JOC Article

Remarkable Reactivity Difference in Oxygen-Substituted versus Non-Oxygen-Substituted Bromoalkynes in Cu(I)-Catalyzed Cross-Coupling Reactions: Total Synthesis of (−)-*S*-18-Hydroxyminquartynoic Acid

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The conjugated tetraacetylenic natural product (*S*)-18-hydroxyminquartynoic acid (**2**) is synthesized in five linear steps and 17.7% overall yield from commercially available 1,2,5,6-*O*-diisopropylidene mannitol. The key step is a one-pot three-component Cadiot−Chodkiewicz reaction affording the tetrayne unit. The oxygen-substituted bromoalkyne **10** was found to react at a much faster rate than the non-oxygen-substituted bromoalkyne **6** in the key step. The undesired symmetric cross-coupling by **10** generates a symmetric tetrayne intermediate, which undergoes a nucleophilic addition by 1 equiv of ethylamine. This side reaction is suppressed by controlling the order and rate of addition of each component and by reducing the amount of ethylamine.

Introduction

Naturally occurring polyacetylenes are an intriguing class of natural products.[1−7] Along with (−)-minquartynoic acid (**1**) and (*E*)-15,16-dihydrominquartynoic acid (**3**), 18-hydroxyminquartynoic acid (**2**) was isolated from a chloroform extract of the twigs of *Ochanostachys amentacea* from southeast Asia.[8] In recent in vitro tests, all three polyacetylenes show potent cytotoxicity against 10 different tumor cell lines.[8] The structures of these polyacetylenes are fascinating. They are optically active, with each compound containing a conjugated polyyne, one or two hydroxy group(s), and a carboxylic acid function, Figure 1.

Widespread interest has recently appeared in the synthetic studies of the natural acetylenic compounds.[9−15]

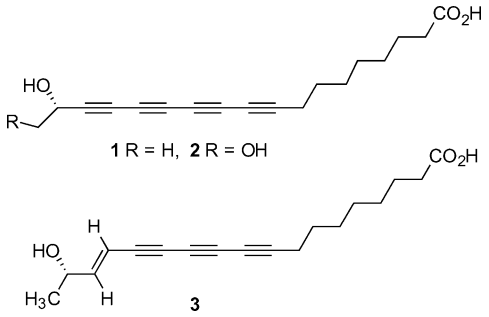

FIGURE 1. Cytotoxic polyacetylenes from *O. amentacea*: minquartynoic acid (**1**), (*S*)-18-hydroxyminquartynoic acid (**2**), and (*E*)-15,16-dihydrominquartynoic acid (**3**).

The main challenge in the total synthesis of these polyyne natural products is the highly reactive nature of the intermediate terminal diynes and triynes.[16−18] Recently, we reported the first total synthesis of (−)-minquartynoic acid (**1**) using a three-component Cadiot−Chodkiewicz reaction,[19] Scheme 1.[18] The idea was to avoid the isolation of the reactive terminal diyne and triyne intermediates

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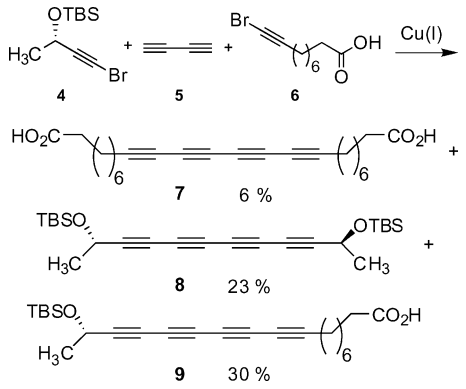
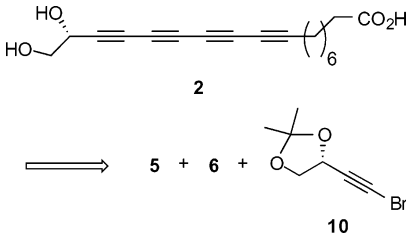
SCHEME 1



SCHEME 2

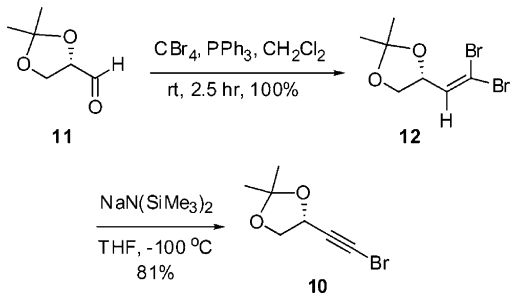


and to obtain the relatively stable internal tetrayne in an one-pot reaction. Such a three-component cross-coupling reaction involves two individual cross-coupling steps. Statistically only one-third of the desired asymmetric cross-coupling product (**9**) is expected and the other two-thirds of the reaction products (**7** and **8**) are the results of two symmetric cross-couplings. This statistical ratio is based on the assumption that the two bromoalkynes (**4** and **6**) involved have identical reactivities. Indeed all three expected products were isolated in our recent synthesis of (−)-minquartynoic acid, Scheme 1.[18] However, when the same conditions were applied in the present study, none of the desired product was isolated. In this manuscript, we wish to report the observation of a remarkable difference in reactivities among the bromoalkynes (**6**, **10**, and **14**) in the Cu(I)-catalyzed cross-coupling reactions, which is at variance with the expectations based on statistics. We also report the conditions for a concise synthesis of (*S*)-18-hydroxyminquartynoic acid (**2**).

Results and Discussion

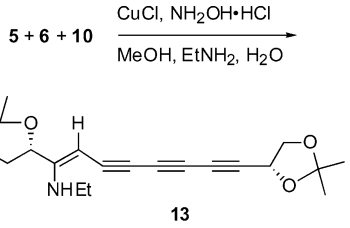
By adopting the same strategy as for the synthesis of (−)-minquartynoic acid (**1**), we had hoped that (−)-18-hydroxyminquartynoic acid (**2**) would be available from a three-component cross-coupling of butadiyne **5** and bromoalkynes **6** and **10**, Scheme 2. The bromoalkyne **10** should be available from D-glyceraldehyde,[20] and butadiyne **5** can be prepared in one step from commercially available 1,4-dichloro-2-butyne.[21] Bromoalkyne **6** is obtained from commercially available azelaic acid monomethyl ester in four steps.[18]

SCHEME 3



Thus, starting from aldehyde **11**,[20] dibromoolefin **12** was obtained quantitatively using a combination of Ph_3P and CBr_4 as shown in Scheme 3.[22] The desired bromoalkyne **10** was obtained by the elimination of one molar HBr from **12** under previously reported conditions.[23]

With bromoalkyne **10** in hand, a Cadiot−Chodkiewicz coupling was attempted with butadiyne **5** and bromoalkyne **6**. Disappointing results were obtained using the conditions for the synthesis of (−)-minquartynoic acid (1 mmol of each of the three reactants were dissolved in a 2 mL 1:1 mixture of methanol and 70% ethylamine aqueous solution with 5 mol % of NH_2OH·HCl and 5 mol % of CuCl, and the mixture was stirred at 0−25 °C for 3 h). Although TLC seemed to show three spots as expected from a statistical cross-coupling of the three components, the most consistent product after workup and chromatographic purification did not contain the fragment from carboxylic acid **6**. Instead, the ^{1}H NMR spectrum of the product shows four different methyl groups. Bromoalkyne **10** undergoes rapid cross-coupling with butadiyne followed by the addition of 1 equiv of ethylamine. The enamine product **13** was consistently obtained in good yield, and its structure was identified by a full battery of spectroscopic methods. There is apparently a large difference in the reactivity between bromoalkyne **10** and bromoalkyne **6**.



The conditions for the three-component couplings were therefore modified on the basis of this analysis. To avoid the addition of the $EtNH_2$ to the tetrayne intermediate, ethylamine was reduced from 1 to 0.3 mL for 1 mmol of each component. It is known that polar terminal alkynes usually afford higher yields in the Cu(I)-catalyzed cross-coupling reactions,[19,24] and we thought that polar 1-bromoalkynes might also react better in polar solvents. The acetal group was removed from bromoalkyne **10**, and

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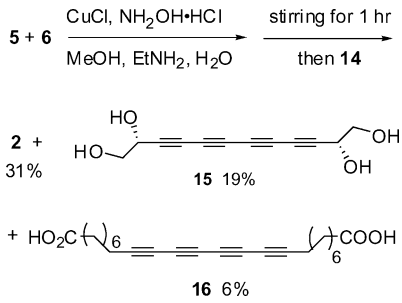
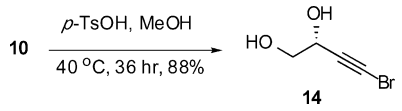
SCHEME 4



diol **14** was obtained by the treatment of **10** with a catalytic amount of *p*-TsOH in MeOH.



Furthermore, the less reactive bromoalkyne **6** was allowed to react with butadiyne **5** for 1 h before bromoalkyne **14** was added to the reaction mixture, Scheme 4. A solid (mp 135 °C) was obtained in 31% yield after column chromatography and gave spectroscopic characteristics identical with those reported for the natural (*S*)-18-hydroxyminquartynoic acid. Even under these conditions, the symmetric coupling product tetraol **15** was isolated in a substantial 19% and the known diacid **16** in just 6% yield.

The proposed mechanism for the Cu(I)-catalyzed cross-coupling of a bromoalkyne with a terminal alkyne involves an acetylenic copper intermediate.[19] We expect that the oxygen substitutions next to the triple bond facilitate the coordination of the intermediate alkynylcopper (R′-≡-Cu) species to the triple bond of the bromoalkyne and subsequent coupling to the other terminal acetylenic carbon, Figure 2.

It seems reasonable to suggest that the remarkable difference in reactivity between bromoalkynes **6** and **10** or **14** is due to the oxygen substitution in the latter. However, very little symmetric cross-coupling of the bromoalkyne **4** was observed in the synthesis of (−)-minquartynoic acid (**1**). Bromoalkyne **4** has one oxygen substituent at the propargylic position and the protecting group is a *tert*-butyldimethylsilyl (TBS) ether. The increased reactivity of **10** or **14** can be attributed to the second oxygen substitution at the homopropargylic carbon as shown in Figure 2. Furthermore, the TBS protecting group in **4** could attenuate the coordination effect because (1) it is a sterically bulky group and (2) silyl ethers are weaker Lewis bases than alkyl ethers.[25] A similar effect of propargylic oxygen coordination to a chromium intermediate was proposed to be responsible for the change of reaction course in carbene-chromium complex/alkyne cycloaddition reactions.[26]

Summary

The condition for a highly efficient synthesis of (*S*)-18-hydroxyminquartynoic acid (**2**) has been found. The total synthesis is completed in a mere five linear steps and 17.7% overall yield from the commercially available 1,2,5,6-*O*-diisopropylidene mannitol. This synthesis confirms the efficiency of the three-component Cadiot−Chodkiewicz coupling reaction in the preparation of conjugated tetraynes. This study also reveals a remarkable difference in the reactivity of oxygen-substituted versus non-oxygen-substituted bromoalkynes. Finally, a solution to circumvent the addition of amines to the tetrayne intermediates is also documented in this report.

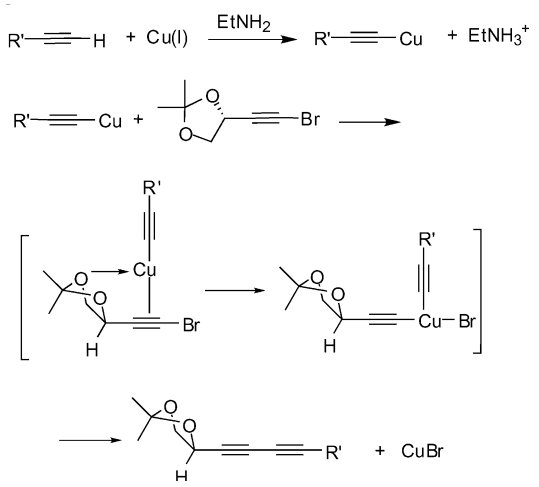
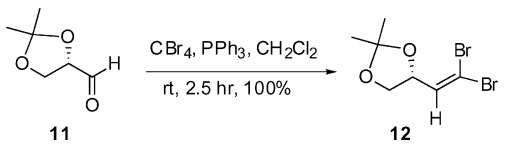


FIGURE 2. Proposed mechanistic pathway for the oxygen substitution accelerated coupling: oxygen functional groups facilitate coordination to the Cu species and hence increase the reaction rate.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources and used directly without further purification. Compounds **5**,[21] **6**,[18] and **11**[20] were prepared according to reported procedures. Purification of reaction products was carried out by flash chromatography using silica gel 40−63 μm (230−400 mesh), unless otherwise stated. Reactiqons were monitored by ^{1}H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% $KMnO_4$ solution followed by heating. Chemical shifts are recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as follows: *s* = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz.

Preparation of 3,4-*O*-Isopropylidene-1,1-dibromobut-1-en-3,4-diol (12).



A 500-mL round-bottom flask was charged with a stirring bar and a solution of PPh_3 (48.6 g, 185 mmol) in 200 mL of CH_2Cl_2. The mixture was stirred and cooled to 0 °C, after which CBr_4 (30.9 g, 92.3 mmol) was added over a period of 15 min. The reaction was allowed to warm to room temperature with stirring for 30 min. It was recooled to 0 °C, and a solution of aldehyde **11** (6 g, 46.1 mmol) in 10 mL of CH_2Cl_2 was added. The reaction mixture was allowed to warm to room temper-

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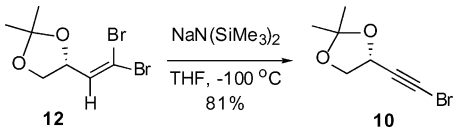
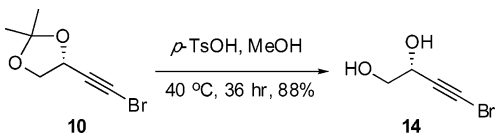
ature with stirring. When the starting material had disappeared (~2 h), the mixture was cooled to 0 °C, and 250 mL of hexanes was added. The mixture was allowed to stir for 1 h and then filtered through a pad of Celite. The cake was washed three times with hexanes. The solvents were removed under reduced pressure (30 mmHg), and the crude mixture was purified by flash column chromatography. A colorless oil (13.13 g, 100% yield) was obtained: $[\alpha]_D$ −15.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.6 (1H, d, J = 8.5 Hz), 4.7 (1H, dd, J = 8.5 Hz, 15.9 Hz), 4.2 (1H, d, J = 6.3 Hz), 3.8 (1H, d, J = 6.8), 1.5 (3H, s), 1.4 (3H, s); ^{13}C NMR (50 MHz,) 137.4, 110.4, 93.1, 76.5, 68.4, 27.0, 26.0; IR (film) 3018, 1709, 1215, 770.

Preparation of 3,4-*O*-Isopropylidene-1-bromobut-1-yn-3,4-diol (10).



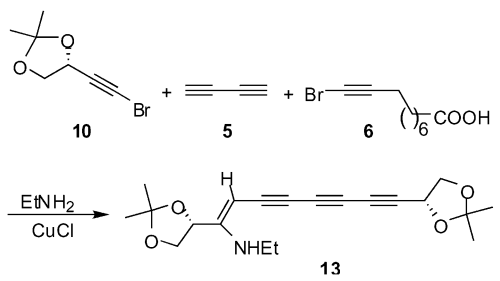
A 300-mL round-bottom flask was charged with a stirring bar and a solution of dibromoalkene **12** (3.0 g, 10.5 mmol) in 110 mL of THF and cooled to −100 °C with stirring. At this temperature, 12.6 mL (12.6 mmol) of $NaN(SiMe_3)_2$ (1 M solution in THF) was added. After 3 h, the reaction mixture was diluted with 200 mL of ether and quenched with 200 mL of saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvents were removed with a rotary evaporator, and the crude mixture was purified using flash column chromatography. A colorless oil (1.78 g. 81%) was obtained: $[\alpha]_D$ −14.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.7 (1H, dd, J = 1.6, 4.5 Hz), 4.1 (1H. dd, J = 6.4, 1.7 Hz), 3.9 (1H, dd, J = 4.3, 6.1 Hz), 3.0 (2H, q, J = 5.4 Hz), 1.5 (3H, s, H-6), 1.4 (3H, s); ^{13}C NMR (50 MHz, acetone-d_6) δ 110.4 (C-5), 79.0 (C-2), 69.9 (C-3) 66.4 (C-4), 46.1 (C-1), 26.1 (C-6), 25.6 (C-7); IR (film) 2900, 2253, 1253, 1096.

Preparation of 4-Bromo-3-butyn-1,2-diol (14).



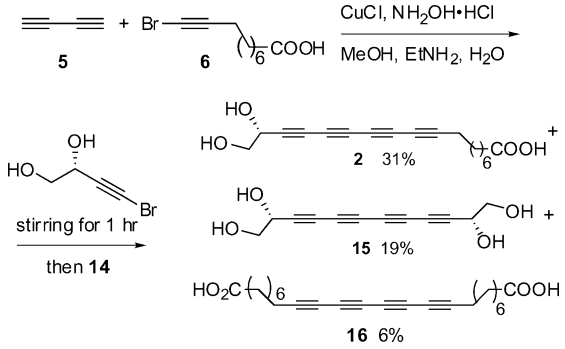
A 50-mL round-bottom flask was charged with a stirring bar, 600 mg (2.94 mmol) of the bromoalkyne **10**, 55 mg (0.29 mmol) of *p*-TsOH, and 25 mL of MeOH. The mixture was stirred at 40 °C for 36 h. The solvent was removed using a rotary evaporator, and the crude mixture was purified using flash column chromatography. A white solid (425 mg, 88%) was isolated: mp 88−91 °C; $[\alpha]_D$ −12.4 (*c* 0.1, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 4.3 (1H, t, J = 5.2 Hz), 3.6 (2H, dd, J = 1.0, 2.4 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 79.4 (C-3), 66.0 (C-1), 63.9 (C-2), 45.0 (C-4); IR (film) 3346, 2212, 1122, 975; HRMS calcd for $C_4H_5O_2Br$ + Na 186.9371, found 186.9363.

Preparation of Enamine (13).



A 10-mL round-bottom flask was charged with a stirring bar, 0.8 mL of MeOH, 0.8 mL of $EtNH_2$ (70% aqueous solution), and an aqueous solution of $NH_2OH{\cdot}HCl$ (2.8 mg, 0.04 mmol) in 0.5 mL of H_2O. A solution of the two bromoalkynes (**10**, 165 mg, 0.81 mmol and **6**, 200 mg, 0.81 mmol) in 2 mL of MeOH was added. The flask was cooled to 0 °C, and a solution of the butadiyne **5** (0.81 mmol, 0.32 mL of 2.5 M solution) in MeOH was added. CuCl (4 mg, 0.04 mmol) was added shortly afterward. The reaction was stirred at 0 °C for 1 h. When the starting materials were consumed, the reaction mixture was diluted with 20 mL of ether and quenched with 20 mL of KCN/NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic extract was washed with brine and dried over $MgSO_4$. Solvents were removed with a rotary evaporator, and the crude mixture was purified with flash column chromatography. A colorless oil was isolated (81 mg, 58% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.14, (1H, t, J = 7.0 Hz), 5.1 (1H, s), 4.9 (1H, t, J = 5.9 Hz), 4.5 (1H, t, J = 5.8 Hz), 4.20 (1H, t, J = 5.9 Hz), 4.16 (1H, s), 4.0 (1H, t, J = 6.0 Hz), 3.8 (1H, dd, J = 1.5, 6.0 Hz), 3.0 (2H, q, J = 5.4 Hz), 1.5 (6H, two -CH_3, s, overlap), 1.46 (3H, s), 1.41 (3H, s), 1.2 (3H, t, J = 7.3); ^{13}C NMR (50M Hz, $CDCl_3$) δ 161.3, 111.2, 110.6, 79.8, 78.1, 78.0, 74.3, 71.9, 70.1, 67.3, 67.0, 66.5, 66.1, 37.9, 32.0, 26.5, 26.4, 26.3, 25.6, 14.0; $[\alpha]_D$ −58.1 (*c* 0.1, $CHCl_3$); IR (film) 3154, 2986, 2986, 2936, 2859, 2253, 2160, 1709, 1589, 1264; UV (MeOH) λ_{max} 373, 350, 330, 278, 264; LCMS calcd for $C_{20}H_{25}NO_4$ + H 344.2, observed 344.2.

Synthesis of (−)-*S*-18-Hydroxyminquartynoic Acid (2).



A 10-mL round-bottom flask was charged with a stirring bar, 3.4 mg (0.10 mmol) of $NH_2OH.HCl$, 1 mL of MeOH, and 0.3 mL of $EtNH_2$ (70% aqueous solution). The flask was cooled to 0 °C, and 1.21 mmol (1.21 M MeOH solution) of butadiyne **5** was added, followed by 6 mg (0.025 mmol) of CuCl. A solution of the bromoalkyne **6** (243 mg, 1.21 mmol) in 1 mL of MeOH was added. After 30 min, a solution of the other bromoalkyne **14** (200 mg, 1.21 mmol) in 1 mL of MeOH was added in three portions over 1 h. The reaction mixture was allowed to warm to room temperature with stirring. After 5 h, it was cooled to 0 °C, and 10 mL of KCN/NH_4Cl solution was added and stirred for 30 min. The mixture was extracted with EtOAc. The aqueous layer was acidified and extracted twice with EtOAc. The combined organic layer was dried over Na_2SO_4. The solvents were removed with a rotary evaporator. Davisil silica gel was used to prepare the flash column, and the mixture was eluted with 5% MeOH/$CHCl_3$. A total of three solids were isolated. The least polar fraction was identified as the known diacid **16** (20 mg, 6%). The most polar fraction was identified as the tetraol **15** (69 mg, 19%): mp 156−161 °C; $[\alpha]_D$ −16.2 (*c* 0.1, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 4.4 (1H, dd, J = 6.0, 5.7 Hz), 3.6 (2H, d, J = 8.2 Hz); ^{13}C NMR (50 MHz, CD_3-OD) δ 79.2, 68.7, 65.6, 63.6, 62.4, 61.4; IR (film) 3383, 2502, 2234, 1458, 1121; UV (MeOH) λ_{max} 218, 230, 236, 238, LCMS calcd for $C_{12}H_{10}O_4$ + Na 241.2, found 241.2. The medium polar fraction is the major product, which was isolated as a white solid **2** (112 mg, 31% yield): mp 132−135 °C (lit. mp 130−135 °C);[8] $[\alpha]_D$ −38.4 (*c* 0.1, MeOH; lit. $[\alpha]_D$ −39);[8] ^{1}H NMR (200

MHz, CD_3OD) δ 4.4 (1H, dd, J = 6.1, 5.7 Hz), 3.6 (2H, d, J = 6.2 Hz) 2.4 (2H, t, J = 2.6 Hz), 2.3 (2H, t, J = 7.5 Hz), 1.6−1.2 (10H, m, overlap); ^{13}C NMR (50 MHz, CD_3OD) δ 176.7, 82.0, 78.2, 68.9, 65.7, 64.8, 63.6, 62.9, 62.7, 59.9, 59.2, 33.9, 29.0 28.8, 28.8, 28.0, 25.0, 18.9; IR (film) 3365, 2934, 2490, 2362, 2225, 2073, 1716, 1100; UV (MeOH) λ_{max} 214, 216, 221, 241; HRMS calcd for $C_{18}H_{20}O_4$ + Na 323.1259, found 323.1241

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Supporting Information Available: ^{13}C NMR spectra for compounds **2**, **11**, and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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