

Full Paper

A Simple and Cost Effective Synthesis of 3,11-Dimethylnonacosan-2-one, A Female Sex Pheromone of the German Cockroach

Kwang-Chan Ahn ¹, Jae-Chul Jung ² and Oee-Sook Park ^{1,*}

¹ Department of Chemistry, Institute for Basic Sciences, College of Natural Sciences, Chungbuk National University, Cheongju 361-763, Chungbuk, South Korea.

² Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, P.O. Box 1848, University, Mississippi 38677-1848, USA. E-mail: jcjung@olemiss.edu

* To whom correspondence should be addressed; E-mail: ospark@chungbuk.ac.kr

Received: 27 September 2006; in revised form: 10 October 2006 / Accepted: 10 October 2006 / Published: 12 October 2006

Abstract: A convenient synthesis of 3,11-dimethylnonacosan-2-one (**1**) is described. Our strategy involves the use of well known C-alkylation and ethyl acetoacetate synthesis reactions as key steps. We expect that this method will prove to be useful for large scale preparation of **1** and modification of dimethylnonacosanones.

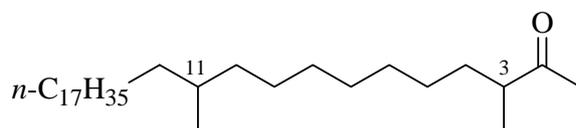
Keywords: 3,11-Dimethylnonacosan-2-one, C-alkylation, Ethyl acetoacetate synthesis, Large scale preparation.

Introduction

Many insects emit precise chemical odors to attract their mates (sex pheromones). Pheromones are naturally occurring, environmentally friendly and species specific compounds that do not result in the development of insecticide resistance [1]. The Nishida group [2] reported the isolation of the female-produced sex pheromone of the German cockroach, *Blattella germanica*, from its cuticular waxes in 1974. The compound, which elicited typical courting behavior in males including wing-raising [3,4], was identified as 3,11-dimethylnonacosan-2-one (**1**, Figure. 1). Since the synthesis of the mixture of diastereomers of **1** was first achieved by Nishida *et al.* [3], a number of syntheses yielding a

diastereomeric mixture of **1** were reported [5]. Bioassay of these four stereoisomers of **1** showed that they were equally active [6]. Most of these methods for the generation of 3,11-dimethylnonacosan-2-one (**1**) are linear synthetic approaches involving expensive reagents and inconvenient handling [5a-b,5f].

Figure 1. Structure of 3,11-dimethylnonacosan-2-one (**1**)

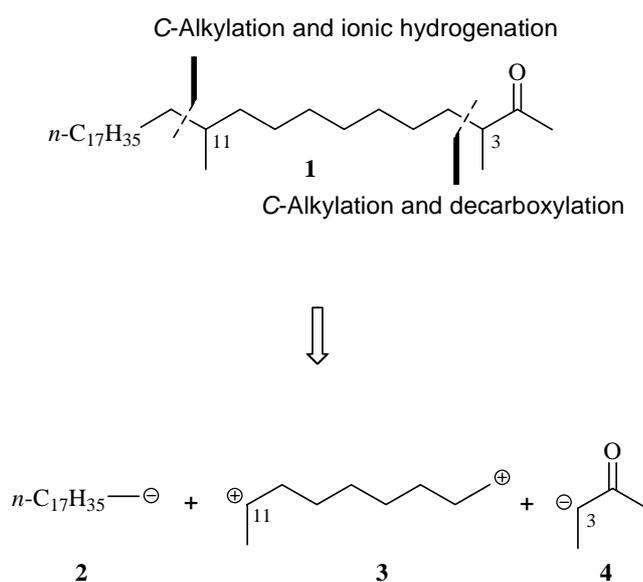


Our research required large quantities of **1** and key fragments **2–4** to serve as potential scaffolds for modification of **1**. We therefore became interested in studying a synthesis of **1** suitable for large scale production. We wish to report herein a convenient new approach to the synthesis of this target molecule via *C*-alkylation–ionic hydrogenation and *C*-alkylation–decarboxylation reactions starting from 1,8-octane-diol (**5**) and 1-octadecanol (**9**).

Results and Discussion

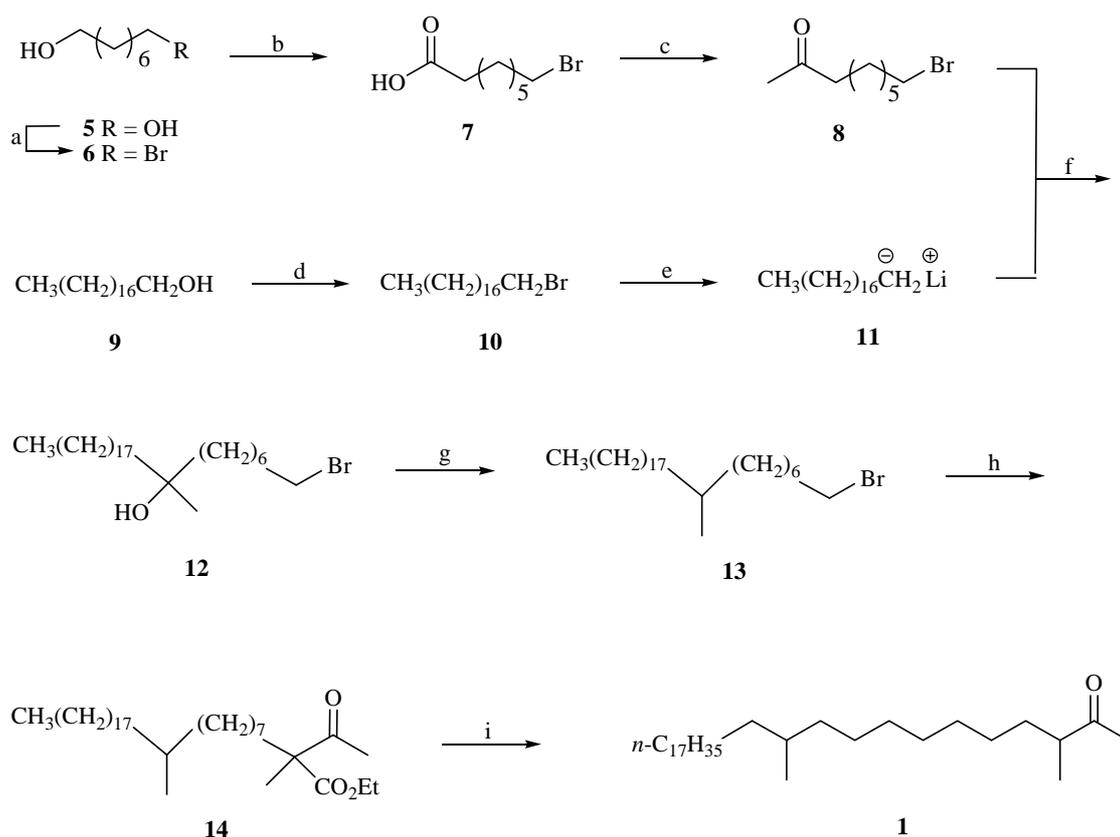
The retrosynthetic analysis for 3,11-dimethylnonacosan-2-one (**1**) is summarized in Scheme 1. The synthetic key strategies involve *C*-alkylation–decarboxylation reaction of unit **3** with acetate anion **4** in order to form the C3–C4 bond, and *C*-alkylation–ionic hydrogenation of alkyl anion **2** with unit **3** for generation of the C11–C12 bond. Units **2** and **4** can be smoothly derived from freshly prepared bromide **10** [7] and commercially available ethyl 2-methylacetoacetate in the presence of base. The electrophilic unit **3** was generated via bromination, oxidation, and methylation of 1,8-octanediol (**5**).

Scheme 1. Retrosynthetic analysis of 3,11-dimethylnonacosan-2-one (**1**).



The synthesis of key fragments **8** and **11** was accomplished as depicted in Scheme 2. Commercially available **5** underwent bromination with aqueous hydrogen bromide (48%) in benzene using a Dean–Stark apparatus to afford a 6:1 ratio (by G.L.C. analysis) of monobromo alkanol **6** and dibromo alkane [8]. Compound **6** was oxidized by Jones reagent at 0 °C in acetone to generate acid **7** in 80% yield [9], which was then treated with methyl lithium (1.4 M solution in ether) in THF to give 9-bromononan-2-one (**8**) in 64% yield [10]. Bromination of alcohol **9** was performed with phosphorus tribromide in ether to produce a 95% yield of bromide **10**, which was treated with Li metal in dry THF to yield anion **11**, which was coupled *in situ* with bromide **8** [11] in DMF to generate tertiary alcohol **12** in 60% yield for two steps. In this bromination reaction the alternate $\text{CBr}_4/\text{PPh}_3$ method proved to be relatively low yielding (80%) [12]. Compound **12** was treated with Et_3SiH in the presence of $\text{BF}_3\cdot\text{OEt}$ in CH_2Cl_2 to afford the product **13** [5a] in 95% yield. Chain-elongation of **13** with ethyl 2-methylacetoacetate was executed employing potassium carbonate as the base to give **14** in 93% yield. Hydrolysis of **14** with concomitant decarboxylation of the resulting acid furnished the final product, 3,11-dimethylnonacosan-2-one (**1**) in 73% yield [5].

Scheme 2. Synthesis of 3,11-dimethylnonacosan-2-one (**1**).



- (a) HBr (48% aq)/benzene, reflux, 18 h, (72%); (b) Jones reagent, acetone, 0 °C to rt, 1 h, (80%); (c) CH_3Li (2 equiv)/THF, -78 °C to 0 °C, 1 h, (64%); (d) PBr_3 /ether, reflux, 2 h, (95%); $\text{PPh}_3, \text{CBr}_4/\text{CCl}_4$, rt, 3 h, (80%); (e) Li/ether, rt, 30 min; (f) **8** + **11**, ether, 0 °C, 3 h, (60%, two steps); (g) Et_3SiH , $\text{BF}_3\cdot\text{OEt}/\text{CH}_2\text{Cl}_2$, 0 °C, 2 h, (95%); (h) ethyl-2-methyl acetoacetate, K_2CO_3 , KI/acetone, reflux, 20 h, (93%); (i) 15% NaOH, (*n*-Bu) $_4\text{NOH}/\text{THF}$, rt, 2 h, (73%).

Conclusions

In summary, we have demonstrated a new and practical large scale route to 3,11-dimethylnonacosan-2-one (**1**) using readily available inexpensive reagents and simple reaction conditions that do not require any special equipment or techniques. We expect that this method will prove to be useful for the large scale preparation of **1** and for modification of dimethylnonacosanones. All physical and spectral data for the synthetically prepared **1** were identical to those reported [3,5].

Experimental

General

Reactions requiring anhydrous conditions were performed following the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates (Analtech) and visualized with 254-nm UV light. Flash chromatography was carried out on silica gel 60 [Scientific Adsorbents Incorporated (SAI), particle size 32–63 μm , pore size 60 \AA]. ^1H -NMR, ^{13}C -NMR, and 2D-NMR spectra were recorded in CDCl_3 on a Bruker DPX 400 instrument operating at 400 MHz (^1H) and 100 MHz (^{13}C), respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Infrared (IR) spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded with a Waters Micromass ZQ LC–Mass system and high resolution mass spectra (HRMS) were measured with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). When necessary, chemicals were purified according to the reported procedures [13].

8-Bromooctan-1-ol (**6**)

To a stirred solution of 1,8-octanediol (**5**, 31.2 g, 213.5 mmol) in benzene (500 mL) was added 48% aqueous HBr (37.5 mL) and the mixture was refluxed for 18 h, while the water formed was trapped using a Dean–Stark water separator. The reaction mixture was washed successively with 6N aqueous NaOH solution (200 mL), 10% HCl aqueous solution (250 mL), water (300 mL) and brine (300 mL). The organic layer was separated, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (b.p. 66–70 $^\circ\text{C}/3$ torr, lit. [8c] b.p. 110–120 $^\circ\text{C}/2$ torr) to give **6** (32.0 g, 72%) as a colorless oil. IR (neat, NaCl) 3455, 2984, 2875, 1142, 1048, 852 cm^{-1} ; ^1H -NMR δ 3.72 (t, $J = 6.8$ Hz, 2H, CH_2Br), 3.45 (t, $J = 7.0$ Hz, 2H, CH_2OH), 1.25–1.15 (m, 12H, $6\times\text{CH}_2$); HRMS calcd. for $\text{C}_8\text{H}_{18}\text{OBr}$: 209.0541 $[\text{M}+\text{H}]^+$, found: 209.0547.

9-Bromononan-2-one (**8**)

A stirred solution of acid **7** (45.0 g, 201.0 mmol) in dry THF (1.4 L) was cooled to -78 $^\circ\text{C}$ and methyllithium (287.5 mL, 402.0 mmol, 1.4 M solution in ether) was added dropwise over 20 min. The

reaction mixture was allowed to warm to 0 °C for 1 h, and quenched with sat'd aqueous NH₄Cl solution (250 mL), followed by extraction with ether (3×300 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% ethyl acetate in hexanes) to give **8** (28.5 g, 64%) as a colorless oil. *R*_f = 0.4 (20% ethyl acetate in hexanes); IR (neat, NaCl) 2977, 2876, 1712, 1518, 1452, 1250, 1068, 781 cm⁻¹; ¹H-NMR δ 3.38 (t, *J* = 6.8 Hz, 2H, CH₂Br), 2.40 (t, *J* = 7.6 Hz, 2H, CH₂CO), 2.11 (s, 3H, CH₃), 1.87–1.77 (m, 2H, CH₂), 1.58–1.49 (m, 2H, CH₂), 1.44–1.36 (m, 2H, CH₂), 1.35–1.18 (m, 4H, 2×CH₂); ¹³C-NMR δ 208.9 (CO), 43.5 (CH₂CO), 33.8 (CH₂Br), 31.9 (CH₃), 30.2 (CH₂), 28.5 (CH₂), 28.1 (CH₂), 26.8 (CH₂), 23.4 (CH₂); HRMS calcd. for C₅H₁₀OBr: 164.9915 [M+H]⁺, found: 164.9908.

1-Bromomethylhexacosan-8-ol (12)

Anhydrous ether (150 mL) was placed in a three-necked flask equipped with a dropping funnel, a N₂ gas inlet and a septum. After the apparatus was swept with dry N₂, lithium wire (1.5 g, 216.0 mmol) was cut into small pieces, which were allowed to fall into the reaction flask. With stirring, a solution of 1-bromooctadecane (**10**, 30.0 g, 90.0 mmol) in anhydrous ether (150 mL) was added. After a period of 1 h, the mixture became slightly cloudy. The reaction mixture then was cooled to -10 °C. The remainder of the 1-bromooctadecane solution was added over a period of 3 h at the same temperature. After addition was completed, the reaction mixture was kept at the same temperature for additional 1 h and then was allowed to warm up to 10 °C with stirring. Over a period of 30 min, the reaction mixture was cannulated to a two-necked flask in which bromide **8** (15.0 g, 60.0 mmol) in ether (75 mL) at 0 °C was placed and the resulting reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched by addition of 50% aqueous NH₄Cl solution (150 mL) and aqueous phase was extracted with ether (180 mL). The combined organic phases were washed with brine (150 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20% hexane in ethyl acetates) to give alcohol **12** (25.5 g, 60%) as a colorless oil. *R*_f = 0.3 (20% hexane in ethyl acetates); IR (neat, NaCl) 3520–2916, 2848 cm⁻¹; ¹H-NMR δ 3.64 (t, *J* = 6.8 Hz, 2H, CH₂Br), 1.65–1.48 (m, 6H, 3×CH₂), 1.32–1.20 (m, 44H, 22×CH₂), 0.88 (t, *J* = 7.2 Hz, 3H, CH₃); HRMS calcd. for C₂₇H₅₆OBr: 475.3515 [M+H]⁺, found: 475.3521.

1-Bromo-8-methylhexacosane (13)

To a stirred solution of 1-bromo-8-methylhexacosan-8-ol (**12**, 24.0 g, 50.0 mmol) in dichloromethane (600 mL) was added triethylsilane (12.0 g, 120.0 mmol), followed by addition of BF₃·OEt (20.0 g, 150.0 mmol) at 0 °C and the mixture was stirred for 2 h. The reaction mixture was diluted with CH₂Cl₂ (400 mL) and washed with sat'd aqueous NH₄Cl solution (500 mL) and brine (500 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in hexanes) to give bromide **13** (22.0 g, 95%) as a colorless oil. *R*_f = 0.5 (5% ethyl acetate in hexanes); IR (neat, NaCl) 2978, 1446, 1062, 838 cm⁻¹; ¹H-NMR δ 3.43 (t, *J* = 6.8 Hz, 2H, CH₂Br),

1.61–1.39 (m, 7H), 1.35–1.21 (m, 43H), 0.89 (t, $J = 7.0$ Hz, 3H, CH₃); HRMS calcd. for C₂₇H₅₆Br: 459.3565 [M+H]⁺, found: 459.3573.

3,11-Dimethyl 3-ethoxycarbonylnonacosan-2-one (14)

To a stirred solution of ethyl 2-methylacetoacetate (9.0 g, 63.0 mmol) in acetone (150 mL) was added K₂CO₃ (18.6 g, 135.0 mmol) and KI (3.0 g, 18.0 mmol) at room temperature. After 10 min, a solution of bromide **13** (27.6 g, 60.0 mmol) in acetone (60 mL) was added and the reaction mixture was rapidly brought to reflux by heating in oil bath. After 20 h, the resultant mixture was cooled to room temperature, diluted with ether (300 mL) and filtered. The residue was washed with sat'd aqueous NH₄Cl solution (150 mL) and brine (150 mL). The organic layer was separated, and the aqueous phase was extracted with ether (150 mL). The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) to give acetate **14** (28.5 g, 93%) as a colorless oil. $R_f = 0.3$ (10% ethyl acetate in hexanes); IR (neat, NaCl) 2924, 2853, 1735 (CO), 1716 (COO), 1458, 1265, 1120 cm⁻¹; ¹H-NMR δ 4.18 (t, $J = 7.0$ Hz, 2H, CH₂), 2.03 (s, 3H, CH₃), 1.86–1.72 (m, 2H, CH₂), 1.48–1.21 (m, 51H, CH, 25×CH₂), 0.85–1.02 (m, 6H, 2×CH₃); HRMS calcd. for C₃₃H₆₅O₃: 509.4934 [M+H]⁺, found: 509.4922.

3,11-Dimethylnonacosan-2-one (1)

To a stirred solution of 3,11-dimethyl-3-ethoxycarbonylnonacosan-2-one (**14**, 15.2 g, 30.0 mmol) in THF (500 mL) was added 15% aqueous NaOH solution (300 mL), followed by addition of tetrabutylammonium hydroxide solution (38.0 g, 150.0 mmol, 1.0 M sol. in water) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (600 mL) and washed with sat'd aqueous NH₄Cl solution (600 mL) and brine (400 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (300 mL). The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) to give **1** (9.8 g, 73%) as a colorless oil. $R_f = 0.3$ (10% ethyl acetate in hexanes); IR (neat, NaCl) 2957, 1729 (CO), 1446, 1285, 1024, 837 cm⁻¹; ¹H-NMR δ 2.55–1.41 (m, 1H, CH), 2.06 (s, 3H, CH₃), 1.72–1.22 (m, 55H), 0.84 (t, $J = 7.0$ Hz, 3H, CH₃); HRMS calcd. for C₃₁H₆₃O: 451.4879 [M+H]⁺, found: 451.4887.

Acknowledgements

This work was supported by Chungbuk National University Grant in 2004.

References

- (a) Eliyahu, D.; Mori, K.; Takikawa, H.; Leal, W. S.; Schal, C. *J. Chem. Ecol.* **2004**, *30*, 1839–1848; (b) Schal, C.; Gu, X.; Burns, E. L.; Blomquist, G. *J. Arch. Insect Biochem. and Physiol.*

- 1994, 25, 375–391; (c) Chase, J.; Touhara, K.; Prestwich, G. D.; Schal, C.; Blomquist, G. J. *P. Nat. Acad. Sci. USA* **1992**, 89, 6050–6054; (d) Place, P.; Roumestant, M. L.; Gore, J. *Tetrahedron* **1978**, 34, 1931–1933.
- Nishida, R.; Fukami, H.; Ishii, S. *Experientia* **1974**, 30, 978–979.
 - Nishida, R.; Fukami, H.; Ishii, S. *Appl. Entomol. Zool.* **1975**, 10, 10–18.
 - Nishida, R.; Sato, T.; Kuwahara, Y.; Fukami, H.; Ishii, S. *J. Chem. Ecol.* **1976**, 2, 449–455.
 - (a) Schwarz, M.; Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1975**, 40, 2410–2411; (b) Burgstahler, A. W.; Weigel, L. O.; Bell, W. J.; Rust, M. K. *J. Org. Chem.* **1975**, 40, 3456–3458; (c) Sato, T.; Nishida, R.; Kuwahara, Y.; Fukami, H.; Ishii, S. *Agric. Biol. Chem.* **1976**, 40, 391–394; (d) Rosenblum, L. D.; Anderson, R. J.; Henrick, C. A. *Tetrahedron Lett.* **1976**, 17, 419–422; (e) Mori, K.; Suguro, T.; Masuda, S. *Tetrahedron Lett.* **1978**, 19, 3447–3450; (f) Mori, K.; Masuda, S.; Suguro, T. *Tetrahedron* **1981**, 37, 1329–1340; (g) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 28, 651–654; (h) Mori, K.; Takikawa, H. *Tetrahedron* **1990**, 46, 4473–4486; (i) Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett.* **1998**, 39, 1823–1826.
 - Nishida, R.; Fukami, H. *Mem. Coll. Agric. Kyoto Univ.* **1983**, 122, 1–24.
 - (a) Easton, C. J.; Xia, L.; Pitt, M. J.; Ferrante, A.; Poulos, A.; Rathjen, D. A. *Synthesis* **2001**, 451–457; (b) Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, 38, 7223–7224; (c) Kulkarni, S. M.; Mamdapur, V. R.; Chadha, M. S. *Indian J. Chem., Section B*: **1983**, 22B, 683.
 - (a) Camps, F.; Gasol, V.; Guerrero, A. *Synthesis* **1987**, 511–512; (b) Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139–141; (c) Kang, S. K.; Kim, W. S.; Moon, B. H. *Synthesis* **1985**, 1161–1162; (d) Nanda, S.; Yadav, S. *Tetrahedron Asymm.* **2003**, 14, 1799–1806.
 - (a) Just, G.; Luthe, C.; Oh, H.; Montgomery, J. *Synth. Commun.* **1979**, 9, 613–617; (b) Allanson, N. M.; Llu, D.; Chi, F.; Jain, R. K.; Chen, A.; Ghosh, M.; Hong, L.; Sofia, M. J. *Tetrahedron Lett.* **1998**, 39, 1889–1892; (c) Petersen, Q. R.; Cambie, R. C.; Russell, G. B. *Aus. J. Chem.* **1993**, 46, 1961–1964.
 - (a) Zhang, W. C.; Li, C. J. *J. Org. Chem.* **2000**, 65, 5831–5833; (b) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. A. *J. Am. Chem. Soc.* **1992**, 114, 9683–9685.
 - Porter, N. A.; Miracle, G. S.; Cannizzaro, S. M.; Carter, R. L.; McPhail, A. T.; Liu, L. *J. Am. Chem. Soc.* **1994**, 116, 10255–10266.
 - (a) Bentz, E. L.; Gibson, H.; Hudson, C.; Moloney, M. G.; Seldon, D. A.; Wearmouth, E. S. *Synlett* **2006**, 247–250; (b) Kasuga, J. I.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2006**, 16, 771–774; (c) Kotha, S.; Anglos, D.; Kuki, A. *Tetrahedron Lett.* **1992**, 33, 1569–1572.
 - Perrin, D. D.; Armarego, L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed; Pergamon Press: New York, **1980**.

Sample Availability: Samples of the compounds are available from authors.