Iodohydrins and Tetrahydrofurans from Lead Tetraacetate–Iodine Oxidation of Terpenic Alcohols

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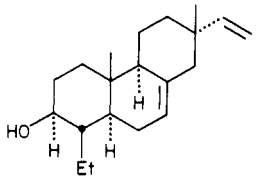
The oxidations of 18-methyl-19-nor-3β-isopimarol, 2β-hydroxymanoyl oxide, 8,9-didehydro-7,8-dihydro-2β-isopimarol, 2β-isopimarol, 13-demethyl-13-devinyl-13-oxonezukol, and 3β-friedanol with lead tetraacetate and iodine have been investigated and the iodohydrin and tetrahydrofuran products are described. The nezukol and friedelin derivatives have yielded long-range oxidation products.

The functionalization of unactivated, saturated carbon sites by the free-radical oxidation of alcohols have been an important method of organochemical synthesis known for some time[2] and applied especially effectively in the steroid field.[3] Thus, for example, the alcohol oxidation with lead tetraacetate and iodine has been shown to yield 1,4-iodohydrins and/or tetrahydrofurans and has been formulated to proceed by way of the thermal (or photochemical) decomposition of a hypoiodite, 1,5-hydrogen shift of the resultant alkoxy radical, and iodination of the thus-produced carbon radical (Scheme I). As the following discussion illustrates, the oxidation was employed on diterpenic substrates, whose products had the potential for conversion into naturally occurring substances.

Since the alkoxy-to-carbon radical transformation requires close proximity of the alkoxy moiety to the saturated carbon–hydrogen bond system, most successful oxidations have involved 1,3-diaxial or peri, 1,3-diequatorial relationships between the interacting groups within a rigid molecular framework. However in the presence of favorable rotamer population preferences the reaction can take place even on fully or partially acyclic systems.[2] Oxidation of alcohol **1**,[4] a substance the methyl group of whose two-carbon side chain can orient itself favorably toward the rigidly held, neighboring, equatorial hydroxy function, with lead tetraacetate and iodine now gave tetrahydrofuran **2** in 67% yield. The ease of this reaction and the facile synthesis of alcohol **1** from virescenol B (**3**)[4] makes the reaction sequence a viable route of synthesis of cafestol-like (**4**)[5] substances.



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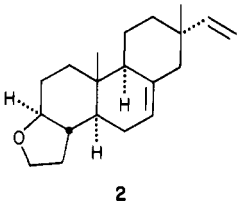

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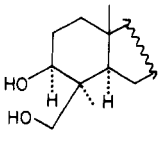

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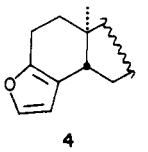

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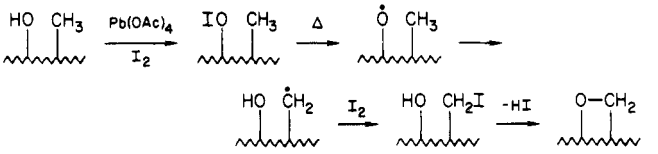
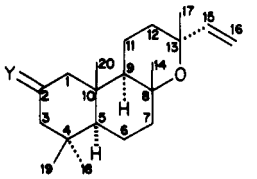
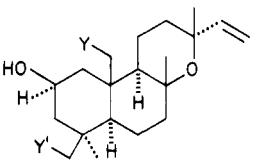
Scheme I



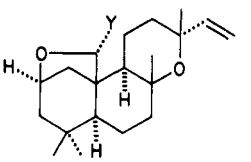
Reduction of 2-ketomomanoyl oxide (**5a**)[6] with lithium tri-*tert*-butoxyaluminum hydride yielded 2β-hydroxymanoyl oxide (**5b**), a conformationally rigid, axial alcohol oriented 1,3-diaxially to two axial methyl groups. Oxidation of the alcohol with lead tetraacetate and iodine in benzene led to three compounds: iodohydrin **6a**, diiodohydrin **6b**, and acetoxytetrahydrofuran **7b** in 24%, 23%, and 20% yields. Treatment of the monoiodohydrin (**6a**) with sodium carbonate in pyridine afforded tetra-



5a, Y = O
b, Y = α-H, β-OH
c, Y = H_2



6a, Y = I, Y' = H
b, Y = Y' = I



7a, Y = H
b, Y = OAc

hydrofuran **7a**. The structures of the four compounds were determined by ^{13}C NMR spectroscopy. Introduction of an axial 2β-hydroxy group into ring A of manoyl oxide (**5c**)[7] causes a δ effect on the 4β- and 10β-methyl groups, which leads to deshielding of these one-carbon units by 3 and 1.7 ppm, respectively. Formation of a ring between the C-(2)-oxygen and a methyl function forces the loss of the 10β-methyl shift and produces shielding of the 4β-methyl group (presumably by a decrease of the δ effects from the 1,3-diaxially interacting groups on ring formation), indi-

(1) Present address: Department of Chemistry (D-006), University of California—San Diego, La Jolla, CA 92093.
(2) Mihailović, M. Lj.; Čeković, Z. *Synthesis* **1970**, 209.
(3) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.
(4) Ceccherelli, P.; Curini, M.; Pellicciari, R.; Baddeley, G. V.; Raju, M. S.; Wenkert, E. *J. Org. Chem.* **1978**, *43*, 4244.
(5) Djerassi, C.; Cais, M.; Mitscher, L. A. *J. Am. Chem. Soc.* **1959**, 81, 2386.
(6) Hosking, J. R.; Brandt, C. W. *Chem. Ber.* **1935**, *68*, 286. Grant, P. K.; Hodges, R. *Chem. Ind. (London)* **1960**, 1300.
(7) Buckwalter, B. L.; Burfitt, I. R.; Nagel, A. A.; Wenkert, E.; Näf F. *Helv. Chim. Acta* **1975**, *58*, 1567. Almquist, S.-O.; Enzell, C. R. *Acta Chem. Scand.* **1975**, *B29*, 695.

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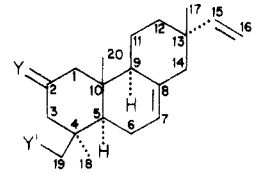
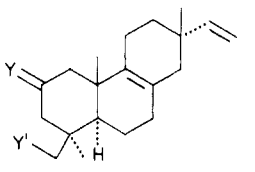
cative of the new bond spanning the 2β-oxy and the 10β-carbon units. Thus ether **7a** and its precursor **6a** possess the structures depicted by their formulas. Ester **7b** has to be related to ether **7a**, as the constancy of most ring A and B carbon shifts suggests, and its acetoxy group is oriented away from rings A and B, as corroborated by a small γ effect on C(1) and shift changes of the ring C methylenes. Both ^1H and ^{13}C NMR spectroscopy verify the locations of the two iodines of diiodohydrin **6b**. The structures of the three products of oxidation of alcohol **5b** reveal the 10β-methyl moiety to be more vulnerable to free-radical oxidation than the 4β-methyl group, a fact ascribable to the angular methyl function being in the midst of the rigid ring skeleton.

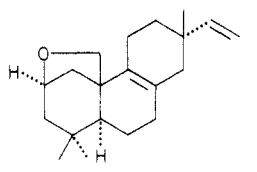
Treatment of olefinic ketone **8a**[8] with acid and reduction of the resultant isomer (**9a**) with lithium triethylborohydride produced axial alcohol **9b**, once again a compound whose hydroxy group was disposed 1,3-diaxially to two axial methyl groups. Oxidation of the alcohol with lead tetraacetate and iodine gave tetrahydrofuran **10** in 60% yield. The structure of the latter was shown to be isomeric with that of ether **11**, which was prepared sequentially by



8a, Y=O, Y'=H
b, Y=O, Y'=OAc
c, Y=α-H, β-OH, Y'=OH
d, Y=α-H, β-OH, Y'=H



9a, Y=O, Y'=H
b, Y=α-H, β-OH, Y'=H
c, Y=α-H, β-OH, Y'=I



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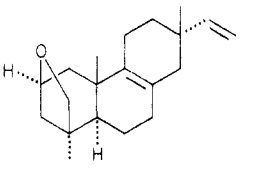

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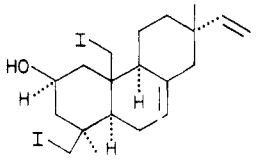

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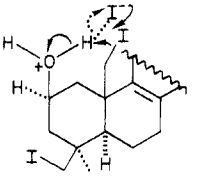

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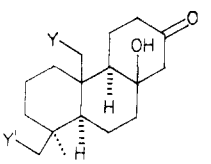
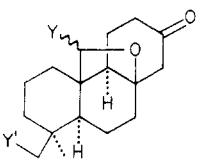
reduction of keto ester **8b**[8] with lithium triethylborohydride and acid-induced dehydration and double-bond isomerization of the resultant diol **8c**. The exclusive formaton of ether **10** represents a second example of more efficient oxidation of the angular methyl group than the 4β-methyl function. The ease of dehydroiodination of the intermediate iodohydrin may reflect double-bond participation in the iodide extrusion, i.e., homoallyl cation formation .

Reduction of olefinic ketone **8a**[8] with lithium triethylborohydride afforded axial alcohol **8d**, whose oxidation with lead tetraacetate and iodine led to diiodohydrin **12**. Unfortunately the latter halide proved to be exceedingly unstable (and thus not available for further chemistry), undergoing spontaneous decomposition even in chloroform solution. The product (**9c**), whose structure was derived from its ^{13}C NMR spectra, was one of double-bond isomerization and monodeiodination. If it be assumed that hydrogen iodide is liberated in the decomposition process and is responsible for the double-bond migration, then formulation **13** constitutes the simplest (albeit not sole) explanation for the reduction phase of the unusual reaction.

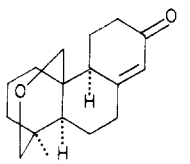
Oxidation of ketol **14a**,[9] a product of oxidative degradation of the diterpene manool, with lead tetraacetate and iodine gave two products, one of which could be identified readily as tetrahydrofuran **15a** (60% yield).[10] The second product was an iodo ether (10% yield), which at first was assumed to possess structure **15b** on the basis of the known



14a, Y=Y'=H
b, Y=I, Y'=H
c, Y=H, Y'=I
d, Y=Y'=I



15a, Y=Y'=H
b, Y=I, Y'=H
c, Y=H, Y'=I



16

proclivity of the reaction to lead to products of overoxidation (α-iodo- and α-acetoxytetrahydrofurans), i.e., the reaction process taking place by way of two consecutive hypoiodite formations and decompositions leading to 4,4-diiodo alcohols followed by one or two iodide displacements. ^1H NMR spectral inspection, however, revealed the iodo ether to be a substance containing two less methyl groups than the starting ketol (**14a**) and incorporating two methylenes attached to heteroatoms. This observation pointed to formula **15c** as best representing the structure of the minor product, a fact which was corroborated by the base-induced transformation of the compound into, inter alia, the enone ether **16**. It is noteworthy that the ring A substitution pattern of the latter is characteristic of that of some diterpenic natural substances.[11]

Whereas keto ether **15a** was a normal product of a single hypoiodite formation and decomposition and subsequent dehydroiodination of the intermediate iodohydrin **14b**, production of the iodo ether **15c** must have involved two hypoiodite operations and the ultimate dehydroiodination of diiodohydrin **14d**. The introduction of iodine on C(19), far from the reaction site, was unprecedented at the time of its discovery[10] and seemed not to fit the reaction requirements of Scheme I. However, a slight elaboration of the latter leads to an understanding of the unusual oxidation result. If it be assumed that intermediate iodohydrin **14b** undergoes hypoiodite formation and decomposition, the resultant iodomethyl radical (i.e., the C(20) radical of **14b**) may be too crowded (being not only axially oriented but also 1,3-diaxially disposed to the 8β-hydroxy and 4β-methyl functions) to permit iodine entry and, instead, performs a 1,5-hydrogen shift with C(19), the new, but less sterically encumbered carbon radical finally interacting with iodine.[12,13] This reaction sequence is il-

(8) Ceccherelli, P.; Pellicciari, R.; Cagnoli-Bellavita, N.; Fringuelli, R. *Ann. Chem. (Rome)* **1975**, *65*, 25.

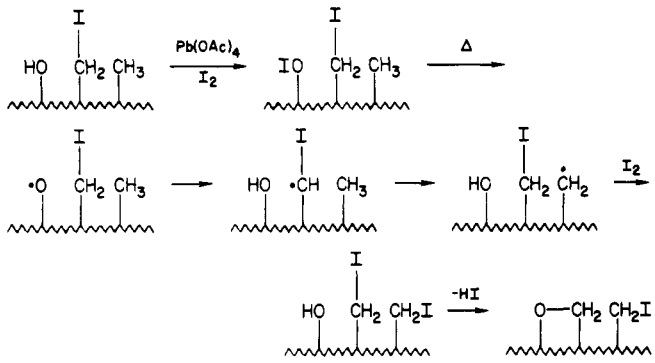
(9) Wenkert, E.; Mahajan, J. R.; Nussin, M.; Schenker, F. *Can. J. Chem.* **1966**, *44*, 2575 and references cited herein.

(10) The results of the oxidations of alcohols **14a** and **17** were presented in preliminary form in Wenkert, E.; Mylari, B. L. *J. Am. Chem. Soc.* **1967**, *89*, 174.

(11) Annonalide, for example (Orsini, F.; Pellizzoni, F.; McPhail, A. T.; Onan, K. D.; Wenkert, E. *Tetrahedron Lett.* **1977**, 1085).

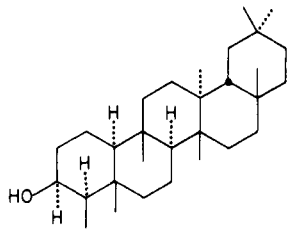
(12) Whereas, in principle, the formation of the diiodohydrin (**14d**) precursor of product **14c** can emanate from monoiodohydrin **14b** or **14c**, the above argument based on steric grounds precludes the intermediacy of iodo alcohol **14c**. Had the latter been an intermediate, it would have been produced with a rate comparable to that of the formation of compound **14b** and thus would have been observed as one of the isolated reaction products.

Scheme II



lustrated in Scheme II.

In order to determine the generality of the new reaction and to ascertain whether it was merely the consequence of the proper bis-1,3-diaxial positioning of a hydroxy and two methyl groups in the starting alcohol, 3β-friedelanol (**17**)[14] was chosen as another test case for the oxidation with lead tetraacetate and iodine.[10,15] Oxidation of the triterpenic alcohol gave a tetrahydrofuran (**18a**) (28% yield), an iodo ether (**18b**) (31%), and an α-acetoxytetrahydrofuran (**18c**) (7%).[16] Thus in this case overoxidation has led to a long-range oxidation product (**18b**) as well as one of the more common type (**18c**).



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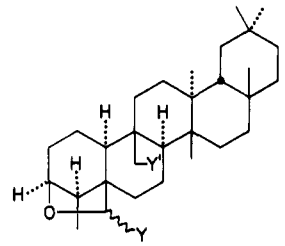

18a, Y = Y' = H
b, Y = H, Y' = I
c, Y = OAc, Y' = H

Experimental Section

Melting points were taken on a Reichert micro hotstage and are uncorrected. Infrared spectra of Nujol mulls were obtained on a Perkin-Elmer 1320 spectrophotometer. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded on a Varian EM-390 spectrometer and ^{13}C NMR spectra of $CDCl_3$ solutions on a Bruker WP 80 sy spectrometer operating at 20.15 MHz in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Column chromatography was carried out on 0.063–0.200-mesh Merck silica gel. All extracts were dried over Na_2SO_4.

Tetrahydrofuran 2. A mixture of 260 mg (0.59 mmol) of lead tetraacetate, 70 mg (0.30 mmol) of iodine, and 260 mg of calcium carbonate in 8 mL of anhydrous benzene was refluxed for 10 min. A solution of 120 mg (0.42 mmol) of alcohol **1** in 4 mL of anhydrous benzene was added, and refluxing was continued for 90 min. The suspension was filtered and the solid washed with benzene. The combined filtrate and washings were washed with saturated sodium thiosulfate solution and with water and then dried. The solution was evaporated and the residue chromatographed. Elution with 50:1 pentane–ethyl acetate gave 80 mg (67%) of semisolid ether **2**: ^{1}H NMR δ 0.88, 0.90 (s, 3 each, methyls), 2.9–3.2 (m, 1, OCH), 3.8–4.1 (m, 2, OCH_2), 4.8–5.1, 5.6–6.0 (m, 3, vinyl Hs), 5.2–5.4 (m, 1, olefinic H).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.62; H, 10.75.

2β-Hydroxymanoyl Oxide (5b). A mixture of 640 mg (17 mmol) of lithium aluminum hydride and 3.2 mL of dry *tert*-butyl alcohol in 32 mL of tetrahydrofuran was stirred at room temperature for 1 h. A solution of 2.00 g (6.6 mmol) of 2-oxomanoyl oxide (**5a**)[6] in 30 mL of dry tetrahydrofuran was added over a 30-min period and the stirring was contined for 4 h. Ice water was added slowly. The mixture was neutralized with 5% sulfuric acid solution and extracted with ether. The extract was washed with water, dried, and evaporated. Chromatography of the residue on neutral alumina (activity IV) and elution with 50:1 hexane–ethyl acetate gave 1.80 g (90%) of crystalline alcohol **5b**: mp 80–82 °C (from ether); ^{1}H NMR δ 0.92, 1.00, 1.06, 1.28, 1.30 (s, 3 each, 5 Me), 4.05 (pent., 1, J = 6 Hz, OCH), 4.5–5.2, 5.6–6.0 (m, 3, vinyl Hs); ^{13}C NMR δ 15.5 (C-11), 18.3 (C-20), 20.1 (C-6), 24.3 (C-19), 25.0 (C-14), 28.5 (C-17), 32.6 (C-4), 32.8 (C-18), 35.9 (C-12), 37.5 (C-10), 42.8 (C-7), 46.1 (C-1 or C-3), 46.7 (C-3 or C-1), 53.5 (C-9), 56.2 (C-5), 67.1 (C-2), 73.1 (C-13), 74.7 (C-8), 109.9 (C-16), 147.9 (C-15).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.26; H, 11.24.

Oxidation of 2β-Hydroxymanoyl Oxide (5b). A mixture of 1.00 g (2.2 mmol) of lead tetraacetate, 280 mg (1.1 mmol) of iodine, and 1.00 g of calcium carbonate in 120 mL of dry benzene was refluxed for 10 min. A solution of 500 mg (1.6 mmol) of alcohol **5b** in 30 mL of dry benzene was added and refluxing was continued for 2 h. Workup as above gave first 200 mg (23%) of liquid 2β-hydroxy-19,20-diiodomanoyl oxide (**6b**): ^{1}H NMR δ 1.10, 1.33, 1.53 (s, 3 each, 3 Me), 3.21 (dd, 1, J = 9, 2 Hz, H of ICH_2), 3.50 (dd, 1, J = 10, 3 Hz, H of ICH_2), 4.04 (d, 1, J = 9 Hz, H of ICH_2), 4.14 (pent., 1, J = 5 Hz, OCH), 4.28 (d, 1, J = 10 Hz, H of ICH_2), 4.7–5.2, 5.6–6.0 (m, 3, vinyl Hs); ^{13}C NMR δ 14.3 (C-11), 19.1 (C-20), 19.9 (C-6), 20.9 (C-19), 24.0 (C-14), 26.4 (C-17), 34.1 (C-18), 36.2 (C-4), 39.0 (C-12), 39.7 (C-10), 43.0 (C-7), 43.5 (C-3 or C-1), 43.6 (C-1 or C-3), 56.2 (C-5), 60.2 (C-9), 67.4 (C-2), 73.5 (C-13), 75.3 (C-8), 110.2 (C-16), 147.6 (C-15). (The compound was too unstable for elemental analysis.)

Further elution led to 120 mg (20%) of crystalline 20-acetoxy-2β,20-oxidomanoyl oxide (**7b**): mp 185–188 °C (from ether); ^{1}H NMR δ 0.98, 1.06, 1.20, 1.32 (s, 3 each, 4 Me), 2.10 (s, 3, COMe), 4.22 (t, 1, J = 6 Hz, OCH), 4.7–5.3, 5.6–6.0 (m, 3, vinyl Hs), 6.05 (s, 1, O_2CH); ^{13}C NMR δ 17.9 (C-11), 21.5 (acetyl Me), 22.1 (C-6), 22.6 (C-19), 26.0 (C-14 or C-17), 26.4 (C-17 or C-14), 33.0 (C-4), 34.0 (C-18), 38.1 (C-12), 39.1 (C-1), 42.3 (C-7), 45.3 (C-3), 49.9 (C-10), 51.0 (C-9), 54.4 (C-5), 73.0 (C-13), 74.4 (C-8), 75.4 (C-2), 97.2 (C-20), 110.1 (C-16), 147.6 (C-15), 169.6 (C=O).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.76; H, 9.51.

Further elution afforded 170 mg (24%) of crystalline 2β-hydroxy-20-iodomanoyl oxide (**6a**): mp 125–127 °C dec (from ether); ^{1}H NMR δ 0.93, 1.08, 1.34, 1.52 (s, 3 each, 4 Me), 3.52 (dd, 1, J = 12, 3 Hz, H of ICH_2), 4.33 (pent., 1, J = 5 Hz, OCH), 4.45 (dd, 1, J = 12, 2 Hz, H of ICH_2), 4.8–5.2, 5.6–6.0 (m, 3, vinyl Hs); ^{13}C NMR δ 16.3 (C-11), 18.8 (C-20), 19.9 (C-6), 23.9 (C-14), 24.1 (C-19), 26.4 (C-17), 32.7 (C-4), 34.3 (C-18), 39.0 (C-12), 39.8 (C-10), 43.4 (C-1,C-7), 46.4 (C-3), 56.8 (C-5), 59.9 (C-9), 67.6 (C-2), 73.4 (C-13), 74.7 (C-8), 110.1 (C-16), 147.7 (C-15). The iodohydrin was dehydrohalogenated without further purification.

2β,20-Oxidomanoyl Oxide (7a). A mixture of 170 mg (0.4 mmol) of iodohydrin (**6a**) and 25 mg of sodium carbonate in 4 mL of dry pyridine was heated at 120 °C for 12 h. It then was neutralized with 5% sulfuric acid solution and extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography and elution with 50:1 hexane–ethyl acetate yielded 80 mg (67%) of liquid tetrahydrofuran **7a**: ^{1}H NMR δ 0.95, 1.00, 1.14, 1.28 (s, 3 each, 4 Me), 3.44 (d, 1, J = 8 Hz, H of OCH_2), 3.78 (d, 1, J = 8 Hz, H of OCH_2), 4.26 (t, 1, J = 6 Hz, OCH), 4.8–5.3, 5.7–6.0 (m, 3 vinyl Hs); ^{13}C NMR δ 15.6

(13) Whereas it was difficult to isolate the iodohydrin (**14b**) precursor of major product **15a**, on the one occasion it was trapped prior to ring closure into a tetrahydrofuran it was oxidized with lead tetraacetate and iodine, affording iodo ether **15c** in 51% yield.

(14) Corey, E. J.; Ursprung, J. J. *J. Am. Chem. Soc.* **1956**, *78*, 5041.

(15) For another long-range iodination by the oxidation of a rigidly held alcohol with lead tetraacetate, see: Corbett, R. E.; Wilkins, A. L. *J. Chem. Soc., Perkin Trans 1* **1975**, 710.

(16) Takahashi and co-workers [Fukuda, T.; Tsuyuki, T.; Tanahashi, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 370. Hoshino, T.; Tsuyuki, T.; Takahashi, T. *Ibid.* **1967**, *40*, 389] have reported this oxidation (in cyclohexane solution and higher concentration of oxidizing agents), followed by chromic acid oxidation of the crude product mixture. The sole product isolated in 22% yield was the γ-lactone corresponding to **18c**, implying that the latter had been their only product of the lead tetraacetate–iodine reaction.

(C-11), 22.2 (C-6), 22.7 (C-19), 25.8 (C-14), 28.3 (C-17), 33.1 (C-4), 34.1 (C-18), 35.7 (C-12), 41.9 (C-1), 42.4 (C-7), 47.0 (C-10), 47.4 (C-3), 47.7 (C-9), 54.1 (C-5), 67.5 (C-20), 73.3 (C-13), 74.6 (C-2), 74.7 (C-8), 110.5 (C-16), 147.8 (C-15).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found C, 78.52; H, 10.25.

8,9-Didehydro-7,8-dihydro-2-oxoisopimaradiene (9a). A solution of 500 mg (1.8 mmol) of ketone **8a** in 150 mL of anhydrous chloroform, saturated with hydrogen chloride gas, was kept at room temperture for 24 h. It then was washed with water and saturated sodium bicarbonate solution and dried. The solution was evaporated and the residue chromatographed. Elution with chloroform gave 450 mg (90%) of solid, whose crystallization from benzene–hexane afforded crystalline ketone **9a**: mp 60–62 °C; ^{1}H NMR δ 0.91, 1.00, 1.00, 1.08 (s, 3 each, methyls), 2.1–2.5 (m, 4, 2 $COCH_2$), 4.7–4.9, 5.5–5.9 (m, 3 vinyl Hs).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.51; H, 10.72.

8,9-Didehydro-7,8-dihydro-2β-isoprimarol (9b). A 1.0 M tetrahydrofuran solution of lithium triethylborohydride, 3.5 mL, was added dropwise to a stirring solution of 500 mg (1.8 mmol) of ketone **9a** in 20 mL of dry tetrahydrofuran under nitrogen at room temperature. After 20 min water was added and the mixture extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with chloroform gave 460 mg (92%) of semisolid alcohol **9b**: ^{1}H NMR δ 0.94, 1.00, 1.08, 1.24 (s, 3 each, methyls), 4.08 (pent., 1, J = 5 Hz, OCH), 4.6–4.9, 5.5–5.9 (m, 3, vinyl Hs); ^{13}C NMR δ 19.0 (C-11), 21.2 (C-6), 22.6 (C-20), 24.2 (C-19), 27.9 (C-17), 32.4 (C-4), 32.6 (C-7), 33.1 (C-18), 35.0 (C-13), 35.1 (C-12), 37.7 (C-10), 42.0 (C-14), 42.9 (C-1), 46.5 (C-3), 50.1 (C-5), 68.0 (C-2), 110.7 (C-16), 124.0 (C-8), 137.1 (C-9), 146.3 (C-15).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.50; H, 11.07.

8,9-Didehydro-7,8-dihydro-2β,20-oxidoisopimaradiene (10). A solution of 500 mg (1.7 mmol) of alcohol **9b** in 30 mL of dry benzene was added to the refluxing mixture of oxidizing agents used for the oxidation of alcohol **5b** (vide supra), and the heating was continued for 90 min. Workup as above and elution with chloroform led to 100 mg of starting alcohol (as second fraction) and 240 mg of colorless, semisolid ether **10**: ^{1}H NMR δ 0.93, 0.98, 1.02 (s, 3 each, 3 Me), 3.38, 3.45, 3.73, 3.80 (4-line AB, 2, OCH_2), 4.31 (m, 1, OCH), 4.6–4.9, 5.5–5.9 (m, 3 vinyl Hs).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.94; H, 10.37.

2β,19-Dihydroxyisopimaradiene (8c). A 1.0 M tetrahydrofuran solution of lithium triethylborohydride, 4 mL, was added dropwise to a stirring, refluxing solution of 500 mg of keto acetate **8b** in 30 mL of dry tetrahydrofuran under nitrogen. After 20 min the mixture was worked up as above. Elution with 30:1 chloroform–methanol produced 350 mg (80%) of colorless, semisolid diol **8c**: ^{1}H NMR δ 0.88, 0.96, 1.13 (s, 3 each, methyls), 3.25, 3.38, 4.07, 4.20 (4-line AB, 2, OCH_2), 4.0–4.3 (m, 1, OCH), 4.8–5.1, 5.6–6.0 (m, 3 vinyl Hs), 5.2–5.5 (m, 1, olefinic H).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.62; H, 10.71.

8,9-Didehydro-7,8-dihydro-2β,19-oxidoisopimaradiene (11). A solution of 100 mg of diol **8c** and 20 mg of *p*-toluenesulfonic acid in 30 mL of chloroform was refluxed for 3 h. The mixture was washed with saturated sodium bicarbonate solution and with water, dried, and evaporated. Chromatography of the residue and elution with chloroform gave 60 mg (64%) of semisolid ether **11**: ^{1}H NMR δ 0.90, 0.94, 1.11 (s, 3 each,methyls), 3.39, 3.48, 3.76, 3.85 (4-line AB, 2, OCH_2), 4.3–4.6 (m, 1, OCH), 4.8–5.1, 5.5–5.9 (m, 3, vinyl Hs).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.71; H, 10.63.

2β-Isopimarol (8d). A 1.0 M tetrahydrofuran solution of lithium triethylborohydride, 8.0 mL, was added dropwise to a stirring solution of 1.00 g (3.6 mmol) of ketone **8a**[8] in 60 mL of dry tetrahydrofuran under nitrogen at room temperature. After 20 min waster was added, and the mixture was extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with chloroform yielded 900 mg (90%) of crystalline alcohol **8d**: mp 105–108 °C (from hexane); ^{1}H NMR δ 0.90, 0.91, 1.11, 1.18 (s, 3 each, 4 Me), 4.20 (pent., 1, J = 6 Hz, OCH), 4.8–5.0, 5.7–5.9 (m, 3, vinyl Hs), 5.3–5.5 (m, 1, olefinic H).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.41, H, 11.02.

8,9-Didehydro-7,8-dihydro-19-iodo-2β-isopimarol (9c). A mixture of 860 mg (1.9 mmol) of lead tetraacetate, 250 mg (1.0 mmol) of iodine, and 1.00 g of calcium carbonate in 100 mL of dry benzene was refluxed for 10 min. A solution of 400 mg (1.4 mmol) of alcohol **8d** in 20 mL of dry benzene was added and refluxing continued for 0.5 h. Workup as above and elution with chloroform gave 220 mg (30%) of colorless, liquid 19,20-diiodo-2β-isopimarol (**12**): ^{1}H NMR δ 0.96, 1.10 (s, 3 each, 2 Me), 3.40 (dd, 1, J = 9, 2 Hz, H of ICH_2), 3.53, 3.66, 3.79, 3.92 (4-line AB, 2, ICH_2), 4.26 (pent., 1, J = 5 Hz, OCH), 4.42 (d, 1, J = 9 Hz, H of ICH_2), 4.8–5.1, 5.6–5.9 (m, 3, vinyl Hs), 5.3–5.6 (m, 1, H-7).

A chloroform solution of the diiodohydrin **12** became red on being kept at room temperature for less than 1 h and the TLC response of the contents showed the presence of two substances. The optimum time for the transformation of alcohol **12** into another compound was 2 days. Purification of the material in a manner in which the diiodohydrin had been purified led to colorless liquid iodohydrin **9c**: ^{1}H NMR δ 0.98, 1.10, 1.27 (s, 3 each, 3 Me), 3.28 (dd, 1, J = 9, 2 Hz, H of ICH_2), 4.19 (pent., 1, J = 5 Hz, OCH), 4.26 (d, 1, J = 9 Hz, H of ICH_2), 4.8–5.0, 5.5–5.9 (m, 3, vinyl Hs); ^{13}C NMR δ 18.6 (C-11), 21.1 (C-6), 22.3 (C-20), 23.6 (C-19), 27.9 (C-17), 32.2 (C-7), 32.4 (C-18), 34.8 (C-12), 34.9 (C-13), 36.0 (C-4), 37.1 (C-10), 41.7 (C-3), 41.8 (C-14), 43.9 (C-1), 50.3 (C-5), 67.8 (C-2), 110.7 (C-16), 123.8 (C-8), 136.9 (C-9), 146.0 (C-15).

Anal. Calcd for $C_{20}H_{33}O_2I$: C, 55.53; H, 7.71. Found: C, 55.12; H, 7.95.

Oxidation of Ketol 14a. A mixture of 680 mg (1.6 mmol) of lead tetraacetate, 200 mg (0.8 mmol) of iodine, and 700 mg of calcium carbonate in 20 mL of dry benzene was refluxed for 10 min. A solution of 200 mg (0.76 mmol) of alcohol **14a** in 10 mL of dry benzene was added and refluxing continued for 1 h. Workup as above and elution with chloroform gave 180 mg of a mixture of two substances, whose rechromatography and elution with 2:1 hexane–ether gave first 120 mg (60%) of keto ether **15a**: mp 87–89 °C (benzene–hexane); IR 5.84 (s, C=O) μm; ^{1}H NMR δ 0.96, 0.96 (s, 3 each, methyls), 2.2–2.5 (m, 4, 2 $COCH_2$), 3.48 3.60, 4.18, 4.30 (4-line AB, 2, OCH_2).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.92; H, 10.06.

The late eluates gave 30 mg (10%) of iodide **15c**: mp 180 °C dec (benzene–hexane); IR 5.85 (s, C=O) μm; ^{1}H NMR δ 1.08 (s, 3, Me), 2.2–2.5 (m, 4, 2 $COCH_2$), 3.39, 3.48, 3.54, 3.63 (4-line AB, 2, ICH_2), 3.54, 3.64, 4.05, 4.15 (4-line AB, 2, OCH_2).

Anal. Calcd for $C_{17}H_{25}O_2I$: C, 52.58; H, 6.50. Found: C, 52.51; H, 6.61.

Keto Oxide 16. A solution of 100 mg of keto ether **15c** and 50 mg of sodium methoxide in 20 mL of dry methanol was refluxed under nitrogen for 12 h. Water, 10 mL, was added and the solution neutralized with 3% sulfuric acid. It then was extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 2:1 hexane–ether, giving 52 mg (70%) of crystalline keto ether **16**: mp 76–77 °C (from hexane); IR 6.01 (s, C=O) μm; ^{1}H NMR δ 0.74 (s, 3, Me), 3.32, 3.46, 3.52, 3.66 (4-line AB, 2, OCH_2 at C-10), 3.67 (s, 2, OCH_2 at C-4), 5.86 (br s, 1, olefinic H).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.35; H, 9.41.

Oxidation of 3β-Friedelanol (17). A mixture of 1.40 g (3.2 mmol) of lead tetraacetate, 400 mg (1.6 mmol) of iodine, and 1.40 g of calcium carbonate in 100 mL of dry benzene was refluxed for 10 min. A solution of 700 mg (1.6 mmol) of alcohol **17** in 20 mL of dry benzene was added and the refluxing mixture was irradiated by a 250-W, all-purpose tungsten lamp for 80 min. Workup as above and elution with 25:1 pentane–ether gave 200 mg of ether **18a**: mp 219–221 °C (methanol) (lit.[17] mp 208–210 °C); IR and ^{1}H NMR spectrally identical with an authentic sample.[17] Further elution yielded 280 mg of iodide **18b**: mp 205–206 °C (methanol); ^{1}H NMR δ 0.9–1.2 (m, 18, methyls), 3.49,

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3.60, 4.32, 4.43 (4-line AB, 2, OCH_2), 3.63, 3.73, 3.88, 3.98 (4-line AB, 2, ICH_2), 3.8–3.9 (m, 1, OCH).

Anal. Calcd for $C_{30}H_{49}OI$: C, 65.19; H, 8.95. Found: C, 64.97; H, 9.04.

Finally, further elution led to 50 mg of semisolid acetate **18c**: IR ($CHCl_3$) 5.77 (s, C=O) μm; ^1H NMR δ 0.9–1.2 (m, 21, methyls), 2.10 (s, 3, COMe), 4.0–4.2 (m, 1, OCH), 6.40 (s, 1, CO_2CH).

Anal. Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.16; H, 10.96.

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Iodination of Vancomycin, Ristocetin A, and Ristocetin Pseudoaglycon

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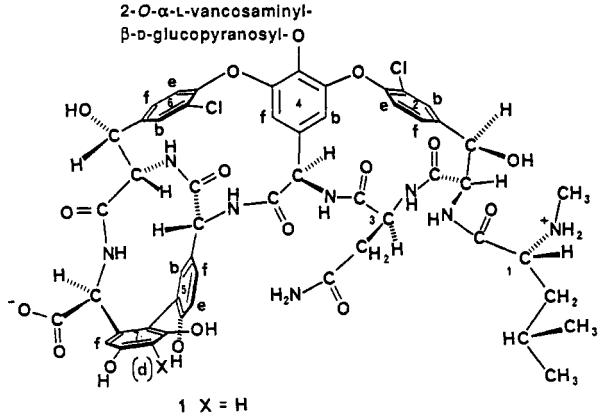
Iodinated derivatives of the glycopeptide antibiotics vancomycin (**1**) and ristocetin A (**2**) have been known for some time; the site(s) of iodination in these compounds have now been determined by NMR and degradation. Vancomycin is iodinated at the para position of the ring in residue 7 (the resorcinol ring of actinoidinic acid). In contrast, ristocetin undergoes iodination predominantly on residue 3 at the ortho position distal to the diphenyl ether linkage. However, if the sugar attached to the aromatic ring of residue 7 is removed as in the pseudoaglycon of ristocetin (Ψ-AGR, **10**) iodination occurs in the same position as in vancomycin, suggesting that in ristocetin the sugar sterically blocks the electronically preferred site of iodination. Peptide binding ability, as measured by K_A determinations for the tripeptide Ac_2-L-Lys-D-Ala-D-Ala, is somewhat diminished by iodination. Iodovancomycin, iodoristocetin, the pseudoaglycon of iodoristocetin and iodinated pseudoaglycon of ristocetin have K_A values ($\sim 10^5$) slightly lower but of the same order of magnitude as the analogous uniodinated compounds.

Vancomycin (**1**) and ristocetin (**2**) are glycopeptide antibiotics, isolated from *Nocardia orientalis* (formerly called *Streptomyces orientalis*) and *Nocardia lurida*, respectively.[1] They are active against Gram-positive bacteria



1 X = H
3 X = I

and the former is used clinically for the treatment of methicillin-resistant *Staphylococcus aureus* infections and *Clostridium difficile* induced pseudomembranous colitis.[2] The antibiotics in this group exert their antibacterial action by binding to peptide intermediates involved in bacterial cell wall synthesis.[3] In vitro these antibiotics bind certain aliphatic peptides, such as *N*-Ac-D-Ala-D-Ala and Ac_2-L-Lys-D-Ala-D-Ala, which are analogues of cell wall precursors.[4] The structures of the glycopeptide antibiotics as well as the nature of the antibiotic–peptide complexes have been the subject of several investigations in recent years.[1,5] High field ^1H NMR studies by Williams,[6] Feeney,[7] and Fesik[8] have revealed many details of the peptide–antibiotic interaction which involves a series of intermolecular hydrogen bonds between the two constituents. It is now of

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