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Tandem Wittig−Ene Reaction Approach to Kainic Acid

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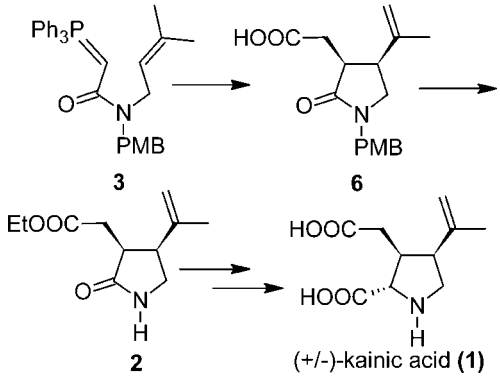

The first example of a tandem Wittig−intramolecular ene reaction approach and its application toward the synthesis of kainic acid is reported. The synthetic pathway involves conversion of prenyl bromide into phosphorane **3**, followed by one-pot Wittig olefination and an ene reaction with glyoxalic acid to give the cis fused pyrrolidine skeleton of kainic acid.

The kainoid group of nonproteinogenic pyrrolidine dicarboxylic acids has attracted considerable interest from synthetic chemists because of its varied neuropharmacological properties as well as its unique and challenging structural features.[1] (−)-α-Kainic acid **1**, isolated from *Digenea simplex*[2] and several other red algae,[3] displays potent neuroexcitatory activity in the mammalian central nervous system and is widely used in the study of neurological disorders such as epilepsy,[4] Alzheimer's disease,[5] Huntington's chorea,[6] and so forth.

Kainic acid is an amino acid with three contiguous stereogenic centers in the pyrrolidine ring. Among these, the C-2, C-3 arrangement is trans while the C-3, C-4 substituents are in a thermodynamically less favorable cis configuration, a factor implicated in its interesting biological properties.[7] The increasing worldwide[8] demand and the challenging cis-3,4 stereochemistry of this molecule have led to the development of several synthetic strategies[9] including the first asymmetric synthesis by Oppolzer and Thirring[10] using a stereocontrolled intramolecular ene reaction.

Continuing our interest in the synthesis of marine natural products and other biologically active compounds,[11] we herein report a facile synthesis of pyrrolidone **2**, a key intermediate in the total synthesis[12] of (−)-α-kainic acid **1**. The preparation of compound **2**, which has substituents at the C-3 and C-4 positions in the desired cis geometry, has been achieved using our newly developed tandem Wittig−intramolecular ene reaction.

In our retrosynthetic analysis, compound **2** was envisioned to result from phosphorane **3** via a tandem Wittig−ene reaction. The phosphorane **3**, in turn, could be obtained from prenyl bromide (Scheme 1).

Thus, N-alkylation of benzylamine with prenyl bromide in the presence of K_2CO_3 followed by treatment of monoalkylated benzylamine with bromoacetyl bromide yielded *N*,*N*-disubstituted bromoacetamide **5a**. Reaction of **5a** with PPh_3 afforded the corresponding Wittig salt, which on deprotonation using NaOH provided the required phosphorane **3a** in good yield (Scheme 2). With a sufficient amount of phosphorane **3a** in hand, our next plan was to prepare the pyrrolidine skeleton. Toward this end, phosphorane **3a** was refluxed with glyoxalic acid in different solvents. As expected, two reactions, that is, the Wittig reaction and the intramolecular ene reaction, took place in a tandem fashion, yielding the desired product **6a** along with its thermodynamically more stable, trans analogue **7a** in varying proportions (Scheme 3 and Table 1).

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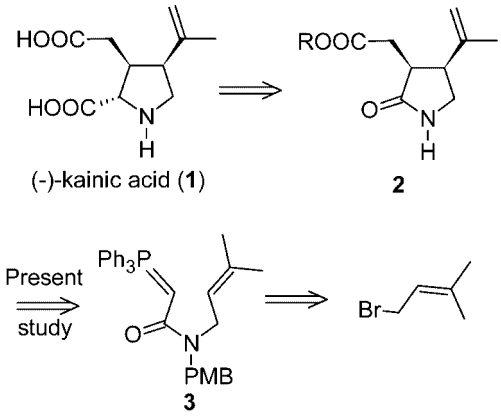
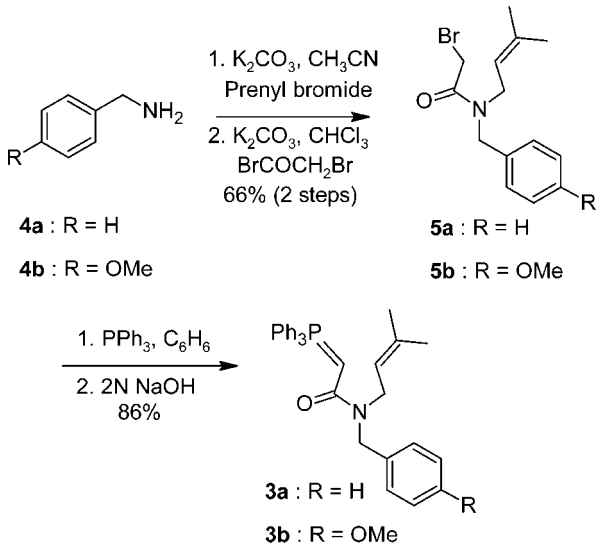
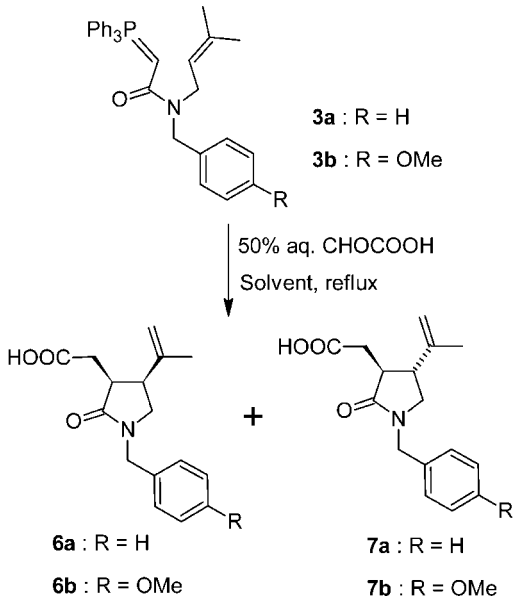
SCHEME 1. Retrosynthetic Analysis Depicting the Tandem Wittig−Intramolecular Ene Reaction



SCHEME 2. Synthesis of Phosphorane



SCHEME 3. Tandem Wittig−Intramolecular Ene Reaction



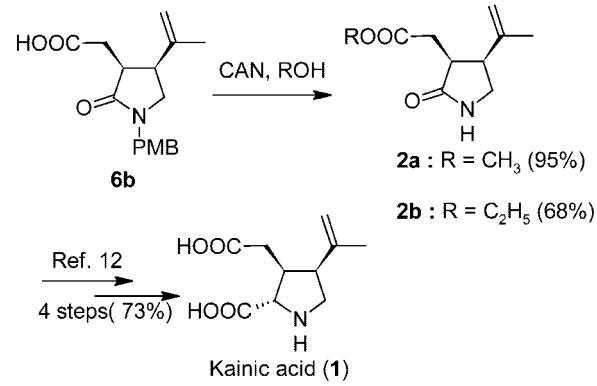
With diphenyl ether as the refluxing solvent (4 h) the products **6a** and **7a** were obtained in the ratio 1:7. The stereochemical assignments were facilitated by the observation that the isopropenyl methyl peaks of cis and trans isomers (**6a** and **7a**) appear at δ 1.46 (s) and 1.70 (s), respectively, in their ^{1}H NMR spectra. Additional proof is provided by the observation that one of the C-3 side chain methylene protons appears significantly upfield (δ 2.43) in the cis as compared (δ 2.60) to the trans isomer.[13] When the reaction was carried out in refluxing toluene or xylene (24 h), the cis/trans ratio was found to be 20:1, as indicated by ^{1}H NMR spectra of the crude products (entries 2 and 3, respectively). These results indicated a possible cis to trans thermally induced isomerization in diphenyl ether (bp 250 °C).

TABLE 1. Tandem Wittig−Intramolecular Ene Reaction

entry	substrate (R)	conditions	products	ratio[a] (% yield)
1.	H	250 °C, PhOPh, 4 h	**6a**:**7a**	1:7 (40)
2.	H	110 °C, toluene, 24 h	**6a**:**7a**	20:1 (60)
3.	H	140 °C, xylene, 24 h	**6a**:**7a**	20:1 (58)
4.	OMe	110 °C, toluene, 24 h	**6b**:**7b**	5:1 (65)

[a] The ratio of diastereomers was calculated on the basis of the ^{1}H NMR.

SCHEME 4. Synthesis of Pyrrolidone



To complete the formal synthesis of the kainic acid, removal of the benzyl group in **6a** was necessary. However, debenzylation using the reported method[14] failed in our hands to provide the desired amide **2**. Subsequently, the modified phosphorane **3b** was prepared (Scheme 2), which, upon treatment with glyoxalic acid in refluxing toluene, provided **6b** (entry 4). CAN oxidation of **6b** resulted in simultaneous deprotection of the PMB group and esterification of the carboxylic acid, giving methyl ester **2a** in good yield (95%). The Ganem's intermediate, ethyl ester **2b**, was obtained in 68% yield (Scheme 4). The spectral data of **2b** were identical to those reported in literature.[12] The above one-pot deprotection and esterification did not affect the stereochemistry of C-3, C-4.

The synthesis of pyrrolidone **2b** constitutes a formal synthesis of kainic acid. The overall yield of the five-step synthesis of pyrrolidone **2b** from prenyl bromide is 25% and is comparable with the literature procedure, that is, 10% in seven steps[9d] from chlorosulfone and 39% in four steps[12] from prenylamine.

In conclusion, the present work demonstrates the feasibility and synthetic utility of a tandem Wittig−ene sequence for the assembly of cis fused 3,4-disubstituted pyrrolidone **6**. The conversion of **6b** to Ganem's advanced intermediate **2b** constitutes a formal synthesis of (±)-kainic acid.

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Experimental Section

General Remarks: Column chromatography was performed by using Merck silica gel 60/120 mesh size. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker 300 instrument. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS), and the coupling constant J is given in Hz. Chemical shifts within square brackets give the values of the amide torsion isomer.

General Procedure for Preparation of *N*,*N*-Disubstituted Bromoacetamide (5): To a stirred solution of benzylamine or *p*-methoxy benzylamine (3 equiv) and K_2CO_3 (1 equiv) in anhyd CH_3CN (10 mL) was added a solution of prenyl bromide (1 equiv) in CH_3CN (2 mL) over a period of 10 min in an ice cold water bath. The reaction mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. Purification of residue by column chromatography on silica gel (hexanes/EtOAc = 7:3) afforded *N*-prenyl benzylamine (the yield of product was calculated on the basis of the recovery of starting benzylamine). To a stirred solution of *N*-prenyl benzylamine (1 equiv) and K_2CO_3 (2 equiv) in $CHCl_3$ (20 mL) was added a solution of bromoacetyl bromide (1.2 equiv) in $CHCl_3$ (1 mL) at 0 °C over a period of 10 min. The reaction mixture was then stirred for 1 h at room temperature and diluted with water (20 mL), and product was extracted with $CHCl_3$ (3 × 20 mL). The organic phase was washed with H_2O (2 × 20 mL), followed by $NaHCO_3$ (2 × 30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuum. Purification of residue by column chromatography on silica gel (hexanes/EtOAc = 7:3) afforded the desired product **5**.

***N*-Benzyl-*N*-prenyl-2-bromoacetamide (5a):** Yield 65% (2 steps); light yellow thick oily compound. IR (ν max): 1647 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60 [1.53] (s, 3H), 1.73 [1.71] (s, 3H), 3.87 [4.01] (d, J = 6.6 Hz, 2H), 3.91 [3.84] (s, 2H), 4.58 [4.55] (s, 2H), 5.11−5.16 (m, 1H), 7.16−7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8, 25.6, 26.3 [26.5], 45.7 [43.5], 48.3 [50.8], 119.3 [118.5], 126.3 [127.3], 127.7 [127.9], 128.5 [128.9], 136.8 [136.2], 137.2, 166.8. HRMS: m/z [M + Na]$^+$ calcd for $C_{14}H_{18}NOBrNa$, 318.0469; found, 318.0474.

***N*-(*p*-Methoxy)benzyl-*N*-prenyl-2-bromoacetamide (5b):** Yield 66% (2 steps); light yellow thick oily compound. IR (ν max): 1647 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 [1.56] (s, 3H), 1.75 [1.73] (s, 3H), 3.80 [3.82] (s, 3H), 3.91 [3.88] (s, 2H), 3.87 [3.99] (d, J = 6.9 Hz, 2H), 4.52 [4.49] (s, 2H), 5.05−5.20 (m, 1H), 6.86 [6.89] (d, J = 8.4 Hz, 2H), 7.18 [7.13] (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.9, 25.7, 26.5, 45.5 [43.3], 47.8 [50.3], 55.2, 114.0 [114.3], 119.5 [118.6], 127.7 [129.4], 128.9 [128.0], 136.7 [137.1], 159.0 [159.2], 166.8. HRMS: m/z [M + Na]$^+$ calcd for $C_{15}H_{20}NO_2BrNa$, 348.0575; found, 348.0566.

General Procedure for Preparation of Phosphorane (3): To a stirred solution of PPh_3 (1.1 equiv) in dry benzene (20 mL) was added *N*,*N*-disubstituted bromoacetamide **5** (1 equiv), and the solution was stirred at room temperature for 8 h. Water (40 mL) was added to the reaction mixture, and the mixture was washed with benzene (3 × 30 mL). Benzene (50 mL) was added to aqueous layer followed by 2 N NaOH with constant shaking to the phenolphthalein end point. The benzene layer was dried over anhyd Na_2SO_4 and concentrated to give a thick liquid **3**.

***N*-Prenyl-*N*-benzyl-2-[triphenylphosphoranylidene] Acetamide (3a):** Yield 85%; yellow color thick liquid. IR (ν max): 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52 [1.48] (s, 3H), 1.66 [1.65] (s, 3H), 2.09 (d, J = 12.6 Hz, 1H), 3.77 [3.99] (d, J = 6.6 Hz, 2H), 4.50 [4.41] (s, 2H), 5.05−5.09 [5.10−5.15] (m, 1H), 7.10−7.51 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8, 25.6, 29.6, 45.6 [42.6], 50.8 [47.7], 119.6, 126.2, 128.3, 128.5, 131.8, 132.0, 132.8, 137.5, 170.5. HRMS: m/z [M + H]$^+$ calcd for $C_{32}H_{33}NOP$, 478.2300; found, 478.2313.

***N*-Prenyl-*N*-(*p*-methoxy)benzyl-2-[triphenylphosphoranylidene] Acetamide (3b):** Yield 86%; yellow color thick liquid. IR (ν max): 1647 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59 [1.48] (s, 3H), 1.67 [1.65] (s, 3H), 2.01 (br s, 1H), 3.78 [3.77] (s, 3H); 3.91 [4.16] (d, J = 6.9 Hz, 2H), 4.38 [4.81] (s, 2H), 4.97 [5.05] (t, J = 6.6 Hz, 1H), 6.76 [6.82] (d, J = 8.4 Hz, 2H), 6.94 [7.11] (d, J = 8.4 Hz, 2H), 7.60−7.85 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.0 [17.8], 25.7 [25.6], 32.6, 44.1 [46.6], 48.2 [50.4], 55.3, 113.9 [114.2], 118.5 [119.0], 119.1, 119.3, 120.2 [120.3] 127.9 [129.2], 128.6 [128.5], 129.8, 129.9, 130.0, 133.6, 133.7, 133.8, 134.4, 137.3 [137.4], 158.9, 164.0 [164.2]. HRMS: m/z [M + H]$^+$ calcd for $C_{33}H_{35}NO_2P$, 508.2405; found, 508.2401.

General Procedure for Preparation of N-Protected 2-Pyrrolidone (6): To a solution of 1.2 equiv of phosphorane **3** in dry toluene (30 mL) was added 1 equiv of glyoxalic acid (50% aq soln), and the mixture was stirred at room temperature for 30 min. The reaction mixture was refluxed in a Dean-stark equipped flask for 24 h. After the reaction was over, it was cooled to room temperature, $NaHCO_3$ (20 mL) was added, and then the mixture was washed with Et_2O (3 × 20 mL). The aqueous layer was neutralized with 2 N HCl (30 mL) and extracted with Et_2O (3 × 20 mL). A combined organic phase was dried over anhyd Na_2SO_4 and concentrated under reduced pressure, and recrystallizaton using hexanes/EtOAc (7:3) afforded the desired product **6**.

***N*-Benzyl-2-pyrrolidone (6a):** Yield 60%; white crystalline solid, mp 113−114 °C. IR (ν max): 3485−2289, 1739, 1639 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 3H), 2.47 (dd, J = 4.5 Hz, 16.2 Hz, 1H), 2.71 (dd, J = 8.7 Hz, 16.2 Hz, 1H), 3.10−3.22 (m, 3H), 3.51−3.56 (m, 1H), 4.50 (s, 2H), 4.75 (s, 1H), 4.85 (s, 1H), 7.29−7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 31.8, 41.1, 42.3, 47.2, 49.6, 115.6, 128.0, 128.7, 128.8, 135.3, 142.2, 175.0, 175.4. HRMS: m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NO_3Na$, 296.1263; found, 296.1253.

***N*-(*p*-Methoxy)benzyl-2-pyrrolidone (6b):** Yield 65%; white crystalline solid, mp 103−104 °C. IR (ν max): 3600−2245, 1722, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (s, 3H), 2.39 (dd, J = 6.6 Hz, 17.1 Hz, 1H), 2.79 (dd, J = 5.4 Hz, 17.4 Hz, 1H), 3.09−3.14 (m, 3H), 3.45−3.48 (m, 1H), 3.80 (s, 3H), 4.37 (d, J = 14.4 Hz, 1H), 4.45 (d, J = 14.1 Hz, 1H), 4.72 (s, 1H), 4.81 (s, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 31.5, 41.2, 42.2, 46.5, 49.4, 55.2, 114.2, 115.5, 127.4, 130.0, 142.3, 159.3, 175.1, 175.5. HRMS: m/z [M + Na]$^+$ calcd for $C_{17}H_{21}NO_4Na$, 326.1368; found, 326.1365.

Preparation of *N*-Benzyl-2-pyrrolidone (7a): To a solution of phosphorane (0.332 g, 0.87 mmol) **3a** in dry diphenyl ether (20 mL) was added glyoxalic acid (0.128 g, 0.87 mmol, 50% aq soln), and the mixture was stirred at room temperature for 30 min. The reaction mixture was refluxed for 4 h. After the reaction was over, it was cooled to room temperature, $NaHCO_3$ (20 mL) was added, and then the mixture was washed with Et_2O (3 × 20 mL). The aqueous layer was neutralized with 2 N HCl (30 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give light yellow color thick liquid **7a** (0.095 g, 40%). IR (ν max): 3485−2289, 1739, 1639 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70 (s, 3H), 2.64 (dd, J = 4.8 Hz, 16.2 Hz, 2H), 2.74−2.83 (m, 1H), 2.89−2.93 (m, 1H), 3.10−3.16 (m, 1H), 3.30−3.36 (m, 1H), 4.42 (d, J = 14.7 Hz, 1H), 4.57 (d, J = 14.7 Hz, 1H), 4.85 (s, 1H), 4.87 (s, 1H), 7.24−7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 34.7, 41.7, 46.4, 47.0, 49.5, 114.0, 127.9, 128.1, 128.7, 128.8, 128.9, 135.5, 142.4, 174.3, 175.7. HRMS: m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NO_3NNa$, 296.1263; found, 296.1260.

General Procedure for the Preparation of 2-Pyrrolidone (2): To an ice cooled solution of N-protected 2-pyrrolidone **6** (1 equiv) in alcohol (5 mL) was added ceric ammonium nitrate (4 equiv), and the mixture was stirred for 1 h at 0 °C. This mixture was further stirred for 12 h at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with EtOAc (3 × 20 mL), and dried over anhyd Na_2SO_4, and solvent was removed in vacuum to afford a crude oil. Further purification was done on silica gel (hexanes/EtOAc = 6: 4) to afford the desired product **2** as a white crystalline solid.

2-Pyrrolidone (2a): Yield 95%; mp 89−90 °C. IR (ν max): 3203, 1732, 1693 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.67 (s, 3H), 2.31 (dd, J = 9.9 Hz, 17.4 Hz, 1H), 2.80 (dd, J = 4.5 Hz, 17.4 Hz, 1H), 3.09 (ddd, J = 4.2 Hz, 4.5 Hz, 9.6 Hz, 1H), 3.26−3.32 (m, 2H), 3.59 (dd, J = 6.6 Hz, 9.9 Hz, 1H), 3.70 (s, 3H), 4.78 (s, 1H), 4.87 (s, 1H), 6.01 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.1, 30.3, 40.4, 44.5, 44.7, 51.7, 114.9, 142.9, 172.8, 178.2. HRMS: m/z $[M + Na]^+$ calcd for $C_{10}H_{15}NO_3Na$, 220.0950; found, 220.0947.

Ganem's Intermediate (2b): Yield 68%; mp 104−105 °C. IR (ν max): 3205; 1730; 1696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.2 Hz, 3H), 1.67 (s, 3H), 2.28 (dd, J = 9.9 Hz, 17.4 Hz, 1H), 2.78 (dd, J = 4.5 Hz, 17.4 Hz, 1H), 3.07 (m, 1H), 3.55−3.60 (m, 2H), 3.57 (dd, J = 6.6 Hz, 9.9 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.78 (s, 1H), 4.86 (s, 1H), 6.37 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 20.2, 30.6, 40.4, 44.6, 44.7, 60.6, 114.8, 143.0, 172.3, 178.0. HRMS: m/z $[M + Na]^+$ calcd for $C_{11}H_{17}NO_3Na$, 234.1106; found, 234.1101.

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Supporting Information Available: Copies of ^1H NMR, ^{13}C NMR of all the compounds, and DEPT spectra of **5a**, **6a**, **7a**, and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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