Acid-Catalyzed Rearrangements of Cyclopropyl Ketones Related to Eudesmane[1]

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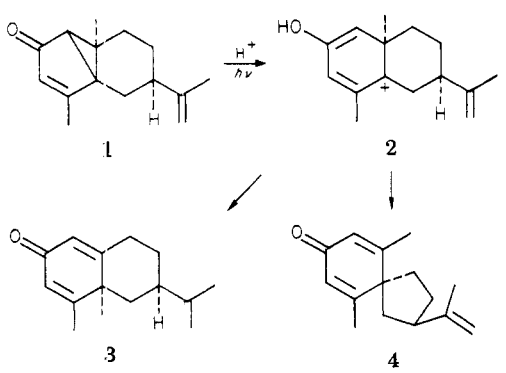
Tricyclodecanones **5**–**7** have been synthesized. Upon reaction with the Lewis acid boron trifluoride in methylene chloride these compounds underwent opening of the cyclopropane ring and rearrangement of the carbon skeleton. Cyclopropyl ketones **5** and **7**, which are stereochemically related to 10-epieudesmane, gave 11,12-dihydronootkatone (**11**) and the octalone derivative **12a**, respectively, as the major products upon treatment with boron trifluoride. In each case these products apparently arose via opening of the internal (2,6) bond of the cyclopropane ring followed by a 1,2-shift of the 1-methyl group to C-6. On the other hand, cyclopropyl ketone **6**, which is stereochemically related to eudesmane, gave 11,12-dihydrosolavetivone (**13**) as the major product upon treatment with boron trifluoride. This spirocyclic enone apparently was produced by opening of the internal bond of the cyclopropane and a 1,2-shift of the 10-methylene group to C-6.

The currently accepted biogenetic pathways for the formation of nootkatone (eremophilane) or spirovetivane sesquiterpenes involve 1,2-methyl or -methylene migrations in bicyclic carbonium ions related to eudesmane.[2] In recent years there has been a considerable amount of interest in the duplication of rearrangements of these types in the laboratory.[3,4] In the preceding paper we reported that nootkatane and spirovetivane sesquiterpenes may be interconverted by photochemical pathways.[4] In this work bicyclic or spirocyclic intermediates containing a cross-conjugated cyclohexadienone chromophore in ring A were converted into the corresponding tricyclodecenone derivatives (lumiproducts) by irradiation in dioxane at 254 nm. These lumiproducts were then irradiated in aqueous acetic acid with greater than 300-nm wavelength ultraviolet light to produce dienone products with the appropiate sesquiterpene skeletons.

The types of photochemical rearrangements described above can be illustrated by using the tricyclodecenone derivative **1**, which is related to 10-epieudesmane. Light-induced cleavage of the internal bond of the cyclopropane ring in **1** apparently leads to the bicyclic carbonium ion **2** which may undergo 1,2-methyl migration to produce dehydronootkatone (**3**) or 1,2-methylene migration to produce anhydro-β-rotunol (**4**). The latter pathway is significantly favored since the initial ratio of **3** to **4** was 1:5.6.[4]



Conjugated cyclopropyl ketones are known to react readily with a variety of electrophilic reagents. Upon treatment with (1) halogen acids in ethanol or acetic acid they undergo ring opening to yield γ-halo ketones,[5] (2) with protic or Lewis acid catalysts in nucleophilic solvents they yield ketones derived from ring opening followed by proton transfer or incorporation of the solvent at the γ-position,[5b,6] and (3) in systems where structural features permit, the ring-opening process may be accompanied by olefin or aryl participation[7] or rearrangement of the carbon skeleton[8] when Lewis acids in aprotic solvents are used as the electrophilic reagents.

The latter results indicated that reactions of tricyclodecanone derivatives related to **1** with Lewis acid catalysts in aprotic solvents might lead to rearrangement products having a nootkatone and/or a spirovetivane ring skeleton. Therefore, we have synthesized the diastereomeric tricyclodecanones **5**[9] and **6**, which have a carbon skeleton related to eudesmane, and the tricyclodecanone **7**, having a 9α- rather than an 8β-isopropyl group, and have investigated the reactions of these compounds with boron trifluoride in methylene chloride.

Cyclopropyl ketone **5** was readily obtained from dienone **1**[4] by catalytic hydrogenation over palladium on carbon in ethanol. Cyclopropyl ketone **7** was prepared in a similar manner by catalytic hydrogenation of the corresponding dienone **8**.[4] Examination of models of both **1** and **8** clearly indicated that the β side of the 4,5 double bond was much less hindered than the α side. The stereochemistry of the 5-methyl groups in **5** and **7** was assigned on the basis of the assumption that hydrogen would add from the less hindered side of the double bond. These assignments were

(1) This investigation was supported in part by Public Health Service Grant No. CA 12193 from the National Cancer Institute and by Grant No. CHE7810044 from the National Science Foundation.

(2) For a recent review, see: Marshall, J. A.; Brady, S. F.; Andersen, N. H. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 283.

(3) For a recent review, see: Coates, R. M. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 73.

(4) Caine, D.; Chu, C. Y.; Graham, S. L. *J. Org. Chem.*, preceding paper in this issue.

(5) (a) Caine, D.; Boucugnani, A. A.; Chu, C. Y.; Graham, S. L.; Smith, T. L., Jr. *Tetrahedron Lett.* **1978**, 2667. (b) Ruppert, J. F.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1976**, 976. (c) Dasgupta, S. K.; Sarma, A. S. *Tetrahedron* **1973**, *29*, 309. (d) Dauben, W. G.; Schutte, L.; Wolf, R. E.; Deviny, E. J. *J. Org. Chem.* **1969**, *34*, 2512. (e) Monti, S. A.; Bucheck, D. J.; Sheppard, J. C. *Ibid.* **1969**, *34*, 3080. (f) Liang, S. B.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 937. (g) Shoulders, B. A.; Kwie, W. W.; Klyne, W.; Gardner, P. D. *Tetrahedron* **1965**, *21*, 2973.

(6) (a) McCurry, P. M., Jr. *Tetrahedron Lett.* **1971**, 1845. (b) Ganter, C.; Utzinger, E. C.; Schaffner, K.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 2403. (c) Wenger, R.; Dulter, J.; Wehrli, H.; Schaffner, K.; Jeger, O. *Ibid.* **1962**, *45*, 2420.

(7) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371. (b) Stork, G.; Gregson, M. *Ibid.* **1969**, *91*, 2373. (c) Stork, G.; Grieco, P. *Ibid.* **1969**, *91*, 2407. (d) Stork, G., Grieco, P. *Tetrahedron Lett.* **1971**, 1807. (e) Corey, E. J.; Balanson, R. D. *Ibid.* **1973**, 3153.

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(9) For a preliminary report on the reaction of **5** with boron trifluoride in methylene chloride, see ref 8a.

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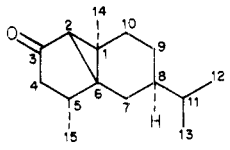

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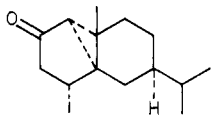

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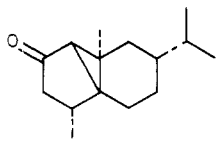

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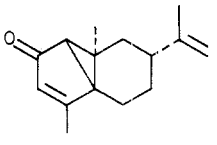
confirmed by the subsequent rearrangement reactions described below.

Cyclopropyl ketone **6** was prepared by conversion of the known enone **9a**[10] into the corresponding cross-conjugated dienone **9b** by the phenylselenylation–selenoxide elimination procedure,[11] photochemical rearrangement of **9b** to the tricyclodecenone **10** by irradiation with 254-nm ul-



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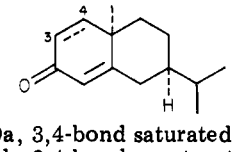
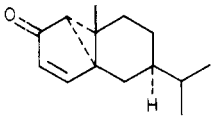


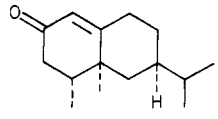
9a, 3,4-bond saturated
b, 3,4-bond unsaturated



10

traviolet light in anhydrous dioxane, and conjugate addition of lithium dimethylcuprate to the enone system, using the procedure of House and co-workers.[12] In the latter reaction a single product was obtained in ca. 95% yield. The 1β-methyl in **10** would provide a considerable amount of steric hindrance to the approach of the cuprate reagent from the β side of the 4,5 double bond. Thus it was assumed that the conjugate-addition product contained a 5α-methyl group, as indicated in **6**. This stereochemical assignment was supported by subsequent experiments.

Ketone **5** was allowed to react with a saturated solution of boron trifluoride in dry methylene chloride for 24 h at room temperature. GLC analysis of the reaction mixture indicated that essentially all of the starting material had been consumed and one major product which made up greater than 65% of the volatile compounds had been formed. The mixture also contained four minor components, but none of these amounted to as much as 10% of the total volatile material. The major product was isolated by chromatography on silica gel. Its spectral properties indicated that it was a bicyclic enone. These properties, as well as the GLC behavior of the product, were found to be identical with those of an authentic sample of 11,12-dihydronootkatone (**11**), which was prepared by selective hydrogenation of natural nootkatone[13] using the homogeneous catalyst tris(triphenylphosphine)rhodium chloride in benzene.[14]



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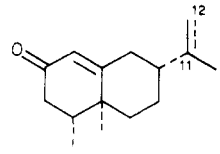

12a, 11,12-bond saturated
b, 11,12-bond unsaturated

The minor components of the reaction of **5** could not be isolated in sufficiently pure form to permit positive identification. However, examination of the spectral properties of partially purified materials indicated that a mixture of unconjugated bicyclic enones, resulting from cleavage of the 2,6-bond of the cyclopropane ring and proton transfer from C-5 and C-7, and a cyclopentenone derivative, resulting from cleavage of the 1,6-bond and migration of the 7-methylene group to C-1, probably were produced. Products of similar structures were observed to be formed in small amounts when a steriodal cyclopropyl ketone related to **5** was reacted with Lewis acids.[8b] No evidence for the formation of any spirocyclic enone which would result from concomitant cleavage of the 2,6-bond and migration of the 10-methylene group to C-6 was obtained.

Cyclopropyl ketone **7** was treated under the same conditions as those described for the isomer **5**. In this case GLC analysis indicated that only two products were formed in an ~9:1 ratio in ~80% yield. The major component was purified by preparative GLC. It exhibited identical GLC behavior and spectral properties with those of a sample of the enone **12a** which was prepared from dienone **12b**[4] by selective hydrogenation of the 11,12 double bond using tris(triphenylphosphine)rhodium chloride in benzene.[14] The minor component of the acid-catalyzed reaction of **7** was not identified. However, GLC and spectral evidence indicated that a spirocyclic product, i.e., 11,12-dihydrosolavetivone (**13**), which could have been formed by opening the 2,6-bond and migration of the 10-methylene group to C-6, was not produced.

The reaction of cyclopropyl ketone **6** with boron trifluoride was investigated next. When treated as described above it yielded one major product and two minor components in an 18:1:1 ratio by GLC. The yield of volatile products was ~80%. The major product was purified by preparative TLC. It exhibited identical spectral properties and chromatographic behavior (GLC and TLC) with an authentic sample of 11,12-dihydrosolavetivone (**13**) which was obtained by selective hydrogenation of the double bond in the isopropenyl group of (−)-solavetivone[15] using tris(triphenylphosphine)rhodium chloride in benzene. Insufficient quantities of the minor components of the reaction of **6** were available to permit identification.

The formation of 11,12-dihydronootkatone (**11**) from cyclopropyl ketone **5** involves cleavage of the internal (2,6) bond of the three-membered ring and migration of the 1-methyl group to C-6. In the relatively nonpolar solvent methylene chloride it is possible that the entire process

(10) (a) Marshall, J. A.; Fanta, W. I.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 1016. (b) Marshall, J. A.; Bundy, G. L.; Fanta, W. J. *Ibid.* **1968**, *33*, 3913.

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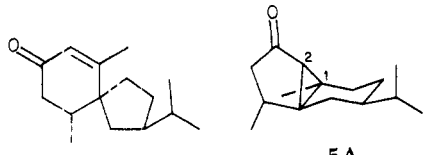
(12) House, H. O.; Chu, C. Y.; Wilkens, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

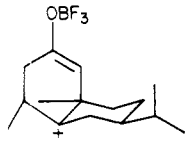
(13) We are grateful to Dr. Ben Clark of the Coca-Cola Company for a sample of pure (+)-nootkatone.

(14) (a) Huffman, J. W. *J. Org. Chem.* **1972**, *37*, 2736. (b) Odom, H. C.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2193.

(15) We are grateful to Dr. Donald M. Gunn (I.C.I., Ltd.) and Dr. James S. Roberts (University of Stirling) for supplying us with an authentic sample of (−)-solavetivone.

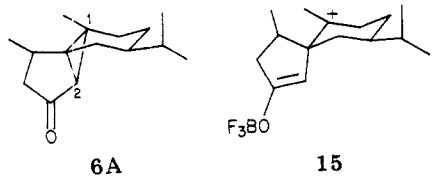


13 5A

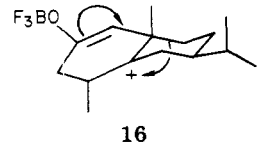


14

is concerted, since bond cleavage and bond formation can occur from the opposite sides of C-6. However, it may be formally represented as proceeding via a bicyclic carbonium ion intermediate. The most favorable conformation of ketone **5** would be expected to be **5A** in which the isopropyl group is equatorial to the six-membered ring. In **5** the external (1,2) bond of the cyclopropane ring overlaps more favorably than the internal bond with the π orbital of the carbonyl group. However, in **5A** cleavage of the 2,6-bond can occur in a diaxial manner, leading to a bicyclic carbonium ion in conformation **14** in which the enolized carbonyl function is axial with respect to the B ring.[6b] In this species, a transition state which allows for maximum orbital overlap during migration to C-6 appears to be much more easily achieved by the methyl group than the methylene group. The establishment of a conjugated enone system apparently provides a strong driving force for a rearrangement reaction as opposed to proton-transfer processes which would lead to unconjugated bicyclic enones.[16] However, as noted above, proton-transfer products were possibly produced in small quantities from **5**. The same conformational and electronic factors which are involved in the arrangement of **5** to **11** also seem to account for the formation of the octalone **12a** from the tricyclodecanone **7**. We were surprised to find that cyclopropyl ketone **6** gave primarily the spiro enone 11,12-dihydrosolavetivone (**13**) on reaction with boron trifluoride. The most favorable conformation of **6** should be as represented in **6A** in which opening of the external (1,2) bond could occur in a diaxial sense. Thus products formally arising from rearrangement via the spiro carbonium ion intermediate **15** were expected in this case.



6A 15



16

Indeed, we have observed that reaction of the 5-normethyl derivative of **6** with hydrogen bromide in acetic acid led mainly to a spirocyclic bromo ketone resulting from opening of the three-membered ring in the diaxial manner.[5a] (In contrast, the normethyl derivative of **5** gave exclusively a bicyclic bromo ketone, again by a pathway also involving cleavage of the ring in a diaxial manner.)[5a] However, it seems that spiro enone **13** would have to arise from migration of the 10-methylene group to C-6 in a bicyclic carbonium ion intermediate. It is possible that the spiro carbonium ion **15** is formed initially but rearranges to a bicyclic species with a conformation such as **16**, in which steric interaction between the methyl group at C-5 and the 7-methylene group is minimized and the 10-methylene group is favorably disposed for migration, faster than other reactions occur.[17] In the conversion of **6** into **13**, cleavage of the 2,6-cyclopropyl bond and formation of the new carbon–carbon bond by methylene migration must occur from the same side of C-6. Therefore, the possibility of a concerted methylene migration seems less likely here than in the systems in which methyl migration was observed.

The above mechanistic arguments are based upon the assumption that the reaction products were produced under kinetic control. The bicyclic and spirocyclic enones which were formed were shown to be stable under the reaction conditions. We cannot rule out the possibility that other undetected conjugated enones or bicyclic or spirocyclic unconjugated enones derived from proton-transfer reactions in carbonium ions such as **14** or **15** were intermediates in these processes. However, in studies on a related cyclopropyl ketone, *cis*-1,7-dimethyltricyclo-[4.4.0.0^{2,6}]decan-3-one, it was found that such unconjugated enones, which could be isolated in low yields, did not give mixtures of rearrangement products of the same composition as those which were obtained from the parent cyclopropyl ketone upon reaction with boron trifluoride in methylene chloride.[18]

If the 11,12-dehydro derivatives of **5** and **6** were to undergo rearrangements analogous to the parent saturated cyclopropyl ketones with Lewis acid catalysts, the natural products nootkatone and solavetivone, respectively, would be produced. Some preliminary experiments have indicated that the rearrangements of these unsaturated systems with boron trifluoride are also accompanied by extensive double bond isomerizations. Therefore, we are looking at reactions of these compounds with other electrophilic reagents which may be less prone to attack the isolated double bond.

Experimental Section[19]

1α,5α-Dimethyl-9α-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (5). A mixture 40 mg of 10% palladium on carbon and 4.0 mL of 95% ethanol was placed under hydrogen at 1-atm pressure and stirred until the uptake of hydrogen ceased. A solution of 0.217

(16) Initially we felt that methyl migration might occur primarily to relieve the 1,3-interaction between the 1α- and 5α-methyl groups in **5**. However, in preliminary experiments it was found that the 5-normethyl derivative of **5**[5a] also yields mainly an octalone derivative derived from methyl migration upon treatment with boron trifluoride in methylene chloride.

(17) The 5-normethyl derivative of **6**[5a] was also found to rearrange largely to the corresponding spiro ketone related to **13** upon reaction with boron trifluoride.

(18) Caine, D.; Chu, C.-Y.; Krueger, L. M.; Gupton, G. T., III, unpublished work.

(19) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^{1}H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (parts per million) relative to Me_4Si as an internal standard. Abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. The ^{13}C chemical shift assignments were consistent with off-resonance decoupling experiments. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7. Gas–liquid chromatography was carried out a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6 ft × 0.125 in. aluminum column packed with 20% Carbowax 20M on acid-washed Chromosorb W (column A) was employed for analytical work and a 10 ft × 0.25 in. stainless-steel column containing the same packing material (column B) was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, GA.

g (0.0010 mol) of 1α,5-dimethyl-9α-(isopropenyl)tricyclo-[4.4.0.0^{2,6}]dec-4-en-3-one (1) in 2.0 mL of 95% ethanol was injected into the mixture via a syringe and stirring was continued until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.200 g (91%) of 5 as a colorless oil: IR (CCl_4) 1716 cm^{-1} (cyclopropyl conjugated C=O); NMR (CCl_4) δ 0.85 (d, J = 6 Hz, 6 H, CH-(CH_3)$_2$), 1.14 (d, J = 6.5 Hz, 3 H, 5-CH_3), 1.32 (s, 3 H, 1-CH_3); mass spectrum, m/e (70 eV) 220.1789 (calcd 220.1821).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.96.

1α,5α-Dimethyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (7). A solution of 0.850 g (0.0039 mol) of the tricyclodecenone derivative 8 in 150 mL of 95% ethanol containing 150 mg of 10% palladium on carbon was shaken in a Parr hydrogenation apparatus under a hydrogen pressure of 25 psi for 3 h. The catalyst was removed by filtration and the solvent was removed in vacuo to give 0.780 g (92%) of 7: bp 120–130 °C (0.1 mm); IR (CCl_4) 1719 cm^{-1} (cyclopropyl conjugated C=O); NMR (CCl_4) δ 0.87 (m, 6 H, CH(CH_3)$_2$), 1.14 (d, J = 7 Hz, 3 H, 5-CH_3), 1.32 (s, 3 H, 1-CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70; H, 10.99.

1β,5α-Dimethyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]decan-3-one (6). n-Butyllithium (20.98 mL of a 2.24 M solution in hexane) was added slowly with stirring to a solution of 6.59 mL (0.047 mol) of dry diisopropylamine and 50 mg of 2,2-bipyridyl in 200 mL of dry tetrahydrofuran (THF) at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C and then cooled to −70 °C. A solution of 8.8 g (0.043 mol) of 3,4,5,6,7,8-hexahydro-4aα-methyl-7β-isopropyl-2(4a*H*)-naphthalenone (**9a**)[10] in 50 mL of dry THF was then added dropwise with stirring and the mixture was stirred for an additional 30 min.

A solution of 7.99 g (0.026 mol) of diphenyl diselenide in 50 mL of dry THF was cooled in a dry ice–acetone bath for a few seconds and 1.32 mL (0.026 mol) of bromine was added with swirling. The solution of benzeneselenenyl bromide thus prepared was transferred to a dropping funnel and added rapidly to the solution of the kinetic dienolate of **9a**. The mixture was stirred and allowed to warm to room temperature and 100 mL of a saturated solution of NH_4Cl was added. The mixture was then extracted with two 100-mL portions of ether and the ether extracts were washed with 150 mL each of 2% ice-cold hydrochloric acid, saturated $NaHCO_3$, and saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The residue was dissolved in 100 mL of methylene chloride and while the temperature of the mixture was maintained below 25 °C a solution of 9.92 g of 30% hydrogen peroxide in 10 mL of water was added slowly with stirring. The mixture was stirred vigorously for an additional 1 h. Water (100 mL) was added, the layers were separated, and the aqueous layer was extracted with 100 mL of methylene chloride. The solvent from the combined methylene chloride extracts was removed in vacuo and the residue was dissolved in 100 mL of ether. After filtration to remove insoluble benzeneselenenic acid, the solution was washed with 100 mL each of saturated $NaHCO_3$ and saturated NaCl.

The solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to give 6.55 g (75%) of 5,6,7,8-tetrahydro-4aα-methyl-7β-isopropyl-2(4a*H*)-naphthalenone (**9b**): mp 83.5–84.3 °C; IR (CCl_4) 1666 (α,β-unsaturated C=O), 1632 and 1608 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 0.79–0.98 (m, 6 H, CH(CH_3)$_2$), 1.30 (s, 3 H, 4a-CH_3), 5.95 (d, J = 1.5 Hz, 1 H, 1-H), 6.02 (d of d, J = 1.5 and 9 Hz, 1 H, 3-H), 6.58 (d, J = 9 Hz, 1 H, 4-H); mass spectrum, m/e (70 eV) 204.1513 (calcd 204.151).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.26; H, 9.88.

A solution of 1.0 g of dienone **9b** in 100 mL of anhydrous dioxane was irradiated for 1 h with a 7-W Hanau NK 20 low-pressure mercury lamp. The mixture was stirred by passage of a stream of dry nitrogen through it during the entire irradiation period. The solvent was removed in vacuo. The combined photomixtures from three identical runs were chromatographed on 70 g of silica gel. Elution with 12% ether–hexane gave 1.26 g (42%) of 1β-methyl-8β-isopropyltricyclo[4.4.0.0^{2,6}]dec-4-en-3-one (**10**): bp 93–97 °C (0.03 mm); IR 1702 cm^{-1} (C=O); NMR (CCl_4) δ 0.9 (d, J = 6 Hz, 6 H, CH(CH_3)$_2$), 1.17 (s, 3 H, 1-CH_3), 5.75 (d of d, J = 1 and 5.5 Hz, 1 H, 4-H), 7.18 (d of d, J = 1 and 5.5 Hz, 1 H, 5-H).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.27; H, 9.88.

The procedure of House and co-workers[12] was used for the conversion of **10** into **6**. Methyllithium (15.22 mmol, 13.83 mL of a 1.1 M solution in ether) was added dropwise with stirring to a solution of 1.71 g (8.32 mmol) of (CH_3)$_2$SCuBr in 15 mL of dimethyl sulfide and 15 mL of anhydrous ether under nitrogen while the temperature was maintained at 20–25 °C. The addition of methyllithium was stopped just at the point when the last of the initially formed yellow precipitate of $(CH_3Cu)_n$ dissolved to form a pale yellow solution. To this solution was added 1.24 g (6.1 mmol) of tricyclodecenone **10** in 5 mL of ether, and the resulting mixture, from which $(CH_3Cu)_n$ separated, was stirred at 25 °C for 45 min. The reaction mixture was partitioned between ether and an aqueous solution (pH 8) of NH_4Cl and NH_4OH. The ether layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo to give 1.27 g (95%) of a pale yellow liquid. GLC analysis indicated that only one product was present. Distillation gave **6**: bp 115–125 °C (0.1 mm); IR (CCl_4) 1726 and 1706 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 0.85 (d, J = 6 Hz, 6 H, CH(C**H**$_3$)$_2$), 1.13 (d, J = 7 Hz, 3 H, 5-CH_3), 1.15 (s, 3 H, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 43.9 (C-1), 46.3 (C-2), 212.6 (C-3), 47.7 (C-4), 39.3 (C-5), 29.5 (C-6), 35.6 (C-7), 32.4 (C-8), 28.0 (C-9), 25.7 (C-10), 31.4 (C-11), 19.7 (C-12 to C-15); mass spectrum, m/e (70 eV) 220.1884 (calcd 220.1827).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.75; H, 11.00.

Reaction of Cyclopropyl Ketone 5 with Boron Trifluoride in Methylene Chloride. Boron trifluoride gas was passed into a solution of 0.107 g of **5** in 5 mL of dry methylene chloride until the solution was saturated. The mixture was then allowed to stand for 24 h at 25 °C and poured into 15 mL of 5% aqueous $NaHCO_3$. After the mixture was shaken, the layers were separated and the aqueous phase was extracted with two 10-mL portions of methylene chloride. The combined organic extracts were washed with two 10-mL portions of saturated NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give 0.097 g of a mixture of products. GLC analysis (column A)[19] of this mixture showed that it contained greater than 65% 11,12-dihydronootkatone (**11**) and four other minor components each of which made up 10% or less of the total volatile material. The actual yield of **11** was determined to be 46%, using pure (+)-nootkatone[13] as an internal standard. A portion of this mixture (80 mg) was chromatographed on 10 g of silica gel. Elution of the column with 20% ether–hexane gave 30 mg (37% from **5**) of 11,12-dihydronootkatone. This sample showed identical spectral properties and GLC behavior with a sample of **11** which was prepared by reduction of the 11,12 double bond in authentic (+)-nootkatone[13] with hydrogen in the presence of tris(triphenylphosphine)rhodium chloride.[14]

Some of the fractions which were eluted from the column with 5% and 10% solutions of ether–hexane contained some of the minor components in partially purified form. One of these showed an IR (CCl_4) absorption at 1714 cm^{-1} (saturated C=O) and NMR (CCl_4) absorptions for a vinyl proton and a vinyl methyl group. This possibly was a mixture of unconjugated octalones derived from opening of the 2,6-bond in **5** followed by proton transfer from C-5 and C-7. Another fraction showed UV absorption at 232 nm and IR absorptions at 1710, 1683, and 1600 cm^{-1}, possibly attributable to a cyclopentenone derivative which could result from cleavage of the 1,6-bond in **5** followed by migration of the 7-methylene group to the 1-position.[8b] However, the quantities of these materials were insufficient to permit their purification and positive identification.

Reaction of Cyclopropyl Ketone 7 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone **7** (200 mg) was reacted with boron trifluoride in 20 mL of methylene chloride in the same manner as that described for **5**. After workup of the reaction mixture in the usual way, 184 mg of an oil, which according to GLC analysis (column A)[19] was a 9:1 mixture of enone **12a** and an unidentified minor component, was obtained. An analytical sample was collected by GLC (column B):[19] IR (CCl_4) 1663 (α,β-unsaturated C=O), 1610 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 0.85–0.97 (m, 9 H, CH(CH_3)$_2$ and 4-CH_3), 1.03 (s, 3 H,

4a-CH_3), 5.58 (br s, 1 H, vinyl H); mass spectrum, m/e (70 eV) 220.1751 (calcd 220.1821).

The GLC behavior and spectral properties of the major rearrangement product of **7** were identical with those of a sample prepared from the corresponding dienone **12b**[4] with an 11,12 double bond as follows. A solution of 75 mg of tris(triphenylphosphine)rhodium chloride in 15 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen had ceased. Then a solution of 110 mg of dienone **12b** in 2 mL of benzene was introduced and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen was absorbed. After filtration of the product through a column the containing 5 g of ammonia, ~60 mg of enone **12a** was isolated as a colorless oil.

Reaction of Cyclopropyl Ketone 6 with Boron Trifluoride in Methylene Chloride. Cyclopropyl ketone **6** (450 mg) was reacted with a saturated solution of boron trifluoride in methylene chloride under the same conditions as those described above for **5** and **7**. After workup of the product in the usual manner, 380 mg of a yellow oil was obtained. GLC analysis (column A)[19] of this material indicated that it contained one major component and two minor components in an 18:1:1 ratio. Preparative GLC (column B)[19] did not permit complete purification of the major component. However, preparative TLC using 0.5-mm silica plates and 20% ether–hexane as the eluant allowed the isolation of an analytical sample of 11,12-dihydrosolavetivone (**13**): UV (95% C_2H_5OH) 242 nm (ϵ 6400); IR (CCl_4) 1670 (α,β-unsaturated C=O), 1616 cm^{-1} (conjugated C=C); ^1H NMR (CCl_4) δ 0.89–1.01 (m, 9 H, $CH(CH_3)_2$ and $CHCH_3$), 1.89 (d, J = 1.2 Hz, vinyl CH_3), and 5.62 (q, J = 1.2 Hz, 1 H, vinyl H); ^{13}C NMR ($CDCl_3$) δ 41.0 (C-1), 47.2 (C-2), 33.4 (C-3), 34.2 (C-4), 50.2 (C-5), 166.0 (C-6), 124.8 (C-7), 198.0 (C-8), 42.8 (C-9), 38.9 (C-10), 32.1 (C-11), 21.4 and 20.8 (C-12 to C-14), 15.9 (C-15); mass spectrum, m/e (70 eV) 220.1813 (calcd 220.1821).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.96.

The sample of **13** obtained above was identical in GLC and TLC behavior and spectral properties with a sample prepared by selective reduction of the 11,12 double bond of (-)-solavetivone.[15] This reduction was performed as follows. A solution of 50 mg of tris(triphenylphosphine)rhodium chloride in 10 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen ceased. Then a solution of 61 mg of (-)-solavetivone in 1 mL of benzene was introduced via a syringe and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen had been absorbed. The solution was then passed through a column containing 5 g of silica gel and the solvent was removed in vacuo to give 54 mg of crude 11,12-dehydrosolavetivone (**13**). A pure sample of **13** was obtained by preparative TLC using 20% ether–hexane as the eluant.

Registry No. **1**, 74431-66-6; **5**, 61187-65-3; **6**, 74431-17-7; **7**, 74397-88-9; **8**, 53768-19-7; **9a**, 16735-08-3; **9b**, 69035-61-6; **10**, 69044-04-8; **11**, 70267-57-1; **12a**, 74397-89-0; **12b**, 74397-90-3; **13**, 74431-18-8.

Synthesis and Stereochemistry of 9-Deoxy-5,9α-epoxyprostaglandins: A Series of Stable Prostacyclin Analogues

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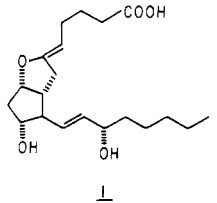
The reaction of *cis*-Δ^4-prostaglandin $F_1\alpha$ methyl ester (**4**) with iodine gave (4*S*,5*S*)-4-iodo-9-deoxy-5,9α-epoxyprostaglandin F_1 methyl ester (**5**) and (4*R*,5*R*)-4-iodo-9-deoxy-5,9α-epoxyprostaglandin F_1 methyl ester (**6**). The reaction of **4** with mercuric acetate followed by reduction with sodium borohydride gave (5*R*)-9-deoxy-5,9α-epoxyprostaglandin F_1 methyl ester (**7**) and (5*S*)-9-deoxy-5,9α-epoxyprostaglandin F_1 methyl ester (**8**). Reductive removal of iodine from **5** gave **7**. The free acids (5*R*)-9-deoxy-5,9α-epoxyprostaglandin F_1 (**9**) and (5*S*)-9-deoxy-5,9α-epoxyprostaglandin F_1 (**10**) were prepared by saponification of **7** and **8**, respectively. The reaction of iodo ether **5** with DBN in warm toluene gave (2*E*,5*S*)-9-deoxy-5,9α-epoxy-Δ^2-prostaglandin F_1 methyl ester (**13**) as the main product together with, after hydrolysis, a small amount of 5-oxoprostaglandin $F_1\alpha$ methyl ester (**14**). The α,β-unsaturated ester **13** was prepared independently from **7** via preparation of the phenyl selenide, oxidation to the selenoxide, and elimination of the selenoxide to give the olefin. Reaction of iodo ether **6** with DBN gave (4*Z*)-9-deoxy-5,9α-epoxy-Δ^4-prostaglandin F_1 methyl ester (**15**), which was converted to the sodium salt **16** by reaction with 1 equiv of sodium hydroxide. Aqueous acid converted **15** to **14**. The configuration at C_5 in **7** and **8** (and all related analogues) was determined by the conversion of both compounds into like-ended molecules, (2*R*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-decahydro-2,7-dipentyl-2*H*-cyclopenta[1,2-*b*:4,3′-*b*]dipyran (**27a**) and (2*S*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-decahydro-2,7-dipentyl-2*H*-cyclopenta[1,2-*b*:4,3′-*b*]dipyran (**27b**), respectively. The ^{13}C NMR spectrum of **27b** contains eleven signals, reflecting the fact that the C_2 symmetry of the molecule reduces to 11 the number of stereochemically different carbons in the skeleton. These results reverse the previous tentative assignment of configuration given to C_5.[6]

Prostacyclin is the most potent, naturally occurring inhibitor of platelet aggregation yet discovered and also is a powerful vasodepressor.[1] The chemical structure of prostacyclin (**1**) features an enol–ether functional group that is susceptible to hydrolysis, giving 6-keto-$PGF_1\alpha$ (**2**).[2] Hydrolysis of the enol–ether is catalyzed by the carboxylic acid group so that prostacyclin has a half-life of only 3–4 min under physiological conditions.[3] Clearly, the preparation of chemically stable analogues of prostacyclin that



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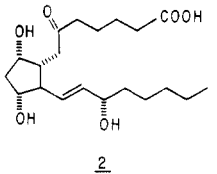

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