Medium-Ring Ketone Synthesis. Total Syntheses of (±)-Isocaryophyllene and (±)-Caryophyllene

Yasuo Ohtsuka,* Setsuko Niitsuma, Hajime Tadokoro, Toshio Hayashi, and Takeshi Oishi*

The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351, Japan

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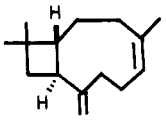
Total syntheses of (±)-isocaryophyllene and (±)-caryophyllene are reported. The key step involves a novel construction of the nine-membered ring in these natural products by a base-induced intramolecular acyl transfer reaction of 13-membered lactam sulfoxides **16** and **41**.

The unusual structures of isocaryophyllene (**1**) and caryophyllene (**2**), possessing fused four- and nine-membered rings, have attracted the attention of many chemists and several syntheses have been reported[1] since the first elegant synthesis by Corey and co-workers in 1964.[1a]



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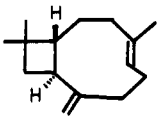
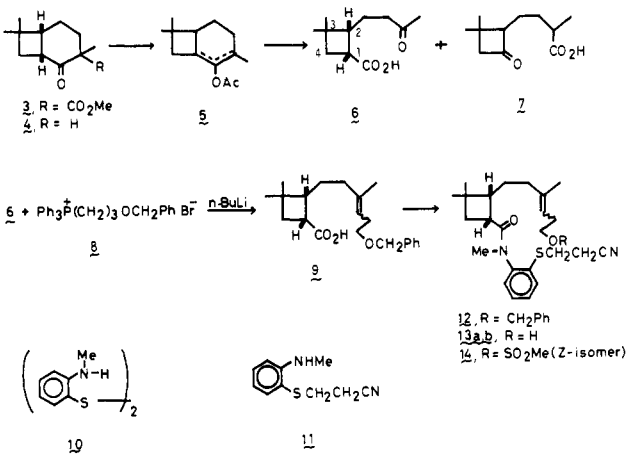


2

Construction of the nine-membered ring constituted the crucial step in the syntheses of **1** and **2**. In previous syntheses the nine-membered ring was generated by bond scission of two fused smaller rings.[1a-c] We focused our attention on a direct closure of the nine-membered ring from a suitable precursor,[1d] by the novel intramolecular cyclization process we developed recently[2] for the preparation of medium-ring ketones. In order to examine the general applicability of this method, total syntheses of **1** and **2** were undertaken.[3]

The Corey intermediate keto ester **3** was chosen as the starting material (Scheme I). Alkaline hydrolysis of **3** followed by decarboxylation gave ketone **4**,[4] which on treatment with isopropenyl acetate gave a mixture of enol acetates **5**.[5] The crude mixture was subjected to ozonolysis, and the resulting mixed anhydrides were hydrolyzed to a mixture of keto acids. Separation of the latter afforded acids **6** and **7** in 46% and 8% yields, respectively.[6-8]

Scheme I



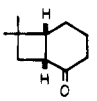
Three-carbon elongation of the acid **6** was effected by a Wittig reaction with the phosphorane derived from [3-(benzyloxy)propyl]triphenylphosphonium bromide (**8**), leading to an *E*/*Z* mixture of acid **9** in 57% yield.[9]

(1) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485. (b) Bertrand, M.; Gras, J.-L. *Tetrahedron* **1974**, *30*, 793. (c) Kumar, A.; Devaprabhakara, D. *Synthesis*, **1976**, 461. (d) After the present work had been completed, a synthesis of isocaryophyllene based on a elegant direct closure of the nine-membered ring was reported: McMurry, J. E.; Miller, D. D. *Tetrahedron Lett.* **1983**, *24*, 1885.

(2) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1979**, 4487; *Chem. Pharm. Bull.* **1983**, *31*, 443, 454.

(3) This work was presented at the 24th Symposium on the Chemistry of Natural Products, Osaka, Japan, 1981; Symposium Papers, p 284.

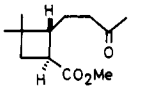
(4) Since the bicyclo[4.2.0]octan-2-one system is known to be most stable in the cis form,[1a] crude ketone **i** was heated slowly to convert the trans isomer contained in it into the cis isomer according to a literature procedure.[1a] Since ketone **4** is derived from **i** it could be assigned a cis bridgehead configuration.



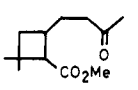
i

(5) Deghenghi, R.; Engel, C. R. *J. Am. Chem. Soc.* **1960**, *82*, 3201.

(6) A minor side product [^{1}H NMR δ 1.12, 1.27 and 2.13 (s, each 3 H)] was shown to be an isomer of **6**. While first considered the trans isomer, this idea was shown to be untenable in view of its methyl ester [obtained on diazomethane treatment; IR 1732, 1725 (sh) cm^{-1}; ^{1}H NMR (400 MHz) δ 1.05, 1.25, 2.12 and 3.66 (s, each 3 H), 2.81 (dd, J = 2.1, 8.7 Hz, 1 H); MS, m/z 212.1382 (M^+, $C_{12}H_{20}O_3$ requires 212.1411)] being different from the keto ester **ii** [IR 1720 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.03, 1.07, 2.13 and 3.67 (s, each 3 H), 2.64 (ddd, J = 9.0, 9.3, 9.8 Hz, 1 H); MS, m/z 181.1212 ($M^+ - CH_3O$, $C_{11}H_{17}O_2$ requires 181.1228)] derived from the ozonolysis of ester **37**. Structure **iii** is assigned tentatively to the isomer.

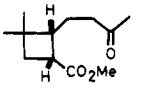


ii



iii

(7) In view of the possibility of an isomerization having taken place in the alkaline hydrolysis phase of the **5** → **6** conversion and in view of the known greater stability of 1,2-disubstituted cyclobutanes in the trans form,[8] it was necessary to determine the behavior of an acid derivative of keto acid **6** toward base. Hence the keto esters **ii** and **iv** were refluxed in 2% potassium hydroxide 9:1 water–ethanol solution for 2 h and the acidic products reesterified with diazomethane. Each ester had maintained its integrity, no isomerization being observed. The lack of identity of esters **ii** [$J_{1,2}$ = 9.3 Hz] and **iv** [$J_{1,2}$ = 10.0 Hz] as well as the later formation of cis ketone **18** are further verification of the stereochemistry of keto acid **6**.

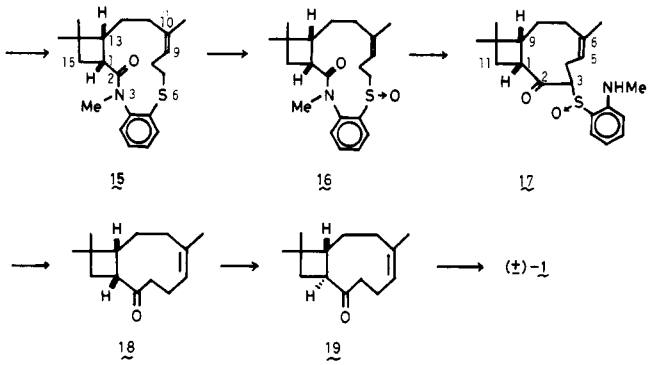


iv

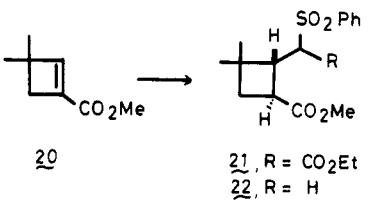
(8) Fonken, G. J.; Sheingthong, S. *J. Org. Chem.* **1963**, *28*, 3435. McCoy, L. L. *Ibid.* **1965**, *30*, 3762.

0022-3263/84/1949-2326$01.50/0

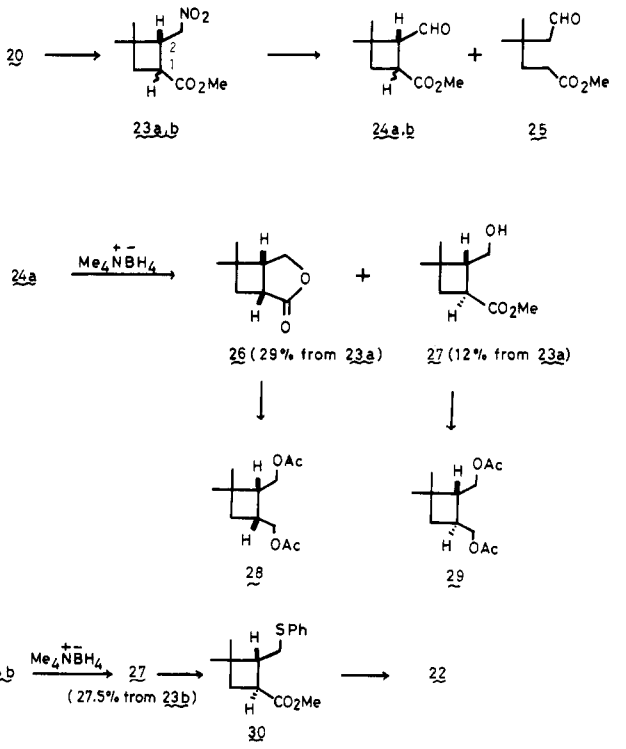
Scheme II



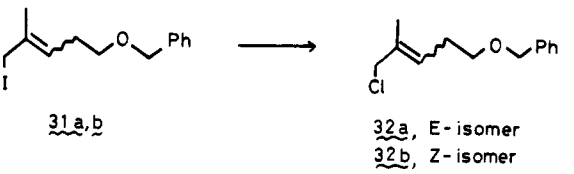
Scheme III



Scheme IV



Scheme V

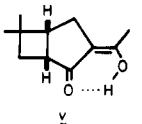


Acids **9** were treated with oxalyl chloride and the resultant acid chlorides with bis(2-methylamino)phenyl disulfide (**10**).[2,10] Since the yield of the desired diamide was less than 25%, the monoamide and some starting acids **9** being recovered, amidation by an *o*-thioaniline containing a different S-protecting group was investigated. When the acid chlorides of **9** were treated with 2-cyanoethyl 2-(methylamino)phenyl sulfide (**11**), amides **12** were obtained in quantitative yield. The latter was treated with dimethyl sulfide and boron trifluoride etherate to remove the benzyl protecting group.[11] Surprisingly, a product lacking a hydroxy group (by IR analysis) and an olefinic function (by ^{1}H NMR analysis) was obtained. On the assumption that the liberated hydroxy group could be trapped prior to interaction with the double bond, acetic anhydride was added to the above reaction mixture. This produced in high yield an acetate, whose hydrolysis with potassium carbonate in methanol gave alcohols **13**. Separation of the double-bond isomers led to a major product with a 1.75 ppm methyl signal in its ^{1}H NMR spectrum and a minor product with a corresponding signal at 1.67 ppm. The two compounds were assigned *Z* (**13a**) and *E* (**13b**) configurations, respectively, by analogy with literature data.[12] Isomer **13a** was then transformed into mesylate **14**, whose treatment with potassium *tert*-butoxide resulted in the removal of the S-protecting group and the concomitant formation of a 13-membered ring sulfide. The yield of lactam sulfide **15** was 57%.

The stage was now set for the crucial intramolecular acyl transfer leading to the nine-membered carbocycle. As a consequence sulfide **15** was converted into sulfoxide **16** by sodium *m*-periodate treatment[13] and the product exposed to lithium diisopropylamide (Scheme II). The reaction gave a quantitative yield of keto sulfoxide **17**, whose desulfurization by aluminum amalgam afforded the nine-membered ring ketone **18** in 81% yield. Treatment of the latter with sodium *tert*-butoxide produced isomer **19**.[1a,14] This ketone was subjected to a Wittig reaction with methylenetriphenylphosphorane,[1a] giving (±)-isocaryophyllene (**1**) in 77% yield.

Since the conversion of *E* isomer **13b** into the corresponding nine-membered ring ketone was unsuccessful,[15]

(9) When the ester iv was subjected to the Wittig reaction under the same conditions, the five-membered ring ketone v [IR 1740 (w), 1720 (w), 1655, 1605 cm^{-1}; ^{1}H NMR δ 1.01, 1.15 and 2.04 (s, each 3 H); gave a positive $FeCl_3$ test] was obtained. Ester ii was unreactive toward the Wittig process.



v

(10) Kiprianov, A. I.; Pazenko, Z. N. *Zh. Obshch. Khim.* **1949**, *19*, 1523; *Chem. Abstr.*, **1950**, *44*, 3487.

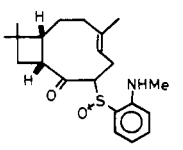
(11) Fujita, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.

(12) Bates, R. B.; Gale, D. M. *J. Am. Chem. Soc.* **1960**, *80*, 5749.

(13) It has been observed in previous experiments[2] that the intramolecular cyclization of this type proceeds well with sulfoxides in the cases of α-mono- and α,α-dialkylated lactams but requires the oxidation level of sulfones in the case of α-unsubstituted lactams.

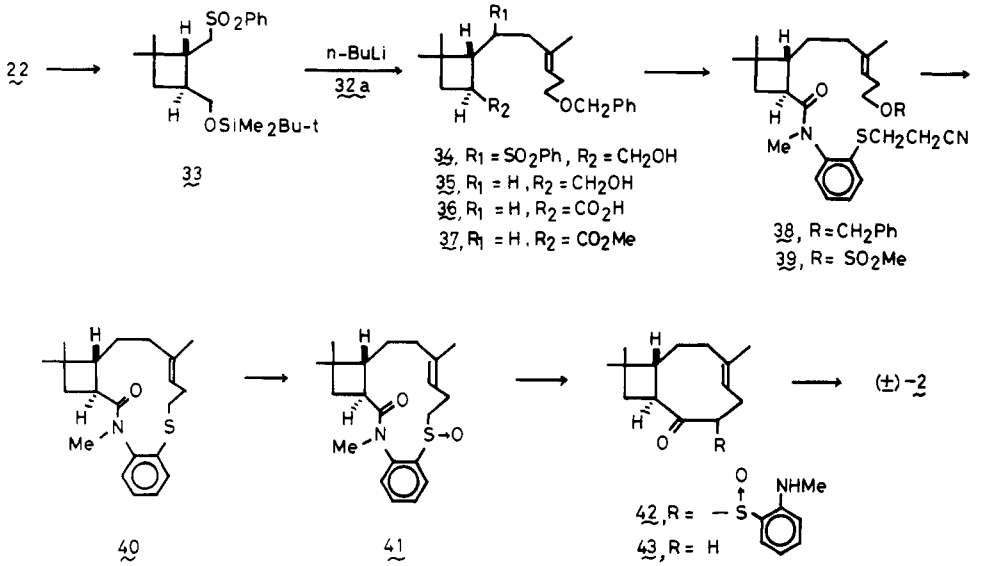
(14) Kaiser, R.; Lampavsky, D. *Helv. Chem. Acta* **1976**, *59*, 1803.

(15) *E*-Isomer **13b** could be converted into a (*E*)-13-membered ring sulfide corresponding to **15** (51% yield), which was successfully transformed into (*E*)-keto sulfoxide vi in the same way as used in the preparation of **17**, although the total yield (44%) was much less than that in the *Z* series (93%). However, an attempted desulfurization of vi with aluminum amalgam brought about only the reduction sulfoxide to sulfide. Since (*E*)-**13b** could only be obtained as a minor product from (*E*)-**9** by a Wittig reaction and the overall yield from (*E*)-**13b** to vi was low, desulfurization of vi was not pursued further.



vi

Scheme VI



a totally different, unequivocal pathway to caryophyllene (2) was investigated and the known four-membered ring ester **20**[16] chosen as starting material.

Addition of ethyl (phenylsulfonyl)acetate to **20** led to **21**, whose hydrolysis, decarboxylation, and reesterification afforded ester **22** (Scheme III). The stereochemistry of the latter was determined as follows. Base-induced addition of nitromethane to **20** afforded nitro esters **23a,b**, whose titanium trichloride treatment[17] led to aldehydes **24a,b**, respectively.[18] Reduction of aldehyde **24a** with tetramethylammonium borohydride afforded γ-lactone **26** and hydroxy ester **27** (Scheme IV). On the other hand, only **27** was produced by the same reduction of **24b**. Lithium aluminum hydride reduction of **26** and **27** followed by acetylation of the resultant diols afforded the isomeric diacetates **28** and **29**, respectively (indicating **26** not to be derived from **27**). Since γ-lactone **26** can exist only in the cis form, **27** should have a trans configuration.[19] Treatment of **27** with diphenyl disulfide and tri-*n*-butylphosphine in pyridine[20] and oxidation of the resultant trans sulfide **30** afforded a sulfone, which was found to be identical with sulfone **22** prepared from **20** via **21**.

Since it was necessary to elongate the C-2 side chain of ester **22**, the known mixture of iodides **31a,b**,[21] was converted into chlorides **32a,b**,[22] respectively, by exposure to lithium chloride in dimethylformamide (Scheme V). The chlorides could be separated and identified by their ^1H NMR spectra (the methyl signal of the major product at 1.73 ppm and that of the minor component at 1.83 ppm identifying **32a,b** as *E* and *Z* isomers, respectively[12]). Interaction of the sulfone anion of ester **22**, prepared by the treatment of the latter with lithium diisopropylamide, with chloride **32a** unfortunately led to an intractable mixture.[23] However, the alkylation of the anion of sulfone **33**, derived from ester **22** on lithium aluminum hydride treatment and subsequent silylation, succeeded, affording sulfone **34** in 98% yield (Scheme VI). Reductive desulfurization of **34** with sodium amalgam in the presence of sodium hydrogen phosphate[24] afforded alcohol **35**. Jones oxidation of the latter produced acid **36**, which was converted into amide mesylate **39** via benzyl ether **38** in the same way as described in the isocaryophyllene synthesis. Removal of the S-protecting group from **39** and base-induced formation of the 13-membered ring sulfide afforded lactam sulfide **40** in 55% yield.

The intramolecular acyl transfer reaction did not take place with sulfoxide **41**, derived from **40** on oxidation, under the conditions used in the reaction of isomer **16**. However, the addition of a small amount of hexamethylphosphoramide[25] to the reaction mixture led to smooth acyl migration even at 0 °C, producing the nine-membered ring keto sulfoxide **42** in quantitative yield. Reductive removal of the phenylsulfinyl group from **42** afforded ketone **43**.[14] The Wittig reaction[1a] of **43** afforded (±)-caryophyllene (**2**) in 80% yield.

Experimental Section

All melting points and boiling points are uncorrected. ^1H NMR spectra were taken on a JEOL MH-60, FX-60, or GX-400 instrument in $CDCl_3$ solution with Me_4Si as an internal standard. A JEOL MH-60 or FX-60 instrument was routinely used. Infrared (IR) spectra were measured in CCl_4 solution with a JASCO A-3 spectrometer. Mass spectra were obtained with a Hitachi RMU-6M mass spectrometer and high-resolution mass spectra were recorded on a Hitachi M-80 GC-MS spectrometer. Analytical gas chromatography (GC) was performed on a Shimadzu GC-4BM gas chromatography by using 2 m × 4 mm column packed with

(16) Brannock, K. C.; Bell, A.; Brupitt, R. D.; Kelly, C. A. *J. Org. Chem.* **1964**, *29*, 801. Brannock, K. C.; Brupitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *Ibid.* **1964**, *29*, 813.

(17) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4637.

(18) Each aldehyde ester was accompanied by a small amount of byproduct **25**.

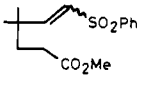
(19) The formation of trans hydroxy ester **27** in the borohydride reduction of cis aldehyde ester **24a** indicates a prior isomerization at position C-1 or C-2. In view of the noted stability of cyclobutane esters ii and iv to mild base,[7] the isomerization must have taken place α to the aldehyde carbon.

(20) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

(21) Sakurai, A.; Hayashi, T.; Hori, I.; Jindo, Y.; Oishi, T. *Synthesis* **1978**, 370 and references cited therein.

(22) Direct separation of a mixture of **31a,b** by silica gel chromatography was difficult because they were found to be unstable to chromatographic conditions.

(23) This result may have been the consequence of a retro-Michael processes leading to ester **20** and/or vii. Either product could have been alkylated by chloride **32a**.



vii

(24) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Venhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(25) Cf. Lavielle, S.; Bory, S.; Moreau, B.; Luche, M. J.; Marquet, A. *J. Am. Chem. Soc.* **1978**, *100*, 1558.

1.5% OV-17 on 80–100 mesh Shimalite W.

3,7,7-Trimethylbicyclo[4.2.0]octan-2-one (4). Keto ester **3**[1a] (8.52 g, 38 mmol) was stirred with 1 N NaOH (190 mL) at 35–45 °C for 24 h. After being cooled, the resulting solution was acidified with 3 N HCl at 0 °C and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated, giving a pale yellow liquid. It was dissolved in pyridine (20 mL) and heated at 107–117 °C (bath temperature) for 1 h under nitrogen. The mixture was poured into 3 N HCl (ca. 85 mL) at 0 °C and extracted with ether. The extract was washed with 3 N HCl and water, dried ($MgSO_4$), and evaporated, affording crude ketone (6.96 g). This material was purified by silica gel chromatography (100:1 hexane–ethyl acetate) to afford ketone **4** (5.22 g, 83% yield) as a colorless liquid: bp 62–63 °C (0.7 torr); IR 1700 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.53; H, 10.98.

2α-(3-Oxobutyl)-3,3-dimethylcyclobutane-1α-carboxylic Acid (6) and 4-(2,2-Dimethyl-4-oxocyclobutyl)-2-methylbutanoic Acid (7). A solution of **4** (4.99 g, 30 mmol) and isopropenyl acetate (50 mL) in benzene (200 mL) was refluxed for 5 h in the presence of concentrated sulfuric acid (0.2 mL). The mixture was diluted with benzene, washed with cold 5% sodium bicarbonate solution and brine, and dried ($MgSO_4$). Removal of the solvent afforded a mixture of enol acetates **5**. A solution of the resulting oil in methanol (80 mL) was treated with ozone at −78 °C until the mixture turned blue (ca. 2 h). After removal of an excess of ozone, methyl sulfide (11 mL) was added at −78 °C and the mixture was stirred overnight at room temperature. Excess methyl sulfide and methanol were evaporated off in vacuo from the mixture. The residue was dissolved in ether and the solution was washed with brine. The solvent was dried ($MgSO_4$) and evaporated to yield a mixture of the mixed anhydrides as an oil (7.88 g). The resulting oil was stirred with 1 N NaOH (180 mL) for 23 h at room temperature under argon. After the mixture was washed with ether, the aqueous solution was acidified with 6 N HCl at 0 °C and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and evaporated to provide a mixture of carboxylic acids, which were chromatographed on silica gel.

The first fraction (3:1 hexane–ethyl acetate) gave a four-membered ring keto acid (0.49 g, 8% yield from **4**), whose structure was assigned as **7**: IR ($CHCl_3$) 1775, 1715 cm^{-1}; ^1H NMR δ 1.14 and 1.48 (s, each 3 H), 1.20 (d, J = 7 Hz, 3 H), 9.00 (br, s, 1 H, OH). Diazomethane treatment of **7** provided the corresponding keto ester: IR 1780, 1740 cm^{-1}; ^1H NMR δ 1.13 and 1.43 (s, each 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.35–2.0 (m, 4 H), 2.3–3.1 (m, 4 H).

The second fraction (2:1 hexane–ethyl acetate) afforded semicrystalline keto acids (3.93 g), which was recrystallized from ether–hexane to provide **6** (2.75 g, 46% yield from **4**) as colorless prisms: mp 76–77 °C; IR 1715 cm^{-1}; ^1H NMR δ 1.07, 1.13 and 2.12 (s, each 3 H), 3.0–3.48 (m, 1 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Foudn: C, 67.02; H, 9.18.

Diazomethane treatment of **6** afforded the corresponding keto ester iv: IR 1735 (sh), 1723 cm^{-1}; ^1H NMR (400 MHz) δ 1.05, 1.12 2.12, and 3.68 (s, each 3 H), 1.80 (ddd, J = 1.2, 8.9, 11.8 Hz, 1 H, C-4-H), 2.12 (ddd, J = 1.0, 6.2, 11.8 Hz, 1 H, C-4-H), 2.25 (br dt, J = 8.1, 10.0 Hz, 1 H, C-2-H), 3.18 (ddd, J = 6.2, 8.9, 10.0 Hz, 1 H, C-1-H); high-resolution mass spectrum, m/z 181.1212 ($M^+ - OCH_3$, $C_{11}H_{17}O_2$ requires 181.1228).

The neutral fraction from the ether extract gave the starting **4** (86 mg, 2% recovery).

[3-(Benzyloxy)propyl]triphenylphosphonium Bromide (8). A mixture of 3-(benzyloxy)propyl bromide (9.77 g, 42.7 mmol) and triphenylphosphine (11.20 g, 42.7 mmol) was heated at 94–96 °C for 27 h and then cooled. The resulting solid was crystallized from methylene chloride–ether, providing **8** (17.29 g, 82% yield) as colorless prisms: mp 145–147 °C; ^1H NMR δ 1.75–2.3 (m, 2 H), 3.83 (t, J = 7.5 Hz, 2 H), 3.85 (t, J = 5 Hz, 2 H), 4.48 (s, 2 H), 7.28 (s, 5 H), 7.5–8.07 (m, 15 H).

Anal. Calcd for $C_{28}H_{28}BrOP$: C, 68.44; H, 5.74; Br, 16.26. Found: C, 68.34; H, 5.72; Br, 16.50.

2α-[6-(Benzyloxy)-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1α-carboxylic Acid (9). A solution of *n*-butyllithium in hexane (2.7 mmol) was added dropwise to a stirring suspension of **8** (1.47 g, 3 mmol) in THF (10 mL) at 0 °C under argon, and the resulting mixture was stirred for 30 min at room temperature. Then, the mixture was cooled to 0 °C and a solution of acid **6** (59 mg, 0.3 mmol) in THF (1.5 mL) was added. After 24 h at room temperature, saturated aqueous ammonium chloride solution was added at 0 °C. The mixture was diluted with brine, acidified with 3 N HCl, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated. Silica gel chromatography (9:1 hexane–ethyl acetate) of the residue provided a mixture of the unsaturated acids **9** (56 mg, 57% yield): IR 1735 (sh), 1705 cm^{-1}; ^1H NMR δ 1.05 and 1.13 (s, each 3 H), 1.68 (br s, 3 H), 2.95–3.6 (m, 1 H), 3.44 (t, J = 7 Hz, 2 H), 4.50 (s, 2 H), 5.13 (t, J = 7 Hz, 1 H), 7.27 (s, 5 H); mass spectrum, m/z 330 (M^+).

The fraction eluted with hexane–ethyl acetate (1:1) gave the starting acid **6** (11 mg, 19% recovery).

2-Cyanoethyl 2-(Methylamino)phenyl Sulfide (11). Acrylonitrile (6.2 mL) was added to a mixture of 2-(methylamino)benzenethiol[10] (4.80 g, 34.5 mmol) and ethanolic 1 N NaOH (2 mL) in benzene (24 mL) at 0 °C with vigorous stirring under nitrogen, and the reaction mixture was stirred overnight at room temperature. The mixture was neutralized with dilute HCl and extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Removal of the solvent gave an oil, whose distillation afforded the pure sulfide **11** (6.10 g, 92% yield) as a yellow oil: bp 165–168 °C (1 torr); IR 3400, 2250 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.28; H, 6.26; N, 14.44; S, 16.60.

***N*-Methyl-2′-[(2-cyanomethyl)thio]-2α-[6-(benzyloxy)-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1α-carboxanilide (12).** Oxalyl chloride (7.30 g, 57.5 mmol) was added dropwise to a stirring solution of acids **9** (3.80 g, 11.5 mmol) in benzene (60 mL) at room temperature. The reaction mixture was stirred for 30 min at room temperature and then heated for 2 h at 60–65 °C. After being cooled, removal of the solvent afforded the corresponding acid chlorides as an oil; IR 1795 cm^{-1}. A solution of the acid chlorides in THF (40 mL) was added to an ice-cooled suspension of **11** (4.42 g, 23 mmol) and anhydrous potassium carbonate (7.95 g, 57.5 mmol) in THF (40 mL). The mixture was stirred for 1.5 h at 0 °C, diluted with benzene (100 mL), and then filtered. The filtrate was washed with brine, 3 N HCl, and again brine, and dried ($MgSO_4$). The solvent was removed to afford a yellow oil (6.9 g), which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1) provided a mixture of amides **12** (5.80 g, 100% yield) as an oil: IR 2280, 1670 cm^{-1}; ^1H NMR δ 1.00, 1.06 and 3.17 (s, each 3 H), 3.48 (t, J = 7 Hz, 2 H), 4.51 (s, 2 H), 5.17 (t, J = 8 Hz, 1 H), 6.9–7.5 (m, 4 H), 7.30 (s, 5 H); mass spectrum, m/z 504 (M^+).

The HCl extract was made alkaline with potassium carbonate and the liberated oil was extracted with benzene. The extract was dried ($MgSO_4$) and evaporated to recover sulfide **11** (1.88 g).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-2α-[(*Z*)-6-hydroxy-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1α-carboxanilide (13a) and *N*-Methyl-2′-[(2-cyanoethyl)thio]-2α-[(*E*)-6-hydroxy-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1α-carboxanilide (13b).** Dimethyl sulfide (2 mL, 27 mmol), acetic anhydride (1 mL, 11 mmol), and boron trifluoride etherate (1.23 mL, 10 mmol) were added successively to a stirring solution of **12** (505 mg, 1 mmol) in methylene chloride (2 mL) at 0 °C under argon. After being stirred for 40 min at 0 °C, the mixture was poured into cold 5% sodium bicarbonate solution and extracted with $CHCl_3$. The extract was washed with 5% sodium carbonate solution and brine and dried ($MgSO_4$). Removal of the solvent afforded a mixture of the corresponding oily acetoxy amides, which were used for the next methanolysis without purification: IR 2260, 1740, 1665 cm^{-1}; ^1H NMR δ 2.05 and 3.19 (s, each 3 H), 4.04 (t, J = 7 Hz, 2 H); mass spectrum, m/z 456 (M^+).

A mixture of the crude acetoxy amides prepared from **12** (505 mg) was stirred with anhydrous potassium carbonate (691 mg, 5 mmol) in methanol (5 mL) at 0 °C for 1 h. The mixture was diluted with benzene (20 mL) and filtered. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The resulting oil was subjected to silica gel column chromatography (1:1 hexane–ethyl acetate), giving a mixture of hydroxy amides (349 mg, 84% yield from **12**), which could be separated into **13a,b** by Lobar column chromatography (1:2 hexane–ethyl acetate). From a mixture of **13a,b** (2.86 g), (*Z*)-hydroxy amide **13a** (1.85 g) was obtained as a less polar oil and (*E*)-hydroxy amide **13b** (702 mg)

was obtained as a more polar oil.

13a: IR 3650, 3500, 2260, 1660 cm^{-1}; ^1H NMR δ 0.99 (s, 3 H), 1.03 and 1.11 (s, total 3 H), 1.75 (br s, 3 H), 3.16 and 3.19 (s, total 3 H), 3.64 (t, J = 6.3 Hz, 2 H), 5.12 (br t, J = 6.8 Hz, 1 H); mass spectrum, m/z 414 (M^+).

13b: IR 3650, 3500, 2260, 1660 cm^{-1}; ^1H NMR δ 0.98 (s, 3 H), 1.03 and 1.11 (s, total 3 H), 1.67 (br s, 3 H), 3.16 and 3.18 (s, total 3 H), 3.63 (t, J = 6.5 Hz, 2 H), 5.15 (br t, J = 6.8 Hz, 1 H); mass spectrum, m/z 414 (M^+).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-2α-[(*Z*)-6-[(methylsulfonyl)oxy]-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1α-carboxanilide (14).** A solution of methanesulfonyl chloride (687 mg, 6 mmol) in methylene chloride (4 mL) was added to a stirring solution of hydroxy amide **13a** (1.00 g, 2.41 mmol) and triethylamine (808 mg, 8 mmol) in methylene chloride (16 mL) at 0 °C under argon, and the resulting mixture was stirred for 30 min at 0 °C. The mixture was diluted with $CHCl_3$ (30 mL), and an excess of the reagent was decomposed with cold 5% sodium bicarbonate solution (45 mL). The organic layer was separated, washed with 5% sodium bicarbonate solution, 3 N HCl, and brine, and dried ($MgSO_4$). Removal of the solvent and subsequent chromatography (silica gel, 3:2 hexane–ethyl acetate) of the residue gave mesylate **14** (920 mg, 77% yield) as an oil: IR 2280, 1663, 1180 cm^{-1}; ^1H NMR δ 0.99 and 3.01 (s, each 3 H), 1.03 and 1.11 (s, total 3 H), 1.75 (d, J = 1 Hz, 3 H), 3.14 and 3.16 (s, total 3 H), 4.17 (t, J = 7 Hz, 2 H), 5.06 (t, J = 6.8 Hz, 1 H); mass spectrum, m/z 492 (M^+).

(*Z*)-1β,7,8,11,12,13β,14,15-Octahydro-3,10,14,14-tetramethyl-4,5-benzo-3-aza-6-thia-2*H*-bicyclo[11.2.0]pentadecen-2-one (15). A solution of **14** (1.36 g, 2.76 mmol) in dioxane (70 mL) was added slowly to a stirring solution of potassium *tert*-butoxide (619 mg, 5.52 mmol) in *tert*-butyl alcohol (130 mL) at 55–60 °C during a period of 16.5 h under nitrogen, and the resulting mixture was stirred for 3 h at the same temperature. The mixture was concentrated in vacuo, diluted with brine, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and evaporated to provide an oil, which was subjected to column chromatography (silica gel, 15:1 hexane–ethyl acetate), affording lactam sulfide **15** (530 mg, 56% yield) as colorless prisms: mp 153–180 °C (ether). TLC of **15** by various solvent systems afforded single spot in every case, but a wide melting point range noted above was not improved after recrystallization: IR 1660 cm^{-1}; ^1H NMR δ 0.94, 0.99, 1.69 and 3.19 (s, each 3 H), 5.03 (t, J = 7.5 Hz, 1 H), 7.0–7.45 (m, 4 H); mass spectrum, m/z 343 (M^+).

Anal. Calcd for $C_{21}H_{29}NOS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.33; H, 8.49; N, 3.97; S, 9.21.

(*Z*)-1β,7,8,11,12,13β,14,15-Octahydro-3,10,14,14-tetramethyl-4,5-benzo-3-aza-6-thia-2*H*-bicyclo[11.2.0]pentadecen-2-one 6-Oxide (16). A solution of sodium *m*-periodate (306 mg, 1.43 mmol) in water (3 mL) was added dropwise to a solution of **15** (409 mg, 1.19 mmol) in methanol (20 mL) at 0 °C under vigorous stirring. After being stirred for 18 h at room temperature, the mixture was diluted with brine and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and evaporated. Silica gel column chromatography (2:1 hexane–ethyl acetate) of the residue gave lactam sulfoxide **16** (399 mg, 93% yield) as colorless prisms; mp 152–157 °C (ether); IR 1665, 1040 cm^{-1}; ^1H NMR δ 0.96, 1.03, 1.55 and 3.20 (s, each 3 H), 5.1–5.6 (m, 1 H), 6.8–7.07 (m, 1 H), 7.3–7.76 (m, 2 H), 7.8–8.0 (m, 1 H).

Anal. Calcd for $C_{21}H_{29}NO_2S$: C, 70.15; H, 8.13; N, 3.90; S, 8.92. Found: C, 70.12; H, 8.16; N, 3.82; S, 8.95.

(*Z*)-1β,3,4,7,8,9β,10,11-Octahydro-6,10,10-trimethyl-3-[[(2-(methylamino)phenyl]sulfinyl]-2*H*-bicyclo[7.2.0]undecen-2-one (17). A solution of **16** (320 mg, 0.89 mmol) in THF (10 mL) was added dropwise to a stirred lithium diisopropylamide solution prepared from diisopropylamine (360 mg, 3.56 mmol) and a solution of *n*-butyllithium and hexane (3.56 mmol) in THF (20 mL) at −78 °C under argon. The reaction mixture was stirred for 40 min at −78 °C, and then saturated aqueous ammonium chloride solution was added. The mixture was diluted with brine, neutralized with 3 N HCl, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The resulting oil was purified by silica gel chromatography (9:1 hexane–ethyl acetate) to afford keto sulfoxide **17** (320 mg, 100% yield) as a pale yellow solid: IR 3310, 1695, 1015 cm^{-1}; ^1H NMR δ 0.82, 0.99 and 1.64 (s, each 3 H), 2.86 (d, J = 4.8 Hz, 3 H), 4.62 (dd, J = 4.8, 9.4 Hz, 1 H), 5.49 (t, J = 8.5 Hz, 1 H), 6.1–6.9 (m, 3 H), 6.9–7.5 (m, 2 H); mass spectrum, m/z 359 (M^+). The crude **17** was subjected to the next reaction without purification.

(*Z*)-1β,3,4,7,8,9β,10,11-Octahydro-6,10,10-trimethyl-2*H*-bicyclo[7.2.0]undecen-2-one (18). Aluminum amalgam prepared from aluminum foil (40 mg) and 2% mercuric chloride solution in the usual manner was added to a solution of **17** (36 mg, 0.1 mmol) in ethanol–water (9:1, 4 mL), and the mixture was stirred for 1 h at room temperature under nitrogen. The same amount of aluminum amalgam was added twice at hourly intervals, and the whole mixture was stirred for an additional 1 h (total 3 h). The mixture was diluted with ether and filtered. The filtrate was washed with cold 3 N HCl and brine, dried ($MgSO_4$), and evaporated. Silica gel column chromatography (30:1 hexane–ethyl acetate) of the resulting oil provided ketone **18** (17 mg, 81% yield) as a colorless oil: IR 1700 cm^{-1}; ^1H NMR δ 0.96 and 1.13 (s, each 3 H), 1.64 (d, J = 1.5 Hz, 3 H), 3.51 (q, J = 8.6 Hz, 1 H), 5.25 (t, J = 6.8 Hz, 1 H); mass spectrum, m/z 206 (M^+).

(*Z*)-1α,3,4,7,8,9β,10,11-Octahydro-6,10,10-trimethyl-2*H*-bicyclo[7.2.0]undecen-2-one (19). According to the procedure reported by Corey and co-workers,[1a] **18** (30 mg, 0.145 mmol) was converted into **19**. Silica gel column chromatography (50:1 hexane–ether) of the crude **19** afforded trans ketone **19** (22 mg, 73% yield) as a colorless oil: IR 1695 cm^{-1}; ^1H NMR δ 0.99 and 1.05 (s, each 3 H), 1.66 (d, J = 0.9 Hz, 3 H), 3.12 (q, J = 8 Hz, 1 H), 5.26 (t, J = 6.8 Hz, 1 H); mass spectrum, m/z 206 (M^+). The ^1H NMR data were found to be identical with those of the reported values of **19**.[14]

(±)-Isocaryophyllene (1). The modified Corey procedure[1a] was used for the Wittig reaction of **19**. A solution of *n*-butyllithium in hexane (0.53 mmol) was added dropwise to a stirring suspension of methyltriphenylphosphonium iodide (257 mg, 0.64 mmol) in THF (1.5 mL) at 0 °C under argon, and the mixture was stirred for 30 min at room temperature. Then the mixture was cooled to 0 °C and a solution of **19** (22 mg, 0.11 mmol) in THF (0.5 mL) was added. After being stirred for 2 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution at 0 °C. Workup of the mixture in the usual manner and subsequent silica gel chromatography (hexane) of the resulting oil afforded (±)-isocaryophyllene (1) (17 mg, 77% yield) as a colorless oil. The spectral data (360 MHz ^1H NMR, mass spectra, and IR (film)) of the product were identical with those of natural isocaryophyllene.

Methyl 3,3-Dimethyl-2α-[(phenylsulfonyl)methyl]cyclobutane-1β-carboxylate (22). A solution of **20**[16] (140 mg, 1 mmol) in THF (2.5 mL) was added to a stirring solution of potassium *tert*-butoxide (59 mg, 0.5 mmol) and ethyl (phenylsulfonyl)acetate (228 mg, 1 mmol) in THF (2.5 mL) containing dimethyl sulfoxide (0.5 mL) under nitrogen. After being stirred for 6 days at room temperature, saturated aqueous ammonium chloride solution was added on an ice bath. The mixture was acidified and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated. The resulting oil (**21**, 357 mg) was treated with 2% KOH in water–ethanol (9:1, 18 mL) solution for 1 h at room temperature and then refluxed for 2 h. The mixture was acidified and extracted with $CHCl_3$. The residual caramel (314 mg) obtained by removal of the solvent was dissolved in pyridine (3 mL), and the solution was refluxed for 2 h under nitrogen. Removal of pyridine gave an oil (300 mg), which was refluxed for 12 h with dimethyl sulfate (0.5 mL) and anhydrous potassium carbonate (2 g) in acetone (25 mL). Workup of the mixture in the usual manner yielded an oil (267 mg), which was chromatographed on silica gel (17:3 hexane–ethyl acetate), affording **22** (182 mg, 61.5% yield from **20**) as a colorless oil: bp 150–150 °C (bath temperature) (0.01 torr); IR 1735–1730, 1320, 1150 cm^{-1}; ^1H NMR δ 1.11 (s, 6 H), 3.0–3.3 (m, 2 H), 3.65 (s, 3 H), 7.4–7.75 (m, 3 H), 7.75–8.05 (m, 2 H); mass spectrum, m/z 296 (M^+).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.78; H, 6.80; S, 10.82. Found: C, 60.68; H, 6.86; S, 10.73.

Benzyl (*E*)-5-Chloro-4-methyl-3-pentenyl Ether (32a) and Benzyl (*Z*)-5-Chloro-4-methyl-3-pentenyl Ether (32b). Iodides **31a,b** were prepared as a mixture of *E*/*Z* isomers from 1-[(benzyloxy)ethyl]-2-methylallyl 1-pyrrolidinecarbodithioate.[21] The crude mixture of **31a,b** (2.22 g) was treated with lithium chloride (1.08 g) in dimethylformamide (21.6 mL) for 18 h at room temperature under nitrogen. Usual workup of the reaction mixture

provided an oil, whose silica gel chromatography (19:1 hexane–ethyl acetate) afforded a mixture of **32a,b** (1.57 g, 100% yield) in a ratio of 3:1, favoring *E* isomer, which again was subjected to Lobar column chromatography. Elution with 19:1 hexane–ethyl acetate afforded successively **32b** (401 mg) as a less polar colorless oil [^{1}H NMR δ 1.83 (d, J = 1.3 Hz, 3 H), 3.48 (t, J = 6.5 Hz, 2 H), 4.05 and 4.50 (s, each 2 H), 5.42 (tq, J = 1.3, 7.4 Hz, 1 H)], a mixture of **32a,b** (360 mg), and **32a** (730 mg) as a more polar colorless oil [^{1}H NMR δ 1.73 (d, J = 1.3 Hz, 3 H), 3.46 (t, J = 6.4 Hz, 2 H), 3.99 and 4.48 (s, each 2 H), 5.56 (tq, J = 1.3, 7.3 Hz, 1 H)].

3,3-Dimethyl-1β-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2α-[(phenylsulfonyl)methyl]cyclobutane (33). Sulfone ester **22** (1.32 g, 4.44 mmol) was added to lithium aluminum hydride (338 mg) in ether (40 mL) and stirred for 20 min on an ice bath. After usual workup, the crude alcohol (1.33 g) was obtained as a colorless oil: ^{1}H NMR δ 1.03 (s, 6 H), 3.17 (d, J = 6.1 Hz, 2 H), 3.4–3.75 (m, 2 H), 7.4–7.75 (m, 3 H), 7.75–8.05 (m, 2 H).

The alcohol (1.33 g) obtained above was treated with *tert*-butyldimethylchlorosilane (810 mg, 1.2 equiv) and imidazole (758 mg, 2.5 equiv) in dimethylformamide (4.6 mL) at room temperature under nitrogen. The mixture was stirred overnight. The crude product obtained by usual workup was subjected to silica gel column chromatography (19:1 hexane–ethyl acetate) affording **33** (1.65 g, 97.1% yield from **22**) as a colorless oil: ^{1}H NMR δ 0.00 and 1.11 (s, each 6 H), 0.89 (s, 9 H), 3.0–3.4 (m, 2 H), 3.4–3.8 (m, 2 H), 7.4–7.8 (m, 3 H), 7.8–8.05 (m, 2 H); mass spectrum, m/z 367 (M^+ − 15).

2α-[(*E*)-6-(Benzyloxy)-3-methyl-1-(phenylsulfonyl)-3-hexenyl]-3,3-dimethyl-1β-(hydroxymethyl)cyclobutane (34). A solution of **32a** (337 mg, 1.5 mmol) in THF (4 mL) and hexamethylphosphoramide (0.5 mL) was added slowly to a stirring solution of the lithium salt prepared from **33** (382 mg, 1 mmol) and a solution of *n*-butyllithium and hexane (1.53 mmol) in THF (4 mL) (−78 °C, 1 h) at −78 °C under argon. The mixture was stirred for 2 h at −78 °C and then 1 h on an ice-salt bath. The reaction was quenched with saturated aqueous ammonium chloride solution at −78 °C, and the mixture was extracted with 1:1 ether–ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (19:1 hexane–ethyl acetate) of the residue afforded the corresponding silyl ether of **34** (567 mg, 99.5% yield from **33**) as a colorless oil: ^{1}H NMR δ 0.00 and 0.03 (s, each 3 H), 0.88 (s, 9 H), 1.22 (s, 6 H), 1.42 (br s, 3 H), 4.51 (s, 2 H), ca. 5.1 (br t, J = 7 Hz, 1 H), 7.34 (s, 5 H), 7.4–7.7 (m, 3 H), 7.7–8.0 (m, 2 H).

A solution of the silyl ether of **34** (567 mg, 0.99 mmol) obtained above in THF (16 mL) was treated with tetra-*n*-butylammonium fluoride (620 mg, 2 mmol) for 3 h at room temperature under nitrogen. After usual workup and subsequent column chromatography on silica gel (3:1 hexane–ethyl acetate), **34** was obtained as a colorless oil (446 mg, 97.8% yield from **33**): IR 3630, 3500, 1305, 1140 cm^{-1}; ^{1}H NMR δ 1.05 and 1.11 (s, each 3 H), 1.40 (br s, 3 H), 4.48 (s, 2 H), ca. 5.2 (br t, J = 8 Hz, 1 H), 7.32 (s, 5 H), 7.4–7.7 (m, 3 H), 7.7–8.0 (m, 2 H); mass spectrum, m/z 456 (M^+).

2α-[(*E*)-6-(Benzyloxy)-3-methyl-3-hexenyl]-3,3-dimethyl-1β-(hydroxymethyl)cyclobutane (35). Pulverized 5% sodium amalgam (7.0 g) was added portionwise to a suspension of **34** (745 mg, 1.63 mmol) and anhydrous sodium hydrogen phosphate (2.8 g) in methanol (37 mL) at 0 °C under nitrogen, and the mixture was stirred for 16 h at room temperature. Sodium hydrogen phosphate (1.4 g) and 5% sodium amalgam (3.5 g) were added again and stirring was continued for 22 h at room temperature. The mixture was poured into ice–water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was subjected to column chromatography on silica gel. The fraction eluted with hexane–ethyl acetate (9:1) afforded **35** as a colorless oil (435 mg, 84.2% yield); IR 3600 cm^{-1}; ^{1}H NMR δ 1.03 (s, 6 H), 1.61 (br s, 3 H), 4.51 (s, 2 H), ca. 5.1 (br t, J = 6 Hz, 1 H), 7.32 (s, 5 H); mass spectrum, m/z 316 (M^+).

2α-[(*E*)-6-(Benzyloxy)-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1β-carboxylic Acid (36). Jones reagent (4 N, 1.85 mL) was added to a solution of **35** (370 mg, 1.17 mmol) in acetone (18.5 mL), and the mixture was stirred for 30 min at 0 °C. After usual workup, the crude acid **36** was obtained as an oil (390 mg): IR 1700 cm^{-1}; ^{1}H NMR δ 1.03 and 1.08 (s, each 3H), 1.59 (br s, 3 H), 3.75 (t, J = 7.1 Hz, 2 H), 4.51 (s, 2 H), ca. 5.1 (br t, J = 7.2 Hz, 1 H). The crude acid **36** was used for the next reaction without purification.

***N*-Methyl-2′-[(2-cyanoethyl)thio]-2α-[(*E*)-6-(benzyloxy)-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1β-carboxanilide (38).** The crude acid **36** (390 mg) obtained from **35** (370 mg, 1.17 mmol) was converted into **38** in the same way as described in the preparation of **12**. Silica gel column chromatography (3:1 hexane–ethyl acetate) of the crude product afforded **38** (550 mg, 91.5% yield from **35**) as a colorless gum: IR 2230, 1660 cm^{-1}; ^{1}H NMR δ 0.80, 1.03 and 3.15 (s, each 3 H), 1.59 (br s, 3 H), 3.46 (t, J = 7.1 Hz, 2 H), 4.51 (s, 2 H), 5.11 (br t, J = 7.2 Hz, 1 H), 7.32 (br s, 9 H); mass spectrum, m/z 504 (M^+).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-2α-[(*E*)-6-[(methylsulfonyl)oxy]-3-methyl-3-hexenyl]-3,3-dimethylcyclobutane-1β-carboxanilide (39).** Benzyl ether **38** (475 mg, 0.94 mmol) was converted into **39** (218 mg, 52.5% yield) as a colorless oil [^{1}H NMR δ 0.79, 1.03, 3.01 and 3.16 (s, each 3 H), 1.60 (br s, 3 H), 4.18 (t, J = 6.9 Hz, 2 H), 5.08 (br t, J = 7 Hz, 1 H)] via the corresponding acetate (**38**, R = $COCH_3$) [IR 2260, 1735, 1660 cm^{-1}; ^{1}H NMR δ 0.80, 1.03, 2.04 and 3.16 (s, each 3 H), 1.59 (br s, 3 H), 4.02 (t, J = 7.1 Hz, 2 H), 5.05 (dd, J = 6.4, 7.5 Hz, 1 H), 6.9–7.6 (m, 4 H)] in the same way as described in the preparation of **14**.

(*E*)-1α,7,8,11,12,13β,14,15-Octahydro-3,10,14,14-tetramethyl-4,5-benzo-3-aza-6-thia-2*H*-bicyclo[11.2.0]pentadecen-2-one (40). Mesylate **39** (175 mg, 0.356 mmol) was converted into **40** in the same way as described in the preparation of **15**. The crude product was purified first roughly by silica gel column chromatography (9:1 hexane–ethyl acetate) and then subjected to Lobar column chromatography (5:1 hexane–ethyl acetate) to afford **40** (67 mg, 54.8% yield) as a colorless gum: ^{1}H NMR δ 0.81, 1.01 and 3.11 (s, each 3 H), 1.59 (br s, 3 H), 3.3–3.8 (m, 1 H), 5.11 (br t, J = 7 Hz, 1 H); mass spectrum, m/z 343 (M^+).

(*E*)-1α,7,8,11,12,13β,14,15-Octahydro-3,10,14,14-tetramethyl-4,5-benzo-3-aza-6-thia-2*H*-bicyclo[11.2.0]pentadecen-2-one 6-Oxide (41). Sulfide **40** (64 mg, 0.187 mmol) was converted into **41** in the same way as described in the preparation of **16**. The crude product was purified by Lobar column chromatography. The fraction eluted with ethyl acetate afforded **41** (60 mg, 89.5% yield) as a colorless powder: IR 1665, 1035 cm^{-1}; ^{1}H NMR δ 0.84, 1.03 and 3.27 (s, each 3 H), 1.57 (br s, 3 H), 5.08 (br t, J = 7.3 Hz, 1 H); mass spectrum, m/z 361 (M^+ + 1), 360 (M^+).

(*E*)-1α,3,4,7,8,9β,10,11-Octahydro-6,10,10-trimethyl-3-[[2-(methylamino)phenyl]sulfinyl]-2*H*-bicyclo[7.2.0]undecen-2-one (42). A solution of **41** (54 mg, 0.15 mmol) in THF (4 mL) and then hexamethylphosphoramide (0.53 mL, 3 mmol) were added slowly to a stirring solution of lithium diisopropylamide (1.5 mmol) in THF (2 mL) at −78 °C under argon. The mixture was stirred for 30 min at −78 °C and for 30 min at 0 °C. After being quenched with saturated aqueous ammonium chloride at −78 °C and neutralized with 10% HCl, the ethereal extract of the mixture was washed with brine, dried ($MgSO_4$), and concentrated. The resulting product **42** (a pale yellow oil, 55 mg) was almost pure from TLC analysis and was used for the next desulfurization without purification: IR 3300, 1690 cm^{-1}; ^{1}H NMR δ 0.82 and 0.90 (s, each 3 H), 1.80 (br s, 3 H), 2.87 (d, J = 5 Hz, 3 H), 4.96 (dd, J = 7.8, 11.2 Hz, 1 H), 5.18 (br t, J = 7.9 Hz, 1 H).

(*E*)-1α,3,4,7,8,9β,10,11-Octahydro-6,10,10-trimethyl-2*H*-bicyclo[7.2.0]undecen-2-one (43). Pulverized 5% sodium amalgam (620 mg) was added portionwise to a mixture of the crude ketone **42** (55 mg) and anhydrous sodium hydrogen phosphate (380 mg) in methanol (5 mL) at 0 °C under nitrogen. After being stirred for 30 min at 0 °C, 5% sodium amalgam (320 mg) was added again and stirring was continued for 30 min. The same workup as described in the preparation of **35** and subsequent silica gel column chromatography (19:1 hexane–ethyl acetate) afforded **43** (21.6 mg, 70% yield from **41**) as a colorless oil; mass spectrum, m/z 206 (M^+). The spectral data (IR and ^{1}H NMR) of the product were identical with those reported in the literature.[14]

(±)-Caryophyllene (2). Ketone **43** (16 mg, 0.08 mmol) was converted into **2** in the same way as described in the preparation of **1**. Silica gel chromatography (hexane) of the crude product afforded **2** (12.6 mg, 79.5% yield) as a colorless oil. The physical data (400 MHz ^{1}H NMR, mass spectra and GC) of the product

were identical with those of authentic natural caryophyllene.

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Registry No. (±)-1, 61217-74-1; (±)-2, 17627-40-6; (±)-3, 90191-48-3; (±)-4, 90107-84-9; 5 (isomer 1), 90107-85-0; 5 (isomer 2), 90107-86-1; (±)-6, 90191-49-4; 7, 90107-87-2; 8, 54314-85-1; (±)-(*E*)-9, 81491-42-1; (±)-(*Z*)-9, 81521-03-1; 10, 3495-63-4; 11, 37845-64-0; (±)-(*E*)-12, 81521-04-2; (±)-(*Z*)-12, 81491-32-9; (±)-13a, 90191-50-7; (±)-13b, 90191-51-8; (±)-14, 81521-07-5; (±)-15, 81491-43-2; (±)-16, 81570-11-8; (±)-17, 81521-10-0; (±)-18, 81521-12-2; (±)-19, 61217-73-0; 20, 37676-91-8; (±)-21, 90107-88-3; (±)-22, 81491-29-4; (±)-23a, 81491-48-7; (±)-23b, 81491-49-8; (±)-24a, 81491-50-1; (±)-24b, 81491-52-3; (±)-26, 81491-53-4; (±)-27, 81491-55-6; (±)-28, 90107-89-4; (±)-29, 90107-90-7; (±)-30, 81491-28-3; 31a, 90107-91-8; 31b, 90107-92-9; 32a, 81491-46-5; 32b, 81491-47-6; (±)-33, 81491-30-7; 34, 90107-93-0; 34 (TBMS ether), 81491-31-8; (±)-35, 81491-33-0; (±)-36, 90191-52-9; (±)-38, 81521-01-9; (±)-39, 90191-53-0; (±)-40, 90191-54-1; (±)-41, 81491-37-4; (±)-42, 81491-38-5; (±)-43, 81491-39-6; (±)-vi, 81521-11-1; ethyl(phenylsulfonyl)acetate, 7605-30-3; diphenyl disulfide, 882-33-7; nitromethane, 75-52-5.

Supplementary Material Available: Experimental procedures and spectroscopic data for compounds 23–30, 37, and vi, and the process of conversion of 30 into 22 (8 pages). Ordering information is given on any current masthead page.

Synthesis of *Z,Z*-Skipped Diene Macrolide Pheromones for *Cryptolestes* and *Oryzaephilus* Grain Beetles (Coleoptera Cucujidae)

Jocelyn G. Millar and Allan C. Oehlschlager*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

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Three macrolide aggregation pheromones for *Cryptolestes pusillus*, *Cryptolestes turcicus*, and *Oryzaephilus mercator* were synthesized stereoselectively from acyclic precursors. The first, 13-methyl-(5*Z*,8*Z*)-tridecadienolide (I), is an aggregation pheromone for *C. turcicus* and had been tentatively identified previously in *Phoracantha synonyma*. The second, 11-methyl-(3*Z*,6*Z*)-undecadienolide (II), is an aggregation pheromone for *O. mercator*. The third, (3*Z*,6*Z*)-dodecadienolide (III) is an aggregation pheromone for *O. mercator* and is also slightly attractive to *C. pusillus*. The racemic and enantiomeric forms of I were synthesized.

During the past several years, our laboratory has been screening insect-produced volatiles from *Cryptolestes* and *Oryzaephilus* species of grain beetles, in a search for aggregation pheromones for these insects. We now report the syntheses of three macrolides isolated from pentane extracts of Porapak Q captured insect and frass volatiles.

The first, 13-methyl-(5*Z*,8*Z*)-tridecadienolide (I), was tentatively identified by others by analysis of its mass spectrum.[1] We have isolated and fully characterized I from *C. turcicus* (Grouvelle), for which it acts as an aggregation pheromone.[2] Macrolide I was also identified by GLC and mass spectral comparisons in *C. ferrugineus* (Stephens)[3] and in *O. mercator* (Fauvel).[4] It has no apparent biological activity in these latter two insects.

The second, 11-methyl-(3*Z*,6*Z*)-undecadienolide (II), was isolated from *C. ferrugineus*[3] and frass volatiles and had no discernable biological activity for these insects. Macrolide II was also found in *O. mercator*,[4] for which it is an aggregation pheromone.

The third compound, (3*Z*,6*Z*)-dodecadienolide (III), was isolated from frass volatiles of *O. mercator*,[4] and *C. pusillus*.[5] Macrolide III is an aggregation pheromone for *O. mercator*,[4] and is also attractive to *C. pusillus*[5] at high concentrations.

Of the various methods available to obtain macrolides, cyclization of appropriate acyclic hydroxy acid precursors offers the advantages of flexibility in terms of substrates and lactonization under mild conditions. One key feature common to I–III is the sensitive skipped diene system, which, in the case of II and III, was also β,γ to a carbonyl, leading to a propensity to isomerize and/or decompose. Several approaches, e.g., Wittig reactions, have been used in syntheses of skipped dienes.[6,7] However, the stereochemical control is not usually absolute. Vinylic organocuprates[8] and organoboranes[9] have been coupled with allylic halides, but these reactions have limitations with respect to compatability with various functional groups. Dibutyl-1,5-stannacyclohexadiene as the synthetic equivalent of (*Z,Z*)-LiCH=CHCH$_2$CH=CHLi has similar drawbacks.[10]

A straightforward method of making *Z,Z*-skipped dienes involves the selective reduction of an appropriate diyne precursor. The required diynes are easily made by coupling a propargyl halide or propargyl tosylate[11,12] with the Grignard derivative of a terminal alkyne, with cuprous salt

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