Interconversion of Cembranolide δ- and γ-Lactones: Synthesis of the C-1 Epimer of Isolobophytolide

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The δ-lactone cembranolide diterpene crassin alcohol (2) has been converted to an isomeric γ-lactone isocrassin alcohol (6) by a sequence involving kinetically controlled addition of benzenethiol to the conjugated lactone double bond followed by base-promoted translactonization and thermal elimination of the derived sulfoxide. Internal displacement of the monomethanesulfonate derivative 7 of lactone diol 6 afforded epoxy lactone 11, the C-1 epimer of isolobophytolide (12). Basic hydrolysis of lactone 6 followed by acidification led back to crassin alcohol (2), thereby completing the cycle.

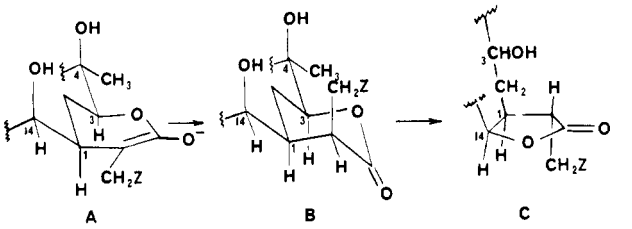
In recent years cembranolides have emerged as a major class of marine natural products.[1] The prototype member, crassin acetate (1), was recognized just over 10 years ago as a constituent of *Pseudoplexaura porosa*, an abundant Caribbean gorgonian.[2] A host of cembranolides were subsequently found in gorgonians and Pacific soft corals.[1]

The ready availability[3] of crassin acetate makes it an attractive starting point for partial synthesis of other less plentiful cembranolides. It also represents a potentially useful model system for chemical examination of the relatively unexplored cembranolide ring system. Pursuant to projects in these areas we wished to develop a scheme for interconverting cembranoid δ- and γ-lactones such as 2 and 6.

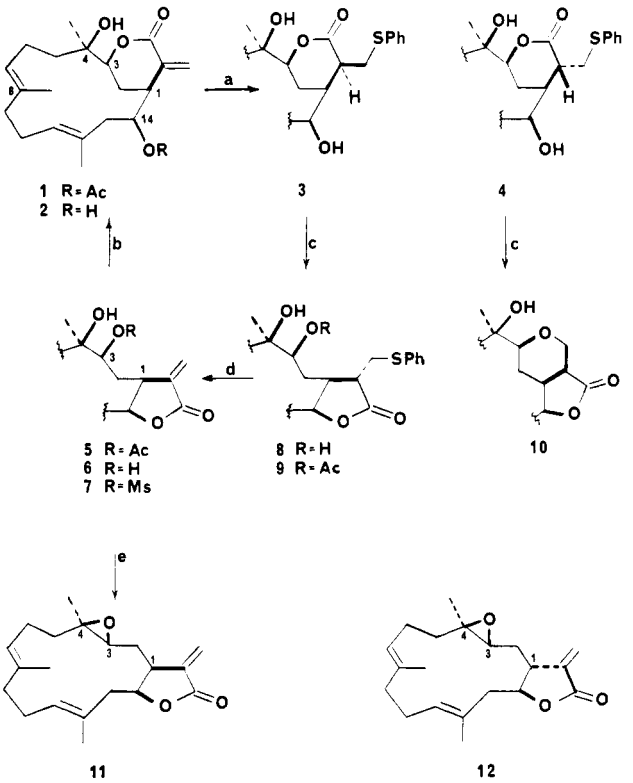
Weinheimer and co-workers saponified crassin acetate (1) and isolated hydroxy lactone 2 (crassin alcohol) upon acidification of the water soluble salt.[1,4] Evidently, in acid the δ-lactone 2 is favored over the γ-lactone 6. In strong base (methanolic sodium methoxide) crassin acetate is converted to the tricyclic γ-lactone ether 10.[5] This ether is also formed upon treatment of crassin alcohol (2) with sodium hydride. Ether 10 is quite stable: elimination to the α-methylene γ-lactone 6 cannot be effected under a variety of acidic and basic reaction conditions.[5]

Weinheimer and co-workers found that selective hydrogenation of crassin acetate followed by saponification and acidification afforded a γ-lactone (8, Sph = H).[1,2] Thus, translactonization of the crassin system can be profoundly influenced by α-substituents on the lactone ring. These findings led us to speculate that cembrane α-methylene δ- and γ-lactones might be interconverted through addition of a removable group (Z, Scheme I) to the α-methylene under conditions favoring kinetic protonation of the intermediate lactone enolate A.[6] The CH_2Z substituent would thereby be forced to assume the more hindered orientation as in B.[6] Isomerization to the γ-lactone isomer C would reorient this group to a less hindered environment and should thus benefit from relief of steric strain.[6] Subsequent elimination of HZ would restore the α-methylene grouping. In this report we detail the successful implementation of this plan.

Scheme I



Scheme II[a]



[a] (a) PhSH, Et_3N, C_6H_6, (b) KOH, H_2O, 10% HCl, (c) NaH, THF, (d) $NaIO_4$, CH_3OH, C_6H_6; CH_3Ph, C_5H_5N, reflux, (e) $Et_4N^+OH^-$, $(CH_3)_2CO$.

Both benzenethiol and benzeneselenol readily add to crassin alcohol (2) to give stable purifiable 1,4-adducts in high yield. In the former case addition at low temperature affords a (kinetic) crystalline adduct (3) in over 90% yield. At 45 °C a new (thermodynamic) epimer (4) is gradually formed and eventually becomes the major product. Both epimers yield crassin alcohol (2) upon saponification followed by acidification. The stereochemical assignments of 3 and 4 can be surmized through high field ^1H NMR

(1) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortsch. Chem. Org. Naturst.* **1979**, *36*, 286.
(2) (a) Sifford, D. Ph.D. Thesis, University of Oklahoma, Norman, OK, 1962. (b) Hossian, M. B.; van der Helm, D. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1413.
(3) Rice, J. R.; Papastephanou, C; Anderson, D. G. *Biol. Bull.* **1970**, *138*, 334.
(4) Reference 1, p 342.
(5) Reference 1, p 343.
(6) The pictured conformation is based on X-ray structure data.[2b] The precise conformation is not crucial to the argument since all conformers related to B will possess a skew $CH_2Z/CHOH$ interaction (or worse) not present in C.

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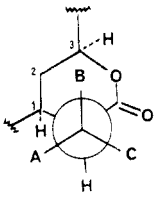
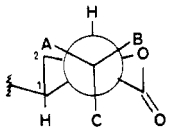
analysis.[7] The kinetic benzenethiol adduct **3** displays two sets of double doublets at 3.58 and 3.19 ppm with geminal coupling of 13.7 Hz and vicinal coupling of 3.9 and 11.3 Hz (CH_2SPh). The corresponding methylene protons of the thermodynamic adduct **4** appear at 3.52 and 3.36 ppm with geminal coupling of 13.6 Hz and vicinal coupling of 3.9 and 5.9 Hz. Newman projections of the two isomeric adducts are shown in **3a–c** and **4a–c**. The vicinal couplings of 3.9 and 11.3 Hz observed for the kinetic adduct **3** are in best agreement with conformer **3a**, whereas those of the thermodynamic adduct **4** (3.9 and 5.9 Hz) are more in line with conformer **4a**.[7] Both conformers **3a** and **4a** would also be expected to show minimum steric interactions for the SPh group.





3a, A = B = H; C = SPh
3b, A = C = H; B = SPh
3c, B = C = H; A = SPh

4a, A = B = H; C = SPh
4b, A = C = H; B = SPh
4c, B = C = H; A = SPh

Lactone **3** readily afforded the γ-lactone **8** upon treatment with sodium hydride. Acetylation followed by periodate oxidation and thermal elimination of the resulting sulfoxide yielded the α-methylene γ-lactone **5** ("isocrassin acetate"). Alternatively, the diol **8** could be oxidized to the sulfoxide which gave lactone **6** ("isocrassin alcohol") upon thermolysis, albeit in rather poor yield.

The thermodynamic benzenethiol adduct **4** was not isomerized by sodium hydride but was slowly transformed to the bridged ether **10**. This conversion may proceed via direct elimination of benzenethiol from **4** to give crassin alcohol (**2**). Translactonization and cyclization of the intermediate γ-lactone **6** ("isocrassin alcohol") would give ether **10**. Alternatively, lactone **4** may initially translactonize to the sterically crowded side chain epimer of lactone **8**, which then affords isocrassin alcohol (**6**) and thence **10**. On one occasion, when 2 molar equiv of sodium hydride was employed, the kinetic benzenethiol adduct **3** yielded the bridged ether **10** as the major product. Isocrassin alcohol **6** seems the likely intermediate here, as well. The aforenoted isomerization of crassin alcohol (**2**) to **10** by sodium hydride may also proceed via **6**.

Coll and co-workers recently proposed structure **11** or the 3,4 (epoxide) epimer for isolobophytolide, a cembranolide isolated from an Australian soft coral.[8] Since lactone diol **6** is clearly related to **11**, a correlation was made in an attempt to resolve the stereochemistry question. Treatment with 1 equiv of methanesulfonyl chloride, followed by base, converted diol **6** to the epoxide **11**. The NMR spectrum of this epoxide differed from that of isolobophytolide, especially in the lactone carbinyl proton region (δ = 4.7 ppm for **11** vs. 4.1 ppm for isolobophytolide). It was subsequently found that isolobophytolide is the trans fused lactone **12** epimeric with lactone **11** at C-1.[9] In preliminary screening at the National Cancer Institute lactone **11** was found to be active against P388 lymphocytic leukemia in mice.

To complete our lactone interconversion studies we wished to transform γ-lactone **6** to the bridged δ-lactone **2** (crassin alcohol). Weinheimers' conversion of crassin acetate (**1**) to **2**[1,4] indicated that the triol acid hydrolysis product would lactonize to the desired δ-lactone, but we were concerned that with lactone **6** unwanted events enroute to this triol, such as closure to the stable bridged ether **10**, might intercede. We were therefore pleased to find that treatment of lactone **6** with aqueous potassium hydroxide followed by acidification led cleanly to crassin alcohol (**2**). The ability to interconvert the δ- and γ-lactone systems **2** and **6** is of great import to current synthetic studies in this area which we will report in due course.[10]

Experimental Section[11]

Crassin Acetate (1). The isolation procedure of Anderson and co-workers[3] was modified as follows. A 1-kg sample of dry powdered cortex of *Pseudoplexaura porosa*[12] was extracted with petroleum ether in a Soxhlet extractor. After four cycles the solvent was changed to ethyl acetate and extraction was continued for 3 h.

The concentrated petroleum ether extracts (55 g of green oil) were filtered through a column containing 300 g of Florisil (bottom half) and 300 g of Fisher alumina (top half), using 50% ethyl acetate–hexane as the eluant. The eluted material (25 g) was dissolved in 250 mL of petroleum ether and refrigerated overnight, whereupon 4.6 g of crystalline crassin acetate was collected by filtration.

The ethyl acetate extracts were concentrated, and the residue was filtered through 700 mL of Florisil, using ethyl acetate as the eluant, to give 20 g of a yellow brown solid. Rechromatography on 700 mL of Florisil, using 50% ethyl acetate–hexane as the eluant, afforded a white solid, which was combined with the crystalline crassin acetate obtained from the above described petroleum ether extracts. The combined solid was recrystallized from petroleum ether–benzene to afford 14.0 g of crassin acetate, mp 141–142 °C (lit.[3] mp 141–142 °C), as slender white needles. A second crop of 2.3 g, mp 140–141 °C, was obtained from the mother liquor.

Crassin Alcohol (2). A. From Crassin Acetate (1). A suspension of 5.65 g (15.0 mmol) of crassin acetate (**1**) in 150 mL of 3% aqueous potassium hydroxide was heated at reflux for 1 h. The resultant solution was cooled to 0 °C and acidified with cold 10% HCl. After the solution was stirred overnight, the milky suspension was extracted with ethyl acetate–ether. The extracts were dried over $MgSO_4$, and the solvent was distilled under reduced pressure, affording a white solid which was recrystallized from 50% ethyl acetate–hexane to afford 4.25 g (85%) of crassin alcohol (**2**), mp 177–178 °C, as small white needles: IR ν 3540, 2850, 1720, 1625, 1100 cm^{-1}; NMR[13a] δ 6.50, 5.70 (d, C=CH_2, J = 2.4 Hz), 5.23 (m, vinyl H), 5.05 (t, vinyl H, J = 7.8 Hz), 4.20 (ddd, H-14, J = 2.5, 5.4, 11.2 Hz), 3.92 (d, H-3, J = 11.2 Hz), 2.53 (ddd, H-1, J = 2.9, 6.3, 12.2 Hz), 2.43 (dd, H-13, J = 4.4, 12.7 Hz), 1.64, 1.57 (vinyl CH_3's), 1.37 (C-4 CH_3).

(7) Cf. Jackman, L. M. "Applications of Nuclear Magnetic Resonance", McMillan: New York, 1964, p 84.
(8) Bowden, B. F.; Brittle, J. A.; Coll, J. C.; Liyanage, N.; Mitchell, S. J.; Stokie, G. J. *Tetrahedron Lett.* **1977**, 3661.
(9) Private communication from J. C. Coll. We thank Dr. Coll for spectra and a sample of isolobophytolide.
(10) Work in progress with Richard D. Royce, Jr.
(11) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 132) was used to maintain an argon or nitrogen atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts overy anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected. High-pressure liquid chromatography (HPLC) was performed on Waters Associates ALC-201 Model 6000 and Model LC500 instruments, using Porasil, μ-Porasil, and Corasil II columns.
(12) The *P. porosa* was collected off Eliot Key near Homestead, FL, in May of 1977 and near Islamorada in June of 1981. We are grateful to Dr. David Anderson for his invaluable assistance.
(13) (a) The 270-MHz NMR spectra were secured from the Yale Regional NMR Facility. (b) The 400-MHz NMR spectra were secured from the South Carolina Regional NMR Facility.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.59; H, 9.13.

B. From Isocrassin Alcohol (6). The above procedure was followed, using 0.19 g (0.5 mmol) of isocrassin alcohol (**6**) in 25 mL of 0.22 M KOH, whereupon 0.14 g (85%) of recrystallized crassin alcohol (**2**), mp 177–178 °C, was obtained. The identity of this material was verified by spectral comparison, mixture melting point, and TLC comparison.

Phenyl Sulfide Adduct 3 of Crassin Alcohol (2). To a solution of 0.79 g (2.34 mmol) of crassin alcohol (**2**) in 25 mL of benzene was added 0.5 mL (3.6 mmol) of triethylamine. The solution was cooled to 10 °C and 0.5 mL (4.9 mmol) of thiophenol was added via syringe. The mixture was stirred at 10 °C for 15 min and poured into a 1:1 water–ether mixture, and the product was extracted with ether. The extracts were washed with 10% aqueous NaOH (2×), 10% aqueous HCl, and saturated brine and dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure from the filtered solution and the product was purified via HPLC, using 3:1 ethyl acetate–hexane as the eluant to afford 0.95 g (92%) of adduct **3** as a white solid. Recrystallization from 1:1 ethyl acetate–hexane gave the analytical sample: mp 170–171 °C: IR ν 3500, 2950, 1740, 1245, 740, 680 cm^{-1}; NMR[13b] δ 7.40–7.22 (m, aromatic H's), 5.20 (m), 5.08 (t, J = 7.4 Hz, vinyl H's), 4.36 (m, H-14), 3.88 (d, H-3, J = 11.7 Hz), 3.58 (dd half of CH_2SPh AB, J_{vic} = 3.9, J_{gem} = 13.7 Hz), 3.19 (dd, half of CH_2SPh AB, J_{vic} = 11.3, J_{gem} = 13.7 Hz), 2.66 (dt, H-15, J = 5.3, 10.5 Hz), 1.76, 1.60 (vinyl CH_3's), 1.33 (C-4 CH_3).

Anal. Calcd for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16. Found: C, 70.25; H, 8.32.

Phenyl Sulfide Adduct 4 of Crassin Alcohol (2). The above experiment was carried out starting with 0.22 g (0.67 mmol) of crassin alcohol (**2**). After 1 min at 10 °C only adduct **3** could be detected by HPLC. Prolonged reaction at 45 °C gradually yielded a mixture of adducts **3** and **4** which was unchanged (30% **3**, 70% **4**) after 90 h. Isolation as above by HPLC yielded 0.048 g of adduct **3** and 0.13 g of adduct **4**. The latter had mp 140–141 °C after recrystallization from ethyl acetate–hexane: IR ν 3450, 2950, 1720, 1440, 760, 680 cm^{-1}; NMR[13b] δ 7.41–7.19 (m, aromatic H's), 5.23 (m), 5.11 (t, J = 7.8 Hz, vinyl H's), 4.06 (d, H-3, J = 11.2 Hz), 3.92 (m, H-14), 3.52 (dd, half of CH_2SPh AB, J_{gem} = 13.6, J_{vic} = 3.9 Hz), 3.36 (dd, half of CH_2SPh AB, J_{gem} = 13.6, J_{vic} = 5.9 Hz), 3.11 (dt, lactone α-H, J = 4.4, 5.9 Hz), 2.46 (dd, H-13, J = 3.4, 13.2 Hz), 1.61 (vinyl CH_3's), 1.37 (C-4 CH_3).

Anal. Calcd for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16. Found: C, 70.46; H, 8.40.

When the adduct **4** was subjected to the above conditions, slow equilibration took place to a mixture of **3** and **4**. After 122 h, HPLC analysis indicated a 1:9 ratio of **3** and **4**.

Isocrassin Acetate (5). To a solution of 0.24 g (0.5 mmol) of acetate **9** in 7 mL of methanol and 0.5 mL of benzene was added 0.14 g (0.65 mmol) of sodium periodate at 0 °C. The stirred mixture was allowed to reach room temperature overnight. Filtration through Celite and extraction with ether afforded 0.25 g of oily sulfoxide diastereoisomers.

The above sulfoxide sample in 5 mL of toluene containing 2 drops of pyridine was heated at reflux for 4 h. Removal of solvent under reduced pressure and recrystallization of the residue from ethyl acetate–hexane afforded 0.13 g (72%) of isocrassin acetate (**5**), mp 120–121 °C, as slender white needles: IR ν 3550, 2950, 1775, 1730, 1250, 985 cm^{-1}; NMR[13a] δ 6.12, 5.52 (C=CH_2, d, J = 2.2 Hz), 5.24 (t, J = 7.0 Hz), 4.95 (m, vinyl H's), 4.86 (dd, H-3, J = 1.5, 10.5 Hz), 4.75 (q, H-14, J = 6.0 Hz), 3.00 (m, H-1), 2.38 (d, H-13, J = 5.9 Hz), 2.06 (CH_3CO), 1.72, 1.60 (vinyl CH_3's), 1.16 (C-4 CH_3).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.92; H, 8.64.

Isocrassin Alcohol (6). A 2.23-g (5.0 mmol) sample of sulfide **8** was oxidized with 1.07 g (5.0 mmol) of sodium periodate in 50 mL of 1:10 benzene–methanol for 50 h as described above to give 2.15 g (93%) of crude solid sulfoxide. A 2.00-g sample of this sulfoxide was heated at reflux for 4 h in toluene–pyridine as described above to give 0.55 g (38%) of isocrassin alcohol, mp 117–118 °C, after recrystallization from ethyl acetate–hexane: IR ν 3560, 3485, 2950, 1760, 1120, 1070, 980 cm^{-1}; NMR[13a] δ 5.76, 6.25 (d, C=CH_2, J = 2.2 Hz), 5.11 (m), 4.76 (m, vinyl H's), 4.71 (m, H-13), 3.50 (dd, H-1, J = 1.5, Hz), 2.23 (m, H-3), 1.94, 1.83 (vinyl CH_3's), 1.40 (C-4 CH_3); mass spectrum,[14] m/e 334.2145 ($C_{20}H_{30}O_4$ requires 334.2145).

γ-Lactone Diol 8. Isomerization of the Kinetic Benzenethiol Adduct 3. To a stirred solution of 4.3 g (9.7 mmol) of sulfide **3** in 100 mL of tetrahydrofuran was added 0.1 g of oil-free sodium hydride. After 10 min, a few drops of water were added, and the solvent was removed under reduced pressure. The solid residue was taken up in ether and washed with water and brine and dried over anhydrous $MgSO_4$. Removal of solvent and recrystallization of the residue from ethyl acetate–hexane afforded 2.6 g (60%) of δ-lactone **8**: mp 125–126 °C; IR ν 3460, 2900, 1755, 1060, 980, 720 cm^{-1}; NMR δ 7.25 (m, aromatic H's), 4.76 (m, vinyl CH's), 3.5–3.0 (m, H-13 and H-3), 1.60, 1.51 (vinyl CH_3's), 1.17 (C-4 CH_3).

Anal. Calcd for $C_{22}H_{36}O_4S$: C, 70.23; H, 8.16. Found: C, 70.51; H, 8.43.

Lactone Ether 10. A. From Sulfide 4. The procedure described above for sulfide **3** was followed, using 0.40 g of sulfide **4**. No reaction took place at room temperature, so the solution was stirred at reflux for 1 h to give ether lactone **10** (quantitative): mp 258–260 °C (sublimed sample); IR ν 3350, 2950, 1775, 1630, 1580, 1160, 1105 cm^{-1}; NMR[13b] δ 5.07 (m, vinyl H's), 4.44 (d, half of CH_2O AB, J = 12.5 Hz), 4.52 (m, H-13), 3.74 (d, half of CH_2O AB, J = 12.5 Hz), 2.93 (dd, H-3, J = 2, 12 Hz), 1.67, 1.55 (vinyl CH_3's), 1.26 (C-4 CH_3): mass spectrum,[14] m/e 334.2157 ($C_{20}H_{30}O_4$ requires 334.2145).

B. From Crassin Alcohol (2). To a stirred solution of 0.50 g of diol **2** in 25 mL of THF was added 0.05 g of sodium hydride. After 12 h water was added and the product was extracted with ether to give 0.50 g of white solid, which was recrystallized from ethyl acetate–hexane, affording 0.46 g (92%) of ether **10**, mp 248–250 °C. The identity of this substance was confirmed through spectra comparison and mixture melting point.

Epoxide 11. To a solution of 0.334 g (1.0 mmol) of diol **6** in 3 mL of pyridine at 0 °C was added 0.16 mL of methanesulfonyl chloride. The mixture was placed in a freezer overnight and extracted with ether to afford the methanesulfonate **7** (0.41 g) as an oil.

To a stirred solution of the crude methanesulfonate **7** in 8 mL of acetone was added 0.5 mL (0.85 mmol) of 20% aqueous tetraethylammonium hydroxide at room temperature. After 4 h an additional 0.5 mL of base was added. After 15 min, the mixture was diluted with water and extracted with ether. The crude neutral product was eluted from silica gel, using 25% ethyl acetate–hexane, to give 0.15 g (52%) of epoxide **11** as an oil: NMR[13a] 6.16, 5.58 (d, C=CH_2, J = 1.8 Hz), 4.98 (m, vinyl H's), 4.80 (m, H-14), 2.83 (dd, H-3, J = 4.5, 4.2 Hz), 1.66, 1.57 (vinyl CH_3's), 1.27 (C-4 CH_3); mass spectrum,[14] m/e 316.2035 ($C_{20}H_{28}O_3$ requires 316.2039).

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Registry No. **1**, 28028-68-4; **2**, 28068-69-1; **3**, 80375-66-2; **4**, 80408-91-9; **5**, 80375-67-3; **6**, 80375-68-4; **7**, 80375-69-5; **8**, 80375-70-8; **9**, 80375-71-9; **10**, 80375-72-0; **11**, 80408-92-0.

(14) High-resolution mass spectra were secured from the University of Pennsylvania Regional Facility.