$KHCO_3$ (0.78 mg, 1 equiv) in water (1.0 mL) was added to form the carboxylate salts. This solution was concentrated under reduced pressure, and the isomers were then separated by HPLC on a reverse-phase column eluting with 20% methanol in 1% ammonium acetate buffer, pH 7.0. The isomers **2a** and **1a** were eluted quantitatively at 6.5 and 7.4 retention volumes, respectively, in the ratio of 1:4.

6-[(*Z*)-Methoxymethylene]penicillanic acid (1a): UV (ammonium salt in water) 245 nm (ϵ 12 400 M^{-1} cm^{-1}); IR (film) 1770, 1752, 1712, 1685, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.65 (s, 3 H), 3.84 (s, 3 H), 4.44 (s, 1 H), 5.87 (d, 1 H, J = 0.7 Hz, 6.96 (d, 1 H, J = 1.7 Hz); mass spectrum (trimethylsilyl ester), m/z 315 (M^+).

6-[(*E*)-Methoxymethylene]penicillanic acid (2a): UV (ammonium salt in water) 252 nm (ϵ 10 300 M^{-1} cm^{-1}); IR (film) 1763, 1745, 1723, 1688, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.65 (s, 3 H), 4.01 (s, 3 H), 4.43 (s, 1 H), 5.65 (s, 1 H), 6.40 (s, 1 H); mass spectrum (trimethylsilyl ester), m/z 315 (M^+).

β-Lactamase Inhibition and Inactivation by 1a. The TEM-2 β-lactamase was purified to homogeneity from *E. coli* W3110 carrying the RP4 plasmid. The inhibition of the β-lactamase by **1a** was followed by assay of the remaining enzyme activity. The enzyme (10–40 μL of a 22 μM solution) was incubated with 6-(methoxymethylene)penicillanic acid (20–50 μL of a 4.7 mM solution). Portions (5 μL) were withdrawn at appropriate intervals and mixed with a buffered solution (3.0 mL) of benzylpenicillin (3 mM), and the hydrolysis of the latter was followed at 240 nm.

Acknowledgment. I would like to thank Jeremy Berg for invaluable assistance with the X-ray crystal structure, Jim Kadonaga for help with the microbiological work, and Alan Barton for advice. I am also grateful to J. R. Knowles (in whose laboratory this work was done) and to E. J. Corey and Y. Kishi for helpful discussions. The comments of the reviewers were especially helpful in revising this manuscript. This work was supported by a grant (to J. R. Knowles) from the National Institutes of Health. I am grateful to Shell for a graduate fellowship.

Supplementary Material Available: Lists of atomic coordinates, thermal parameters, bond distances, bond angles (4 pages). (Observed and calculated structure factors are available from the author.) Ordering information is given on any current masthead page.

Total Synthesis of (±)-Isoclovene

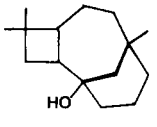
Pier Giovanni Baraldi,† Achille Barco,‡ Simonetta Benetti,‡ Gian Piero Pollini,*,† Eleonora Polo,‡ and Daniele Simoni†

Istituto Chimica Farmaceutica e Tossicologica, Università degli Studi, Ferrara, Italy, and Istituto Chimico, Università degli Studi, Ferrara, Italy

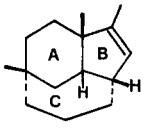
Received April 17, 1984

A total synthesis of racemic isoclovene (**2**), the most abundant sesquiterpene artifact derived from acid treatment of caryolan-1-ol (**1**), is presented. The characteristic tricyclo[6.2.2.$0^{5,12}$]dodecane skeleton of **2** has been set up creating the seven-membered ring C through an internal Michael addition of the suitably functionalized hydrindenone system **5**. The latter was in turn obtained starting from the readily available *cis*-4,5,6,7,8,9-hexahydro-8-methylindan-1,5-dione (**7**) in 15 steps, the most significant of which was a [3,3]-sigmatropic rearrangement which allowed the establishment of the correct stereochemistry of the quaternary center at C-5.

Acid treatment of caryolan-1-ol **1** represents a source of a wide variety of rearranged sesquiterpene artifacts, all but one featured by basic carbon frameworks common to many other natural compounds.[1] In fact only isoclovene **2** incorporates an unprecedented and unusual tricyclo[6.2.2.$0^{5,12}$]dodecane skeleton. Its structure was determined by X-ray crystallographic analysis of the crystalline derivative resulting by addition of hydrogen chloride.[2] Its possible mode of formation from **1** was investigated and a plausible mechanistic scheme was proposed.[3] The rarity of the carbon skeleton of **2** unlike the other compounds having the same origin, probably accounts for the limited literature on its chemistry.[4-7] The year 1983 marked a



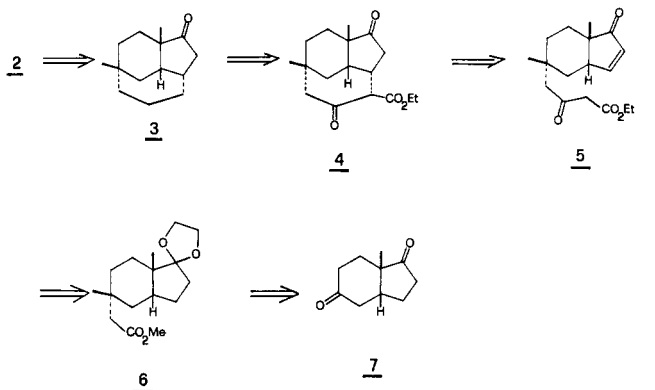
1



2

renaissance of interest in the chemical synthesis of **2** and two confirmatory syntheses of its structure, tackling the problem from a significantly different point of view, were reported by Kellner and Loewenthal[8] and by our group.[9]

Scheme I

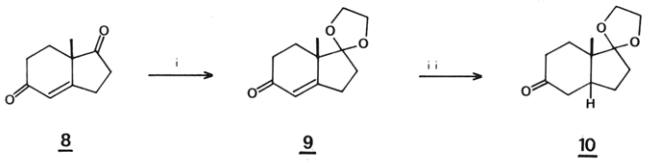


† Istituto Chimica Farmaceutica e Tossicologica.
‡ Istituto Chimico.

(1) Lutz, A. W.; Reid, E. B. *J. Chem. Soc.* **1954**, 2265. Henderson, G. G.; McCone, R. O. O. *Ibid.* **1929**, 1368.
(2) Clunie, J. S.; Robertson, J. M. *J. Chem. Soc.* **1961**, 4382.
(3) Crane, R. I.; Eck, C.; Parker, W.; Penrose, A. B.; McKillop, T. F. W.; Hawley, D. M.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 385.
(4) Traverso, G.; Bothner-By, A. A.; Pollini, G. P.; Barco, A., II *Farmaco, Ed. Sci.* **1966**, *21*, 645.

0022-3263/85/1950-0023$01.50/0

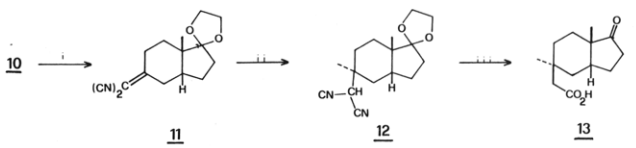
Scheme II[a]



8 9 10

[a] Reagents: i, MED, ii, H_2/Pd.

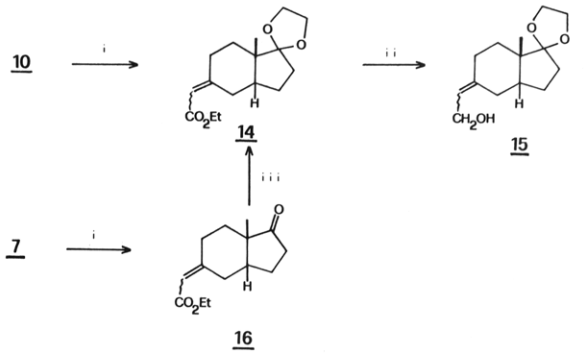
Scheme III[a]



11 12 13

[a] Reagents: i, $CH_2(CN)_2$, AcOH, $AcONH_4$; ii, Me_2LiCu; iii, KOH, $(CH_2OH)_2$.

Scheme IV[a]



14 15 16

[a] Reagents: i, $(C_6H_5)_3P{=}CHCO_2Et$; ii, $LiAlH_4$; iii, $(CH_2OH)_2$, *p*-toluenesulfonic acid.

We detailed in this paper the results of the studies that have culminated in a total synthesis of **2** as its racemate. Our approach to **2** is retrosynthetically outlined in Scheme I. We chose to follow a route for assembling the tricyclo[6.2.2.$0^{5,12}$]dodecane skeleton involving the suitable functionalization of a preexisting AB unit, followed by an intramolecular cyclization providing the seven-membered C ring and thus completing the tricyclic frame. We were intrigued by the possibility of employing as the cornerstone of our strategy an internal Michael addition, already successfully operating in the construction of five- and six-membered rings.[10-12] Based on this analysis, four objectives were defined for the successful completion of the project: (i) preparation of a suitable starting material; (ii) construction of the quaternary center at C-5 possessing the correct stereochemistry; (iii) elaboration of the donor–acceptor system to allow the crucial Michael step; (iv) final elaboration of the derived tricyclic intermediate to complete the synthesis of **2**.

The Starting Material. The readily available **8** was chosen as a convenient starting point. Well-established procedure[13] allows chemoselective differentiation of the two carbonyl groups by ketal exchange with 2-methyl-2-ethyl-1,3-dioxolane (MED) to produce the monoketal **9** and to secure the requisite cis stereochemistry of the ring junction through catalytic reduction to give **10** (Scheme II). Both carbonyls are strategically located at C-5 and C-1, the first in an ideal position to become a precursor of the quaternary center, the second with a dual function, first in the elaboration of the $\alpha\beta$-unsaturated system and later as synthon for the ultimate introduction of the methyl group.

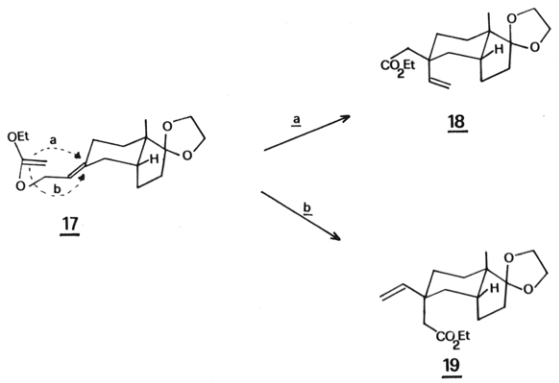
Construction of the Quaternary Center at C-5. The creation of the quaternary center at C-5 with the correct stereochemistry provides the key hurdle that a successful synthesis of **2** must surmount. In a first attempt we tried to perform this crucial operation through the conjugate addition of lithium dimethylcopper to the Knovenagel product **11** obtained by reaction of **10** with malononitrile in the presence of acetic acid–ammonium acetate. The addition of the organocuprate proceeded with high stereospecificity producing a good yield of a 1,4-adduct **12** as the sole isolable product. Its saponification under severe conditions (sodium hydroxide in refluxing ethylene glycol) took place with concomitant decarboxylation affording after acidification the crystalline keto acid **13** (Scheme III).

We expected that the known[14] stereospecificity of addition of organocuprates to an alkylidene derivative like **11** should form an adduct in which the newly introduced methyl group possessed a cis relationship with the angular group deriving by a preferred attack from the less hindered face. In contrast, the structure of **13**, determined unambiguously by X-ray crystallographic analysis,[15] showed that the reaction occurred in the opposite way, that is from the more hindered convex side producing the undesired compound **12**. The remarkable stereoselectivity of the addition can be explained assuming that a complexation of the organometallic reagent with the oxygen atom of the ketal moiety is involved. We therefore turned our attention to alternative methods to achieve our goal and we felt that the Claisen rearrangement of allyl vinyl ethers, which found a widespread utilization in natural products chemistry because it makes possible the buildup of desired stereochemistry at quaternary centers,[16] could be ideally suited to our purposes. To this end we transformed **10** into the allylic alcohol **15** by a two-step sequence involving prior reaction with (carbethoxymethylene)triphenylphosphorane to afford the ketal ester **14** as a 1:1 E/Z mixture, successively converted into **15** by reduction with lithium aluminum hydride (Scheme IV). [At this point we found it more convenient to reduce the starting material **8** to the known[13] dione **7**, having discovered that the two carbonyls reacted chemoselectively with (carbethoxymethylene)triphenylphosphorane to give **16**, and then convert it to **14** by standard ketalization conditions, $(CH_2OH)_2$, *p*-toluensulfonic acid, and benzene.]

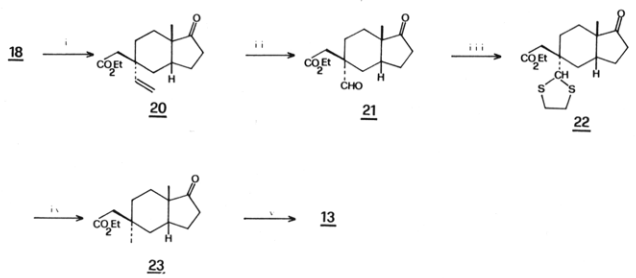
It is well-known that the Claisen rearrangement is a concerted intramolecular process involving a cyclic six-centered transition state. House et al.[17] investigated the question whether the involvement of such a transition state

(5) Mahalanabis, K. K. *Indian J. Chem.* **1967**, *5*, 124.
(6) Traverso, G.; Pollini, G. P.; Barco, A.; Anastasia, M.; Bothner-By, A. A. *Gazz. Chim. Ital.* **1969**, *99*, 863.
(7) Goswami, P.; Venkateswaran, R. V.; Dutta, P. C. *Indian J. Chem.* **1976**, *14*, 299.
(8) Kellner, D.; Loewenthal, H. J. E. *Tetrahedron Lett.* **1983**, *22*, 3397.
(9) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1983**, *22*, 5669.
(10) Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978**, 2445.
(11) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776.
(12) Stork, G.; Shiner, S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.
(13) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.
(14) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128.
(15) Bertolasi, V.; Ferretti, V.; Gilli, G. *Cryst. Struct. Commun.* **1982**, *11*, 1459.
(16) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. "Synthesis of Natural Compounds through Pericyclic Reactions"; American Chemical Society: Washington, D.C., 1983; ACS Monograph No. 180.
(17) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.

Scheme V



Scheme VI[a]

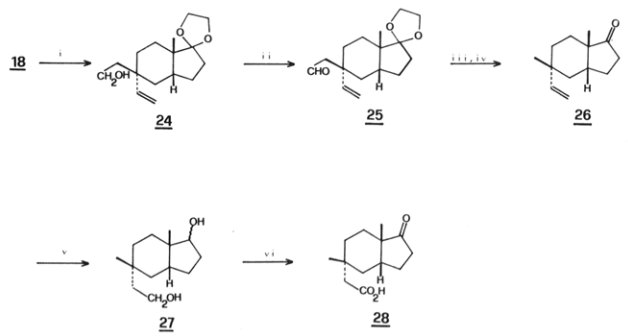


[a] Reagents: i, H^+, H_2O; ii, O_3; iii, $(CH_2SH)_2$, $BF_3 \cdot Et_2O$; iv, Ni-Raney; v, K_2CO_3, H_2O.

may exhibit a selectivity for either axial or equatorial attack at a double bond exocyclic to a cyclohexane ring and found that in the two cases studied there was a slight preference for attack to form a new equatorial bond. However, although the stereochemical outcome of this rearrangement was not safely predictable, we were encouraged to examine the behavior of **15** since, whatever the experimental result may have been, both substituents introduced were amenable for a degradation to a methyl group. The rearrangement of the allyl vinyl ether **17**, deriving from **15** by treatment with ethyl orthoacetate in the presence of propionic acid as catalyst at 140–145 °C, may evolve along the two pathways indicated as a and b by dotted lines, the former originating a new carbon–carbon bond to give **18**, the latter to yield **19** (Scheme V).

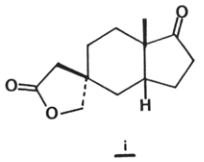
We observed that the reaction took place with a very high degree of stereoselectivity producing a 98:2 mixture of C-5 epimers **18** and **19**. In order to establish the configuration of the major component **18** the shortest route seemed to be the transformation of the vinyl group into a methyl group, through ozonolytic cleavage to furnish an intermediate aldehyde, further converted into the corresponding thioketal for the final desulfurization. To this end the rearranged ester **18** was deketalized by brief acid treatment to give **20** (to avoid the subsequent possible trans-acetalization with the incoming aldehydic group) and submitted to ozonolysis followed by quenching with dimethyl sulfide. The derived aldehyde **21** could be selectively thioketalized by treatment with stoichiometric quantities of ethanedithiol in the presence of boron trifluoride–ether complex to give the corresponding thioketal **22**. Its reductive desulfurization was readily achieved by action of Raney Ni in boiling ethanol, thus completing the conversion of the original vinyl group into a methyl group. Mild basic treatment of **23** resulted in the formation of the crystalline keto acid **13** which was shown to be identical in all respects to that obtained by the previously described route, showing that the carbon–carbon-forming step of the Claisen rearrangement occurred through a preferred attack

Scheme VII[a]



[a] Reagents: i, $LiAlH_4$; ii, PCC; iii, C/Pd, heat; iv, 10% H_2SO_4; v, B_2H_6; vi, Jones.

from the less hindered side. The overall sequence is outlined in Scheme VI. [Ozonolysis of **18** followed by reductive treatment with sodium borohydride and brief acid treatment gave the crystalline lactone i, the structure of which has been established unambiguously by X-ray crystallographic analysis.[15]]

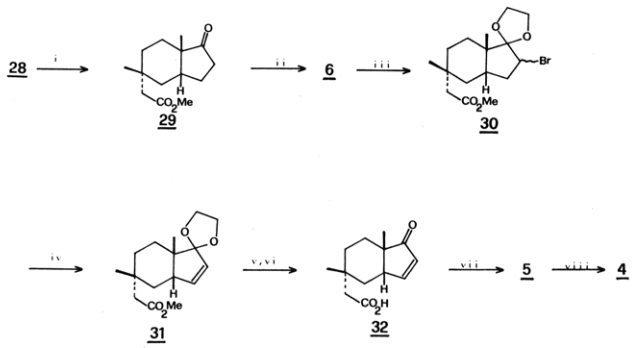


After the stereochemistry of the quaternary center at C-5 was defined, the next operations followed consequently. Thus **18** was converted to the aldehyde **25** by reduction with lithium aluminum hydride followed by oxidation of the alcohol **24** with pyridinium chlorochromate. Thermal decarbonylation of **25** was smoothly achieved by heating at 200–210 °C in the presence of C/Pd, affording **26** in high yield after deketalization by brief acid treatment. **26** was successively hydroborated to afford the diol **27** and eventually oxidized with Jones reagent to the desired acid **28**. The whole sequence is summarized in the Scheme VII.

Elaboration of the Donor–Acceptor Michael Components. We first proceeded to the construction of the acceptor partner for the planned intramolecular Michael addition. Esterification of the keto acid **28** with ethereal diazomethane produced the corresponding keto ester **29**, successively ketalized under standard conditions to afford **6**. The latter was converted to the α,β-unsaturated keto acid **32** by bromination with pyridine hydrobromide perbromide in THF solution to give the bromo compound **30** which, without any purification, was submitted to dehydrohalogenation by refluxing for 8 h in xylene solution in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene to produce **31**. Alkaline hydrolysis of **31** with a methanolic solution of potassium carbonate was followed by exposure to aqueous acid to effect deketalization producing the α,β-unsaturated keto acid **32**. Having the keto acid **32** in hand, we were ready to extend the acetic chain by two carbons in order to obtain the synthon **5**. The chain elongation was accomplished following the elegant procedure introduced by Masamune et al.,[18] which activates the carboxylic function as imidazolide by treatment with carbonyldiimidazole in THF solution to promote the nucleophilic attack of the magnesium salt of monoethyl malonate under essentially neutral conditions. An easy

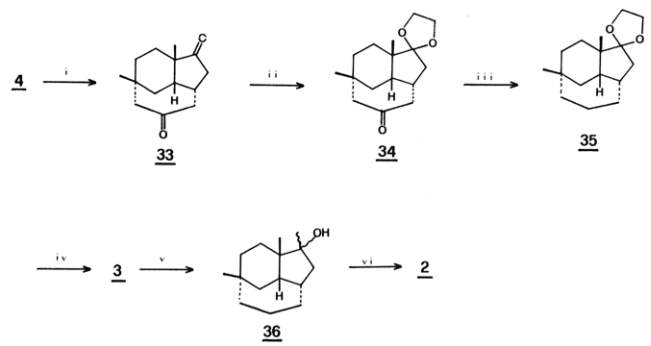
(18) Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72.

Scheme VIII[a]



[a] Reagents: i, MeOH, H^+; ii, $(CH_2OH)_2$, *p*-toluenesulfonic acid; iii, $PyH^+Br_3^-$; iv, DBU; v, K_2CO_3; vi, H^+, H_2O; vii, Im-CO-Im, $EtO_2CCH_2CO_2H$, $Mg(OEt)_2$; viii, K_2CO_3, EtOH.

Scheme IX[a]



[a] Reagents: i, Me_2SO, NaCl; ii, MED; iii, $NH_2NH_2 \cdot H_2O$, KOH, diethylene glycol; iv, H^+, H_2O; v, MeMgI; vi, I_2, catalyst.

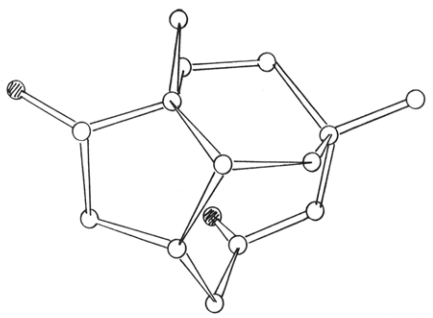


Figure 1. A view of compound **33** showing the different structural environment between the seven- and five-membered carbonyls.

intramolecular Michael addition readily took place when the crude **5** was exposed to ethanolic potassium carbonate giving the crystalline tricyclic compound **4** in high yield. Although **5** could be isolated as pure compound from a byproduct deriving by addition of imidazole itself to the α,β-unsaturated moiety, the latter suffering retro-Michael reaction on treatment with potassium carbonate, it is more convenient to utilize the crude mixture. Scheme VIII summarizes the sequence.

Final Elaboration of the Tricyclic Intermediate 4 to the Target 2. The completion of the isoclovene synthesis, requires two separate structural modifications: (a) removal of the β-keto ester moiety of the seven-membered ring; (b) conversion of the carbonyl group of the cyclopentane nucleus into a methyl-substituted endocyclic olefin. Deethoxycarbonylation was effected in a straightforward fashion by heating **4** in dimethyl sulfoxide in the presence of NaCl.[19] In this fashion the tricyclic diketone **33** was obtained in essentially quantitative yield as a beautiful crystalline compound. The less hindered cyclopentanic carbonyl group (Figure 1), reacted rapidly with the ketal technique exchange with 2-methyl-2-ethyl-1,3-dioxolane producing the monoketal **34** which was submitted to Wolff–Kishner reduction to afford **35**.

After acid treatment to remove the protective group the ketone **3** was obtained in 80% yield. The final stage of the synthesis was achieved conventionally by reaction of **3** with methylmagnesium iodide to give the tertiary carbinol **36** followed by iodine-promoted dehydration to afford eventually **2**. Its spectroscopic data were identical with those of a sample prepared starting from caryolan-1-ol **1** (Scheme IX).

The more significant feature of the ^1H NMR spectrum of isoclovene **2** is the double doublet of the vinylic methyl group coupled to both vinylic and allylic protons. Decoupling of this double doublet shows a coupling constant of 3 Hz for the vinylic proton and of 2 Hz for the allylic proton.

(19) Krapcho, A. P. *Synthesis* **1982**, 805.

Experimental Section

Melting and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by TLC on precoated silica gel 60 F_{254} plates (Merck). Infrared spectra were measured on a Perkin-Elmer 237 spectrometer. Nuclear Magnetic Resonance (^1H NMR) spectra were obtained with a Perkin-Elmer R32, and peak positions are given in parts per millions downfield from tetramethylsilane as an internal standard. All drying operations were performed over anhydrous magnesium sulfate. Petroleum ether refers to the fraction of boiling range 40–60 °C.

(3′aα,7′aα)-Octahydro-7′a-methyl-5′-(dicyanomethylene)spiro[1,3-dioxolane-2,1′-[1*H*]indene] (11). A solution of **10** (4.2 g, 20 mmol) in dry benzene (60 mL) containing malononitrile (2.8 g, 42 mmol), ammonium acetate (0.7 g, 9.1 mmol), and acetic acid (0.86 mL) was refluxed for 6 h in a Dean–Stark apparatus. The cooled mixture was successively washed with 5% aqueous sodium bicarbonate solution (20 mL) and water (20 mL) and dried. Removal of the solvent gave 4.1 g of **11** (79%): mp 69–71 °C (from ether–petroleum ether 1:9); IR (Nujol) 1660 and 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 3.9 (s, 4 H). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 67.74; H, 7.02; N, 10.85. Found: C, 67.58; H, 7.16; N, 10.69.

(3′aα,5′β,7′aα)-Octahydro-5′,7′a-dimethyl-5′-(dicyanomethyl)spiro[1,3-dioxolane-2,1′-[1*H*]indene] (12). Lithium dimethylcuprate was prepared from copper(I) iodide (1.5 g, 7.75 mmol) in dry ether (20 mL) at 0 °C by dropwise addition of methyllithium solution (10 mL) (2 N in *n*-hexane) until the initially yellow precipitate just dissolved. To this was added a solution of **11** (2 g, 7.75 mmol) in ether at 0 °C. The solution was stirred at 0 °C for 2.5 h, poured into saturated aqueous ammonium chloride, and extracted with ether and dichloromethane; subsequently the extracts were dried. Removal of the solvents afforded **12** (1.7 g, 80%) as an oil: IR (film) 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 3.9 (s, 4 H). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.81; H, 8.35; N, 10.05.

(3aα,5β,7aα)-Octahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5-acetic Acid (13). To a solution of potassium hydroxide (2 g, 36 mmol) in ethylene glycol (6 mL) was added **12** (2 g, 7.3 mmol) and the mixture refluxed for 6 h. Water (20 mL) was added to the cooled mixture which was then acidified with 6 N HCl. The precipitated acid was extracted with ether (3 × 25 mL), and the extracts were dried and concentrated to afford 1.4 g of **13** (86%): mp 131–132 °C (ether–petroleum ether 3:2); IR (Nujol) 1700 and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 2.3 (m, 2 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.64; H, 9.03.

(3aα,7aα)-5-(Carbethoxymethylene)octahydro-7a-methyl-1*H*-inden-1-one (16). A solution of **7** (3 g, 18 mmol) in dry toluene (30 mL) was added with [(ethoxycarbonyl)-methylene]triphenylphosphorane (11 g, 30 mmol) and heated at reflux for 20 h. The solvent was removed in vacuo and the residue

treated with petroleum ether (50 mL). The precipitated solid was removed by filtration and the filtrate evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (eluant, petroleum ether:ether 2:1) to give 3.2 g (75%) of **16** as an oil: IR (film) 1650, 1710 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 4.1 (q, 2 H, J = 7 Hz), 5.72 (m, 1 H). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.36; H, 8.41.

(3'aα,7'aα)-Octahydro-7'a-methyl-5'-(carbethoxymethylene)spiro[1,3-dioxolane-2,1'-[1*H*]indene] (14). A solution of **16** (3 g, 13 mmol) in dry benzene (30 mL) containing ethylene glycol (1.08 mL, 19 mmol) was refluxed in the presence of *p*-toluenesulfonic acid (0.05 g) in a Dean–Stark apparatus for 15 h. The cooled mixture was washed with 5% aqueous sodium bicarbonate solution (20 mL) and then with saturated brine (20 mL). The organic layer was dried and evaporated to give 2.98 g (83%) of **14** as an oil: IR (film) 1650 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 3.9 (s, 4 H), 4.1 (q, 2 H, J = 7 Hz), 5.6–5.75 (m, 1 H). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.82; H, 8.51. The same product was obtained by treatment of **10** with [(ethoxycarbonyl)-methylene]triphenylphosphorane as above.

(3'aα,7'aα)-Octahydro-7'a-methyl-5'-(2-hydroxyethylidene)spiro[1,3-dioxolane-2,1'-[1*H*]indene] (15). A solution of **14** (2 g, 7.1 mmol) in dry ether (20 mL) was added to an ice-cooled and well stirred slurry of $LiAlH_4$ (0.4 g, 10 mmol) in ether (2 mL) and the mixture was left at room temperature for 2 h. Careful addition of water (2 mL) allowed the separation of the organic layer from inorganic salts, which were washed with chloroform (3 × 25 mL) by decantation. The combined organic extracts were dried and evaporated in vacuo to yield 1.65 g (98%) of **15** as an oil: IR (film) 1670 and 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 3.9 (s, 4 H), 4.15 (m, 2 H), 5.45 (m, 1 H). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.66; H, 9.44.

(3'aα,5'β,7'aα)-Octahydro-7'a-methyl-5'-vinylspiro[1,3-dioxolane-2,1'-[1*H*]indene]-5'-acetic Acid Ethyl Ester (18). A mixture of 1.5 g (6.3 mmol) of the allylic alcohol **15**, 2.00 mg of propionic acid, and 5.84 g (36 mmol) of freshly distilled ethyl orthoacetate was heated at 140–150 °C with continous removal of EtOH until no more EtOH distilled (4 h). The solution was treated with 5% sodium bicarbonate solution, extracted with ether (2 × 25 mL), and dried. The solvent was removed under reduced pressure. The residual oil was purified by chromatography on silica gel (eluant, petroleum ether:ether, 5:1) to give 0.98 g (65.5%) of **18**: IR (film) 1730 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.2 (t, 3 H, J = 7 Hz), 2.20 (m, 2 H), 3.8 (s, 4 H), 4.00 (q, 2 H, J = 7 Hz), 4.8–5.2 (m, 2 H), 5.8 (dd, 1 H, J = 10 Hz, J = 18 Hz). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.94; H, 9.27.

(3aα,5β,7aα)-Octahydro-7a-methyl-1-oxo-5-vinyl-1*H*-indene-5-acetic Acid Ethyl Ester (20). A mixture of **18** (2 g, 6.5 mmol) in MeOH (10 mL) was treated with 10% sulfuric acid at room temperature for 5 h. Water (5 mL) was added and the mixture extracted with ether (3 × 25 mL). Concentration of the dried extracts in vacuo gave **20** as an oil (1.66 g, 97%): IR (film) 1640 and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 2.37 (s, 2 H), 4.1 (q, 2 H, J = 7 Hz), 4.8–5.25 (m, 2 H), 5.6–6.1 (m, 1 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.60; H, 9.03.

(3aα,5β,7aα)-Octahydro-7a-methyl-1-oxo-5-formyl-1*H*-indene-5-acetic Acid Ethyl Ester (21). A cold (−78 °C) solution of 1.2 g (4.54 mmol) of **20** in 80 mL of CH_2Cl_2 was treated with a stream of O_2 containing 3.4% O_3 until a blue color in the solution indicated excess O_3. After the cold solution had been purged with O_2 to remove the excess O_3, a solution of triphenylphosphine (1.18 g, 4.54 mmol) in CH_2Cl_2 (10 mL) was added and the solution allowed to warm to 0 °C. The solvent was removed under reduced pressure, the residue was treated with ether–petroleum ether 8:1 (20 mL), and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was concentrated to give **21** (1.2 g), which was used without further purification: IR (neat) 1730 and 2700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 2.65 (s, 2 H), 4.15 (q, 2 H, J = 7 Hz), 9.55 (s, 1 H).

(3aα,5β,7aα)-Octahydro-5-(1,3-dithiolan-2-yl)-7a-methyl-1-oxo-1*H*-indene-5-acetic Acid Ethyl Ester (22). To a stirred solution of **21** (1.29 g) in tetrahydrofuran (10 mL) containing 1,2-ethanedithiol (0.38 mL, 4.54 mmol) were added 0.4 mL of boron trifluoride etherate and the mixture was left at room temperature for 24 h. The reaction mixture was poured into 15 mL of saturated aqueous Na_2CO_3 and extracted with ether (3 × 10 mL). After being dried, the solvents were concentrated under reduced pressure to leave **22** (1.4 g, 90%) as an oil: IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.27 (t, 3 H, J = 7 Hz), 2.5 (s, 2 H), 3.15 (s, 4 H), 4.15 (q, 2 H, J = 7 Hz), 4.9 (s, 1 H).

(3aα,5β,7aα)-Octahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5-acetic Acid Ethyl Ester (23). A mixture of crude **22** (1.4 g, 4.06 mmol) and 3 g of W-2 Raney nickel in absolute EtOH was refluxed for 3 h, then filtered on Celite, and concentrated to give 0.48 g (70%) of **23**: IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.02 (s, 3 H), 1.27 (t, 3 H, J = 7 Hz), 2.27 (s, 2 H), 4.12 (q, 2 H, J = 7 Hz). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.56; H, 9.83. The ester **23** (0.3 g, 1.9 mmol) dissolved in MeOH (3 mL) was refluxed for 1 h with K_2CO_3 (0.5 g) in H_2O (3 mL). The cooled mixture was acidified with 5% sulfuric acid and the precipitated crystalline acid, collected by filtration in quantitative yield, was identical with **13** previously described.

(3'aα,5'β,7'aα)-Octahydro-7'a-methyl-5'-vinylspiro[1,3-dioxolane-2,1'-[1*H*]indene]-5'-ethanol (24). A solution of **18** (1 g, 3.24 mmol) in ether (10 mL) was added dropwise to an ice-cooled slurry of $LiAlH_4$ (0.2 g, 5.27 mmol) in ether (15 mL) and the mixture stirred at room temperature for 1.5 h. The excess of reagent and the complex were then decomposed by addition of aqueous sodium hydroxide. Anhydrous sodium sulfate was then added and the solution was filtered and evaporated, yielding **24** as an oil (0.9 g, 93.8%): IR (film) 1635, 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H), 3.4–3.82 (m, 3 H), 3.9 (s, 4 H), 4.85–5.37 (m, 2 H), 5.55–6.07 (m, 1 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.83; H, 9.67.

(3'aα,5β,7'aα)-Octahydro-7'a-methyl-5'-vinylspiro[1,3-dioxolane-2,1'-[1*H*]indene]-5'-acetaldehyde (25). Pyridinium chlorochromate (1.2 g, 5.64 mmol) in dichloromethane (8 mL) was added to a stirred solution of the alcohol **24** (1 g, 3.76 mmol) in dichloromethane (3 mL) and the mixture stirred for 1.5 h at room temperature. Ether (10 mL) was added and the mixture was filtered through a short column of Florisil to give a solution which, on concentration under reduced pressure, gave pure **25** (0.82 g, 83%) as an oil: IR (film) 1640 and 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 2.37 (m, 2 H), 3.92 (s, 4 H), 4.97–5.4 (m, 2 H), 5.72–6.2 (m, 1 H), 9.8 (t, 1 H, J = 3 Hz). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.85; H, 9.01.

(3aα,7aα)-Octahydro-7a,5α-dimethyl-5β-vinyl-1*H*-inden-1-one (26). A mixture of **25** (1 g, 3.78 mmol) and 0.15 g of 10% palladium on charcoal was heated at a bath temperature of 200–210 °C for 3 h. The cooled mixture was treated with ether (25 mL) and filtered on Celite and the filtrate concentrated under reduced pressure. The residue dissolved in THF (5 mL) was treated with 10% sulfuric acid at room temperature for 3 h. The mixture was concentrated at reduced pressure and extracted with CH_2Cl_2. Elimination of the solvent yielded 0.63 g of **26** as an oil (87%): IR (film) 1640, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.00 (s, 3 H), 4.75–5.17 (m, 2 H), 5.77 (dd, 1 H, J = 10 Hz, J = 18 Hz). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.08; H, 10.39.

(3aα,5α,7aα)-Octahydro-5,7a-dimethyl-1-hydroxy-1*H*-indene-5-ethanol (27). A solution of **26** (1.53 g, 7.9 mmol) in dry THF (60 mL) was stirred and cooled at 0 °C as a stream of diborane was passed for 3 h. The mixture was poured carefully in ice–water, 9.3 mL of 20% sodium hydroxide and 9.3 mL of 30% hydrogen peroxide were added, and the reaction mixture was stirred vigorously for an additional 0.5 h. The mixture was extracted with CH_2Cl_2 (2 × 25 mL), and the organic extracts were washed with saturated sodium chloride, dried, and evaporated. The residue was chromatographed on silica gel eluting with ether to yield 1.17 g (70%) of **27**: IR (film) 3440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (m, 6 H), 2.62 (sb, 2 H), 3.65 (t, 2 H, J = 7 Hz), 4.22 (t, 1 H, J = 8 Hz). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.69; H, 11.19.

(3aα,5α,7aα)-Octahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5-acetic Acid (28). To a solution of **27** (1.7 g, 7.02 mmol) in acetone (150 mL) cooled at −10 °C was added Jones reagent dropwise until a reddish color persisted. After excess oxidant was quenched with ethyl alcohol, anhydrous $MgSO_4$ was added and

the green mixture was filtered through Celite. Removal of the solvent in vacuo gave **28** (1.34 g, 75%) as a white solid: mp 112 °C (ether); IR (Nujol) 1740, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 6 H), 9.82 (s, 1 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.64; H, 8.95.

(3aα,5α,7aα)-Octahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5-acetic Acid Methyl Ester (29). The acid **28** (2 g, 8.9 mmol) was refluxed for 4 h with MeOH (50 mL) containing concentrated sulfuric acid (0.3 mL). Most of the solvent was removed in vacuo and water (15 mL) was added, followed by extraction with ether (2 × 20 mL). The combined extracts were washed with 5% sodium bicarbonate solution, dried, and concentrated to give quantitatively **29** as an oil: IR (film) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 2.25 (m, 2 H), 3.65 (s, 3 H). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.22; H, 9.06.

(3'aα,5'α,7'aα)-Octahydro-5',7'a-dimethylspiro[1,3-dioxolane-2,1'-[1*H*]indene]-5'-acetic Acid Methyl Ester (6). A solution of **29** (2 g, 8.4 mmol) in benzene (35 mL) containing ethylene glycol (0.7 mL, 1.27 mmol) was refluxed in the presence of *p*-toluenesulfonic acid (0.05 g) in a Dean–Stark apparatus for 16 h. Usual workup provided **6** (1.45 g, 61%) as an oil: IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.02 (s, 3 H), 2.25 (s, 2 H), 3.65 (s, 3 H), 3.87 (m, 4 H). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.29; H, 9.08.

(3'aα,5'α,7'aα)-Octahydro-2'-bromo-5',7'a-dimethylspiro-[1,3-dioxolane-2,1'-[1*H*]indene]-5'-acetic Acid Methyl Ester (30). A solution of **6** (1.5 g, 5.3 mmol) in THF (25 mL) was added with pyridinium hydrobromide perbromide (1.94 g, 6.1 mmol), stirred at room temperature for 1 h, filtered, and concentrated in vacuo. The residue was treated with 10% sodium bicarbonate solution (20 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with saturated sodium thiosulfate solution, dried, and concentrated to give 1.6 g of **30** (70%), after column chromatography on silica gel eluting with petroleum ether: ether 4:1: IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.05 (s, 3 H), 2.23 (s, 2 H), 3.65 (s, 3 H), 4.00 (m, 4 H).

(3'aα,5'α,7'aα)-3'a,4',5',6',7',7'a-Hexahydro-5',7'a-dimethylspiro[1,3-dioxolane-2,1'-[1*H*]indene]-5'-acetic Acid Methyl Ester (31). A solution of **30** (1.00 g, 2.7 mmol) in xylene (3 mL) containing 1,5-diazabicyclo[5.4.0]undec-5-ene (4 mL, 27 mmol) was heated at 160 °C for 8 h. Ether (30 mL) was added to the cooled mixture and the solution washed with water (3 × 15 mL). The dried extracts were concentrated and the residue purified by flash chromatography (eluant:ether) to give **31** (0.58 g, 75%) as an oil: IR (film) 1612, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.05 (s, 3 H), 2.24 (m, 2 H), 2.5 (m, 1 H), 3.64 (s, 3 H), 3.93 (s, 4 H), 5.64 (dd, 1 H, J = 8 Hz, J = 3 Hz), 6.11 (dd, 1 H, J = 8 Hz, J = 2 Hz). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.66; H, 8.50.

(3aα,5α,7aα)-3a,4,5,6,7,7a-Hexahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5-acetic Acid (32). A solution of **31** (1 g, 3.6 mmol) in MeOH (6 mL) and 2.32 g (16.8 mmol) of potassium carbonate in 15.5 mL of water was heated at 90 °C for 4 h. The cooled mixture was acidified with 10% hydrochloric acid, stirred at room temperature for 3 h, and extracted with $CHCl_3$ (3 × 15 mL). Concentration of the dried extracts affords **32** (0.78 g, 98%) as an oil: IR (film) 1580, 1700, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 3 H), 1.13 (s, 3 H), 2.2 (s, 3 H), 2.68 (m, 1 H), 6.13 (dd, 1 H, J = 6 Hz, J = 2 Hz), 7.7 (dd, 1 H, J = 6 Hz, J = 3 Hz), 9.83 (s, 1 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.16; H, 8.31.

(3aα,5α,7aα)-3a,4,5,6,7,7a-Hexahydro-5,7a-dimethyl-1-oxo-1*H*-indene-5β-oxobutyric Acid Ethyl Ester (5). Carbonyldiimidazole (0.92 g, 5.7 mmol) was added to a solution of keto acid **32** (1 g, 4.5 mmol) in THF (15 mL). After the mixture was stirred at room temperature for 5 h, the magnesium salt of ethyl malonic acid half ester [prepared by stirring monoethyl malonate (1.32 g, 10 mmol) and magnesium ethoxide (0.72 g, 6.3 mmol) in THF (20 mL) for 1 h at room temperature] was added and the mixture left at room temperature overnight. The solvent was removed at reduced pressure and the residue was treated with 5% hydrochloric acid (20 mL) and ether (25 mL). The aqueous layer was further extracted with $CHCl_3$ (2 × 25 mL) and the combined extracts were washed with aqueous saturated sodium bicarbonate solution and dried. Evaporation of the solvents in vacuo left as residue **5**, which was used without further purification.

(1α,3aβ,7α,8aβ)-3,3a,6,7,8,8a-Hexahydro-4-carbethoxy-1,7-dimethyl-1,7-ethanoazulene-2(1*H*),5(4*H*)-dione (4). A solution of crude **5** (1.25 g) in ethanol (5 mL) was added to a suspension of potassium carbonate (0.7 g) in ethanol (40 mL) and the mixture stirred at room temperature for 3 h and then filtered. The solvent was removed in vacuo and water (10 mL) and 5% hydrochloric acid (10 mL) were added, followed by extraction with $CHCl_3$ (3 × 30 mL). The dried extracts were concentrated in vacuo to give **4** (1 g, 80%): mp 77 °C (ether); IR (Nujol) 1650, 1700, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.10 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 4.17 (q, 2 H, J = 7 Hz), 4.24 (m, 1 H). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.79; H, 8.26.

(1α,3aβ,7α,8aβ)-3,3a,6,7,8,8a-Hexahydro-1,7-dimethyl-1,7-ethanoazulene-2(1*H*),5(4*H*)-dione (33). A mixture of **4** (0.88 g, 3 mmol), NaCl (0.176 g, 3 mmol), and water (0.11 mL, 6 mmol) in Me_2SO (2.5 mL) was heated at 160 °C for 3 h, diluted with H_2O (30 mL), and extracted with ether (3 × 25 mL). Evaporation of the washed (H_2O) and dried extracts gave quantitatively **33** (0.62 g): mp 95–96 °C (ether); IR (Nujol) 1695, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 6 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.34; H, 9.18.

(1'α,3'aβ,7'α,8'aβ)-1',2',3',3'a,6',7',8',8'a-Octahydro-1',7'-dimethylspiro[1,3-dioxolane-2,2'-[1,7]ethanoazulen]-5(4*H*)-one (34). A mixture of **33** (0.39 g, 1.8 mmol), 2-methyl-2-ethyl-1,3-dioxolane (3 mL), ethylene glycol (0.06 mL), and a few crystals of *p*-toluenesulfonic acid was stirred at room temperature for 8 h. Triethylamine (0.15 mL) was added, followed by benzene (20 mL) and water (20 mL). The organic layer was separated, dried, and concentrated to give **34**, mp 119–120 °C (ether), in essentially quantitative yield: IR ($CHCl_3$) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 1.02 (s, 3 H), 3.92 (m, 4 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.61; H, 9.13.

(1'α,3'aβ,7'α,8'aβ)-Decahydro-1',7'-dimethylspiro[1,3-dioxolane-2,2'-[1,7]ethanoazulene] (35). A solution of **34** (0.3 g, 1.2 mmol) in ethylene glycol (3 mL) containing 2 pellets of KOH was heated at reflux for 4 h. The cooled mixture was diltued with water (4 mL) and extracted with ether (3 × 15 mL). Evaporation of the dried extracts gave **35** (0.21 g, 78%) as an homogeneous oil: ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H), 0.92 (s, 3 H), 3.92 (s, 4 H). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.59; H, 10.62.

(1α,3aβ,7α,8aβ)-3,3a,4,5,6,7,8,8a-Octahydro-1,7-dimethyl-1,7-ethanoazulen-2(1*H*)-one (3). A solution of **35** (0.3 g, 1.2 mmol) in MeOH (6 mL) was stirred at room temperature with 10% H_2SO_4 (2 mL) for 4 h. Dilution with water (5 mL), followed by extraction with ether (3 × 10 mL) and evaporation of the dried extracts in vacuo afforded **3** (0.2, 80%): IR (Nujol) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.07 (s, 3 H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.70; H, 10.82.

(1α,3aβ,7α,8aβ)-1,3a,4,5,6,7,8,8a-Octahydro-1,2,7-trimethyl-1,7-ethanoazulene (Isoclovene) (2). A solution of **3** (0.15 g, 0.73 mmol) in ether (5 mL) was added to a solution of methylmagnesium iodide [from magnesium (0.16 g) and MeI (1 mL)] in ether and the mixture stirred at 30 °C for 1.5 h. The mixture was poured in ice–water, solid NH_4Cl was added, the organic layer separated, and the aqueous phase extracted with ether (3 × 15 mL). The combined dried extracts were evaporated in vacuo to give **36** as an oil, which was treated without purification with a crystalline of iodine at 110 °C for 1 h. The cooled mixture was taken up with ether (15 mL), and the solution was washed with saturated aqueous sodium thiosulfate, dried, and evaporated in vacuo to give **2**, identical in any respect with a sample of natural compound obtained by reported procedure: ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.02 (s, 3 H), 1.58 (dd, 3 H, J = 3 Hz, J = 2 Hz), 2.8–3.12 (m, 1 H), 5.12 (m, 1 H).

Acknowledgment. We thank the Consiglio Nazionale delle Ricerche (Rome) and Ministero Pubblica Istruzione for partial financial support and Centro di Strutturistica Diffrattometrica of University of Ferrara for X-ray analysis.

Registry No. **2**, 87727-65-9; **3**, 87702-67-8; **4**, 89951-19-9; **5**, 89951-18-8; **6**, 89951-16-6; **7**, 25222-16-6; **10**, 93564-75-1; **11**, 89951-23-5; **12**, 93564-76-2; **13**, 90025-54-0; (*E*)-**14**, 93564-77-3;

(Z)-14, 93564-77-3; 15, 93711-46-7; 16, 93564-78-4; 17, 93564-79-5; 18, 89951-15-5; 19, 93711-47-8; 20, 93564-80-8; 21, 93564-81-9; 22, 93564-82-0; 23, 93564-83-1; 24, 93564-84-2; 25, 93564-85-3; 26, 93564-86-4; 27, 93564-87-5; 28, 90025-53-9; 29, 93564-88-6; 30, 93564-89-7; 31, 93564-90-0; 32, 89951-17-7; 33, 89951-20-2; 34, 89951-21-3; 35, 93564-91-1; 36, 89951-22-4; malononitrile, 109-77-3; [(ethoxycarbonyl)methylene]triphenylphosphorane, 1099-45-2; ethyl orthoacetate, 78-39-7.

Model Studies of a Conceptually New Approach to the Total Synthesis of Quinine

Philip L. Stotter*[1a] and Martin D. Friedman[1b]

Division of Earth and Physical Sciences, The University of Texas at San Antonio, San Antonio, Texas 78285, and Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

David E. Minter*[1a]

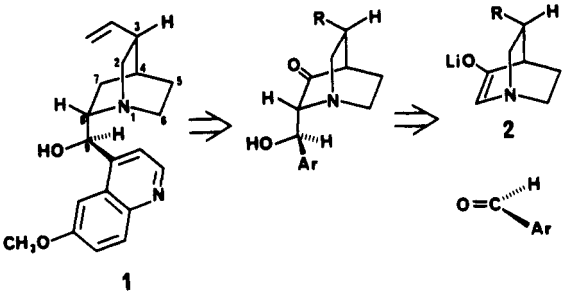
Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

Received May 30, 1984

3-Quinuclidinone was converted to diastereomer-pure racemic *erythro*-2-(α-hydroxybenzyl)quinuclidine (**9**) in 40% yield over five steps. Erythro stereochemistry was established by using a stereoselective aldol condensation of the lithium enolate of 3-quinuclidinone with benzaldehyde at −78 °C. Hydride reduction of the intermediate β-ketoalkoxide afforded a single diastereomer of the resulting diol. Reductive removal of the C-3 hydroxyl led to **9**. This model study demonstrates a conceptually new approach to the total synthesis of quinine.

Although several total syntheses of quinine (**1**) have been reported,[2] none of these has satisfactorily demonstrated solutions to two sets of related stereochemical problems: efficient generation of C-8/C-9 erythro stereochemistry and communication of configurational control from C-3/C-4 to C-8 during or prior to formation of the N-1/C-8 bond. An alternative (Scheme I) to these "classical" methodologies[2] could avoid the troublesome aspects of this step altogether by employing a substrate[3] which contains an intact quinuclidine ring system. A diastereoselective aldol condensation[4] of enolate **2** with an appropriate aldehyde[5] under aprotic, kinetic conditions could, in fact, establish the desired C-8/C-9 erythro stereochemistry of **1**; and these

Scheme I



new chiral centers should also have the correct relationships to those already present in **2**, *if* R (vinyl or vinyl group equivalent) were sufficiently bulky to force the condensation to occur only from the opposite side of the C-2/C-3 bridge. Although the latter aspect of our stereochemical hypothesis has not yet been demonstrated, the viability of this new approach has now been illustrated in part (for the specific case **3**: i.e., **2** where R = H) by the conversion of 3-quinuclidinone to *erythro*-2-(α-hydroxybenzyl)quinuclidine (**9**) in 40% overall yield (Scheme II).

The enolate **3** was generated by reaction of 3-quinuclidinone hydrochloride[6] with 2 equiv of lithium diisopropylamide (LDA) and condensed with benzaldehyde at −78 °C. After workup, the resulting erythro β-ketol **4** (structure confirmed by single-crystal X-ray analysis[7a]) was produced with at least 90% stereoselectivity.[8] Unfortunately, **4** was not particularly stable in solution; substantial equilibration of **4** with its threo isomer via epimerization at C-2 was observed by NMR spectrometry after several

(1) (a) Direct correspondence either to P.L.S. at The University of Texas at San Antonio or to D.E.M. at Texas Christian University. (b) Current address: Manager, Research and Development, AMSPEC, At the foot of Water Street, Gloucester City, NJ 08030.

(2) (a) Woodward, R. B.; Doering, W. von E. *J. Am. Chem. Soc.* **1944**, *66*, 849; **1945**, *67*, 860 and references cited therein. (b) Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425 and references cited therein. (c) Uskokovic, M. R.; Gutzwiller, J.; Henderson, T. *J. Am. Chem. Soc.* **1970**, *92*, 203 and references cited therein. (d) Gutzwiller, J.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 204; **1978**, *100*, 576 and references cited therein. (e) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 205 and references cited therein. (f) Uskokovic, M. R.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1971**, *93*, 5903 and references cited therein. (g) Grethe, G.; Lee, H. L.; Mitt, T.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 5904; **1978**, *100*, 581; **1978**, *100*, 589 and references cited therein. (h) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1972**, *94*, 6218 and references cited therein. (i) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571 and references cited therein.

(3) For two different approaches to the preparation of C-3/C-4 diastereomer-pure 3-functionalized 7-quinuclidinones (quinine numbering) which may serve as useful precursors to enolate **2** where R ↛ H, see: (a) Coffen, D. L.; McEntee, T. E., Jr. *J. Chem. Soc. D.* **1971**, 539. (b) Friedman, M. D. Ph.D. Dissertation, 1978, The University of Texas at Austin.

(4) For an excellent review and leading references, see: Mukaiyama, T., *Org. React. (N.Y.)* **1982**, *28*, 203.

(5) (a) The aldol condensation of **3** with 6-methoxyquinoline-4-carboxaldehyde[11] proved analogous to that of **3** with benzaldehyde (the latter described in the text for preparation of β-ketol **4**). However, for a variety of reasons, 6-methoxyquinoline-4-carboxaldehyde proved unsuitable in the corresponding condensation/reduction (analogous to the preparation of diol **5** reported in the text). Preliminary results suggest that **3** and *N*-carbomethoxy-6-methoxy-1,2-dihydroquinoline-4-carboxaldehyde[5b] can be used in a condensation/reduction and that a product analogous to *erythro-trans*-**5** is formed. (b) Prepared via mild acid hydrolysis of the corresponding dioxolane (reported as **9g** in Minter, D. E.; Stotter, P. L. *J. Org. Chem.* **1981**, *46*, 3965).

(6) Obtained from either Aldrich or Fluka, or by synthesis as described: Daeniker, H. U.; Grob, C. A. *Org. Synth.* **1964**, *44*, 86.

(7) Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Commun.* (a) **1976**, *5*, 465; (b) **1976**, *5*, 785.

(8) As demonstrated in the text, the exact stereoselectivity (at or near 100%) of the aldol condensation which generated erythro β-ketol **4** was obscured by subsequent equilibration (an artifact of workup). In most cases, less than 10% of the threo diastereomer was observed as a contaminant in the NMR spectrum of crude **4** when precautions were taken to isolate the β-ketol from solution as rapidly as possible. Note that complete equilibration of purified *erythro*-**4** could be effected within 48 h at ambient temperature in $CDCl_3$ containing trace DCl and produced a 1:1 mixture of erythro and threo isomers.

0022-3263/85/1950-0029$01.50/0