89%) as a colorless solid.

Mp 149−153 °C; IR ($CHCl_3$) ν 3025, 2927, 2847, 1565, 1514, 1457, 1406, 1327, 1253, 1121, 785 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 7.21 (s, 1H), 7.11 (s, 1H), 6.79 (s, 2H), 6.54 (s, 2H), 4.30 (t, J = 7.7 Hz,

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1H), 3.81 (s, 6H), 3.74 (s, 6H), 3.34 (dd, J = 10.1, 8.2 Hz, 1H), 2.43 (dq, J = 9.6, 6.9 Hz, 1H), 2.04−1.94 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz) δ 15.4 (q), 17.1 (q), 42.3 (d), 51.2 (d), 56.9 (q, 2C), 57.1 (q, 2C), 74.3 (t), 91.5 (s), 106.0 (d, 2C), 106.4 (d, 2C), 135.7 (s), 136.2 (s), 137.1 (s), 139.4 (s), 148.0 (s, 2C), 148.4 (s, 2C) ppm; ESI-MS m/z 427.2 (29%, $[M + Na]^+$), 405.4 (100%, $[M + 1]^+$). Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.25; H, 7.11.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, full characterization for all new compounds, and ^{1}H, ^{13}C NMR, and MS spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

§Dedicated to Professor M. Nagarajan on the occasion of his 60th birthday.

■ REFERENCES

(1) Gan, L.-S.; Yang, S.-P.; Fan, C.-Q.; Yue, J.-M. *J. Nat. Prod.* **2005**, *68*, 221.

(2) (a) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1615. (b) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705.

(3) (a) Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317. (b) Gurjar, M. K.; Karumudi, B.; Ramana, C. V. *J. Org. Chem.* **2005**, *70*, 9658.

(4) For synthesis of eupomatilones see: (a) Hong, S. P.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19. (b) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025. (c) Kabalka, G. W.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 7325. (d) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6177. (e) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (f) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514. (g) Mitra, S.; Gurrala, S. R.; Coleman, R. S. *J. Org. Chem.* **2007**, *72*, 8724. (h) Zhang, J.; Blazecka, P. G.; Curran, T. T. *Tetrahedron Lett.* **2007**, *48*, 2611. (i) Hirokawa, Y.; Kitamura, M.; Kato, C.; Kurata, Y.; Maezaki, N. *Tetrahedron Lett.* **2011**, *52*, 581.

(5) Connors, W. J.; Ayers, J. S.; Sarkanen, K. V.; Gratzl, J. S. *Tappi* **1971**, *54*, 1284.

(6) (a) Pettit, B. R. G.; Baumann, M. F.; Rangammal, K. N. *J. Med. Pharm. Chem.* **1962**, *5*, 800. (b) Rye, C. E.; Barker, D. *Synlett* **2009**, 3315.

(7) Juhasz, L.; Dinya, Z.; Antus, S.; Gunda, T. E. *Z. Naturforsch., B* **2001**, *56*, 554.

(8) Xie, X.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 2661.

(9) Li, G. Q.; Li, Z.; Fang, X. H. *Synth. Commun.* **1996**, *26*, 2569.

(10) (a) Helion, F. G.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109. (b) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.

(11) (a) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910. (b) Pétrier, C.; Einhorn, C.; Luche, J.-L. *Tetrahedron Lett.* **1985**, *26*, 1449. (c) For reviews, see: Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley & Sons: New York, 1997; Chapter 4. (d) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996; Chapter 4.

(12) For selected examples on reverse Wacker oxidation for γ-butyrolactone synthesis see: (a) Wenzel, T. T. *J. Chem. Soc., Chem. Commun.* **1993**, 862. (b) Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem.—Eur. J.* **2006**, *12*, 949. (c) Muzart, J. *Tetrahedron* **2007**, *63*, 7505.

(13) (a) Meulemans, T. M.; Kiers, N. H.; Feringa, B. L.; Leeuwen, P. W. N. M. V. *Tetrahedron Lett.* **1994**, *35*, 455. (b) Weiner, B.; Baeza, A.; Jerphagnon, T.; Feringa, B. L. *J. Am. Chem. Soc.* **2009**, *131*, 9473.

(14) (a) Balogh, V.; Fétizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339. (b) Ramana, C. V.; Suryawanshi, S. B. *J. Org. Chem.* **2009**, *74*, 2843.

(15) Uenishi, J.; Tatsumi, Y.; Kobayashi, N.; Yonemitsu, O. *Tetrahedron Lett.* **1995**, *36*, 5909.