that they could be kairomones which induce settling and metamorphosis in larvae of the dorid nudibranchs known to be associated with the genus *Dysidea*.[8-11]

The presence of both the 5α,6β and 5β,6α hydroxylated sterol series in the same sponge suggests a 5α,6α epoxide precursor to both groups. Such a compound could undergo either electrophilic or nucleophilic ring opening to give rise to both sets of steroids. Since Djerassi has suggested[4] that 5β-stanols are most likely the product of bacterial conversion of 5α-stanols in *P. ficiformis*, it is possible that **2-4** are derived from bacterial conversion of appropriate precursors in *D. etheria*. This sponge does contain a substantial community of bacteria.[12]

Although the trans-AB steroid **1** was moderately cytotoxic,[2] the 5β steroid **3** was inactive (IC_{50} = 26 μg/mL in the KB assay, >10 μg/mL PS). Neither group of steroids elicited any reproducible effect upon larvae of the tobacco hornworm, *Manduca sexta*, whether incorporated into an agar-based diet (250 ppm) or injected subcutaneously (100-μg dose).

Experimental Section

General. One-dimensional NMR spectra were recorded on a Bruker WM-250 spectrometer; COSY and HMQC 2D experiments were done on a Varian VXR-500 instrument; chemical shifts are reported in δ units relative to tetramethylsilane (δ = 0) with pyridine-d_5 as the solvent and internal standard. ^{13}C NMR and ^1H NMR assignments were made by using 2D COSY and 2D HMQC sequences and by comparison of chemical shift data with those in the literature. Mass spectra were determined on a VG-7070 EHF mass spectrometer in the fast atom bombardment (FAB) mode, using a 0.14 M RbI in glycerol matrix to obtain $(M + Rb)^+$ adduct ions. Optical rotations were obtained on a Perkin-Elmer 241 MC polarimeter. All HPLC separations were carried out on a Perkin-Elmer series 3B liquid chromatograph. A Knauer differential refractometer was used for detection in all HPLC steps.

Collection, Extraction, and Initial Fractionation. The collection, extraction, partitioning, and initial chromatographic separations of *D. etheria* have been reported in detail.[2]

Isolation of 2-4. The third fraction from an isocratic LPLC silica gel column (Whatman LPS-2, 2.5 × 25 cm), using $CHCl_3$-iPrOH-MeOH (15:5:1) as eluent, was dissolved in MeOH and subjected to semipreparative HPLC on a Hamilton PRP-1 (C_{18}) column (30 × 0.7 cm) using CH_3CN-H_2O (1:1) as the mobile phase. Further purification of the three major fractions from this separation was achieved by HPLC on an analytical β-cyclodextrin HPLC column (ASTEC, 250 × 4.6 mm), with different mixtures of CH_3CN-H_2O (4:1, **2**), (1:1, **3** and **4**).

5β-Cholest-7-ene-2β,3α,5β,6α,9α,11α,19-heptol (2): yield, 1 × 10^{-2}% dry wt; mp 230-250 °C dec; $[\alpha]^{25}_D$ +23.1° (*c* 0.78, EtOH); ^1H NMR (250 MHz, pyridine-d_5, exchanged with MeOH-d_4) δ 0.75 (3 H, s, H-18), 0.84 (6 H, d, *J* = 6.6, H-26,27), 0.92 (3 H, d, *J* = 5.3, H-21), 1.08 (3 H, m, H-23,24), 1.28 (6 H, m, H-16,17,20,22,23), 1.52 (3 H, m, H-15,25), 1.83 (1 H, m, H-16), 2.10 (1 H, t, *J* = 11.6, H-4α), 2.55 (2 H, m, H-1β, H-4β), 2.76 (1 H, dd, *J* = 11.9, 23.9, H-12α), 2.85 (1 H, m, H-14), 2.99 (1 H, m, H-12β), 3.20 (1 H, dd, *J* = 2.7, 10.0, H-1α), 4.69 (3 H, m, H-6, and H-19 methylene protons—coalesced AB pattern), 4.82 (2 H, m, H-2,3), 5.38 (1 H, dd, *J* = 4.1, 11.9, H-11), 5.71 (1 H, s, H-7); FAB-MS, *m/z* 567 $(M + Rb^+, 1.7)$.

24-Methyl-5β-cholest-7-ene-2β,3α,5β,6α,9α,11α,19-heptol (3): yield, 1 × 10^{-2}% dry wt; mp 240-260 °C dec; $[\alpha]^{25}_D$ +18.2° (*c* 0.28, EtOH); ^1H NMR δ 0.75 (3 H, s, H-18), 0.78 (3 H, d, H-27), 0.79 (3 H, d, H-28), 0.82 (3 H, d, *J* = 6.9, H-26), 0.92 (3 H, d, *J* = 4.4, H-21), 1.0-1.6 (11 H), 1.84 (1 H, m, H-16), 2.10 (1 H, t, *J* = 11.7, H-4α), 2.57 (2 H, m, H-1β, H-4β), 2.82 (1 H, dd, *J* = 11.9, 23.9, H-12α), 2.86 (1 H, m, H-14), 2.99 (1 H, m, H-12β), 3.20 (1 H, dd, *J* = 3.0, 13.1, H-1α), 4.68 (3 H, m, H-6, and H-19 methylene protons—coalesced AB pattern), 4.83 (2 H, m, H-2,3), 5.38 (1 H, dd, *J* = 4.7, 12.1, H-11), 5.71 (1 H, s, H-7); FAB-MS, *m/z* 581 $(M + Rb^+, 0.7)$.

24-Ethyl-5β-cholest-7-ene-2β,3α,5β,6α,9α,11α,19-heptol (4): yield, 1 × 10^{-2}% dry wt; mp 235-245 °C dec; $[\alpha]^{25}_D$ +17.7° (*c* 1.3, EtOH); ^1H NMR δ 0.75 (3 H, s, H-18), 0.8124 (9 H, m, H-26,27,29), 0.94 (3 H, d, *J* = 4.1, H-21), 1.0-1.6 (13 H), 1.83 (1 H, m, H-16), 2.11 (1 H, t, *J* = 11.7, H-4α), 2.56 (2 H, m, H-1β), 2.76 (1 H, dd, *J* = 12.0, 23.8, H-12α), 2.86 (1 H, m, H-14), 2.98 (1 H, m, H-12β), 3.20 (1 H, dd, *J* = 3.0, 13.2, H-1α), 4.67 (3 H, m, H-6, and H-19 methylene protons—coalesced AB pattern), 4.82 (2 H, m, H-2,3), 5.37 (1 H, dd, *J* = 4.4, 12.2, H-11), 5.71 (1 H, s, H-7); FAB-MS, *m/z* 595 $(M + Rb^+, 1.1)$.

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Registry No. **2**, 120711-48-0; **3**, 120711-49-1; **4**, 120711-50-4.

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A Subtotal Synthesis of Methynolide via an Electrophilic Spirocyclization Reaction

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As the aglycon of the simplest member of the macrolide class of antibiotics, methynolide, **1**, has served as a proving ground in the development of stereochemical methods for synthesis of this family of natural products.[1-8] Most routes to methynolide involve the assembly of two optically active fragments in order to control the relationship between the stereocenters in the right half of the molecule (C-2 to C-6) and those in the left (C-10 and C-11). Exceptions are the synthesis reported by Vedejs et al.,[6] in which the C-10 and C-11 stereocenters are introduced on a macrocyclic intermediate, and the formal synthesis by Ireland et al.,[4] in which they are assembled on the rigid, spirocyclic framework of intermediate **2**.

We have developed a number of methods for the stereocontrolled construction of cyclic ethers via electrophilic cyclization of unsaturated alcohols and derivatives.[9-11]

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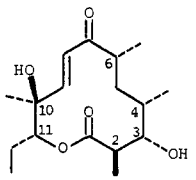
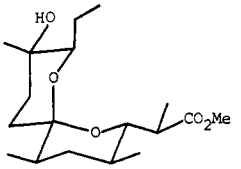
0022-3263/89/1954-3236$01.50/0



1



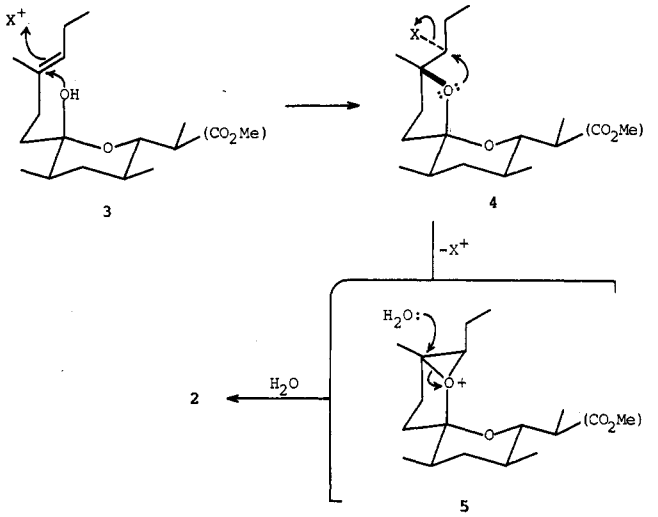
2

The fundamental principle in these transformations has been the transmission of stereochemical information from the carbinol (or related) stereocenter to the newly generated stereocenter(s) because of the conformational preference of the nascent ring.[12] If an anomeric hydroxyl group were to function in a similar fashion, a concise synthesis of the Ireland spiroketal, **2**, could be envisaged as outlined in Scheme I. Both the stereo- and regiochemical course of the proposed cyclization and ring expansion had been demonstrated in our previous work.[9,11] The key questions to be answered with the present system were (1) whether the anomeric effect could be utilized to relay the stereochemical information from the substituents on one ring to the other and (2) whether participation of the ketal oxygen in the solvolysis process, presumably via the oxiranium ion **5**, would lead to the desired ring expansion or cleavage of the ketal bond. This report describes the successful resolution of both of these questions.

A latent form of the Prelog–Djerassi lactone, **9**,[13] was selected as the precursor to the C-1 → C-7 fragment. The remaining carbons were introduced via the unsaturated lithium reagent, **8**, which was prepared from the corresponding bromide **7** as shown in Scheme II. Cyclopropanation[14] of 2-methyl-1-penten-3-ol[15] provides the cyclopropyl carbinol **6**, which undergoes rearrangement in the presence of PBr_3 and zinc bromide[16] to give the homoallylic bromide **7** as a 94:6 ratio of *E*:*Z* isomers.

Addition of the lithium reagent **8** to lactone **9** at −78 °C affords hemiketal **10** in 57% yield (30% recovery of lactone). ^1H and ^{13}C NMR analyses indicate that **10** exists predominantly in the cyclic form as a 10:1 mixture of anomers. The predominant isomer is assigned the axial hydroxyl configuration in view of the anomeric effect and the clear preference for equatorial disposition of the alkyl substituents. Treatment of **10** with *N*-iodosuccinimide in CH_2Cl_2 at 0 °C gives a mixture of spirocyclic iodides in the approximate ratio of 10:1:1:1 by ^1H NMR; the major isomer is isolated by chromatography in 61% yield. That this material is **11**, the product of Markovnikov cyclization, rather than the spiro[5.5] isomer, is demonstrated by the ^1H NMR resonance at δ 4.06 ppm (dd, J = 2.1, 11.5 Hz) for the proton adjacent to the iodide; in the ring-expanded alcohol **12** (see below), the corresponding hydrogen resonates at δ 3.28 (dd, J = 1.7, 10.6 Hz).[17]

Scheme I



3 4 5

Iodo ether **11** undergoes solvolysis and ring expansion on treatment with silver tetrafluoroborate in wet acetone at room temperature.[10] ^1H NMR analysis of the crude product indicates that the anticipated spiroketal **12** and an isomer are formed in a 10:1 ratio; the desired isomer is isolated in 75% yield after chromatographic purification. The ketal oxygen thus participates normally in the cyclization/ring expansion sequence. The "subtotal" synthesis[18] of methynolide is completed by oxidative cleavage of the vinyl group ($RuCl_3$–$NaIO_4$[19]) and esterification with diazomethane, which provides ester **2** in 77% yield. The ^1H NMR spectrum of our racemic material indicates that it has the same relative stereochemistry as the optically active form described by Ireland et al.[4b,20] A fairly concise route to methynolide has therefore been established in which all of the stereocenters are generated with relative asymmetric induction.

Experimental Section

General. All reactions were performed under a dry nitrogen atmosphere. THF, diethyl ether, and benzene were dried by distillation from sodium benzophenone ketyl immediately prior to use; CH_2Cl_2 and acetonitrile were distilled from CaH_2 and DMF from $CaSO_4$. Unless otherwise indicated, reaction workups culminated in washing the organic layer with brine, drying over $MgSO_4$, and removal of the solvent on a rotary evaporator under reduced pressure and finally under vacuum. Chromatography was performed on Silica Gel 60, 100–120 mesh (E. Merck, Darmstadt), with the indicated eluting solvent. ^1H NMR spectra were acquired at 500 MHz in $CDCl_3$ solvent and are reported as

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(13) Yamamoto, Y.; Yatagi, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. Compound **9** is reported to be formed in a highly stereoselective manner. However, after considerable experimentation, we were only able to obtain a 3:1 ratio of **9** and its diastereomer; the desired isomer was isolated in pure form by chromatography.

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(18) While we doubt that this usage will gain acceptance, we think it appropriate to refer to a route that starts with one person's intermediate and ends with someone else's as a "subtotal synthesis" of the ultimate target.

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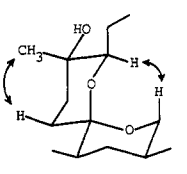
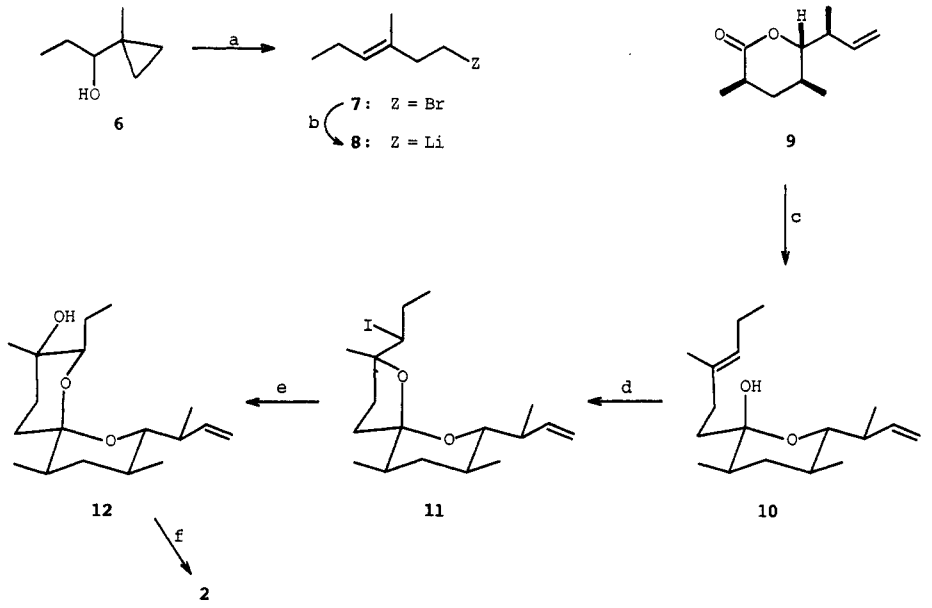
(20) All chemical shifts agreed within 0.03 ppm, with the exception of the resonance for the C-13 methyl group, which appeared at 1.03 ppm in our spectrum of **2** rather than 1.09 ppm as reported.[4b] As additional confirmation of the indicated structure, in initial work we had prepared the model compound i using the same iodocyclization/ring expansion sequence; the configuration of this material was conclusively demonstrated by observation of the indicated NOE interactions.



i

Scheme II[a]



[a] (a) PBr_3, collidine, $ZnBr_2$, ether, 0–21 °C (62%); (b) Li (1% Na), ether; (c) **8**, ether, −78 °C (57%); (d) NIS, CH_2Cl_2, 0 °C (61%); (e) $AgBF_4$, aqueous acetone (75%); (f) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$; CH_2N_2, ether (77%).

follows: chemical shift relative to internal $(CH_3)_4Si$ as 0.0 ppm (multiplicity, number of protons, coupling constants in hertz); ^{13}C NMR spectra were acquired at 51 or 125 MHz using broad-band ^1H decoupling and are reported relative to $CDCl_3$ solvent as 77.0 ppm. IR spectra were obtained on samples prepared as thin films on NaCl plates. Elemental analyses were performed by the Microanalytical Laboratory in the College of Chemistry, University of California, Berkeley.

Methyl [αR*-[2a(S*),3b,5b,6b(8R*,9S*)]]-8-Ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (2). To a two-phase solution of spiroketal **12** (see below) (22.6 mg, 0.08 mmol) and sodium periodate (70 mg, 0.33 mmol) in 0.6 mL of carbon tetrachloride, 0.6 mL of acetonitrile, and 0.9 mL of water was added $RuCl_3 \cdot (H_2O)_3$ (0.5 mg, 2 mol %) at room temperature. After being stirred for 1.5 h, the mixture was diluted with 5 mL of water and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude oil was diluted with ether, filtered through a pad of Celite to remove the ruthenium residue, and concentrated to give 21 mg of a crude oil. This material was dissolved in 5 mL of ether and treated with excess diazomethane at 0 °C. After 10 min, the excess of diazomethane was quenched with glacial acetic acid, and the reaction mixture was concentrated to give 23.5 mg of an oil, which gradually crystallized. The crude product was purified by chromatography on silica gel (20% ethyl acetate/hexane) to give 20.1 mg (77% yield) of a white solid: mp 83–84 °C (recrystallized from pentane); IR 3590, 3500, 1735, 1460, 1000 cm^{-1}; ^1H NMR δ 3.74 (dd, 1, *J* = 3.1, 10.3), 3.70 (s, 3), 3.14 (dd, 1, *J* = 1.8, 10.8), 2.71 (dq, 1, *J* = 3.1, 7.0), 1.24–1.82 (b m, 11), 1.12 (d, 3, *J* = 7.0), 1.08 (s, 3), 1.03 (d, 3, *J* = 7.3), 0.88 (d, 3, *J* = 6.7), 0.82 (d, 3, *J* = 6.6); ^{13}C NMR δ 175.5, 100.0, 76.0, 74.6, 69.4, 51.5, 40.5, 38.2, 36.7, 35.5, 32.0, 30.3, 21.4, 19.3, 17.0, 16.0, 11.0, 8.6.

1-(1-Methylcyclopropyl)-1-propanol (6). A suspension of zinc–copper couple (16.4 g, 250 mmol) and diiodomethane (16.1 mL, 200 mmol) in 100 mL of ether was heated at reflux for 0.5 h. 2-Methyl-1-penten-3-ol[15] (5.0 g, 50 mmol) in 15 mL of ether was added over a 15-min period. After 1 h at reflux, the reaction mixture was poured into 100 mL of saturated NH_4Cl, and the organic layer was extracted with three 20-mL portions of ether. The combined organic layer was washed four times with saturated K_2CO_3 and worked up. The crude product was distilled to give 4.60 g (80% yield) of the title compound as a colorless oil: bp 72–78 °C (25 Torr); IR 3380, 3080, 2980, 1460, 1020, 860 cm^{-1}; ^1H NMR δ 2.74 (t, 1, *J* = 6.9), 1.66 (s, 1), 1.59 (quintet, 2, *J* = 7.4), 1.02 (s, 3), 0.96 (t, 3, *J* = 7.4), 0.23–0.44 (m, 4); ^{13}C NMR δ 80.3, 27.0, 20.0, 16.9, 11.5, 11.2, 10.7. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.36; H, 12.25.

(E)-1-Bromo-3-methyl-3-hexene (7). To $ZnBr_2$ (20.2 g, 100 mmol) in 200 mL of acetonitrile in a 1-L three-neck round-bottom flask equipped with a mechanical stirrer was added 150 mL of ether, alcohol **6** (2.28 g, 20 mmol) in 50 mL of ether, and 5.0 mL (40 mmol) of *s*-collidine at room temperature; the mixture was cooled to −78 °C with a dry ice–methanol bath. After 30 min, PBr_3 (2.0 mL, 20 mmol) in 10 mL of ether was added over a period of 5 min. The cooling bath was exchanged with an ice–water bath, and the reaction mixture was stirred for 4 h at 0 °C and for 2 h at room temperature. Pyridine (2.4 mL) and 400 mL of water were added, the organic layer was separated, and the aqueous layer was extracted with two 40-mL portions of ether. The combined organic layer was washed twice each with 200 mL of 1 N HCl and water and worked up. The residual oil was distilled with a Kugelrohr oven to give 2.2 g (62% yield) of the bromide **7** as a colorless oil: bp 100–110 °C (40 Torr) (bath temperature); IR 2960, 1670, 1450 cm^{-1}; ^1H NMR δ 5.23 (t, 1, *J* = 7.1), 3.43 (t, 2, *J* = 7.5), 2.52 (t, 2, *J* = 7.5), 2.01 (quintet, 2, *J* = 7.3), 1.67 (s, 3), 0.95 (t, 3, *J* = 7.5); ^{13}C NMR δ 130.9, 129.5, 42.8, 31.5, 21.1, 15.3, 14.0. Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.86; H, 7.36.

(2R*,3S*,5R*,6R*)-Tetrahydro-3,5-dimethyl-2-hydroxy-2-(3-methyl-3(E)-hexenyl)-6-[(1R*)-1-methyl-2-propenyl]-2H-pyran (10). To a solution of lactone **9**[13] (182 mg, 1.0 mmol) in 5 mL of THF was added 6 mL of 0.2 M lithium reagent **8** in ether (prepared from bromide **7** and lithium dispersion containing 1% of sodium) at −78 °C in 1 min. After 15 min, the reaction mixture was poured into 20 mL of saturated NH_4Cl and extracted with three 10-mL portions of ether. The combined organic layer was worked up to give 250 mg of a slightly yellow oil. The crude product was purified by chromatography (hexane:ether = 10:1 to 5:1) to give 55 mg (30% yield) of starting lactone **9** and 160 mg (57% yield) of hemiketal **10**: IR 3510, 2980, 1690, 1670, 1640, 1450, 1380, 920, 850 cm^{-1}; ^1H NMR δ 5.96 (ddd, 1, *J* = 7.2, 10.2, 17.4) and 5.80 (m, 1) in 10:1 ratio, 5.24 (t, 1, *J* = 7.0) and 5.13 (t, 1, *J* = 7.0) in 10:1 ratio, 4.99 (dd, 1, *J* = 0.9, 17.4) and 5.06 (m, 1) in 10:1 ratio, 4.94 (dd, 1, *J* = 0.9, 10.2), 3.46 (d, 1, *J* = 10.2), 2.39 (m, 1), 2.24 (m, 1), 1.92–2.17 (m, 3), 1.18 (m, 1), 1.50–1.72 (m, 4), 1.62 (s, 3), 1.42 (m, 1), 1.31 (m, 1), 0.97 (d, 3, *J* = 6.9), 0.93 (t, 3, *J* = 7.5), 0.90 (d, 3, *J* = 6.8), 0.82 (d, 3, *J* = 6.5); ^{13}C NMR δ 144.0, 135.3, 127.2, 112.6, 98.5, 77.7, 38.4, 37.8, 37.2, 33.3, 33.0, 21.2, 17.2, 16.4, 15.6, 14.2, 12.2. Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.89; H, 11.51.

[2a(R*),3b,5b,6b(8S*)]-8-[(1R*)-1-Iodopropyl]-3,5,8-trimethyl-2-[(1R*)-1-methyl-2-propenyl]-1,7-dioxaspiro[5.4]decene (11). To a solution of hemiketal **10** (110 mg, 0.39 mmol)

in 5 mL of CH_2Cl_2 was added *N*-iodosuccinimide (10.6 mg, 0.47 mmol) in one portion at −78 °C, and the mixture was stirred at 0 °C for 2 h in the dark. The reaction mixture was diluted with 20 mL of CH_2Cl_2, washed with 10 mL of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Analysis of the crude product by ^1H NMR indicated that **11** and three other isomers were present in a 10:1:1:1 ratio. Purification by flash chromatography (hexane) gave 97 mg (61% yield) of **11** as a colorless oil: IR 2980, 1640, 1460, 1110, 1020, 990, 920 cm^{-1}; ^1H NMR δ 5.89 (ddd, 1, *J* = 8.3, 10.2, 17.3), 5.01 (dd, 1, *J* = 1.8, 10.2), 4.95 (dd, 1, *J* = 1.8, 17.3), 4.06 (dd, 1, *J* = 2.1, 11.5), 3.21 (dd, 1, *J* = 2.4, 10.1), 2.34 (m, 1), 2.10 (ddd, 1, *J* = 7.4, 11.5, 19.2), 1.90–2.02 (m, 3), 1.62–1.76 (m, 3), 1.48–1.60 (m, 1), 1.42–1.48 (m, 1), 1.31 (s, 3), 1.12–1.22 (m, 1), 1.01 (t, 3, *J* = 7.2), 0.93 (d, 3, *J* = 6.9), 0.85 (d, 3, *J* = 6.7), 0.79 (d, 3, *J* = 6.6); ^{13}C NMR δ 144.0, 113.1, 109.1, 86.3, 78.4, 52.7, 40.0, 38.9, 38.1, 36.4, 33.9, 32.4, 28.8, 20.6, 17.2, 16.4, 14.7, 12.2. Anal. Calcd for $C_{18}H_{31}O_2I$: C, 53.21; H, 7.69; I, 31.23. Found: C, 52.95; H, 7.57; I, 30.88.

[2a(*R),3b,5b,6b(8*S**,9*R**)]-8-Ethyl-3,5,9-trimethyl-2-[(1*R**)-1-methyl-2-propenyl]-1,7-dioxaspiro[5.5]undecan-9-ol (12).** To a solution of iodoketal **11** (77 mg, 0.19 mmol) in 5 mL of acetone and 0.25 mL of water was added $AgBF_4$ (44 mg, 0.23 mmol). After being stirred for 3 h at room temperature in the dark, the reaction mixture was diluted with 20 mL of ether, and 0.1 g of $NaHCO_3$ and 1 g of $MgSO_4$ were added. The mixture was filtered and concentrated. Analysis of the crude product by ^1H NMR indicated that **12** and an isomer were present in a 10:1 ratio. Purification by chromatography (5% ethyl acetate/hexane) gave 42 mg (75% yield) of **12** as a colorless oil: IR 3400, 2990, 1640, 1460, 1380, 1110, 980, 920 cm^{-1}; ^1H NMR δ 6.02 (ddd, 1, *J* = 7.7, 10.3, 17.6), 5.00 (dd, 1, *J* = 17.6, 1.1), 4.98 (dd, 1, *J* = 10.3, 1.1), 3.28 (dd, 1, *J* = 1.7, 10.6), 3.24 (dd, 1, *J* = 2.5, 10.1), 2.40 (m, 1), 1.79–1.92 (m, 2), 1.66–1.70 (m, 1), 1.50–1.58 (m, 3), 1.39–1.46 (m, 2), 1.22–1.35 (m, 2), 1.10 (s, 3), 1.09 (b s, 1), 0.97 (d, 3, *J* = 6.9), 0.96 (t, 3, *J* = 7.4), 0.88 (d, 3, *J* = 6.7), 0.80 (d, 3, *J* = 6.6); ^{13}C NMR δ 143.9, 112.8, 96.6, 76.9, 76.0, 67.9, 38.6, 31.1, 37.3, 35.7, 32.2, 30.6, 21.4, 19.1, 17.2, 16.0, 11.9, 11.3. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.76; H, 10.77.

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Cross Coupling of Allylic Derivatives. 15. Regio- and Stereospecific Cross-Coupling Reactions of Dienyl Allylic *N*-Phenylcarbamates with Phenylcopper Reagents

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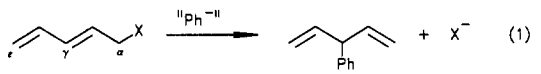
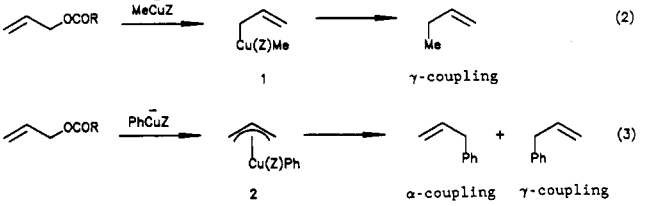
In connection with another study, we required a method to regiospecifically[1] γ-phenylate an allylic dienyl system. Such a transformation would yield an unconjugated diene as illustrated by eq 1.

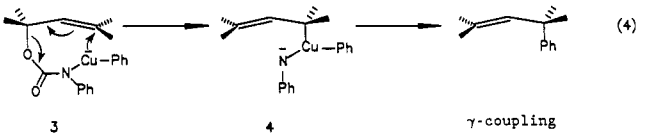


(1)

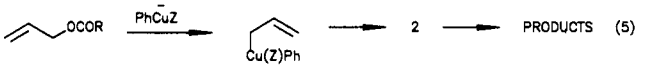
We have recently reported that the mechanism of cross coupling allylic carboxylates with phenyl(sp^2)copper reagents is remarkably different than similar reactions using alkyl(sp^3)copper reagents.[2] Cross coupling allylic carboxylates with alkyl(sp^3)copper reagents can be highly regiospecific (γ-alkylation) and evidently proceeds via a σ-allylcopper(III) intermediate (**1**) as shown by eq 2,[3] but cross coupling with phenyl(sp^2)copper reagents is nonregiospecific and evidently proceeds via a π-allylcopper(III) complex **2** as shown by eq 3.[2] The most compelling evidence for intermediate **2** is that in unbiased systems (such as α-deuterio-2-cyclohexenyl mesitoate) cross coupling with phenylcopper reagents is entirely nonregiospecific,[2,3] and in cis allylic systems (such as *cis*-cinnamyl pivalate), cross coupling gives only cis-α-coupling product (i.e., the original β,γ-double-bond configuration is preserved).[2]



We now report that reaction of allylic dienyl carbamates with phenylcopper reagents according to Gallina's method[4] or a modification that we reported earlier[5] occurs with complete regio- and stereospecificity (syn-γ-coupling) and evidently occurs by a cyclic mechanism illustrated by eq 4. This mechanism involves conversion of the carbamate to a mixed cuprate **3**, which undergoes a cyclic intramolecular oxidative addition of the γ-carbon to give a σ-allylcopper(III) complex **4**.[5] Reductive elimination converts the latter to the syn γ-coupling product.[5] This mechanism parallels that proposed earlier for alkylation of allylic carboxylates with alkyl(sp^3)copper reagents (eq 2).[2,5,6] This is apparently the first instance in which a phenylcopper reagent regiospecifically cross couples with an allylic system; evidently, a σ-allylcopper(III) complex (**4**) is involved in this transformation.



This result is significant in connection with the mechanistic details of cross-coupling reactions of phenyl(sp^2)copper reagents with allylic carboxylates. Heretofore, we were unable to distinguish between (a) direct formation of a π-allylcopper(III) complex (**2**, eq 3) or (b) initial formation of a σ-allylcopper(III) complex (**5**, eq 5) with subsequent complete isomerization to π-allyl complex **2**.[2] The present results indicate that a σ-allylcopper(III) complex (**4**), when formed, undergoes reductive elimination to give the corresponding cross-coupled product. Thus, nonregiospecific cross-coupling reactions of allylic carboxylates with phenyl(sp^2)copper reagents (eq 3) evidently involve direct formation of a π-allylcopper(III) complex **2**.



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(1) The terms regiospecific and regioselective are used as defined in footnote 3 of Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531.

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(4) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093.

(5) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715.

(6) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1988**, *53*, 1140, and earlier papers in this series.

0022-3263/89/1954-3239$01.50/0