The amine and **9** in the molar ratio 1:5 were refluxed in dry benzene for 6 hr. By working up as for the above procedure (B) the corresponding *N*-alkyl derivatives were isolated. The results obtained are reported in Table III.

Acknowledgment. The authors are grateful to Professor V. Carelli for his helpful suggestions. This work was supported by a research grant from CNR, Rome, Italy.

Registry No.—**1a,** 49634-65-3; **1b,** 19195-32-5; **1c,** 25069-59-4; **2a,** 49634-66-4; **2b,** 25069-68-5; **2c,** 25069-64-1; **3a** (R = CH_3), 56553-67-4; **3c** (R = H), 49634-64-2; **3c** (R = CH_3), 56553-68-5; **4a,** 62-53-3; **4b,** 100-61-8; **4c,** 122-39-4; **4d,** 110-89-4; **4e,** 111-92-2; **5** (R = Et; R_1 = Ph; R_2 = Pr), 2217-07-4; **5a** (R = CH_3), 103-69-5; **5a** (R = C_2H_5), 622-80-0; **5b** (R = C_2H_5), 13395-54-5; **5b** (R = C_6H_5), 614-30-2; **5b** (R = $C_{15}H_{31}$), 56553-69-6; **5c** (R = CH_3), 606-99-5; **5c** (R = CH_2Cl), 42393-65-7; **5c** (R = $C_{15}H_{31}$), 51580-76-8; **5d** (R = CH_3), 766-09-6; **5e** (R = CH_3), 4458-33-7; **6a** (R = C_2H_5), 620-71-3; **6c** (R = CH_3), 519-87-9; **6d** (R = C_2H_5), 14045-28-4; **7a,** 135-19-3; **7b,** 91-01-0; **8a** (R = CH_3), 1523-11-1; **8b** (R = CH_3), 954-67-6; **9** (R = H), 56553-59-4; **9** (R = CH_3), 56553-60-7; **9** (R = CH_2Cl), 56553-61-8; **9** (R = C_6H_5), 56553-62-9; acetic acid, 64-19-7; formic acid, 64-18-6; propionic acid, 79-09-4; palmitic acid, 57-10-3; benzoic acid, 65-85-0; monochloroacetic acid, 79-11-8; 2,2′-dithiodianiline, 56553-70-9; *N,N′*-diethyl-2,2′-dithiodianiline, 1141-88-4; *N,N′*-dibenzyl-2,2′-dithiodianiline, 56553-71-0.

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Synthesis of 3,11-Dimethyl-2-nonacosanone, a Contact Courting Pheromone of the German Cockroach[1]

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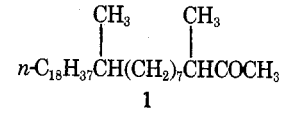
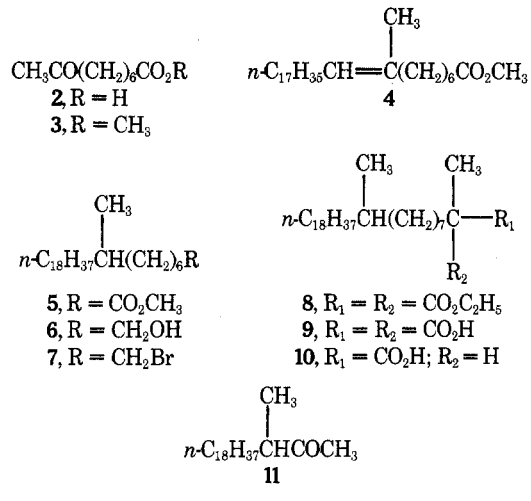
From the cuticle of sexually mature female German cockroaches (*Blattella germanica*), Ishii and coworkers recently isolated a contact chemoreceptive agent, identified as 3,11-dimethyl-2-nonacosanone (**1**), which was shown to elicit typical courting behavior, including wing raising, in males.[2] As part of a program of research on the properties and functions of cockroach pheromones,[3] we undertook and now describe a synthesis of **1**. After completion and submission of this work for publication, an account with limited experimental details of a synthesis of **1** along somewhat similar lines by Ishii and coworkers appeared.[4]



1

As starting material in our synthesis we employed 8-oxononanoic acid (**2**), prepared from ϵ-caprolactone by modifications of the route of Kameoka et al.[5] via 6-bromohexanoic acid, esterification, and acetoacetic ester synthesis. Treatment of the methyl ester **3** in polar solvent with the Wittig reagent derived from octadecyltriphenylphosphonium bromide gave, in 48% yield, methyl 8-methyl-8-hexacosenoate (**4**), apparently mainly (by GLC) the *Z* isomer.[6] Hydrogenation of **4** afforded the saturated ester **5**, which, after $LiAlH_4$ reduction to the corresponding alcohol **6** and conversion into the bromide **7**, was used to alkylate diethyl methylmalonate. Hydrolysis of the resulting diester **8** and decarboxylation of the acid **9** gave 2,10-dimethyloctacosanoic acid (**10**), which, with two widely separated asymmetric centers, was undoubtedly a mixture of the two possible diastereoisomers. Treatment of **10** with 2 mol of methyllithium then furnished the desired ketone **1**, mp 28–31° (lit.[4] 29–31°), in 50% overall yield from the Wittig product **4**.



2, R = H
3, R = CH_3

4

5, R = CO_2CH_3
6, R = CH_2OH
7, R = CH_2Br

8, R_1 = R_2 = $CO_2C_2H_5$
9, R_1 = R_2 = CO_2H
10, R_1 = CO_2H; R_2 = H

11

Although spectral data indicate that the synthetic and natural ketones are structurally identical, our method of synthesis, like that of Ishii and coworkers,[4] undoubtedly afforded a mixture of the two possible diastereoisomers of **1**. It is not surprising, therefore, that the natural product has a different melting point (45–46°), even though it appears to be optically inactive.[2,4]

Previous studies have shown that courting behavior in the German cockroach includes antennation (antennal stroking) of the female by the male, presumably allowing the latter to perceive sex pheromone on the cuticular surface of the female.[7] In our bioassay of synthetic **1** we used antennae ablated from American cockroaches (*Periplaneta americana*) to eliminate any possible stimuli associated with German cockroach antennae. Control antennae, dipped only in carbon tetrachloride, evoked no response. Antennae dipped in a 70 μg/ml solution of synthetic **1** in carbon tetrachloride elicited typical wing raising and other features of courting display[7] in 5% of a group of males (n = 60) kept isolated from females. At a higher concentration of 500 μg/ml the response was 70% in a group of isolated

males (n = 40) showing 80% response when presented with a mature virgin female.

These findings are comparable to those of Ishii and coworkers,[2,4] who reported that purified natural ketone 1 exhibited "distinct activity" in antennal testing at a concentration as low as 50 μg/ml in carbon tetrachloride. Interestingly, we found a lower molecular weight analog of 1, 3-methyl-2-heneicosanone (11), to be completely devoid of activity. Moreover, synthetic 1 failed to excite male American (*Periplaneta americana*) or Cuban (*Byrsotria fumigata*) cockroaches.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137B Infracord or a Beckman IR-5 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were taken on a Varian A-60A or HA-100 instrument in carbon tetrachloride with tetramethylsilane as internal reference except where noted otherwise. Electron impact mass spectra were obtained at 70 eV with a Varian CH-5 spectrometer by Mr. Robert Drake, University of Kansas Department of Chemistry. Decolorizations were done with Nuchar C-190N. Anhydrous magnesium sulfate was used for drying organic extracts. "Pentane" and "hexane" refer to dry, redistilled Skellysolve F (bp 39–50°) and Skellysolve B (bp 64–68°), respectively. Homogeneity assays were made by TLC (silica gel 60F-254) or GLC (Varian A90-P3 instrument, 8-ft glass column packed with 10% SE-30 on 60–80 Gas-Chrom Q). Elemental analyses were run on an F & M 185 CHN analyzer by Mr. Dennis Eisele, University of Kansas Department of Medicinal Chemistry microanalyst.

8-Oxononanoic Acid (2). The route of Kameoka et al.[5] was modified to give a 3.25-fold improvement in overall yield. A mixture of 400 g (3.50 mol) of ε-caprolactone (Aldrich Chemical Co.), 600 ml of 48% hydrobromic acid, and 185 ml of concentrated sulfuric acid was refluxed for 5.5 hr and cooled to 15°. After separation of the upper layer, the lower layer was treated with 600 ml of saturated sodium chloride solution and extracted with three 150-ml portions of ether. The combined dark ether extracts and original upper layer were washed with four 200-ml portions of 20% aqueous sodium chloride solution and once with 200 ml of saturated sodium chloride solution. The ether layer was then decolorized and dried. Filtration and concentration afforded 641 g of crude 6-bromohexanoic acid, which was distilled rapidly at 1 mm; the fraction boiling at 139–140° [lit.[5] bp 150–152° (13 mm)] was collected to yield 533 g (78%) of purified acid, mp 36–38° (lit.[8] mp 35°). Esterification of 460 g (2.36 mol) of this acid with 1150 ml of absolute ethanol and 9.2 ml of concentrated sulfuric acid as catalyst gave, after removal of excess ethanol, extraction into methylene chloride, and distillation, 476 g (90%) of ethyl 6-bromohexanoate, bp 87–88° (0.75 mm) [lit.[5] bp 117–120° (4 mm)]. This ester (450 g, 2.02 mol) was added dropwise at 25–30° to a mechanically stirred solution of the sodium enolate of 276 g (2.12 mol) of ethyl acetoacetate [generated at 10–15° in a suspension of 50.5 g (2.12 mol) of sodium hydride] in 2 l. of dry benzene and 0.5 l. of dimethylformamide under an inert (argon) atmosphere. After stirring for 41 hr at 55° the mixture was concentrated under reduced pressure to ca. 1 l. and stirred for 2 hr longer. Aqueous work-up followed by extraction with benzene and distillation furnished 417 g (76%) of alkylated ethyl acetoacetate, bp 149–150° (1 mm). For conversion into 2, 310 g (1.14 mol) of this ester was dissolved in 700 ml of acetic acid to which was added 450 ml of water and 82 ml of concentrated sulfuric acid. The mixture was refluxed vigorously with stirring for 2.75 hr and cooled to 5°, after which it was poured into 2 l. of ice water saturated with sodium chloride. The oily product was extracted with three 200-ml portions of ether, washed twice with an equal volume of saturated sodium chloride solution, and dried. The solution was concentrated at 45° under water aspirator vacuum and the residue was taken up in 400 ml of 1:1 ether–hexane, after which it was decolorized, filtered, and slowly cooled, with stirring, to ca. −25°. After crystallization was complete, rapid collection of the colorless, fine plates on a precooled Büchner funnel gave 119 g (61%) of 8-oxononanoic acid (2), mp 39–40.5° (lit.[5] mp 40°). Further hydrolysis and decarboxylation of the vacuum-distilled mother liquors (52 g) afforded an additional 19 g (mp 35–39°) of this acid, making the total yield 70%.

Methyl 8-Oxononanoate (3). Esterification of 100 g (0.58 mol) of acid 2 with ethereal diazomethane at 5° gave 103 g (95%) of distilled 3, bp 95° (0.65 mm) [lit.[9] bp 104° (3 mm)]. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.56; H, 9.78.

Methyl 8-Methyl-8-hexacosenoate (4). Triphenyloctadecylidenephosphorane (0.100 mol) was generated in 100 ml of dimethyl sulfoxide by the method of Greenwald, Chaykovsky, and Corey[10] from octadecyltriphenylphosphonium bromide (mp 93–95°, prepared in refluxing xylene). To this deep orange, slightly soluble ylide was added, with stirring, 100 ml each of dry dimethylformamide and tetrahydrofuran, followed by slow addition at 25° of 18.6 g (0.100 mol) of methyl 8-oxononanoate (3). After stirring under argon for 36 hr at 25°, the mixture was poured into 1.5 l. of 15% aqueous sodium chloride solution and extracted with five 100-ml portions of pentane. The combined pentane extracts were washed with three 100-ml portions of water and 200 ml of saturated sodium chloride solution, dried, cooled to 0°, filtered through 15 mm of alumina (Alcoa F-20, 45 g), and evaporated to give 26.2 g (62%) of crude 4 containing small amounts of recovered 3 and traces of triphenylphosphine oxide. Elution of 15.0 g of this product from 200 g of neutral alumina (Woelm, activity grade 2.5) with 1.2 l. of pentane gave 11.7 g (48%) of analytically pure methyl 8-methyl-8-hexacosenoate (4), apparently mainly the Z isomer by GLC analysis: ir (thin film) 3050 (=CH, very weak), 1740 (ester), no absorption at 1715 cm^{-1}; ^{1}H NMR δ 5.11 (1 H, t, J = 7.5 Hz, =CH–), 3.60 (3 H, s, –OCH_3); mass spectrum m/e (rel intensity) 422 (1.6, M^+), 152 (78), 137 (71), 129 (86), 111 (64), 97 (100, base), 71 (43), 69 (93), 57 (71), 55 (64). Anal. Calcd for $C_{28}H_{54}O_2$: C, 79.56; H, 12.88. Found: C, 79.77; H, 12.95.

Methyl 8-Methylhexacosanoate (5). The above ester (11.7 g, 27.6 mmol) was hydrogenated at 1 atm in 150 ml of acetic acid with 400 mg of prereduced platinum oxide until hydrogen uptake was complete (ca. 3 hr). The filtered solution was concentrated at the aspirator to 30 ml, diluted with 100 ml of pentane, and washed successively with 100-ml portions of water, 2% sodium bicarbonate, and saturated sodium chloride. After drying, the solution was evaporated to yield 11.7 g (99%) of 5 as a colorless oil which slowly solidified (mp 31–33°). An analytical sample crystallized from pentane at −10° had mp 33–34°; ir (thin film) 1740 cm^{-1} (ester); ^{1}H NMR δ 3.61 (3 H, s, –OCH_3), 2.22 (2 H, t, J = 7.2 Hz, –$CH_2CH_2CO_2$–); mass spectrum m/e (rel intensity) 424 (2.1 M^+), 423 (37), 310 (33), 143 (100, base), 87 (57), 75 (43), 74 (76), 57 (39), 55(71), 43 (27). Anal. Calcd for $C_{28}H_{58}O_2$: C, 79.18, H, 13.29. Found: C, 79.27; H, 13.48.

8-Methyl-1-hexacosanol (6). A solution of 11.3 g (25.6 mmol) of ester 5 was stirred at 25° for 6 hr with 1.5 g of lithium aluminum hydride in 100 ml of dry ether. After acidic work-up, extraction of the product into hexane, concentration of the dried extracts to 40 ml, and cooling to −10°, 10.0 g (98%) of nearly pure alcohol 6, mp 51–53°, was isolated. Recrystallization from hexane gave an analytical sample: mp 52–53°; ir (CCl_4) 3600–3400 (–OH), no absorption at 1740, 1050 cm^{-1} (C–O); ^{1}H NMR δ 3.55 (2 H, 5, J = 7.0 Hz, –CH_2CH_2O–), 3.02 (1 H, s, –OH); mass spectrum m/e (rel intensity) 396 (0.04, M^+), 125 (48), 97 (44), 85 (37), 83 (56), 71 (56), 69 (74), 57 (100, base), 43 (41), 28 (56). Anal. Calcd for $C_{27}H_{56}O$: C, 81.74; H, 14.23. Found: C, 81.84; H, 14.33.

1-Bromo-8-methylhexacosane (7). A mixture of 10.0 g (25.2 mmol) of 6, 16 ml of 48% hydrobromic acid, and 2.8 ml of concentrated sulfuric acid was stirred vigorously under reflux for 5 hr. The mixture was then cooled, diluted with 150 ml of water, and extracted with ether. After drying and evaporation of the ether extracts, the product was purified by elution with pentane from 100 g of alumina (Alcoa F-20) to give 10.1 g (88%) of bromide 7, 94% pure by GLC: ir (thin film) no absorption at 3600–3500 cm^{-1}; ^{1}H NMR δ 3.30 (2 H, 5, J = 6.8 Hz, –CH_2CH_2Br); mass spectrum m/e (rel intensity) 460 (0.47, M^+ + 2), 458 (0.43, M^+), 125 (21), 99 (22), 97 (26), 85 (47), 83 (42), 71 (68), 69 (47), 57 (100, base), 55 (31), 43 (38), 29 (58). Anal. (after molecular distillation, 0.5 mm). Calcd for $C_{27}H_{55}Br$: C, 70.55; H, 12.06. Found: C, 70.96; H, 12.24.

2,10-Dimethyloctacosanoic Acid (10). To 27.8 mmol of the sodio derivative of diethyl methylmalonate (Aldrich Chemical Co., generated with sodium hydride) in 30 ml of 1:1 benzene–dimethylformamide was added over 15 min, with stirring, 4.50 g (9.80 mmol) of bromide 7. The mixture was stirred under argon for 36 hr at 55°, cooled to 15°, poured into 250 ml of cold 2% acetic acid, and extracted with three 50-ml portions of ether. The combined extracts were washed and concentrated to yield a mixture of diester 8 and recovered diethyl methylmalonate, which was refluxed for 3 hr in 60 ml of 10% ethanolic potassium hydroxide with efficient stirring. After cooling, the mixture was acidified and extracted with ether to yield the crude diacid 9, used without further purification (mp 64–67° after crystallization from acetone). When heated to

180–185° for 45 min under mild aspirator vacuum, **9** furnished 3.34 g (75% yield from **7**) of 2,10-dimethyloctacosanoic acid (**10**) as a colorless, waxy solid: mp 49–51° (after crystallization from acetone); ir (CCl_4) 3500–2400 and 1712 cm^{-1} (carboxyl); ^1H NMR δ 12.30 (1 H, s, $-CO_2H$), 2.33 (1 H, m, >CHCO–); mass spectrum *m/e* (rel intensity) 452 (42, M^+), 143 (21), 130 (26), 97 (22), 87 (43), 74 (100, base), 71 (47), 69 (43), 57 (67), 43 (21). Anal. (vacuum sublimed sample). Calcd for $C_{30}H_{60}O_2$: C, 79.58; H, 13.36. Found: C, 79.77; H, 13.63.

3,11-Dimethyl-2-nonacosanone (1). Over a period of 45 min, 9.0 ml of 1.26 *M* methyllithium in ether was added under argon to a rapidly stirred solution of 2.50 g (5.53 mmol) of acid **10** in 35 ml of dry ether cooled to −10°. The mixture was stirred at −10 to −5° for 20 min and then at 25° for 4 hr, after which it was poured slowly, with stirring, into 100 ml of ice-cold 5% hydrochloric acid. Extraction with two 50-ml portions of ether followed by washing with 5% sodium bicarbonate, saturated sodium chloride, decolorization, drying, and evaporation yielded 2.25 g of colorless and nearly pure (by TLC and GLC) ketone **1**, which partially solidified at 25° (mp 24–28°). For purification, 2.20 g of this product was chromatographed on 150 g of silica (Mallinckrodt SilicAR CC-7). After elution with 200 ml of hexane, 1.91 g (78%) of purified **1** (homogeneous by TLC and GLC) was collected with 600 ml of 5% ether in hexane as a waxy solid with a very faint, thionyl chloride-like odor: mp 28–31° (lit.[4] 29–31°); ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) and ^{13}C NMR (Bruker HX-90, $CDCl_3$) spectra indistinguishable from those reported[2,4] for the natural pheromone; mass spectrum *m/e* (rel intensity) 450 (3, M^+), 85 (9), 72 (100, base), 71 (6), 69 (5), 57 (11), 55 (6), 43 (14). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{31}H_{62}O$: C, C, 82.59; H, 13.86. Found: C, 82.81; H, 14.13.

The 2,4-DNP of **1** crystallized from methanol–ethyl acetate in fine yellow needle clusters, mp 56–62° (lit.[4] mp of natural pheromone 2,4-DNP, 55–56°). Anal. Calcd for $C_{37}H_{66}N_4O_4$: C, 70.43; H, 10.54; N, 8.88. Found: C, 70.20; H, 10.65; N, 8.89.

3-Methyl-2-heneicosanone (11) (with David J. Clymer). Under the same conditions used to prepare ketone **1** from acid **10**, 3.00 g (9.20 mmol) of 2-methyleicosanoic acid[11] [mp 60–61° (lit.[11] mp 61.5–62°)] in 125 ml of ether was allowed to react with 16.3 ml of 1.25 *M* methyllithium in ether to yield 2.44 g (78%) of chromatographed ketone **11**: mp 29–29.5°; ir (CCl_4) 1723 cm^{-1} (ketone); ^1H NMR δ 2.39 (1 H, m, J = 6.8 Hz, >CHCO–) 2.01 (3 H, s, CH_3CO–), 1.02 (3 H, d, J = 6.8 Hz, CH_3CHCO–); mass spectrum *m/e* (rel intensity) 324 (1.3, M^+), 85 (13), 72 (100, base), 57 (15), 55 (10), 43 (15), 28 (19). Anal. (after evaporative distillation, 0.5 mm). Calcd for $C_{22}H_{44}O$: C, 81.41; H, 13.66. Found: C, 81.38; H, 13.87.

The 2,4-DNP of **11** crystallized from ethanol in yellow spores, mp 77–78°. Anal. Calcd for $C_{28}H_{48}N_4O_4$: C, 66.63; H, 9.59. Found C, 66.68; H, 9.97.

Acknowledgments. We thank Dr. B. A. Pearson, Department of Chemistry, The University of Iowa, for the ^{13}C NMR spectrum and Professor R. G. Carlson, Department of Chemistry, The University of Kansas, for helpful suggestions and advice. We also thank Messrs. David J. Clymer and Chung Shih for experimental assistance and Professor S. Ishii for information concerning his investigations.

Registry No.—**1**, 53623-10-2; **1** 2,4-DNP, 56629-71-1; **2**, 25542-64-7; **3**, 34455-70-4; **4**, 56599-03-2; **5**, 56599-04-3; **6**, 56599-05-4; **7**, 55590-34-6; **9**, 56599-06-5; **10**, 56599-07-6; **11**, 56599-08-7; **11** 2,4-DNP, 56599-09-8; 2-methyleicosanoic acid, 56599-10-1.

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Synthesis of Aflatoxin Q_1

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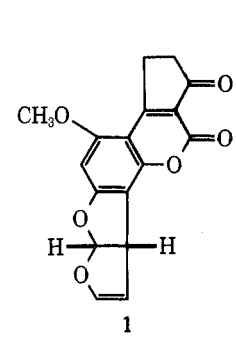
To interpret differences in susceptibility of various animal species to the carcinogenic effects of aflatoxin B_1 (**1**) a knowledge of its metabolic fate is of much importance.[1] The in vitro metabolism of the carcinogen by liver homogenates of duck, rat, mouse, monkey, and human has been investigated and a major, new metabolite called aflatoxin Q_1 (**2**) was isolated and identified structurally by three groups of investigators using monkey[2,3] and human liver.[4] To decide whether the hydroxylation of B_1 (**1**) represents an activation or a detoxification mechanism substantial quantities of Q_1 (**2**) are needed for physiological evaluation. We have developed two simple chemical methods which transform B_1 (**1**) to the metabolite Q_1 (**2**).



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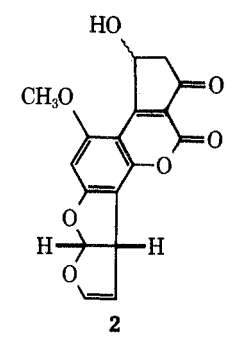

2

The presence of the enol ether function in the starting material **1** made most presently known methods unsuitable for direct hydroxylation and our efforts, accordingly, centered about oxidation of carbanions, derived from starting material by proton abstraction. Small, but detectable amounts of Q_1 (**2**) were formed by oxidation of B_1 (**1**) in *tert*-butyl alcohol solution with oxygen, *tert*-butyl hydroperoxide, or hydrogen peroxide in the presence of potassium *tert*-butoxide. Oxidation of a lithium diisopropylamide generated anion with MoO_5·Py·HMPA[5] afforded similar results. Substantial quantities of Q_1 (**2**) were produced when solutions of B_1 (**1**) in methylene chloride–methanol containing aqueous sodium hydroxide were exposed to either silver(II) or -(I) oxide. Efforts to replace silver oxide with copper(I) or -(II) species, manganese dioxide, and thallium(III) nitrate failed and as a result the reaction parameters of the silver oxide oxidation were examined in some detail with the more readily available model compound **3**.[6] Silver(I) oxide proved to be superior and gave the alcohol **5** in 38% yield while 17% of the starting material **3** was recoverable by chromatography. The structure of the alcohol **5** was determined by NMR spectroscopy and catalytic hydrogenation, proceeding with the consumption of 3 equiv of hydrogen, to 5,7-dimethoxycyclopenteno[2,3-*c*]coumarin (**4**).