Utilization of [2 + 1] Cycloaddition Reactions of 1-Seleno-2-silylethenes: A Novel Synthesis of 2-Substituted 1-Aminocyclopropane-1-carboxylic Acids

Shoko Yamazaki,* Takashi Inoue, Taro Hamada, and Takashi Takada

Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8258, Japan

Kagetoshi Yamamoto

Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

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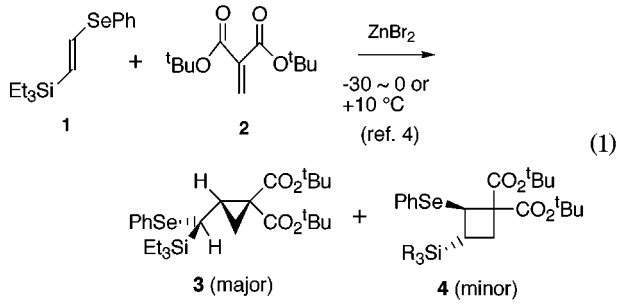
Introduction

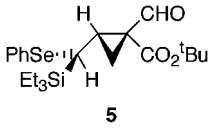
Functionalized cyclopropanes are useful synthetic intermediates for natural and unnatural biologically active cyclopropanes, which possess a large spectrum of biological properties.[1] Among them, 1-aminocyclopropane-1-carboxylic acids, ACCs (2,3-methanoamino acids), are particularly biologically important compounds.[2] Their incorporation into peptides, utilizing their conformational restriction properties is also an active research area.[2a,3] Therefore, new methodologies for synthesis of functionalized cyclopropanes and stereoselective conversion to substituted ACCs are much attracting attention. We have recently reported the reaction of 1-seleno-2-silylethene **1** and methylenemalonate ester **2** in the presence of Lewis acid to provide a highly functionalized cyclopropane **3** (eq 1).[4] This new approach to cyclopropane



construction is based on a selenium-stabilized 1,2-silicon migration process.[5] In this paper, the cyclopropane product **3** is transformed to various 1-aminocyclopropane-1-carboxylic acid (ACC) derivatives stereoselectively utilizing the functionality masked in its structure. Compound **3** is shown to be a general synthetic intermediate for (*E*)-2-substituted ACC derivatives such as (±)-coronamic acid and its alkyl derivative and a 2,3-methanoaspartic acid derivative.

Results and Discussion

The selenium- and silicon-containing cyclopropane **3** was prepared along with the cyclobutane byproduct **4** (**3**:**4** = ca. 7:3) by the reaction of 1-(phenylseleno)-2-(triethylsilyl)ethene (**1**) and di-*tert*-butyl methylenemalonate (**2**) in the presence of $ZnBr_2$ in high total yield (90−98%), according to the procedure described in our previous paper (eq 1).[4] Compounds **3** and **4** were also prepared by the reaction of **1** and **2** in the presence of ZnI_2 in 83% total yield with a **3**:**4** ratio of ca. 7:3 under similar conditions (−30 °C, 1.5 h, 0 °C, 0.5 h). The conversion of the highly functionalized cyclopropane **3** into (±)-coronamic acid (**12**) was next examined. After extensive experimentation under various conditions, stereoselective reduction of the less hindered ester function trans to the (phenylseleno)(triethylsilyl)methyl group in **3** to yield alcohol **6** was performed by a two-step procedure as follows. Reduction of **3** with $LiAlH_4$ at −78 °C gave a mixture of monoaldehyde **5**[6] and monoalcohol **6**. The



mixture of **5** and **6** without separation was treated with $NaBH_4$ at −30 °C to give mono alcohol **6** in 87% yield from **3**. The high stereoselection in the mono reduction probably derives from the bulk of the (phenylseleno)-(triethylsilyl)methyl group.

Compound **6** was protected by the *tert*-butyldimethylsilyl (TBDMS) group to give **7** in 95% yield. NOESY spectra for **6** and protected compound **7** confirmed the stereochemistry.[7] NOEs were observed between H_{2a} (δ 1.48−1.54) and H_{3a} (δ 1.20), between H_{2a} (δ 1.48−1.54) and C*H*$_2$OH (δ 3.35 and 3.60), between H_{3b} (δ 1.33−1.39) and H_4 (δ 2.84), and between H_4 (δ 2.84) and O^{t}Bu (δ 1.44) in **6**. NOEs were observed between H_{2a} (δ 1.57) and C*H*HOTBDMS (δ 3.42), between H_4 (δ 2.91) and O^{t}Bu (δ 1.41), and between O^{t}Bu (δ 1.41) and *o*-SePh (δ 7.54−

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(2) For reviews, see: (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575. (c) Kodama, H.; Shimohigashi, Y. *Yuki Gosei Kagaku Kyokaishi* **1994**, *52*, 180; *Chem. Abstr.* **1994**, *120*, 299214r. (d) Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.

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(6) Reaction of **3** with $LiAlH_4$ at −78 °C for 1 h and separation by column chromatography gave **5** and **6** in 40 and 33% yields, respectively. For **5**: R_f = 0.5 (hexane:ether = 4:1); pale yellow oil (including a trace amount of unidentified impurity); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.564−0.686 (m, 9H), 0.941 (t, J = 7.8 Hz, 6H), 1.48 (s, 9H), 1.71 (dd, J = 7.8, 2.7 Hz, 1H), 1.91−2.07 (m, 2H), 2.94 (d, J = 11.7 Hz, 1H), 7.22−7.25 (m, 3H), 7.50−7.55 (m, 2H), 10.10 (s, 1H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 3.2, 7.6, 24.4, 28.3, 28.5, 41.2, 43.5, 82.5, 127.9, 128.9, 129.1, 135.8, 168.1, 199.0; IR (neat) 2956, 2878, 1698 cm^{-1}.

(7) Stereochemistry concerning the relative configuration between C_2 and C_4 (see Scheme 1 for the numbering) of **6** and **7** was assumed as (*R*,*R*) and (*S*,*S*), which retains that of **3**. The assignment of the stereochemistry of **3** was discussed in our previous paper.[4]

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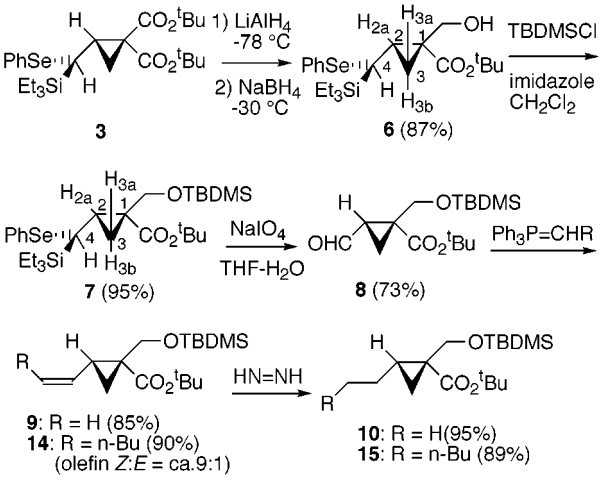
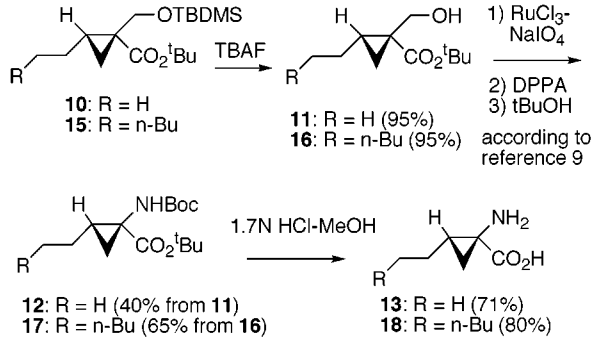
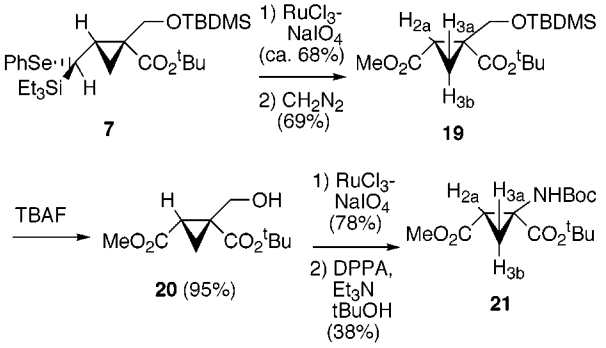
Scheme 1



Scheme 2



Scheme 3



7.56) in **7**. Compound **7** was oxidized with $NaIO_4$ in THF−H_2O solution at room temperature to give aldehyde **8** in 73% yield.[8] Wittig reaction of **8** with methylenetriphenylphosphorane in THF gave **9** in 85% yield. Next, **9** was converted by diimide reduction to give **10** in 95% yield (Scheme 1).

The obtained **10** is the racemic analogue of a synthetic intermediate of (−)-coronamic acid, which was reported by Charette.[9] Compound **10** was converted to protected coronamic acid **12**, following Charette's method (Scheme 2). Compound **12** was finally deprotected to give (±)-coronamic acid (**13**).[10] This approach promises to be a general solution to (*E*)-2-alkyl ACC derivatives. To show the utility of **8** as a synthetic intermediate for (*E*)-2-alkyl ACC derivatives, **8** was reacted with pentylenetriphenylphosphorane to give **14** in 90% yield. The same sequence leads to (*E*)-1-amino-2-hexylcyclopropane-1-carboxylic acid **18**. Thus, diverse 2-substituted cyclopropanes corresponding to **10** (such as **15**) can be prepared by two steps including Wittig reaction from the common intermediate **8**. On the other hand, using Charette's method, to obtain analogues of **10**, diverse starting alkenes which require multistep conversion, including the carbenoid addition, are necessary. Therefore, our method involves a more efficient series of manipulations than that of Charette and has advantages for preparation of diverse 2-substituted ACC derivatives, although our method only creates racemic products at this stage.

Next, synthesis of a protected (*E*)-2,3-methanoaspartic acid was demonstrated. In the literature, stereoselective syntheses of a (*Z*)-2,3-methanoaspartic acid derivative and of a mixture of (*E*) and (*Z*)-derivatives have been reported;[2a−b,11] however, no stereoselective synthesis of a (*Z*)-2,3-methanoaspartic acid derivative has been described yet. Direct oxidation of **7** to carboxylic acid was achieved using $RuCl_3$−$NaIO_4$ in CCl_4−CH_3CN−H_2O.[12,13] Thus, a selenosilylmethyl group can be considered as not only a formyl group equivalent, but also a carboxyl group equivalent. Treatment of the carboxylic acid with diazomethane in ether gave methyl ester **19** in 69% yield. A similar procedure was applied to the synthesis of amino- and dicarboxyl-protected (*E*)-2,3-methanoaspartic acid **21**. For the final Curtius rearrangement, the one-step method (diphenylphosphoryl azide (DPPA), Et_3N in *t*-BuOH)[14] from the carboxylic acid intermediate was adopted because of difficulty in the purification of the azide intermediate. NOESY spectra for both **19** and **21** confirmed the stereochemistry. NOEs were observed between H_{2a} (δ 1.99) and H_{3a} (δ 1.24), between H_{2a} (δ 1.99) and C*H*HOTBDMS (δ 3.69), and between O^{t}Bu (δ 1.43) and OMe (δ 3.67) in **19**. NOEs were observed between H_{2a} (δ 2.26) and NBoc O^{t}Bu (δ 1.46) and between ester O^{t}Bu (δ 1.43) and OMe (δ 3.70) in **21**.[15] Thus, a novel stereoselective synthesis of protected (*E*)-2,3-methanoaspartic acid **21** was achieved. Since spontaneous ring opening of the free amine forms of 2,3-methanoaspartic acid has been reported,[2a−b,16] incorporation of 2,3-methanoaspartic acid into peptides needs some indirect

(8) A two-step ($LiAlH_4$−$NaBH_4$) reduction starting from the mixture of cyclopropane **3** and cyclobutane **4** without separation, subsequent protection by *tert*-butylchlorodimethylsilane (TBDMSCl) and oxidation by $NaIO_4$ gave **8** without decreasing the yield, and **8** was isolated at this stage. Thus, the somewhat tedious MPLC separation of **3** and **4** can be avoided.

(9) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721.

(10) (a) Ichihara, A.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, 269. (b) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. *Tetrahedron Lett.* **1985**, *26*, 481. (c) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

(11) (a) Godier-Marc, E.; Aitken, D. J.; Husson, H.-P. *Tetrahedron Lett.* **1997**, *38*, 4065. (b) Wick, L.; Tamm, C.; Boller, T. *Helv. Chim. Acta* **1995**, *78*, 403. (c) Jiménez, J. M.; Rifé, J.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 537. (d) A single stereoisomer (12% yield) without assignment of stereochemistry. Horikawa, H.; Nishitani, T.; Iwasaki, T.; Inoue, I. *Tetrahedron Lett.* **1983**, *24*, 2193.

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(13) The reaction can be carried out using crude **7**, which was prepared from the mixture of cyclopropane **3** and cyclobutane **4** without separation, and was purified from the small amount of impurity arising from **4** at this stage. See also ref 8.

(14) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(15) ^{1}H NMR chemical shifts of N−Boc O^{t}Bu and ester O^{t}Bu in **21** were assigned as follows. The N−Boc O^{t}Bu appeared as a broad singlet and has HMBC correlation with a broad peak in ^{13}C (80.4 ppm) which is assigned as N−Boc OC$(CH_3)_3$. The broadening may be due the rotation barrier of the carbamate moiety. Broadening of ^{13}C peaks of *N*-Boc *C*=O, *N*-Boc OC$(CH_3)_3$, and cyclopropyl carbons were observed for Boc-protected ACCs, **12**, **17**, and **21**.

(16) Taylor, E. C.; Hu, B. *Synth. Commun.* **1996**, *26*, 1041.

approaches.[11a,17] Incorporation of **21** and related analogues into peptides is under way.

In summary, new methodologies for stereoselective synthesis of (*E*)-2-substituted ACCs have been demonstrated. The [2 + 1] cycloadduct derived from reaction between 1-(phenylseleno)-2-(triethylsilyl)ethene (**1**) and di-*tert*-butyl methylenemalonate (**2**) in the presence of ZnX_2 (X = Br, I) was transformed to several ACC derivatives stereoselectively. The selenosilylmethyl group in **3** functioned as a stereocontrolling group for mono reduction and as a formyl or carboxyl group equivalent. Compound **3** can also be a general synthetic intermediate for (*Z*)-2-substituted ACC derivatives by alternative transformation of the other carboxyl group to an amino group.[9] Application of this methodology to other aminocyclopropanecarboxylic acid derivatives, and development of a chiral version are currently under investigation in our laboratory.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded in the FT mode. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200, 400, or 600 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50.1 or 100.6 MHz. Chemical shifts are reported in ppm relative to Me_4Si or residual nondeuterated solvent. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. All reactions were carried out under a nitrogen atmosphere. MPLC was performed with a UV detector at 254 nm and a flow rate of 15 mL/min using a Michel-Millor column (20ϕ × 30 cm).

The cyclopropane **3** was prepared according to the procedure described in our previous paper,[4] as a mixture with the cyclobutane byproduct **4** (**3**:**4** = ca. 7:3) by the reaction of 1-(phenylseleno)-2-(triethylsilyl)ethene (**1**) and di-*tert*-butyl methylenemalonate (**2**) in the presence of $ZnBr_2$ or ZnI_2. Compounds **3** and **4** were separated by MPLC (Wakogel LP-60, cyclohexane:CH_2Cl_2 = 9:1). Alternatively, the mixture of **3** and **4** was used without separation.[8,13]

(±)-(*Z*)-*tert*-Butyl 1-(Hydroxymethyl)-2-[(phenylseleno)-(triethylsilyl)methyl]cyclopropane-1-carboxylate (6). A solution of **3** (isolated, 1.025 g, 1.95 mmol) in ether (2.5 mL) was added to $LiAlH_4$ (325 mg, 8.6 mmol) in ether (4 mL) with stirring at −78 °C. The mixture was stirred for 45 min. Saturated aqueous Na_2SO_4 was then added to the mixture, the mixture was extracted with ether, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in ^{i}PrOH (3 mL) and cooled to −30 °C, and 0.1 M $NaBH_4$ in ^{i}PrOH (7.2 mL, 0.72 mmol) was then added to the solution. The reaction mixture was stirred for 1 h, and then saturated aqueous Na_2SO_4 was added to the mixture. The mixture was extracted with ether, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give **6** (776 mg, 87%). Crude product is pure enough for use in the next step. For **6**: R_f = 0.15 (hexane:ether = 4:1); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.508−0.632 (m, 9H), 0.909 (t, J = 7.8 Hz, 6H), 1.20 (dd, J = 8.8, 4.4 Hz, 1H), 1.33−1.39 (m, 1H), 1.44 (s, 9H), 1.48−1.54 (m, 1H), 2.51 (broad dd, J = 7.2, 5.3 Hz, 1H), 2.84 (d, J = 12.2 Hz, 1H), 3.35 (dd, J = 12.0, 7.2 Hz, 1H), 3.60 (dd, J = 12.0, 5.3 Hz), 7.20−7.24 (m, 3H), 7.58−7.63 (m, 2H); selected observed NOEs were between δ 1.20 and 1.33−1.39, δ 1.20 and 1.48−1.54, δ 1.33−1.39 and 2.84, δ 1.44 and 2.84, δ 1.44 and 7.58−7.63, δ 1.48−1.54 and 3.35, δ 1.48−1.54 and 3.60, δ 2.84 and 7.58−7.63.; ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 3.2 (t, J = 116 Hz), 7.6 (q, J = 124 Hz), 23.2 (t, J = 163 Hz), 25.3 (d, J = 133 Hz), 28.2 (q, J = 127 Hz), 31.0 (d, J = 157 Hz), 33.3 (s), 67.0 (t, J = 143 Hz), 81.7 (s), 127.2 (d, J = 159 Hz), 128.7 (d, J = 158 Hz), 129.5 (s), 134.7 (d, J = 164 Hz), 171.6 (s); IR (neat) 3414, 2956, 2878, 1713 cm^{-1}; MS (EI) m/z 456; exact mass M$^+$ 456.1578 (calcd for $C_{22}H_{36}O_3SeSi$ 456.1599). Anal. Calcd for $C_{22}H_{36}O_3SeSi$: C, 58.00; H, 7.96. Found: C, 58.14; H, 7.99.

(±)-(*Z*)-*tert*-Butyl 1-((*tert*-Butyldimethylsilyl)oxy)methyl-2-[(phenylseleno)(triethylsilyl)methyl]cyclopropane-1-carboxylate (7). TBDMSCl (374 mg, 2.5 mmol) was added to a solution of **6** (757 mg, 1.7 mmol) in CH_2Cl_2 (15 mL), followed by imidazole (163 mg, 2.4 mmol). The mixture was stirred for 25 h. Saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was extracted with ether, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give **7** (896 mg, 95%). For **7**: R_f = 0.8 (hexane:ether = 4:1); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.025 (s, 3H), 0.037 (s, 3H), 0.563−0.632 (m, 6H), 0.867 (s, 9H), 0.917 (t, J = 8.0 Hz, 9H), 1.21−1.25 (m, 2H), 1.41 (s, 9H), 1.57 (ddd, J = 12.4, 8.9, 7.4 Hz, 1H), 2.91 (d, J = 12.4 Hz, 1H), 3.42 (d, J = 10.2 Hz, 1H), 3.93 (d, J = 10.2 Hz, 1H), 7.17−7.21 (m, 3H), 7.54−7.56 (m, 2H); selected observed NOE's were between δ 1.21−1.25 and 1.57, δ 1.21−1.25 and 2.91, δ 1.41 and 2.91, δ 1.41 and 7.54−7.56, δ 1.57 and 3.42, δ 2.91 and 7.54−7.56; ^{13}C NMR (50.1 MHz, $CDCl_3$) δ −5.4 (q, J = 119 Hz), 3.3 (t, J = 116 Hz), 7.6 (q, J = 124 Hz), 18.1 (s), 20.6 (t, J = 161 Hz), 25.3 (d, J = 133 Hz), 25.8 (q, J = 125 Hz), 28.1 (d, J = 153 Hz), 28.2 (q, J = 126 Hz), 32.3 (s), 62.7 (t, J = 144 Hz), 80.4 (d, J = 4.4 Hz), 127.0 (dt, J = 161, 7.3 Hz), 128.5 (d, J = 157 Hz), 129.8 (s), 134.9 (d), 171.1 (s); IR (neat) 2958, 2936, 2878, 1713 cm^{-1}; MS (EI) m/z 570; exact mass M$^+$ 570.2473 (calcd for $C_{28}H_{50}O_3SeSi_2$ 570.2464). Anal. Calcd for $C_{28}H_{50}O_3SeSi_2$: C, 59.02; H, 8.84. Found: C, 59.24; H, 8.89.

(±)-(*Z*)-*tert*-Butyl 1-((*tert*-Butyldimethylsilyl)oxy)methyl-2-formylcyclopropane-1-carboxylate (8). To a solution of **7** (174 mg, 0.3 mmol) in THF (8 mL) were added water (4 mL) and $NaIO_4$ (332 mg, 1.6 mmol). The mixture was stirred for 6 h at room temperature. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The mixture was extracted with ether, and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give **8** (71 mg, 73%). For **8**: R_f = 0.3 (hexane:ether = 4:1); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.048 (s, 6H), 0.867 (s, 9H), 1.45 (s, 9H), 1.53 (dd, J = 8.2, 4.3 Hz, 1H), 1.93−2.11 (m, 2H), 3.75 (d, J = 10.4 Hz, 1H), 3.96 (d, J = 10.4 Hz, 1H), 9.30 (d, J = 6.1 Hz, 1H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ −5.5 (q, J = 118 Hz), 15.9 (t, J = 166 Hz), 18.2 (s), 25.8 (q, J = 125 Hz), 28.0 (q, J = 127 Hz), 32.9 (dd, J = 169, 26 Hz), 35.9 (s), 61.8 (t, J = 144 Hz), 82.2 (s), 169.2 (s), 200.0 (d, J = 180 Hz); IR (neat) 2958, 2934, 2862, 1715 cm^{-1}; MS (FAB) m/z 315 (M$^+$ + 1). Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 60.99; H, 9.62.

(±)-(*Z*)-*tert*-Butyl 1-((*tert*-Butyldimethylsilyl)oxy)methyl-2-ethenylcyclopropane-1-carboxylate (9). A solution of *n*-BuLi (1.46 M in *n*-hexane, 1.7 mL, 2.4 mmol) was added dropwise to a stirred and ice-cooled suspension of methylenetriphenylphosphonium bromide (862 mg, 2.4 mmol) in THF (10 mL). The mixture was stirred at 0 °C for 15 min. A solution of **8** (309.1 mg, 0.98 mmol) in THF (4 mL) was added to the mixture at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 3 h. After the reaction mixture was cooled to 0 °C, water was added and the mixture was extracted with ether. The ether layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give **9** (261 mg, 85%). For **9**: R_f = 0.9 (hexane:ether = 9:1); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.044 (s, 6H), 0.877 (s, 9H), 1.18 (dd, J = 8.7, 4.5 Hz, 1H), 1.37−1.49 (m, 1H), 1.44 (s, 9H), 1.83 (ddd, J = 8.7, 8.6, 8.1 Hz, 1H), 3.47 (d, J = 10.3 Hz, 1H), 4.13 (d, J = 10.3 Hz, 1H), 5.01 (d, J = 10.3 Hz, 1H), 5.17 (d, J = 16.1 Hz, 1H), 5.69 (ddd, J = 16.1, 10.3, 8.6 Hz, 1H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ −5.3 (q, J = 119 Hz), 17.0 (t, J = 163 Hz), 18.4 (s), 25.9 (q, J = 125 Hz), 27.6 (d, J = 163 Hz), 28.3 (q, J = 125 Hz), 34.0 (s), 63.8 (t, J = 155 Hz), 80.7 (s), 115.8 (t, J = 155 Hz), 135.7 (d, J = 155 Hz), 170.7 (s); IR (neat) 2960, 2934, 2862, 1723, 1636 cm^{-1}; MS (EI) m/z 312. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.16; H, 10.42.

(±)-(*Z*)-*tert*-Butyl 1-((*tert*-Butyldimethylsilyl)oxy)methyl-2-ethylcyclopropane-1-carboxylate (10). To **9** (61.7 mg, 0.2 mmol) in MeOH (0.9 mL) was added dipotassium azodicarboxylate (155 mg, 0.8 mmol) followed by dropwise addition of

(17) Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *Tetrahedron*, **1997**, *53*, 17417.

acetic acid (92 mg, 1.5 mmol) in MeOH (0.15 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. H_2O (1.5 mL) and CH_2Cl_2 (3.8 mL) were added. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give **10** (59 mg, 95%). For **10**: R_f = 0.7 (hexane:ether = 9:1); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.033 (s, 6H), 0.873 (s, 9H), 0.87−1.09 (m, 6H), 1.37−1.55 (m, 2H), 1.45 (s, 9H), 3.28 (d, J = 10.3 Hz, 1H), 4.15 (d, J = 10.3 Hz, 1H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ −5.3 (q, J = 118 Hz), 14.0 (q, J = 125 Hz), 16.7 (t, J = 162 Hz), 18.4 (s), 20.9 (t, J = 126 Hz), 25.9 (q, J = 127 Hz), 26.6 (d, J = 160 Hz), 28.2 (q, J = 125 Hz), 32.0 (s), 65.6 (t, J = 146 Hz), 80.2 (s), 171.8 (s); IR (neat) 2962, 2862, 1721 cm^{-1}; MS (FAB) m/z 315 (M^+ + 1); MS (EI) m/z (rel intensity) 315 (28) M^+ + 1, 259 (100). Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.71; H, 11.04.

(±)-(*E*)-*tert*-Butyl 1-(N−(*tert*-Butoxycarbonyl)amino)-2-ethylcyclopropane-1-carboxylate (12). To a solution of **10** (220 mg, 0.7 mmol) in dry THF (1.40 mL) was added glacial acetic acid (40 μL, 42 mg, 0.7 mmol) followed by a 1.0 M solution of TBAF in THF (1.5 mL, 1.5 mmol). The reaction mixture was stirred at 42 °C for 11 h. After the reaction mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with ether. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes:ether to give (*E*)-*tert*-butyl 1-(hydroxymethyl)-2-ethylcyclopropane-1-carboxylate (**11**) (133 mg, 95%) (R_f = 0.3, hexane:ether = 2:1). Compound **11** was converted to **12**, using the procedure described by Charette[9] (yield (40% from **11**)). For **12**: R_f = 0.3 (hexane:EtOAc = 9:1); colorless crystals; mp 103 °C (8% EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.955 (t, J = 7.4 Hz, 3H), 1.17 (m, 1H), 1.31−1.63 (m, 4H), 1.45 (s, 9H), 1.46 (s, 9H), 5.10 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7, 20.4, 22.6, 28.2, 28.4, 32.7, 39.6, 79.6, 81.1, 156.0, 170.8 {the ^{13}C NMR spectra were in accord with the reported data for (2*R*,3*R*)-**12**};[9] IR (KBr) 3348, 2976, 1717, 1692, 1516, 1371, 1350, 1276, 1160, 843 cm^{-1}; MS (FAB) m/z 286 (M^+ + 1). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.30; H, 9.59; N, 4.95.

(±)-Coronamic Acid (13). To a solution of 1.7 N HCl in MeOH (3.4 mL, 5.8 mmol) at 0 °C was added **12** (24 mg, 0.08 mmol), and the mixture stirred for 24 h at the same temperature, followed by removal of the solvent. The residue was dissolved in H_2O (0.25 mL), loaded on a Dowex column (H^+-form, 50W-8 100−200 mesh, 0.9 × 2.4 cm), and eluted with H_2O until neutral and chloride-free ($AgNO_3$ test). The product was then eluted with 2 N NH_3/H_2O (8 mL). Evaporation gave **13** (7 mg, 71%).[10] For **13**: white solid; mp sublimed at ca. 170−190 °C; ^{1}H NMR (400 MHz, D_2O) δ 0.867 (t, J = 7.2 Hz, 3H), 1.20−1.25 (m, 2H), 1.36−1.62 (m, 3H); ^{13}C NMR (100.6 MHz, D_2O) δ 13.6, 17.9, 20.8, 28.6, 40.6, 175.4; IR (KBr) 3400, 3150−2950, 2100, 1640−1522, 1441, 1396, 1296, 1222 cm^{-1}; MS (FAB) m/z 130 (M^+ + 1).

(±)-(*Z*)-*tert*-Butyl 1-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-2-(1′-(*Z*)-hexenyl)cyclopropane-1-carboxylate (14). A solution of *n*-BuLi (1.54 M in *n*-hexane, 1.04 mL, 1.6 mmol) was added dropwise to a stirred and ice-cooled suspension of pentylenetriphenylphosphonium bromide (663 mg, 1.6 mmol) in THF (5.4 mL). The mixture was stirred at 0 °C for 15 min. A solution of **8** (194 mg, 0.62 mmol) in THF (1.2 mL) was added to the mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2.5 h. After the reaction mixture was cooled to 0 °C, water was added and the mixture was extracted with ether. The ether layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane:ether to give **14** (205 mg, 90%). For **14**: R_f = 0.6 (hexane:ether = 9:1); pale yellow oil (olefin *Z*:*E* = ca. 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) (peaks for the major *Z* olefin isomer) δ 0.045 (s, 3H), 0.051 (s, 3H), 0.882 (s, 9H), 0.900 (t, J = 7.0 Hz, 3H), 1.19 (dd, J = 8.8, 4.4 Hz, 1H), 1.29−1.39 (m, 5H), 1.43 (s, 9H), 1.98 (ddd, J = 8.9, 8.8, 7.6 Hz, 1H), 2.11 (dtd, J = 7.6, 7.2, 1.4 Hz, 2H), 3.53 (d, J = 10.3 Hz, 1H), 4.10 (d, J = 10.3 Hz, 1H), 5.24 (ddt, J = 10.4, 8.9, 1.4 Hz, 1H), 5.45 (dt, J = 10.4, 7.6 Hz, 1H); selected observed NOE is between δ 5.24 and 5.45; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (peaks for the major *Z* olefin isomer) −5.3, 14.0, 17.6, 18.4, 22.2, 22.3, 25.9, 27.3, 28.3, 31.9, 33.9, 63.8, 80.5, 126.9, 132.1, 171.1; IR (neat) 2960, 2932, 2862, 1725 cm^{-1}; MS (EI) m/z 368; exact mass M^+ 368.2748 (calcd for $C_{21}H_{40}O_3Si$ 368.2746).

(±)-(*Z*)-*tert*-Butyl 1-(((*tert*-Butyldimethylsilyl)oxy)-methyl)-2-(1′-hexyl)cyclopropane-1-carboxylate (15). To **14** (151 mg, 0.41 mmol) in MeOH (1.8 mL) was added dipotassium azodicarboxylate (318 mg, 1.6 mmol) followed by dropwise addition of acetic acid (184 mg, 3.1 mmol) in MeOH (0.3 mL) at 0 °C. The mixture was allowed to warm to 50 °C and stirred for 48 h. Dipotassium azodicarboxylate (318 mg, 1.6 mmol) and acetic acid (184 mg, 3.1 mmol) in MeOH (0.3 mL) were added to the reaction mixture, and the reaction was stirred at 50 °C for an additional 26.5 h. Dipotassium azodicarboxylate (318 mg, 1.6 mmol) and acetic acid (184 mg, 3.1 mmol) in MeOH (0.3 mL) were then added to the mixture and stirred at 50 °C for an additional 1.5 h (disappearance of **14** was checked by GC). H_2O (1.8 mL) was added to the reaction mixture, followed by extraction with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexanes: ether to give **15** (187 mg, 89%). For **15**: R_f = 0.7 (hexane:ether = 9:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.028 (s, 3H), 0.030 (s, 3H), 0.865−0.889 (m, 4H), 0.872 (s, 9H), 1.03−1.09 (m, 2H), 1.23−1.40 (m, 8H), 1.41−1.44 (m, 2H), 1.45 (s, 9H), 3.30 (d, J = 10.3 Hz, 1H), 4.13 (d, J = 10.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.3 (q), 14.2 (q), 16.8 (t), 18.4 (s), 22.7 (t), 25.0 (d), 26.0 (q), 27.6 (t), 28.3 (q), 29.2 (t), 29.8 (t), 32.0 (s), 32.0 (t), 65.5 (t), 80.2 (s), 171.9 (s); ^{13}C multiplicities were determined by DEPT; IR (neat) 2960, 2930, 2862, 1721 cm^{-1}; MS (EI) m/z (rel intensity) 371 (4.3) (M^+ + 1), 297 (14), 259 (100).

(±)-(*Z*)-*tert*-Butyl 1-(Hydroxymethyl)-2-(1′-hexyl)cyclopropane-1-carboxylate (16). Compound **16** was prepared from **15** using the procedure described for **11** (yield (95%)). For **16**: R_f = 0.5 (hexane:ether = 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.860−0.918 (m, 4H), 1.12−1.20 (m, 2H), 1.27−1.39 (m, 8H), 1.43−1.49 (m, 2H), 1.48 (s, 9H), 2.63 (dd, J = 8.7, 4.9 Hz, 1H), 3.35 (dd, J = 11.9, 8.7 Hz, 1H), 3.68 (dd, J = 11.9, 4.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2, 18.9, 22.7, 27.6, 27.7, 28.3, 29.2, 29.8, 31.8, 32.0, 68.1, 81.4, 173.0; IR (neat) 3418, 2962, 2930, 2862, 1719 cm^{-1}; MS (EI) m/z (rel intensity) 215 (1.3) (M^+ − 41), 200 (100), 183 (78).

(±)-(*E*)-*tert*-Butyl 1-((*N*-*tert*-Butoxycarbonyl)amino)-2-(1′-hexyl)cyclopropane-1-carboxylate (17). Compound **16** (76 mg, 0.30 mmol) was dissolved in a mixture of CH_3CN (1.0 mL), CCl_4 (1.0 mL), and H_2O (1.3 mL). $NaIO_4$ (254 mg, 1.2 mmol) was then added followed by $RuCl_3 \cdot xH_2O$ (3 mg, ca. 0.014 mmol). After 2.5 h of stirring at room temperature, the solution was diluted with CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was filtered on a short plug of silica gel that was washed with EtOAc:hexane:AcOH (69:30:1) to give the acid (72 mg, 90%). To a solution of the acid (71 mg, 0.26 mmol) in toluene (3.2 mL) at 0 °C was added triethylamine (0.17 mL, 125 mg, 1.2 mmol) followed by diphenylphosphoryl azide (136 μL, 173 mg, 0.63 mmol). The ice bath was removed, and the reaction mixture was stirred for an additional 3.5 h at room temperature. Ether and H_2O were then added, and the layers were separated, and the aqueous layer was extracted with ether twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane: ether to give the acyl azide (66 mg, 85%). The acyl azide (66 mg, 0.22 mmol) in *tert*-butyl alcohol (2.1 mL) was heated at 110 °C for 48 h. The *tert*-butyl alcohol was evaporated in vacuo, and the residue was purified by column chromatography over silica gel eluting with hexane:ether (9:1) to give 17 (65 mg, 85%). For **17**: R_f = 0.4 (hexane:ether = 2:1); colorless crystals; mp 83 °C (10% ether/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.873 (t, J = 6.7 Hz, 1H), 1.19−1.61 (m, 13H), 1.449 (s, 9H), 1.454 (s, 9H), 5.08 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 22.7 (t), 27.0 (t), 28.1 (q), 28.4 (q), 29.1 (t), 29.4 (t), 30.8 (d), 31.9 (t), 39.5 (s), 79.5 (s), 81.0 (s), 156.0 (s), 170.8 (s); ^{13}C multiplicities were determined by DEPT; IR (neat) 3346, 2926, 1723, 1694 cm^{-1}; MS (FAB) m/z 342 (M^+ + 1). Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.83; H, 10.33; N, 4.10. Found: C, 66.44; H, 10.34; N, 4.08.

(±)-(*E*)-1-Amino-2-hexylcyclopropane-1-carboxylic Acid (18). Compound **18** was prepared from **17** using the procedure described for **13** (yield (80%)). For **18**: amorphous white solid; mp 228−230 °C (dec); ^{1}H NMR (400 MHz, CF_3CO_2D) δ 0.729 (t, J = 6.9 Hz, 3H), 1.12−1.42 (m, 8H), 1.56−1.69 (m, 3H), 1.75−1.79 (m, 1H), 1.91−1.99 (m, 1H); ^{13}C NMR (100.6 MHz, CF_3CO_2D) δ 14.0 (q), 22.2 (t), 23.7 (t), 28.0 (t), 30.1 (t), 30.2 (t), 32.7 (d), 32.9 (t), 41.4 (s), 176.1 (s); ^{13}C multiplicities were determined by DEPT; IR (KBr) 3420, 3100−2962, 2924, 2858, 1638−1524, 1439, 1408, 1299, 1218 cm^{-1}; MS (FAB) m/z 186 ($M^+ + 1$).

(±)-(*Z*)-1-*tert*-Butyl 2-Methyl 1-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclopropane-1,2-dicarboxylate (19). Compound **7** (containing a small amount of impurity arising from cyclobutane **4**)[13] (200 mg, ca. 0.35 mmol) was dissolved in a mixture of CH_3CN (6.0 mL), CCl_4 (6.0 mL), and H_2O (3.0 mL). $NaIO_4$ (653 mg, 3.05 mmol) was then added followed by $RuCl_3 \cdot xH_2O$ (7 mg, ca. 0.033 mmol). After 5 h of stirring at room temperature, the solution was diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with EtOAc:hexane:AcOH (69:30:1) to give the acid (79 mg, ca. 68%) (R_f = 0.5, hexane:ether = 1:1). The acid (79 mg, 0.24 mmol) was treated with diazomethane in ether. Purification by column chromatography (silica gel, hexanes:ether) gave **19** (57 mg, 69%). For **19**: R_f = 0.5 (hexane:ether = 4:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.041 (s, 3H), 0.049 (s, 3H), 0.869 (s, 9H), 1.24 (dd, J = 8.6, 4.6 Hz, 1H), 1.43 (s, 9H), 1.69 (dd, J = 6.5, 4.6 Hz, 1H), 1.99 (dd, J = 8.6, 6.5 Hz, 1H), 3.67 (s, 3H), 3.69 (d, J = 10.3 Hz, 1H), 4.00 (d, J = 10.3 Hz, 1H); selected observed NOEs were between δ 1.24 and 1.69, δ 1.24 and 1.99, δ 1.43 and 3.67, δ 1.99 and 3.69; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.41, −5.39, 15.0, 18.3, 24.0, 25.9, 28.0, 35.1, 51.9, 62.8, 81.3, 169.1, 171.0; IR (neat) 2956, 2934, 2862, 1740, 1730 cm^{-1}; MS (FAB) m/z 345 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{42}O_3Si$: C, 68.05; H, 11.42. Found: C, 67.57; H, 11.35.

(±)-(*Z*)-1-*tert*-Butyl 2-Methyl 1-(Hydroxymethyl)cyclopropane-1,2-dicarboxylate (20). Compound **20** was prepared from **19** using the procedure described for **11** (yield (95%)). For **20**: R_f = 0.1 (hexane:ether = 2:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (dd, J = 8.7, 5.0 Hz, 1H), 1.45 (s, 9H), 1.83 (ddd, J = 6.9, 5.0, 0.7 Hz, 1H), 2.02 (dd, J = 8.7, 6.9 Hz, 1H), 2.50 (bs, 1H), 3.57 (bdd, J = 11.7, 6.8 Hz, 1H), 3.67 (s, 3H), 3.71 (bdd, J = 11.7, 2.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.7, 26.7, 28.0, 34.7, 52.1, 66.4, 82.3, 169.8, 170.2; IR (neat) 3500, 2984, 1734, 1717 cm^{-1}; MS (FAB) m/z 231 ($M^+ + 1$); MS (EI) m/z (rel intensity) 175 (25) ($M^+ - 55$), 157 (100) 143 (40).

(±)-(*E*)-1-*tert*-Butyl 2-Methyl 1-((*N*-*tert*-Butoxycarbonyl)amino)cyclopropane-1,2-dicarboxylate (21). Compound **20** (125 mg, 0.54 mmol) was dissolved in a mixture of CH_3CN (5.7 mL), CCl_4 (5.7 mL), and H_2O (7.3 mL). $NaIO_4$ (1.393 g, 6.5 mmol) was then added followed by $RuCl_3 \cdot xH_2O$ (15 mg, ca. 0.072 mmol). After 5 h of stirring at room temperature, the solution was diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was filtered through a short plug of silica gel that was washed with EtOAc:hexane:AcOH (69:30:1) to give the acid (104 mg, 78%). To a solution of the acid (51 mg, 0.21 mmol) in *tert*-butyl alcohol (1.0 mL) was added triethylamine (32.0 μL, 23 mg, 0.23 mmol) followed by diphenylphosphoryl azide (48.6 μL, 62 mg, 0.23 mmol). The mixture was heated at 110 °C for 5.5 h. After cooling to room temperature, the reaction mixture was diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane:ether to give **21** (25 mg, 38%). For **21**: R_f = 0.4 (hexane:ether = 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.42−1.48 (m, 1H), 1.46 (s, 9H), 2.04 (m, 1H), 2.26 (dd, J = 9.0, 9.0 Hz, 1H), 3.70 (s, 3H), 5.16 (bs, 1H); selected observed NOEs were between δ 1.42−148 and 2.04, δ 1.43 and 3.70, δ 1.46 and 2.26; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.2 (t), 27.9 (q), 28.3 (q), 31.6 (d), 40.8 (s), 52.2 (q), 80.4 (s), 82.3 (s), 155.5 (s), 168.5 (s), 168.6 (s); ^{13}C multiplicities were determined by DEPT; IR (neat) 3350, 2982, 1734, 1715, 1696 cm^{-1}; MS (EI) m/z 315; exact mass M^+ 315.1696 (calcd for $C_{15}H_{25}O_6N$ 315.1682).

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Supporting Information Available: Copies of 2D-NOESY spectra for compounds **7** and **21** and HMBC spectra for **21** (10 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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