Studies on the Synthesis of Pinnaic Acid and Halichlorine. Stereoselective Preparation of a (*Z*)-δ-Chloro-γ,δ-unsaturated-β-keto Phosphonate as a Side Chain Synthon

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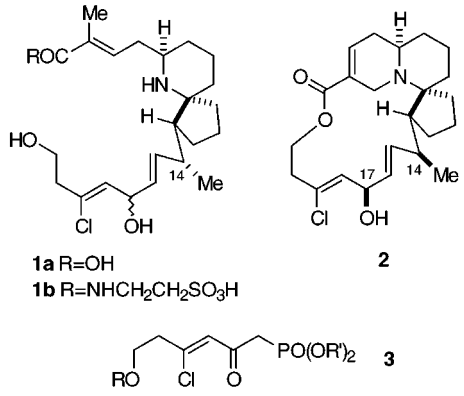
Pinnaic acid (**1a**) and tauropinnaic acid (**1b**) (Chart 1) are newly discovered marine alkaloids produced by the Okinawan bivalve *Pinna muricata*.[1a] A structurally related compound, halichlorine (**2**), was isolated by the same research group from the marine sponge *Halichondria okadai* Kadota.[1b] The relative stereochemistry of these metabolites was established by NMR methods, except for the configuration at the hydroxyl-bearing C17 of **1a/b**, which is at present indeterminate. Moreover, pinnaic acid and halichlorine appear to be epimeric at C14, although these assignments are characterized as being only tentative at this point.[2] The absolute stereochemistry of halichlorine was recently determined by chemical correlation of a degradation product,[1c] and one might reasonably assume that pinnaic acid has the same configuration. Pinnaic acid and tauropinnaic acid were found to have activity against phospholipase A_2. This sort of enzyme inhibitor has potential in the treatment of inflammation. Moreover, halichlorine was found to be an active inhibitor of VCAM-1 (vascular cell adhesion molecule-1). Such compounds are potentially useful in treatment of atherosclerosis, angina, and coronary artery disease.

We have recently been interested in devising a route for total synthesis of these unique molecules and considered the possibility of a convergent appoach for introduction of the C15−C21 chlorinated divinyl alcohol chain via a Wadsworth−Emmons−Horner reaction of an aldehyde with a highly fuctionalized unsaturated keto phosphonate like **3**. This strategy also appeared attractive since it would potentially allow control of the double bond geometry at both olefinic sites.[3] It might be noted that we had some initial concerns regarding the possibility that a keto phosphonate such as **3**, or one of its synthetic precursors, might be prone to undergo facile elimination of HCl and/or ROH or to 1,4-addition/elimination processes.[4] In this note we report that this type of Wadsworth−Emmons−Horner synthon can in fact be easily prepared and smoothly undergoes the desired stereoselective coupling with aldehydes.

The synthesis commenced with commercially available 3-butyn-1-ol (**4**), which could be lithiated and carboxylated to afford 5-hydroxy-2-pentynoic acid (**5**) (Scheme 1).[5] Stereoselective additions of HCl to propiolic acid and its esters have been previously reported,[6] but additions to higher homologues have received little attention.[7,8] We have found that the procedure of Kurtz *et al.*,[6a] which has been used for CuCl-catalyzed addition of HCl to simple propiolic acid derivatives, when applied to acid **5** stereoselectively affords the desired *Z* adduct **6** (anti addition), thus providing very simple access to the correct trisubstituted vinyl chloride stereochemistry. The geometry of **6** was established by a ^{1}H NMR NOE experiment.

Chart 1



To further test the generality of this methodology, 2-heptynoic acid (**7**) was subjected to similar reaction conditions, affording *Z* adduct **8**, along with only a trace of the *E* isomer (>20:1 from ^{1}H NMR) (eq 1 of Scheme 1). In this case dioxane was needed as a cosolvent to help dissolve the substrate.

Continuing the sequence, hydroxy acid **6** was bissilylated to afford **9**, which upon basic hydrolysis gave acid TBS ether **10** (Scheme 2). This acid could then be converted to the corresponding *N*-methoxy-*N*-methyl amide **11**.[9] Addition of dimethyl (lithiomethyl)phosphonate[10] to amide **11** gave an inseparable ∼2:3 mixture of the desired product **14** and the corresponding acetylenic keto phosphonate **13** formed by loss of HCl. However, use of the corresponding Grignard reagent **12**, prepared by exchange of the lithium compound with $MgBr_2$,[11] led to the requisite β-keto phosphonate **14** in good yield,

(1) (a) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871. (b) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (c) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.

(2) See footnote 6 in ref 1c.

(3) Geometrically pure cross-conjugated dienones have been previously made by this type of coupling. See for example: Friesen, R. W.; Blouin, M. *J. Org. Chem.* **1996**, *61*, 7202 and references cited.

(4) Cf.: Vedejs, E.; Bershas, J. P. *Tetrahedron Lett.* **1975**, 1359.

(5) Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. *J. Am. Chem. Soc.* **1979**, *101*, 5364. Hydroxy acid **5** has previously been prepared by a similar but less convenient route: Haynes, L. J.; Jones, E. R. H. *J. Chem Soc.* **1946**, 503. Haynes, L. J.; Jones, E. R. H. *J. Chem Soc.* **1946**, 954.

(6) (a) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141. (b) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1993**, *49*, 5225. (c) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.

(7) Shinada, T.; Yoshihara, K. *Chem. Pharm. Bull.* **1996**, *44*, 264. Application of this procedure to acetylenic acid **5** gave a complex mixture.

(8) For stereoselective additions of HI to propiolates and higher homologues see: Meyer, C.; Marek, I.; Normant, J.-F. *Synlett* **1993**, 386. Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 5329. Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1996**, *74*, 194. Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816.

(9) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. For a review see: Sibi, M. *Org. Prep. Proc. Int.* **1993**, *25*, 15.

(10) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

(11) Hoffmann, R. W.; Ditrich, K. *Liebigs Ann. Chem.* **1990**, 23.

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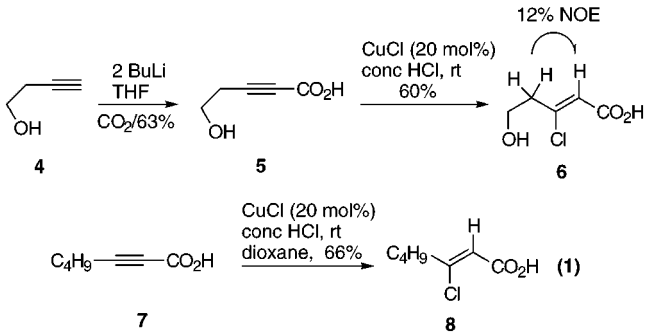
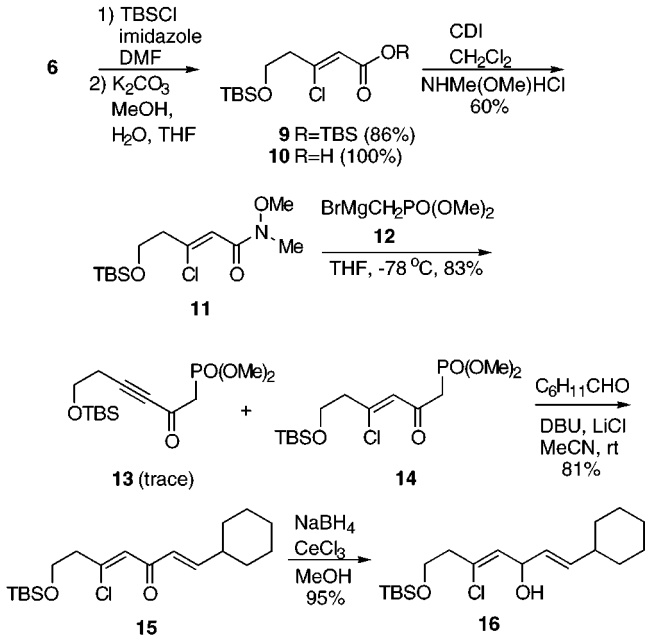
Scheme 1



Scheme 2



contaminated with only a trace (~6%) of the alkynyl keto phosphonate as determined by ^{1}H NMR.

We have tested the behavior of this keto phosphonate in a Wadsworth−Emmons−Horner reaction. Thus, using the condensation conditions developed by Roush and Masamune,[12] with employment of cyclohexanecarboxaldehyde as a model, **14** could be converted to dienone **15**, formed exclusively as the *Z*,*E*-stereoisomer. In addition, dienone **15** can be cleanly reduced[13] to yield the divinyl alcohol **16**, which is stable to chromatography and normal handling procedures.

In summary, the well-behaved (*Z*)-δ-chloro-γ,δ-unsaturated-β-keto phosphonate **14** can be prepared in a short sequence from acetylenic acid **5**. This compound undergoes stereoselective Wadsworth−Emmons−Horner condensation with an aldehyde and is a potentially useful synthon for construction of the C15−C21 dienol segment of pinnaic acid and halichlorine.

Experimental Section

Preparation of 5-Hydroxypent-2-ynoic Acid (5). 3-Butyn-1-ol (**4**, 8.98 g, 128 mmol) and THF (250 mL) were added to a 500 mL three-necked flask equipped with a mechanical stirrer. The stirred solution was cooled to −40 °C, and *n*-butyllithium (100 mL, 2.56 M in hexanes, 256 mmol) was then added dropwise. Once the addition was complete, the reaction mixture was stirred at −40 °C for 1 h and carbon dioxide gas was then bubbled through the pale yellow suspension for 1 h, maintaining the temperature at −40 °C. The resulting reaction mixture was poured onto crushed dry ice (20 g), acidified with 6 M aqueous HCl (40 mL), and then extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The oily solid isolated was washed with CH_2Cl_2 (2 × 15 mL) to give acid **5** (9.22 g, 63%) as a beige solid (mp 54−56 °C): IR (Nujol mull) 3650−2400, 2240, 1700 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.71 (t, J = 6.5 Hz, 2 H), 2.56 (t, J = 6.5 Hz, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 154.4, 87.4, 74.7, 60.2, 23.2; CIMS *m*/*z* (relative intensity) 115 (MH^+, 22), 97 ($MH^+ - H_2O$, 100).

Preparation of (*Z*)-3-Chloro-5-hydroxypent-2-enoic Acid (6). To a solution of acid **5** (1.98 g, 17.4 mmol) in concentrated HCl (9 mL) was added CuCl (345 mg, 3.5 mmol). After being stirred at room temperature for 15 h, the reaction mixture was diluted with water (20 mL). The aqueous solution was then washed with CH_2Cl_2 (5 × 20 mL) and extracted with EtOAc (5 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to yield acid **6** (1.57 g, 60%) as a viscous yellow oil: IR (neat) 3650−2400, 1704, 1641 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.21 (t, J = 0.9 Hz, 1 H), 3.81 (t, J = 6.1 Hz, 2 H), 2.68 (td, J = 6.1, 0.9 Hz, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 164.9, 147.6, 118.9, 59.4, 44.9; CIMS *m*/*z* (relative intensity) 151 (MH^+, 100), 133 ($MH^+ - H_2O$, 70).

Addition of HCl to Hept-2-ynoic Acid (7). To a solution of acid **7** (1.07 g, 8.5 mmol) in 1,4-dioxane (3 mL) was added CuCl (166 mg, 1.7 mmol) and concentrated HCl (4.5 mL). After being stirred at room temperature for 30 h, the reaction mixture was diluted with water (20 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield acid **8** (0.90 g, 66%, *Z*:*E* > 20:1) as a colorless oil: IR (neat) 3500−2400, 1698, 1633 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.06 (s, 1 H), 2.48 (t, J = 7.4 Hz, 2 H), 1.69−1.57 (m, 2 H), 1.42−1.31 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 169.5, 153.8, 115.5, 41.2, 29.2, 21.6, 13.6.

Preparation of *tert*-Butyldimethylsilyl (*Z*)-5-(*tert*-Butyldimethylsiloxy)-3-chloropent-2-enoate (9). To a solution of acid **6** (1.31 g, 8.7 mmol) and imidazole (2.42 g, 35.6 mmol) in DMF (9 mL) was added *tert*-butyldimethylsilyl chloride (2.75 g, 18.2 mmol). The resulting solution was stirred for 15 h, poured into water (50 mL), and then extracted with hexanes (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield silyl ester **9** (2.82 g, 86%) as a colorless oil: IR (neat) 1715, 1692, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 1 H), 3.85 (t, J = 6.0 Hz, 2 H), 2.62 (t, J = 6.0 Hz, 2 H), 0.95 (s, 9 H), 0.88 (s, 9 H), 0.30 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 146.6, 119.9, 59.7, 44.5, 25.8, 25.5, 18.2, 17.5, −4.8, −5.5; CIMS *m*/*z* (relative intensity) 379 (MH^+, 100), 321 ($MH^+ - Me_3CH$, 44).

Preparation of (*Z*)-5-(*tert*-Butyldimethylsiloxy)-3-chloropent-2-enoic Acid (10). To a solution of silyl ester **9** (2.27 g, 6.0 mmol) in THF (15 mL) and MeOH (45 mL) was added 1 M aqueous K_2CO_3 (13 mL, 13 mmol). After being stirred for 1 h, the reaction mixture was diluted with brine (50 mL), cooled to 0 °C, and then acidified by addition of 1 M aqueous $KHSO_4$ (40 mL). The resulting cloudy mixture was extracted with ether (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield acid **10** (1.58 g, 100%) as a colorless semisolid: IR (neat) 3400−2300, 1698, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 3.87 (t, J = 6.0 Hz, 2 H), 2.66 (t, J = 6.0 Hz, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 150.1, 117.5, 59.8, 44.8, 25.8, 18.2, −5.5; CIMS *m*/*z* (relative intensity) 265 (MH^+, 56), 247 ($MH^+ - H_2O$, 20), 207 ($MH^+ - Me_3CH$, 42), 145 (88), 89 (100).

Preparation of (*Z*)-5-(*tert*-Butyldimethylsiloxy)-3-chloro-*N*-methoxy-*N*-methylpent-2-enamide (11). A solution of 1,1′-carbonyldiimidazole (972 mg, 6.0 mmol) in CH_2Cl_2 (10 mL) was added, via a cannula, to a stirred solution of acid **10** (1.57 g, 5.9 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred for 1 h, and *N*,*O*-dimethylhydroxylamine hydrochloride (589 mg, 6.0

(12) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(13) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

mmol) was then added. After being stirred for a further 15 h, the reaction mixture was diluted with ether (75 mL) and washed sequentially with 0.1 M aqueous HCl (60 mL), saturated aqueous $NaHCO_3$ (2 × 25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a yellow oil. Purification of this material by flash column chromatography (1:1 ether/hexanes) afforded amide **11** (1.09 g, 60%) as a colorless oil: IR (neat) 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (br s, 1 H), 3.87 (t, J = 6.1 Hz, 2 H), 3.68 (s, 3 H), 3.24 (s, 3 H), 2.64 (t, J = 6.1 Hz, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 142.8, 117.4, 61.4, 59.8, 44.1, 31.8, 25.7, 18.0, −5.6; CIMS *m*/*z* (relative intensity) 308 (MH^+, 100), 250 ($MH^+ - Me_3CH$, 26).

Preparation of Dimethyl (*Z*)-6-(*tert*-Butyldimethylsiloxy)-4-chloro-2-oxohex-3-enylphosphonate (14). To a stirred solution of dimethyl methylphosphonate (190 mg, 1.53 mmol) in THF (15 mL) was added *n*-butyllithium (0.61 mL, 2.5 M in hexanes, 1.53 mmol) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a solution of magnesium bromide−diethyl etherate (442 mg, 1.71 mmol) in ether (15 mL) was added. The cooling bath was removed, and the cloudy reaction mixture was stirred for 10 min. The resulting clear solution was recooled to −78 °C, and a solution of amide **11** (235 mg, 0.76 mmol) in THF (10 mL), cooled to −78 °C, was added via a cannula. Once the addition was complete, the cooling bath was removed and the stirred reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (10 mL), diluted with water (20 mL), and extracted with CH_2Cl_2 (2 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield a pale yellow oil. Purification by flash column chromatography (EtOAc) afforded keto phosphonate **14** (235 mg, 83%, contaminated with 6% of alkyne **13**) as a colorless oil: IR (neat) 3478, 1697, 1609, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1 H), 3.87 (t, J = 6.1 Hz, 2 H), 3.80 (d, J = 11.2 Hz, 6 H), 3.23 (d, J = 22.4 Hz, 2 H), 2.64 (t, J = 6.1 Hz, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9 (d, J = 6 Hz), 146.3, 124.7 (d, J = 2 Hz), 59.6, 52.9 (d, J = 6 Hz), 44.6, 42.2 (d, J = 129 Hz), 25.6, 18.0, −5.7; CIMS *m*/*z* (relative intensity) 371 (MH^+, 100), 313 ($MH^+ - Me_3CH$, 29).

Preparation of (1*E*,4*Z*)-7-(*tert*-Butyldimethylsiloxy)-5-chlorohepta-1,4-dien-3-one (15). To a stirred suspension of LiCl (87 mg, 2.05 mmol) and phosphonate **14** (178 mg, 0.48 mmol) in MeCN (20 mL) was added DBU (0.073 mL, 0.49 mmol) and cyclohexanecarboxaldehyde (0.079 mL, 0.65 mmol). After being stirred at room temperature for 22 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ether/hexanes) to yield dienone **15** (139 mg, 81%) as a colorless oil: IR (neat) 1666, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, J = 15.9, 6.8 Hz, 1 H), 6.47 (s, 1 H), 6.18 (dd, J = 15.9, 1.3 Hz, 1 H), 3.87 (t, J = 6.0 Hz, 2 H), 2.63 (t, J = 6.0 Hz, 2 H), 2.24−2.08 (m, 1 H), 1.83−1.59 (m, 5 H), 1.40−1.07 (m, 5 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 153.8, 142.7, 128.4, 124.6, 59.8, 44.4, 40.6, 31.6, 25.8 (2C), 25.6, 18.1, −5.5; CIMS *m*/*z* (relative intensity) 357 (MH^+, 100), 323 (35), 299 ($MH^+ - Me_3CH$, 35).

Preparation of (1*E*,4*Z*)-7-(*tert*-Butyldimethylsiloxy)-5-chlorohepta-1,4-dien-3-ol (16). Sodium borohydride (14 mg, 0.37 mmol) was carefully added over 5 min to a stirred solution of dienone **15** (127 mg, 0.36 mmol) and $CeCl_3 \cdot 7H_2O$ (133 mg, 0.36 mmol) in MeOH (3 mL). After the reaction mixture was stirred for a further 5 min, water (5 mL) was added and the resulting mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield a pale yellow oil which was purified by flash column chromatography (1:6 ether/hexanes) to afford dienol **16** (121 mg, 95%) as a colorless oil: IR (neat) 3340, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (ddd, J = 15.5, 6.5, 0.9 Hz, 1 H), 5.62 (d, J = 7.9 Hz, 1 H), 5.44 (ddd, J = 15.5, 6.5, 1.3 Hz, 1 H), 5.06−4.98 (m, 1 H), 3.80 (t, J = 6.4 Hz, 2 H), 2.56−2.49 (m, 2 H), 2.03−1.88 (m, 1 H), 1.79−1.57 (m, 6 H), 1.35−1.00 (m, 5 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 132.8, 129.1, 127.1, 70.3, 60.2, 42.9, 40.2, 32.6, 26.1, 26.0, 25.9, 18.2, −5.4; FAB+ MS *m*/*z* (relative intensity) 359 (MH^+, 5), 341 ($MH^+ - H_2O$, 66), 209 ($MH^+ - H_2O$ − TBSOH, 37), 173 ($MH^+ - H_2O$ − TBSOH − HCl, 46), 145 (85), 115 (75), 105 (100).

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Supporting Information Available: Copies of the proton and carbon NMR spectra of new compounds (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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