acid was added, followed by 1.00 mL of "color reagent" prepared immediately before use by mixing equal volumes of 4% sodium nitroprusside and 4 N NaOH. The tubes were shaken and stored for 25 min, and the absorbance was measured at 625 nm. The reference cell contained a solution prepared from 0.50 mL of 4 N NaOH, 3.4 mL of 3 M acetic, and 1.00 mL of color reagent. Absorbance readings were converted to micromoles of cycloserine by use of a standard curve.[1] The average yield of two separate experiments (14 tubes) was 45.5% (SD 0.70). That the product of the ring-closure reaction was cycloserine and not α-*N*-acetycycloserine (which also gives the same color reaction) was established by TLC on unactivated silica gel sheets (Eastman), using propanol/H_2O (5:1, v/v) as solvent. Compounds were visualized as blue spots by spraying with a solution of 14 mL of 3 M acetic acid and 2 mL of 4 N NaOH to which was added directly before spraying a solution of 2 mL of 4 N NaOH and 4 mL of 4% sodium nitroprusside, mixed immediately before use.

Attempted Cleavage of 8 with TFA. To each of six centrifuge tubes was added 100 μL of a methanol solution containing 606 μg (1.91 μmol) of **8**. The solvent was evaporated and 0.20 mL of a 25% (v/v) solution of freshly distilled TFA in CH_2Cl_2 was added to each tube. The tubes were stored at room temperature and at successive 30-min intervals the contents of a tube was evaporated by a stream of nitrogen. When this process had been completed the contents of the tubes were analyzed by the NaOH–sodium nitroprusside method described above. No color was obtained. TLC analysis of the reaction products after treatment with TFA showed no differences from **8**.

Registry No. **1**, 51541-28-7; **2**, 75975-46-1; **3**, 75975-47-2; **4**, 75975-48-3; **5**, 51541-31-2; **6**, 75975-49-4; **7**, 75975-50-7; **8**, 75975-51-8; **9**, 62214-22-6; **10**, 68-41-7; *tert*-butoxycarbonyl chloride, 24608-52-4; D-cycloserine, 51541-30-1; butylamine, 109-73-9.

Intramolecular Carbonylation of Vinyl Halides To Form Methylene Lactones

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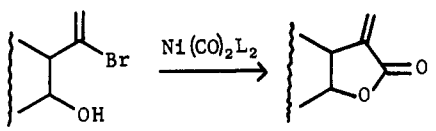
Received June 23, 1980

Sesquiterpene α-methylene lactones continue to serve as stimuli for testing of new strategies for organic synthesis.[2] We have been interested in construction of the α-methylene lactone functionality by use of selective transition-metal-mediated methods.[3,4] For application in a specific synthesis project, we have developed an intramolecular carbonylation procedure (e.g., eq 1) which is



(1)

general and efficient.[5] This process is a variation of the base-promoted carboxylation of vinyl and aryl halides using nickel carbonyl which was discovered by Corey and Hegedus.[6-8] Here we report the formation of five- and six-membered lactones with a convenient nickel reagent and preliminary applications in a two-step cyclization–carbonylation procedure.

A test case is 2-bromo-5-hydroxy-1-pentene (**1**). In direct analogy with the alkoxide-promoted reaction,[6] we first used sodium hydride or *n*-butyllithium to generate the alkoxide. Then, reaction with nickel carbonyl proceeded slowly in tetrahydrofuran, giving carbonylation products **7** (see Chart I) in 20–50% yield after 0.5–1.0 h at 60 °C. Isomerization of the double bond to an endocyclic position was significant using sodium hydride (Table I, entry 1).[9] In

Table I. Carbonylation/Lactonization of 1–6

entry	substr	conditions[a]	product (yield, %)
1	1	$Ni(CO)_4$, NaH, 48 °C, 12 h	7 (25)[b,g]
2	1	$Ni(CO)_4$, BuLi, 59 °C, 1 h	7 (50)
3	1	$Ni(CO)_2L_2$[c], BuLi, 51 °C, 24 h	7 (42)
4	1	$Ni(CO)_4$, reflux, 1.1 h	7 (48), 9 (36)[h]
5	1	$Ni(CO)_4$, 55 °C, 112 h	7 (97),[d] 9 (3)
6	1	$Ni(CO)_2L_2$, 52 °C, 3 h	7 (64), 9 (7)
7	1	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	7 (64), 9 (0)
8	2	$Ni(CO)_4$, reflux, 1 h	8 (54),[i] 10 (28)[h]
9	2	$Ni(CO)_2L_2$, reflux, 1 h	8 (52), 10 (17)
10	2	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 5 min	8 (55)
11	3	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 1 min	11 (76)[j]
12	4	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 1 min	12 (76–80)[j]
13	4	$Ni(CO)_4$, Et_3N,[e] benzene, 50 °C, 2 h	12 (95)
14	5	$Ni(CO)_4$, Et_3N,[e] benzene, 50 °C, 2 h	13 (96)[f]
15	5	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	13 (56)
16	6	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	14 (51)

[a] The solvent is THF unless otherwise noted. $Ni(CO)_4$ is used in 6-fold molar excess, and $Ni(CO)_2L_2$ is used in 1.1- to 2-fold molar excess. [b] The product consists of the *exo*-methylene product **7** and the corresponding endocyclic isomer in a ratio of 2:5. [c] L symbolizes triphenylphosphine. [d] Conversion was 57%. [e] Two molar equivalents with respect to vinyl bromide. [f] Conversion was 90%. [g] A. D. Harmon and C. R. Hutchinson, *J. Org. Chem.*, **40**, 3474 (1975). [h] J. Falbe, N. Hupper, and F. Korte, *Chem. Ber.*, **97**, 863 (1964). [i] C. R. Hutchinson, *J. Org. Chem.*, **39**, 1845 (1974). [j] J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

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(2) For recent examples and leading references, see: (a) F. Kido, K. Tsutsumi, A. Maruta, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **101**, 6420 (1979); (b) R. H. Schlessinger and coworkers, *ibid.*, **101**, 7626, 7627 (1979).

(3) M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, **98**, 3384 (1976).

(4) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and K. Hirotsu, *J. Am. Chem. Soc.*, **100**, 5565 (1978).

(5) A portion of this work was presented at the 178th National Meeting of the American Chemical Society, Washington, DC; Abstract ORGN 98.

(6) E. J. Corey and L. Hegedus, *J. Am. Chem. Soc.*, **91**, 1233 (1969).

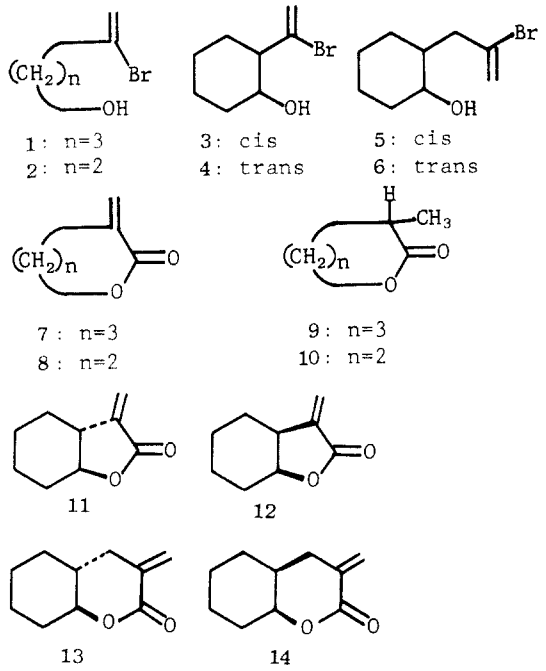
(7) An efficient palladium-promoted carbonylation procedure which effects conversions parallel with that represented in eq 1 has been discovered by Norton, Shenton, and Schwartz [*Tetrahedron Lett.*, 52 (1975)] and developed by Norton and co-workers: T. F. Murray and J. R. Norton, *J. Am. Chem. Soc.*, **101**, 4107 (1979).

(8) (a) Closely related results were reported after this work was largely complete: I. Matsuda, *Chem. Lett.*, 773 (1978). (b) An equivalent transformation has been carried out on hydroxyvinyl bromides related to **3** and **4** in methyl alcohol, producing the corresponding hydroxy esters which were induced to lactonize: R. K. Boeckman and M. Ramaiah, *J. Org. Chem.*, **42**, 1583 (1977).

(9) The yields quoted are of material purified by short-path distillation or sublimation. The difference between the yield of a component in the crude product mixture and of isolated product is often significant for these easily polymerized compounds.

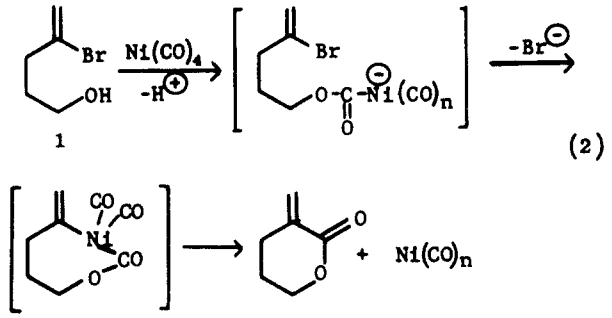
0022-3263/81/1946-1723$01.25/0

Chart I



general, the yields starting from the alkoxide were not satisfactory.

The reaction proceeds at a slightly slower rate but with higher efficiency in the absence of base (Table I, entries 4 and 5). Bis(triphenylphosphine)nickel dicarbonyl [Ni(CO)$_2$L$_2$] was, in general, as effective as nickel carbonyl, even with only a small molar excess. This reagent is more convenient than Ni(CO)$_4$, since it is a nonvolatile, air-stable, crystalline solid.[10] A reasonable mechanism for the reaction involves initial addition of the hydroxy unit to the nickel reagent, either by attack at nickel followed by CO migration or by direct addition to one of the CO units (eq 2).[11] The byproducts are HBr and zerovalent

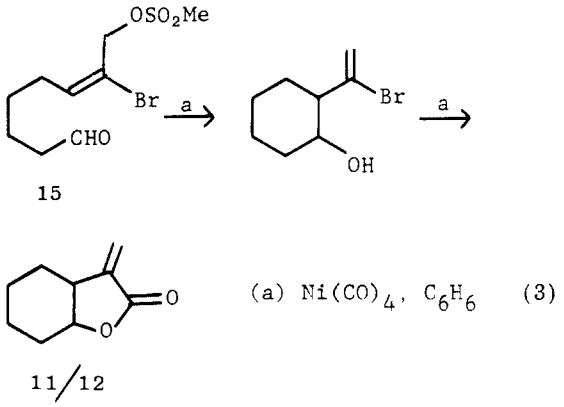


nickel, so the process is formally catalytic in nickel. However, attempts to define a truly catalytic cycle have failed; reaction with 0.1 molar equiv of Ni(CO$_2$)L$_2$ with 1 in the presence of 1 atm of CO effected only stoichiometric conversion to 7. Consistent with a mechanism involving initial addition of the hydroxyl oxygen to Ni(CO)$_4$ is the observation that the acetate of 1 is inert to Ni(CO)$_4$ under conditions where 1 reacts rapidly.

With both nickel reagents, the reaction in the absence of base produced a new byproduct, the saturated lactone **9**, in variable yield, sometimes as high as 36% (entry 4). When the reaction was run under minimum conditions of time and temperature, the yield of saturated lactone was minimized (entries 5 and 6). With the other substrates (**2–6**), the corresponding saturated lactones were formed in less than 5% yield. The mechanism of formation of the saturated lactones has been probed by using the monodeuterio analogue of **1** (eq 1). The product (**9**) shows partial deuteration of the CH_3 and methine H adjacent to the carbonyl group,[12] consistent with hydrogenation involving the hydrogen bromide generated from the hydroxyl hydrogen.

One molar equivalent of triethylamine in the solution completely suppressed the reduction reaction and strongly accelerated carbonylation (entry 7). There appears to be an induction period in the reactions promoted by triethylamine, and a short time (2–5 min) at reflux in THF gave excellent results. The reaction is efficient for five- and six-membered-ring lactones, both simple monocyclic (**7** and **8**) and cis and trans ring-fused derivatives (**11–14**). As before for **1**, while the reaction does proceed in the absence of base, fast, efficient carbonylation occurred in the presence of triethylamine.

The intramolecular carbonylation involves zero valent nickel, as does a related reductive cyclization method for ring closures in α-methylene lactone synthesis.[3,4] Development of the carbonylation procedure now allows a combination ring closure–carbonylation sequence (eq 3) where



the zero valent reagent serves two different roles. Treatment of allylic methanesulfonate ester **15a** with excess nickel carbonyl under conditions favoring complete conversion (95 h, 65 °C, benzene) gave a mixture of **11** and **12** (2:1 ratio) in 58% yield. At shorter reaction times, the intermediate vinyl bromide alcohols (**3** and **4**) can be isolated. Treatment of **15b** with nickel carbonyl for 28 h at 65 °C in benzene afforded **3** and **4** (2:1, 49% isolated yield) and minor amounts of **11** and **12** (2:1, 9%).

We are studying the factors which control the ring-fusion stereochemistry in **11**/**12** and applications in the synthesis of natural α-methylene lactones.

Experimental Section

General Methods. The bis(triphenylphosphine)dicarbonylnickel was either purchased from Alfa or synthesized from nickel tetracarbonyl and 2 equiv of triphenylphosphine in refluxing ether by the method of Rose and Stathom.[14] Nickel tetracarbonyl was

(10) Bis(triphenylphosphine)nickel dicarbonyl is likely to be toxic, similar to nickel carbonyl, but the low volatility makes it easy to avoid ingestion. It is commercially available and easily prepared.

(11) This mechanism is essentially an adaptation of that proposed by Hegedus: L. S. Hegedus, Ph.D. Thesis, Harvard University, 1969.

(12) Treatment of deuterio alcohol **1** (78% OD by ^{1}H NMR integration) with nickel carbonyl in tetrahydrofuran at reflux for 1.0 h yielded **9** as a mixture of deuterium-labeled isomers: ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 2.1 H, CH_3), 1.3–2.3 (m, 4.2 H, $OCH_2CH_2CH_2$), 2.4–2.8 (m, 0.4 H, $CHCO_2$), 4.30 (t, J = 6 Hz, 2.0 H, OCH_2); mass spectrum, m/e (relative intensity) 116 (7.6, parent-d_2), 115 (10.2, parent-d), 114 (4.3, parent), 56 (100).

(13) Coupling of allylic halides with nickel carbonyl is a general process: (a) I. D. Webb and G. T. Borcherdt, *J. Am. Chem. Soc.*, **73**, 2654 (1951); (b) M. F. Semmelhack, *Org. React.*, **19**, 162 (1972).

obtained from Matheson, delivered into an argon-filled flask, and then transferred via syringe to the reaction mixture. The tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl just prior to use.

Example of Carbonylation with Nickel Carbonyl. Conversion of 3 to 11. A 100-mL, three-necked flask equipped with a reflux condensor with a three-way stopcock and gas balloon, a magnetic stirrer, a rubber septum, and a stopper was charged with 0.139 g (0.68 mmol) of vinyl bromide alcohol **3**, and the system was evacuated (0.02 torr) and filled with argon (repeated three times). Via syringe was added 50 mL of dry benzene, and the system was alternately evacuated (until the solvent vigorously frothed) and then filled with argon (repeated five times). Via syringe was introduced 2 molar equiv of triethylamine (0.19 mL, 0.136 g, dried by passage through a short column of basic, activity grade I alumina), followed by the addition of 6 molar equiv of nickel carbonyl (0.5 mL, 0.64 g). The solution was heated at 65 °C. After ca. 2 min, the solution developed a yellow color, and over the course of 5 min underwent the following color changes: yellow to brown to black, at which point a black solid precipitated from the solution. The mixture was stirred an additional 5 min at 65 °C and was then allowed to cool to ca. 30 °C, at which point the excess nickel carbonyl was removed via aspirator pressure over 20 min into a liquid nitrogen trap and destroyed by reaction with excess iodine at 25 °C. The residue in the reaction flask was rinsed into a separatory funnel with 25 mL of benzene, and the benzene layer was washed with 1 N aqueous hydrochloric acid (2 × 50 mL, the black solid readily dissolved). The combined aqueous layers were extracted with ether (4 × 20 mL), and then the combined organic layers were washed with saturated aqueous sodium bicarbonate followed by saturated sodium chloride solution. After having been dried ($MgSO_4$), the solution was concentrated by rotary evaporation to give a light yellow liquid which crystallized on standing. The crude product was sublimed [30 °C (0.05 torr)] to give colorless crystals (0.099 g, 95%) of **11**.

Example of Carbonylation with Bis(triphenylphosphine)dicarbonylnickel. Conversion of 5 to 13. A 100-mL, three-necked flask equipped with a reflux condenser, an argon inlet, a rubbet septum, and a magnetic stirrer was charged with 0.979 g (1.53 mmol, 1.1 molar equiv) of bis(triphenylphosphine)dicarbonylnickel and 0.309 g (1.41 mmol) of **5**. The system was alternately evacuated (0.02 torr) and filled with argon three times. Via syringe was introduced 20 mL of dry tetrahydrofuran, the system was alternately evacuated (until the solvent vigorously frothed) and filled with argon five times, and 0.4 mL (0.29 g, 2.9 mmol, 2 molar equiv) of triethylamine was added. The mixture was heated at reflux for 2 min, during which the color changed from yellow to orange to brown and finally to green. The mixture was cooled to 25 °C, poured into 50 mL of ether, and washed with two 20-mL portions of aqueous 1 N hydrochloric acid. The combined aqueous layers were extracted with ether (4 × 20 mL), and then the combined organic layers were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Having been dried ($MgSO_4$), the organic solution was concentrated by rotary evaporation to yield a heterogeneous green residue. The product was isolated by sublimation [ca. 80 °C (0.003 torr)] to give 0.132 g (56%) of a white crystalline solid, mp 63.5–67 °C.

Characterization Data for Compounds in Table I. 4-Bromopenten-1-ol (1): colorless liquid; bp 70–71 °C (3.8 torr); ^{1}H NMR ($CDCl_3$) δ 5.53 (m, 1.0 H, HC=CBr, anti), 5.33 (d, J = 2 Hz, 0.9 H, HC=CBr, syn), 3.58 (t, J = 6.5 Hz, 2.0 H, CH_2O), 3.50 (s, 1.0 H, OH), 2.50 (t with additional coupling, J = 7 Hz, 1.9 H, C=CCH_2), 1.77 (quintet with additional coupling, J = 7 Hz, 1.9 H, $CH_2CH_2CH_2$); IR ($CHCl_3$) 3620 (m) and 3450 (br, m, OH), 1635 (m, C=C), 1433 (w), 1040 (br, s), 933 (w), 890 (s) cm^{-1}; mass spectrum, no molecular ion, m/e (relative intensity) 148, 146 (2, $M^+ - H_2O$), 135, 133 (1), 122, 120 (17), 84 (43), 39 (100).

Anal. Calcd for C_5H_9BrO: C, 36.39; H, 5.50; Br, 48.42. Found: C, 36.78; H, 5.59; Br, 48.07.

3-Bromo-3-buten-1-ol (2): Colorless liquid; bp 64–65 °C (8.55 torr); ^{1}H NMR ($CDCl_3$) δ 5.62 (m, 1.0 H, HC=CBr, anti), 5.43 (d, J = 2 Hz, 1.0 H, HC=CBr, syn), 3.97 (s, 1.1 H, OH), 3.72 (t, J = 6.3 Hz, 2.2 H, CH_2O), 2.62 (t, J = 6.3 Hz, 2.0 H, CH_2C=C); IR ($CHCl_3$) 3600 (w) and 3400 (br, w, OH), 1635 (m, C=C), 1212 (s), 1050 (m, br), 895 (m) cm^{-1}; mass spectrum, m/e (relative intensity) 152, 150 (9, M^+), 122, 120 (50), 76 (29), 41 (83), 40 (100).

Anal. Calcd for C_4H_7OBr: C, 31.82; H, 4.67; Br, 52.92. Found: C, 46.91; H, 6.40; Br, 38.91.

***trans*-2-(1-Bromovinyl)cyclohexanol (3)**: colorless crystals; mp 87–90 °C; ^{1}H NMR ($CDCl_3$) δ 5.76 (d, J = 1.9 Hz, 1.0 H, HC=CBr, anti), 5.52 (d, J = 1.8 Hz, 1.0 H, HC=CBr, syn), 3.53 (br m, 1.0 H, CHO), 2.33 (s, 1.2 H, OH), 2.3–1.1 (m, 9 H, cyclohexyl); IR ($CHCl_3$) 3570 (w) and 3450 (w, br, OH), 1620 (m, C=C), 1450 (m), 1052 (m), 1042 (m), 900 (m) cm^{-1}; mass spectrum, m/e (relative intensity) 206, 204 (1, M^+), 125 (89), 107 (55), 55 (100), 43 (99.7).

Anal. Calcd for $C_8H_{13}OBr$: C, 46.85; H, 6.39; Br, 38.96. Found: C, 46.80; H, 6.45; Br, 39.04.

***cis*-2-(1-Bromovinyl)cyclohexanol (4)**: colorless solid; mp 36–38 °C; ^{1}H NMR ($CDCl_3$) δ 5.63 (m, 2.0 H, C=CH_2), 4.29 (m, 1.0 H, CHO), 2.4 (m, 1 H, CHC=C), 2.1–1.1 (m, 9 H, cyclohexyl and OH); IR (film) 3230 (br, m, OH), 1635 (m, C=C), 1450 (m), 1125 (m), 970 (s), 885 (m) cm^{-1}; mass spectrum, m/e (relative intensity) 206, 204 (0.5, M^+), 160, 158 (6), 159, 157 (4), 125 (100), 107 (41).

Anal. Calcd for $C_8H_{13}OBr$: C, 46.85; H, 6.39; Br, 38.96. Found: C, 46.91; H, 6.40; Br, 38.91.

***trans*-2-(2-Bromo-2-propenyl)cyclohexanol (5)**: colorless liquid; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.58 (td, J = 1.5 Hz, J' = 0.6 Hz, 1 H, HC=CBr, anti), 5.44 (dd, J = 1.5 Hz, J' = 2.7 Hz, 1 H, H_ACC=C, deshielded by hydroxyl O), 2.13 (dd, J = 14 Hz, J' = 9 Hz, HCC=C), 1.95 (s, 1 H, OH), 2.0–0.8 (m, 9 H, cyclohexyl); ^{13}C NMR ($CDCl_3$) 133.4, 117.8, 74.1, 44.6, 43.4, 35.8, 29.6, 25.3, 24.8; IR (film) 3350 (br, s, OH), 1630 (m, C=C), 1450 (m), 1205 (m), 1060 (m), 1035 (m), 880 (m) cm^{-1}; mass spectrum, no molecular ion, m/e (relative intensity) 202, 200 (1.5, $M^+ - H_2O$), 139 (47), 121 (29), 98 (77), 39 (100).

***cis*-2-(2-Bromo-2-propenyl)cyclohexanol (6)**: colorless liquid; bp 60 °C (0.003 torr); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.60 (distorted d, J = 2 Hz, 1 H, HC=CBr, anti), 5.44 (distorted d, J = 2 Hz, 1 H, HC=CBr, syn), 3.92 (br, s, 1 H, CHO), 2.48 (symmetrically disposed m of seven signals with 7-Hz spacing, 2 H, allylic CH_2), 2.0–1.0 (m, 10 H, alicyclic H and OH); IR (film) 3420 (br, m, OH), 1629 (m, C=C), 978 (m), 888 (m) cm^{-1}; mass spectrum, no molecular ion, m/e (relative intensity) 202, 200 (0.1, $M^+ - H_2O$), 163 (3), 149 (9), 139 (39), 121 (25), 98 (73), 81 (100).

Anal. Calcd for $C_9H_{15}BrO$: C, 49.33; H, 6.90; Br, 36.47. Found: C, 49.44; H, 6.96; Br, 35.91.

Anal. Calcd for $C_9H_{15}BrO$: C, 49.33; H, 6.90; Br, 36.47. Found: C, 49.68; H, 6.97; Br, 36.02.

α-Methylene-*trans*-2-hydroxycyclohexanepropionic acid δ-lactone: colorless crystalline solid; mp 34–36 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.42 (m, 1.0 H, HC=CCO, syn), 5.55 (m, 1.0 H, HC=CCO, anti), 3.95 (td, J = 10.0 Hz, J' = 4.0 Hz, CHO, 1.0 H), 2.66 (ddd, J = 15 Hz, J' = 4 Hz, J'' = 0.5 Hz, CHC=C, 1.1 H), 2.38 (dt, J = 13 Hz, J'' = 2.5 Hz, 1 H, CHC=C), 2.3–1.1 (m, 9 H, cyclohexyl); IR ($CHCl_3$) 1715 (δ lactone), 1630 (C=C), 1180 cm^{-1}; mass spectrum, m/e (relative intensity) 166 (100, M^+), 138 (6, $M^+ - 28$); ^{13}C NMR ($CDCl_3$) 165.6, 134.3, 127.7, 83.0, 38.9, 35.1, 32.1, 30.8, 24.8, 24.0.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.86; H, 8.52.

α-Methylene-*cis*-2-hydroxycyclohexanepropionic acid δ-lactone (14): colorless crystalline solid; mp 63.5–67 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.43 (m, 1.2 H, OCC=CH, syn), 5.55 (m, 1.0 H, OCC=CH, anti), 4.59 (m, 1.1 H, CHO), 2.75 (d of quintets, J = 15 Hz, J' v 2.5 Hz, 1.1 H, CHC=C), 2.52 (d of quintets, J = 16 Hz, J' = 1.5 Hz, 1.1 H, CHC=C), 2.2–1.85 (m, 2 H, diaxial cyclohexyl H's), 1.9–1.2 (m, 7 H, cyclohexyl H); IR ($CHCl_3$) 1710 (δ-lactone), 1628 (C=C), 1305, 1180, 1145, 995 cm^{-1}; mass spectrum, m/e (relative intensity) 166 (M^+), 138 (M - CO); ^{13}C NMR ($CDCl_3$) 165.9, 132.6, 128.5, 78.6, 33.7, 33.5, 30.5, 25.6, 24.2, 19.6.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.55.

Compound 15a: light yellow oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.76 (t, J = 1.5 Hz, 1 H, CHO), 6.23 (tt, J = 7.0 Hz, J' = 0.9 Hz, 1 H, vinyl H), 4.85 (d, J = 0.9 Hz, 2 H, C=CCH_2O), 3.08 (s, 3 H, OSO_2CH_3), 2.48 (td, J = 7 Hz, J' = 1.6 Hz, 2 H, CH_2C=O),

(14) A. A. Rose and A. A. Stathom, *J. Chem. Soc.*, 69 (1950).

2.3–2.1 (m, 2 H, $CH_2C{=}CBr$), 1.8–1.3 (m, 4 H, $CH_2CH_2CH_2C{=}O$); ^{13}C NMR ($CDCl_3$) 201.9, 136.3, 118.7, 74.0, 43.2, 38.4, 30.6, 27.1, 21.3; IR (film) 2720 (w, CHO), 1720 (s, C=O), 1640 (w, C=C), 1355 (s, br), 1175 (s), 940 (s) cm^{-1}.

Acknowledgment. Financial support of this program by the National Institutes of Health is gratefully acknowledged.

Registry No. 1, 64180-78-5; 2, 76334-36-6; 3, 76334-37-7; 4, 76334-38-8; 5, 76334-39-9; 6, 76334-40-2; 7 (isomer 1), 42023-19-8; 7 (isomer 2), 72649-02-6; 8, 547-65-9; 9, 10603-03-9; 10, 1679-47-6; 11, 3727-53-5; 12, 16822-06-3; 13, 51043-42-6; 14, 51043-43-7; 15a, 76346-78-6; nickel carbonyl, 13463-39-3; bis(triphenylphosphine)dicarbonylnickel, 13007-90-4.

Stereospecific Synthesis of the Marine Sterol Stellasterol, (22*E*,24*S*)-5α-Ergosta-7,22-dien-3β-ol

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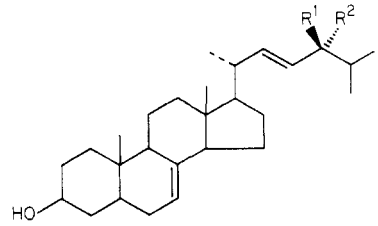
The name stellasterol was coined by Kossel and Edlbacher[2] for a sterol, isolated from the starfish *Asterias rubens*, to which Bergmann and Stansbury[3] attributed the structure **1a** but which they believed to have the 20*S* configuration.

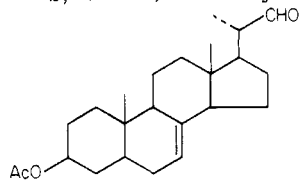
More recently Kobayashi et al.[4,5] isolated a sterol from the starfish *Asterias amurensis* to which they assigned the structure of (22*E*,24*S*)-5α-ergosta-7,22-dien-3β-ol (**1a**). Smith et al. also assigned the structure **1a** to a C_{28} sterol isolated from the starfish *Asterias rubens*.[6] In all cases the structure was assigned on the basis of differences in chemicophysical properties between **1a** and 24*R* epimer **1b** obtained from ergosterol.[7]

We now report the first synthesis of **1a**. The sterol was prepared from the aldehyde **2**,[8] using the method developed by Sucrow and co-workers.[9] This method permits the construction of the chiral center at C-24 in a predictable way from a *Z* allylic C-22 alcohol via a Claisen rearrangement as recently confirmed by us[10] and by others[11,12] in the synthesis of two side-chain models of oogoniols.

Aldehyde **2** reacted with (3-methylbutynyl)magnesium bromide to give a 3:2 mixture of the (22*S*)- (**3a**) and (22*R*)-(**3b**) 3β-acetoxy-5α-cholest-7-en-23-yne-3,22-diols which were separated by chromatography. The 22*R* configuration



1a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$



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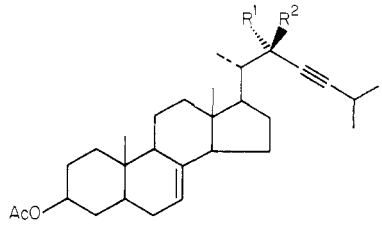
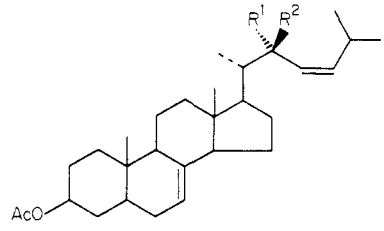
was assigned to the more polar major component **3b** and consequently the 22*S* to the less polar component **3a** on the basis of the usually observed polarities of epimeric pairs of 22-alcohols.[13] Half-hydrogenation of the acetylenic alcohols **3a** and **3b** over Lindlar catalyst gave the desired 22*R* and 22*S* allylic alcohols **4a** and **4b** with the 23*Z* stereochemistry, as established by ^1H NMR analysis. Attempts to support the configurations at C-22 of **4a** and **4b** by application of the 2-nitrobenzoate chirality rule[14] to the CD spectra of 2-nitrobenzoate **4c** and **4d** were unsuccessful. In fact both derivatives show a positive Cotton effect.



3a, $R^1 = OH$; $R^2 = H$
b, $R^1 = H$; $R^2 = OH$



4a, $R^1 = OH$; $R^2 = H$
b, $R^1 = H$; $R^2 = OH$
c, $R^1 = 2\text{-}NO_2\text{-}C_6H_4CO_2$; $R^2 = H$
d, $R^1 = H$; $R^2 = 2\text{-}NO_2\text{-}C_6H_4CO_2$

Claisen rearrangement of the *Z* allylic alcohol 22*R* (**4a**) with triethyl orthoacetate gave in good yield the *E* ester **5a**. The geometry of the Δ^{23} double bond was indicated by the appropriate ^1H NMR constants and by an infrared band at 970 cm^{-1}. Consideration of the mechanism of the Claisen rearrangement[15,16] suggests that the configurations

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