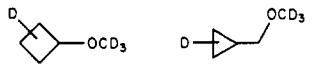
white precipitate was also observed.

Photolysis of 1 in Methanol-d_4. Photolysis of 12 mg of 1 in 0.5 mL of CD_3OD with ~5 mg of $NaHCO_3$ at room temperature produced a mixture which was analyzed by ^1H NMR and GC. Bicyclo[1.1.0]butane (16): yield (by NMR) 79% (1 h photolysis), 65% (3 h), 61% (5 h). Cyclobutene (17): yield ~2% (5 h). Methyl-d_3 4-pentenoate-2-d (14) (see section C): yield 16% (5 h). Cyclobutyl-d methyl-d_3 ether (24): ^1H NMR δ 1.5 (m, ~1 H), 1.7 (m, ~0.3 H), 1.85 (q, ~1.8 H), 2.2 (m, ~2 H), 3.85 (p, 1 H); yield ~6% (5 h). Cyclopropylcarbinyl-d methyl-d_3 ether (25): ^1H NMR δ 0.2 (m, 1.2 H), 0.5 (d, 1.9 H), 1.0 (sextet, 1 H), 3.2 (d, 2 H); yield ~6% (5 h). Retention times for 24 and 25 are 1.8 and 1.9 min but are unassigned. In the absence of $NaHCO_3$, no 16 was observed, and instead 24 and 25 were each obtained in 44% yield. In this case, the observed product distribution of 24-25 is identical with that reported by Wiberg and Szeimies[44] for the hydrolysis of bicyclobutane to the corresponding alcohols of 24-25. The observed labeling patterns are also nearly identical.



24 25

1,1-Di(methoxy-d_3)bicyclo[1.1.1]pentane (19) was formed in up to 43% yield from photolysis without $NaHCO_3$ at slightly below room temperature and was the sole observed product from photolysis at 35-40 °C. ^1H NMR δ 1.4 (s, 2 H), 2.0 (s, 2 H), 2.8 (s, 2 H); t_R 3.7 min.

Control Photolysis of 22. 1,3-Butadiene (~1 mg) in cyclohexane-d_{12} was photolyzed through Vycor for 8.5 h at room temperature. ^1H NMR and GC analysis showed that the yield of cyclobutene was less than 20% and that most of the starting material was unchanged.

Gas-Phase Photolysis of 1. Photolysis of 1-3 mg of 1 in an evacuated ESR tube with vacuum stopcock for durations up to 54 h at room temperature followed by vacuum transfer of benzene-d_6 into the tube, produced bicyclo[1.1.0]butane and 1,3-butadiene as products in a ratio which varied from experiment to experiment, with increasing pressure producing greater quantities of bicyclobutane. A colorless film was also formed on the sides of the tube (detected by filling the empty tube with 5% HF). Photolysis without the Vycor filter increased the rate, and the film on the sides of the tube was yellow instead of colorless.

Control Photolysis of 16. Bicyclo[1.1.0]butane (~6 mg) was photolyzed in the gas phase for 48 h at room temperature. Benzene-d_6 was vacuum transferred into the tube and the solution pipeted into an NMR tube. Only 16 was observed.

F. ESR Experiments. All samples were prepared and degassed (5 cycles) in 5-mm o.d. quartz ESR tubes equipped with high vacuum stopcocks. Samples typically contained 3-8 mg of 1 and 0.5 mL of solvent. 2-Methyltetrahydrofuran (MTHF), cyclohexane, benzene-d_6, and hexafluorobenzene were used as solvents. One sample was made in MTHF with a small amount of mercury as photosensitizer.

A Varian E-9 spectrometer and an Air Products and Chemicals Helitran liquid helium transfer apparatus were used.[58] The samples were photolyzed in the cavity by using an Oriel 200-W mercury-xenon lamp, operated between 150 and 180 W. The light was filtered with water in a quartz vessel.

The cavity temperature was measured using a calibrated chromel vs. gold (with 0.7% iron) thermocouple fitted inside a sample tube. The experiments were run in the temperature range from 9 to 12 K. Some samples exhibited doublet signals upon photolysis, but no signal which could be attributed to a triplet biradical was observed.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for support of this work.

(58) The assistance of Gary J. Snyder is gratefully acknowledged.

Stereospecific Transformation of Grindelic Acid into the Antifeedant 6α-Hydroxygrindelic Acid, Its 6β-Epimer, and Other Related Natural Diterpene Acids

Manuel González Sierra,* María I. Colombo, Alejandro C. Olivieri, Marta E. Zudenigo, and Edmundo A. Rúveda*

Instituto de Química Orgánica de Síntesis (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Casilla de Correo 991, Suipacha 531, 2000 Rosario, Argentina

Received April 24, 1984

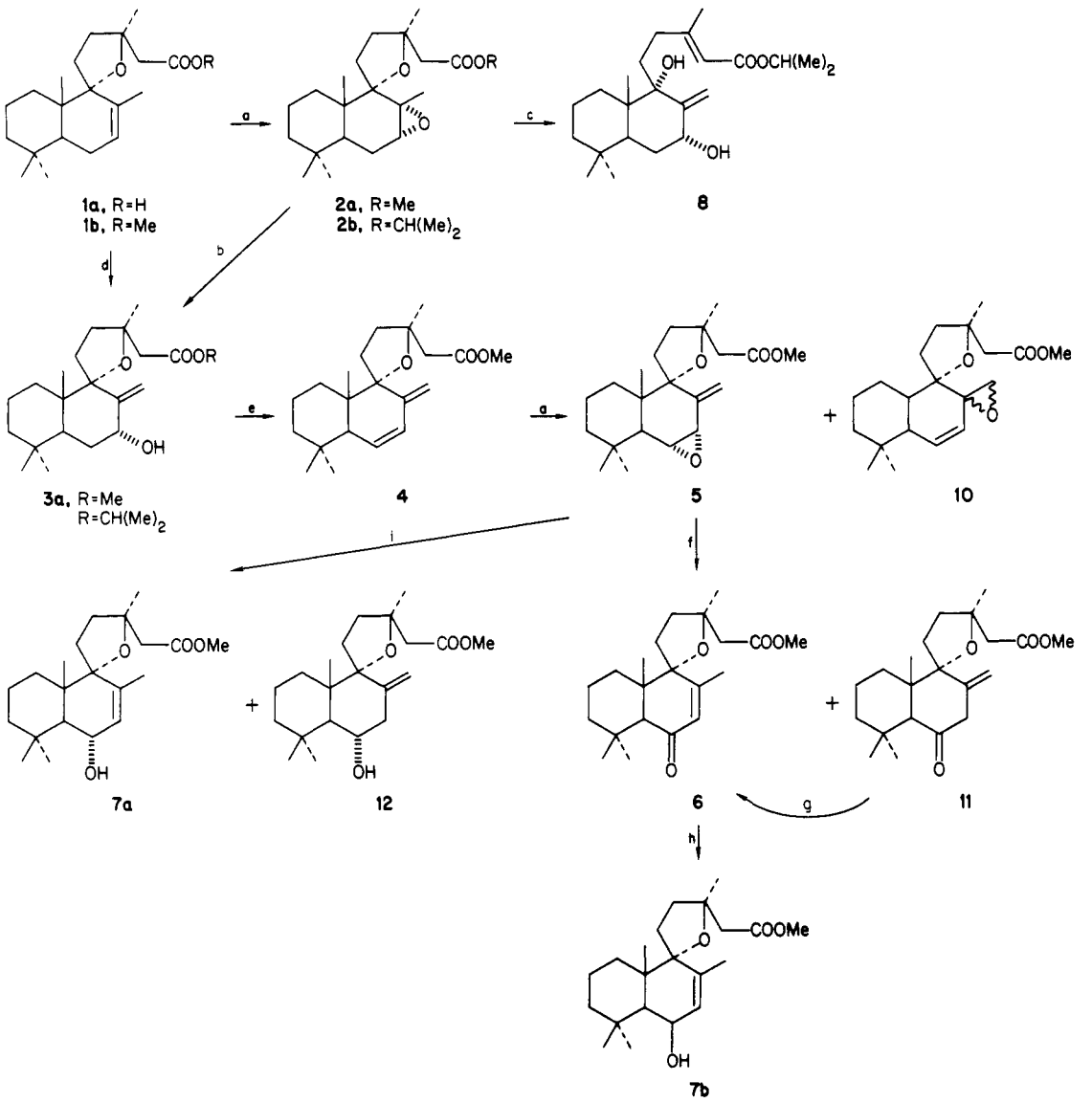
The synthesis of the methyl esters of several natural diterpene acids related to grindelic acid (**1a**), including methyl 7α,8α-epoxygrindelate (**2a**), methyl 7α-hydroxy-8,17-didehydrogrindelate (**3a**), methyl 6,7,8,17-tetradehydrogrindelate (**4**), methyl 6-oxogrindelate (**6**), and methyl 6α-hydroxygrindelate (**7a**), through a common sequence is reported. The unusual, simultaneous, and stereospecific opening of the oxirane and tetrahydrofuran rings of the methyl 7α,8α-epoxygrindelate (**2a**) by aluminum isopropoxide to produce isopropyl 7α,9α-dihydroxylabda-8(17),13(*E*)-dien-15-oate (**8**) is also reported.

Some time ago as part of our research interest in transformations of natural products, we became aware of grindelic acid (**1a**), the most abundant diterpene acid from several *Grindelia* species.[1] Recently we decided to include 6-hydroxy derivatives of **1a** in a program designed to explore alternative methods of insect control.[2-4] Unfortunately our attempts to get the 6-hydroxy compounds through simple allylic oxidations of **1b** failed completely or led to useless complex mixtures. Apparently, oxidation occurs preferably on the allylic methyl group.[5]

(1) Guerreiro, E.; Kavka, J.; Saad, J. R.; Oriental, M. A.; Giordano, O. S. *Rev. Latinoam. Quim.* **1981**, *12*, 77.
(2) Rose, A. F. *Phytochemistry* **1980**, *19*, 2689.
(3) Rose, A. F.; Jones, K. C.; Haddon, W. F.; Dreyer, D. L. *Phytochemistry* **1981**, *20*, 2249.
(4) In an early stage of our study, a careful analysis of the spectroscopic data from the literature and the use of related model compounds allowed us to postulate different structures and stereochemistry for a couple of the reported compounds. Such observations have been already reported in a previous publication: González Sierra, M.; Colombo, M. I.; Zundenigo M. E.; Rúveda, E. A. *Phytochemistry* **1984**, *23*(8), 1685.
(5) Bruun, T.; Jackman, L. M.; Stenhagen, E. *Acta Chem. Scand.* **1962**, *16*, 1675.

0022-3263/84/1949-4984$01.50/0

Scheme I[a]

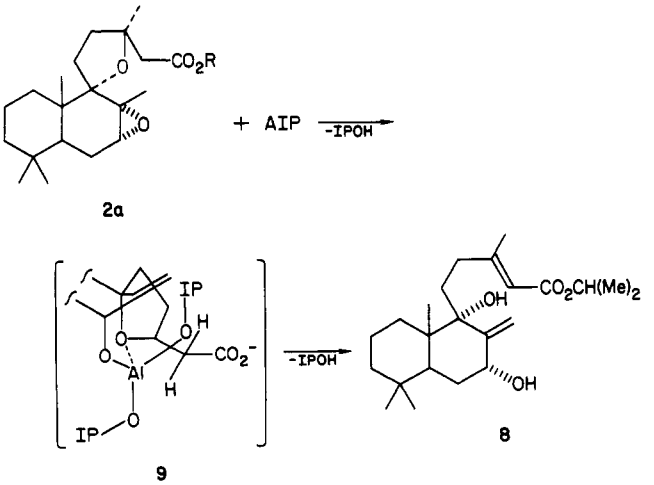


[a] (a) MCPBA, CH_2Cl_2, 0 °C; (b) aluminum isopropoxide (AIP) cat, toluene, reflux; (c) AIP equimolecular, xylene, reflux; (d) *hν*, $^1O_2$, *meso*-tetraphenylporphine, CCl_4; (e) HOTs, benzene, reflux; (f) $BF_3 \cdot Et_2O$, benzene, room temperature; (g) basic Al_2O_3, CH_2Cl_2, reflux; (h) $Zn(BH_4)_2$, Et_2O; (i) PtO_2, EtOH, H_2 atm.

A search for an alternative path led us to consider the sequence shown in Scheme I. Although the sequence is rather long, it also provides the partial synthesis of compounds **2**, **3**, **4**, and **6**, which are also methyl esters of naturally occurring diterpene acids.[1,6-8] Besides, the use of carefully chosen reagents and conditions in the last steps led to complete control of the stereochemistry of the final products.

Epoxidation of **1b** with *m*-chloroperoxybenzoic acid produced exclusively and α epoxide **2a**, as described previously.[4] Of the variety of reagents available to isomerize the oxirane to the allylic alcohol we first used aluminum isopropoxide. Under the conditions described by Eschinasi,[9] no reaction was observed. A 9:1 mixture of the transesterification product **2b** and the allylic alcohol **3b** was obtained by using toluene as solvent and raising the reaction temperature. Other attempts to favor the production of the desired alcohol by changing the reaction conditions or increasing the proportion of aluminum isopropoxide led exclusively to the formation of a new

Scheme II



(6) Bohlmann, F.; Ahmed, M.; Borthakur, N.; Wallmeyer, M.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1982**, *21*, 167.
(7) Hoffmann, J. J.; McLaghlin, S. P.; Jolad, S. D.; Schram, K. H.; Tempesta, M. S.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 1725.
(8) Timmermann, B. N.; Luzbetak, D. J.; Hoffmann, J. J.; Jolad, S. D.; Schram, K. H.; Bates, R. B.; Klenck, R. E. *Phytochemistry* **1983**, *22*, 523.
(9) (a) Eschinasi, E. H. *Isr. J. Chem.* **1968**, *6*, 713. (b) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1598.

Table I. Carbon Shifts of Natural and Synthetic Derivatives of Methyl Grindelate

C	3a	4	5	6	7a	7b	8	11	12
C-1	33.0	31.0	30.8	32.9	33.3	32.4	31.4	31.3	32.5
C-2	18.9	18.8	18.6	18.1	18.7	18.6	19.0	18.4	18.9
C-3	41.7	40.8	41.1	43.0	42.9	44.4	41.5	42.2	43.4
C-4	33.3	33.0	33.2	32.6	33.3	32.4	33.0	32.2	33.7
C-5	40.4	46.6	46.2	56.6	51.0	46.8	39.7	58.6	51.9
C-6	31.8	130.1	54.2	200.1	67.9	65.7	31.5	208.7	71.2
C-7	75.1	129.0	56.4	130.0	130.4	128.3	76.1	51.9	36.5[a]
C-8	147.7	146.9	144.5	154.1	136.6	137.0	146.1	146.2	148.0
C-9	93.3	88.9	88.7	90.6	89.1	90.1	81.0	90.1	90.1
C-10	41.9	41.3	40.8	45.6	42.9	44.4	43.9	43.8	41.9
C-11	26.3	27.3	26.1	28.5	27.6	28.8	27.5	25.3	27.0
C-12	37.4	37.5	36.6	38.9	38.0	38.0	35.5	39.9	36.7[a]
C-13	82.3	81.8	82.0	82.5	81.3	81.7	160.8	81.8	81.2
C-14	46.5	47.8	46.4	47.6	47.4	47.8	115.3	46.4	46.5
C-15	171.2	171.7	171.7	174.2	171.4	171.5	166.4	171.2	171.6
C-16	25.6	25.6	27.2	28.9	27.3	27.3	19.1	26.9	25.4
C-17	111.0	110.8	118.1	21.7	22.6	25.2	113.2	109.4	108.3
C-18	33.1	32.6	32.2	33.7	35.3	33.6	33.6	32.5	36.5
C-19	21.9	22.2	22.3	20.9	20.5	21.1[a]	21.5	21.5	22.4
C-20	16.6	17.2	18.3	19.8	18.9	20.1[a]	15.9	19.3	18.5
OMe	51.3	51.1	51.0	51.3	51.3	51.3		51.2	51.2
$CHMe_2$							66.5, 21.9		

[a] Assignments may be reversed.

product, spectroscopically characterized as the diol **8**.

The easy opening of the tetrahydrofuran ring is probably a consequence of the favorable arrangement of the oxygen atoms allowing the intramolecular coordination of the aluminum atom in the rigid intermediate **9**, as shown in Scheme II, which is capable of suffering the stereospecific opening to **8**.[10] Supporting this explanation are the facts that no opening occurs for a similar system when the stereochemistry of the epoxide is opposite[11] nor when methyl grindelate (**1b**) was submitted to the same reaction conditions. Other conditions (H_2SO_4–H_2O, $ISi(Me)_3$) failed to isomerize the epoxide to allylic alcohol.

At this point we considered the alternative of using a sensitized photooxygenation, followed by reduction,[12] to produce the desired allylic alcohol **3a**. Although **1b** did not readily undergo photooxygenation, we finally produced **3a** in better than 80% yield by using *meso*-tetraphenylporphine in carbon tetrachloride,[13] followed by trimethyl phosphite reduction. Compound **3a**, in turn, was easily dehydrated (TsOH, benzene) to produce diene **4**, whose epoxidation with *m*-chloroperoxybenzoic acid in dichloromethane at 0 °C proceeded regio- and stereospecifically producing one major compound, spectroscopically characterized as the epoxide **5** and assumed to possess the α configuration based on mechanistic considerations[4,10] (a minor amount, less than 10%, of the epoxide mixture **10** was also produced).

With epoxide **5** in hand, we immediately thought of rearranging it to ketone **6** on the basis of our previous experience on the reduction of solidagenone[4] to the closely related 6-hydroxy compounds. The rearrangement of epoxide **5** was straightforward and produced a mixture of the desired ketone **6** plus the unconjugated enone **11**, which was easily converted into **6** by basic alumina isomerization. The reduction of **6**, however, was not as easy as expected and, of the several reducing agents tried ($NaBH_4$/EtOH/NaOH, AlH_3/Et_2O, Dibal, etc.), only $Zn(BH_4)_2$[14] produced a moderate yield of an allylic alcohol, whose ^1H NMR analysis showed clearly the presence of a 6-axial hydroxyl group (δ 4.37, (J_{5-6} = 4.5 Hz)), as expected for the **7b** isomer. In view of those results, we decided to try the reductive opening of epoxide **5** as a direct route toward the natural allylic alcohol **7a**. What we needed was a 1,4-addition to get, simultaneously, the opening of the epoxide and the shift of the exocyclic double bond. Although there are a great number of reagents capable of producing such type of openings, our system has an additional tetrahydrofuran ring and, being doubly allylic, proved to be extremely reactive, producing only complex mixtures of over-reduced deoxygenated compounds with several reagents ($NaCNBH_3$, $BF_3{\cdot}Et_2O$, Li, NH_3 (liquid), H^+, or sodium benzoate).[15-20] Finally, catalytic hydrogenation (PtO_2, EtOH, H_2, 1 atm) produced a 8:3 mixture of two alcohols, the desired **7a** and presumably the 1,2-addition product, characterized as **12** by analysis of its ^1H and ^{13}C NMR spectra. The spectroscopic data found for compounds **2a**, **3a**, **4**, **6**, and **7a** are in good agreement with those reported in the literature.[1,6-8] The carbon shifts for the natural products and the synthetic intermediates are listed in Table I.[21]

Experimental Section

Melting points were determined on an Ernst Leitz hot-stage microscope and are uncorrected. Infrared spectra were measured with a Beckman Acculab 8 spectrophotometer as solids in KBr disks unless specified otherwise. NMR spectra were recorded on a Bruker WP 80 SY spectrometer in $CDCl_3$ solutions. The ^1H NMR spectra were measured at 80.13 MHz and Me_4Si was used as an internal standard; chemical shifts are expressed in δ; J and half-band widths ($W_{1/2}$) are given in hertz. The ^{13}C NMR spectra were measured at 20.15 MHz and the δ values are in parts per million downfield from Me_4Si ($\delta(Me_4Si) = \delta(CDCl_3) + 76.9$). Silica gel GF_{254}(Type 60) was utilized for thin-layer plates (TLC) and

(10) Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909.
(11) Schulte-Elte, K. H.; Gautschi, F.; Renold, W.; Hauser, A.; Frankhauser, P.; Limacher, J.; Ohloff, G. *Helv. Chim. Acta* **1978**, *61*, 1125.
(12) De Miranda, D. S.; Brendolan, G.; Imamura, P. M.; González Sierra, M.; Marsaioli, A. J.; Rûveda, E. A. *J. Org. Chem.* **1981**, *46*, 4851.
(13) Matsumoto, M.; Kuroda, K. *Synth Commun.* **1981**, *11*, 987.
(14) Naito, T.; Nakata, T.; Akita, H.; Oishi, T. *Chem. Lett.* **1980**, *21*, 445. We thank Dr. Oishi for the experimental details of this reaction.
(15) Brown, H. C.; Krishnamurty, S. *J. Am. Chem. Soc.* **1973**, *95*, 8486.
(16) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214.
(17) Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1978**, *43*, 1096.
(18) Otter, B. A.; Falco, E. A.; Fox, J. J. *J. Org. Chem.* **1975**, *40*, 2530.
(19) Lenox, R. S.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 957.
(20) Hall, S. S. *J. Org. Chem.* **1973**, *38*, 1738.
(21) As a consequence of our study mentioned in ref 4 we concluded that the signals for several carbons in compounds **3a**, **4**, and **6** have been misassigned in ref 7 and 8.

spots were visualized by staining with anisaldehyde–sulfuric acid.[22] Combustion analyses were carried out by UMYMFOR (Unidad de Microanálisis y Métodos Físicos en Química Orgánica, Universidad de Buenos Aires).

Methyl Grindelate (1b). It was prepared as described in ref 1 and showed IR (film) and ^{1}H NMR spectra identical with those reported.

Methyl 7α,8α-Epoxygrindelate (2a). It was prepared as described in ref 4: mp 58–59 °C $[\alpha]_D$ −74.8 (*c* 1.1, $CHCl_3$) (lit.[23] mp 58–60 °C; $[\alpha]_D$ −82.1). It showed IR and ^{1}H NMR spectra identical with those reported.[1,23]

Aluminum Isopropoxide Treatment of 2a (2a → 8). A stirred solution of **2a** (370 mg, 1.1 mmol) and freshly distilled AIP (612 mg, 3 mmol) in xylene (13 mL) was heated at 160 °C (oil bath) and the progress of the reaction was monitored by TLC. After 3 h and 14 h, additional amounts of AIP were added (612 mg, 3 mmol) in 3 mL of xylene, each time) and the heating was continued for 19 h in total. The crude product obtained by evaporation of the solvent was taken up with a mixture of Et_2O (30 mL) and 30% aqueous NaOH (35 mL) and the aqueous phase was further extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue over silica gel (15 g) with mixtures of hexane and increasing amounts of EtOAc afforded **2a** (108 mg, 28%) and the diol ester **8** (205 mg, 54%) as a crystalline solid. Recrystallization of **8** from MeOH afforded the following material: mp 157.5–159.9 °C; $[\alpha]_D$ + 10.7 (*c* 1.8, $CHCl_3$); IR 3400, 3000–2820, 1680, 1640, 1385, 1240, 1170, 1110, 1005, 935 cm^{-1}; ^{1}H NMR δ 0.79, 0.85, 0.92 (C-4 and C-10 Me), 1.25 (d, *J* = 7, Me_2), 2.17 (d, *J* = 2, C-13 Me), 2.64 (d, OH), 3.94 (s, OH), 4.46 (m, $W_{1/2}$ = 9.6, H-7), 4.84 (br s, H-17), 5.03 (m, $OCHMe_2$), 5.17 (br s, H-17), 5.65 (d, *J* = 2, H-14). Irradiations at δ 1.25 and at δ 2.64 transform the multiplet at δ 5.03 and the signal at δ 4.46 into sharp and broad singlets, respectively. By addition of D_2O the signals at δ 2.64 and 3.94 slowly decreased in intensity. Mass spectrum, *m/e* (relative intensity) 378 (M^+, 2), 360 (27), 300 (73), 258 (23), 237 (15), 236 (20), 205 (100), 177 (18), 149 (7), 141 (11), 135 (16), 123 (30), 109 (52), 100 (17), 95 (30), 81 (40); found for M^+, *m/e* 378.2766 ($C_{23}H_{38}O_4$ requires *m/e* 378.2767) and found for $M^+ - H_2O$, 360.2680 ($C_{23}H_{36}O_3$ requires *m/e* 360.2676). Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 73.20; H, 10.10.

Photooxygenation of Grindelic Acid (1a → 3a). A solution of **1a** (0.3 gr 0.9 mmol) and *meso*-tetraphenylporphine (1 mg) in CCl_4 (7 mL) in a photooxygenation cell similar to that described by Frimer[24] was irradiated with two 1000-W halogen lamps placed at about 15 cm from the cell, while oxygen was bubbled through the reaction mixture. After ca. 18 h the solvent was removed under vacuo and the residue was taken up in hexane (10 mL) and was stirred with trimethyl phosphite (0.15 mL, 1.27 mmol) at room temperature for 18 h. The organic solution was extracted with aqueous 10% NaOH (2 × 5 mL). The combined alkaline extracts were acidified with 5% HCl to pH 3 and extracted with ether (3 × 5 mL). The combined ethereal extracts were washed with brine until neutral, dried (Na_2SO_4), and treated at 0 °C with an excess of etheral diazomethane. The progress of the reaction was monitored by TLC, and when complete, a few drops of HOAc were added and the solvent was evaporated. The oily residue (0.270 g) was purified by silica gel column chromatography (hexane and hexane–EtOAc) affording pure **3a** (0.22 g, 73%), as a colorless oil, which crystallized on standing: $[\alpha]_D$ −4.3 (*c* 1.86, Cl_3CH); IR (CCl_4) 3520, 3040–2860, 1750, 1650, 1470, 1450, 1390, 1185, 1105, 1070, 1050, 930 cm^{-1}; ^{1}H NMR δ 0.77, 0.83, 0.92 (C-4 and C-10 Me), 1.32 (C-13 Me), 2.62 (s, H-14), 3.67 (OMe), 4.26 (ddd with appearance of two triplets, H-7), 4.56 (d, OH), 4.90 (s, H-17), 5.10 (s, H-17); MS, *m/e* (relative intensity) 350 (M^+, 2.86), 335 (1.28), 332 (2.05), 318 (0.44), 277 (0.5), 276 (0.4), 265 (1.55), 258 (4.9), 236 (100), 205 (10.8), 201 (18.6), 197 (19.5), 194 (22.8), 187 (11.5), 171 (24.8), 155 (40.9), 138 (82.2), 123 (68.6), 117 (52.0), 109 (85.0), 95 (74.5), 85 (70), 69 (92), 55 (95.4).

Diene 4 (1a → 4). The photooxygenation reaction, as described above, was carried out on **1a** (3 g, 9.37 mmol) and the resulting, crude **3a** (2.7 g, ~90%) dissolved in benzene (250 mL); *p*-toluenesulfonic acid (100 mg) and the reaction mixture were then stirred at reflux under a Dean–Stark trap for ca. 48 h (until TLC analysis showed that all **3a** had disappeared). The cooled reaction was then washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a silica column (hexane and mixtures of hexane–EtOAc) to afford pure **4** (1.725 g, 5.196 mmol, 55.5% starting from **1a**) as an oil: $(\alpha)_D$ −22.4 (*c* 0.625, $CHCl_3$); IR (CCl_4) 3100, 3050–2880, 1750, 1600, 1475, 1450, 1390, 1360, 1325, 1105, 1065, 1045, 1030, 905 cm^{-1}; ^{1}H NMR δ 0.72, 0.85, 0.99 (C-4 and C-10 Me), 1.32 (C-13 Me), 2.55 (s, H-14), 3.61 (OMe), 4.89 (br s, H-17), 5.05 (br s, H-17), 5.77 (brd, H-7), 6.09 (dd, H-6); mass spectrum, *m/e* (relative intensity) 332 (M^+, 39), 317 (5), 299 (4), 247 (4), 200 (13), 197 (10), 187 (100), 171 (10), 145 (18), 105 (10), 91 (7).

Epoxide (5). *m*-Chloroperoxybenzoic acid (85% 303 mg) was added to a cold stirred solution of **4** (450 mg) in dry CH_2Cl_2 (30 mL), and the mixture was allowed to stand at 5 °C for 8 h. The CH_2Cl_2 solution was then washed successively with saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine until neutral, dried (Na_2SO_4), and evaporated. Chromatography of the residue (390 mg) over silica gel (20 g) with mixtures of hexane and increasing amounts of EtOAc afforded epoxide **10** (42 mg) as a mixture of stereoisomers, a mixture of **10** and **5** (20 mg), and pure **5** (295 mg, 62%): $(\alpha)_D$ −63.6 (*c* 0.8, $CHCl_3$), IR 3100, 3000–2880, 1745, 1470, 1450, 1355, 1200, 1100, 1040, 940 cm^{-1}; ^{1}H NMR δ 0.76, 0.96, 1.10 (C-4 and C-10 Me), 1.28 (C-13 Me), 2.60 (s, H-14), 3.15 (dd, H-6), 3.46 (d, H-7), 3.63 (OMe), 5.37 (br s, H-17), 5.44 (br s, H-17); mass spectrum, *m/e* (relative intensity) 348 (M^+, 62), 319 (48), 234 (47), 223 (37), 203 (39), 197 (100), 163 (78), 123 (84), 95 (82), 69 (65), 43 (67); found for M^+, *m/e* 348.2290 ($C_{21}H_{32}O_4$ requires *m/e* 348.2300).

Methyl 6α-Hydroxygrindelate (7a). To a solution of epoxide **5** (150 mg) in EtOH (15 mL) were added platinum oxide (30 mg and the mixture was hydrogenated for 4 h at atmospheric pressure. After filtration of the catalyst through a Celite pad, the filtrate was concentrated to dryness. Chromatography of the crude product (145 mg) over silica gel (10 g) with hexane and with mixtures of hexane and increasing amounts of EtOAc resulted in the isolation of the oily alcohols **12** (38 mg) and **7a** (85 mg). Alcohol **12**: IR (film) 3450, 3100, 3000–2880, 1750, 1650, 1450, 1390, 1350, 1325, 1260, 1240, 1105, 1020, 905 cm^{-1}; ^{1}H NMR δ 0.76, 0.99, 1.17 (C-4 and C-10 Me), 1.30 (C-13 Me), 2.52 (br s, H-14 and m, H-7), 3.65 (OMe), 3.75 (m, H-6), 4.75 (br s, H-17), 4.86 (br s, H-17).

Methyl 6α-hydroxygrindelate (**7a**): $(\alpha)_D$ −64.2 (*c* 0.60, $CHCl_3$) (lit.[3,6] $(\alpha)_D$ −28.2, $(\alpha)_D$ −24); IR (film) 3420, 2990–2870, 1740, 1465, 1445, 1380, 1100, 1020, 980 cm^{-1}; ^{1}H NMR δ 0.84, 1.01, 1.13 (C-4 and C-10 Me), 1.33 (C-13 Me), 1.77 (br s, C-8 Me), 2.55 (ABq, *J* = 13.6, H-14), 3.65 (OMe), 4.00 (brd, H-6), 5.50 (m, H-7); mass spectrum, *m/e* (relative intensity) 350 (M^+, 8), 332 (4), 317 (2), 299 (1), 277 (2), 266 (2), 226 (69), 208 (51), 197 (45), 147 (36), 135 (100), 95 (65), 69 (69).

Ketones 6 and 11. Freshly distilled $BF_3{\cdot}Et_2O$ (4 mL) was added to a stirred solution of **5** (560 mg, 1.6 mmol) in benzene (15 mL) at room temperature and under N_2. After the reaction had stirred for 2 min, an aqueous saturated $NaHCO_3$ solution (10 mL) was added. The organic solution was then washed with brine until neutral, dried (Na_2SO_4), and evaporated. Application of the product (520 mg) to a column of silica gel and elution with hexane and mixtures of hexane–EtOAc afforded the oily keto esters **6** (52 mg) and **11** (336 mg, 61%). Keto ester **11**: $(\alpha)_D$ +61.7 (*c* 0.7, $CHCl_3$); IR 3000–2860, 1750, 1720, 1650, 1180, 1030, 895 cm^{-1}; ^{1}H NMR δ 0.74, 1.00, 1.17 (C-4 and C-10 Me), 1.37 (C-13, Me), 2.56 (s, H-14), 2.72, 2.76, 2.89 (2 H, H-5, H-7), 3.64 (OMe, 1 H, br d, *J* = 14, H-7), 4.83 (unresoved dd, H-17); mass spectrum, *m/e* (relative intensity) 348 (M^+, 93), 333 (10.5), 275 (27), 234 (76), 197 (100), 196 (98), 164 (29), 163 (25), 151 (14), 150 (14), 123 (25), 95 (36); found for M^+, *m/e* 348.2280 ($C_{21}H_{32}O_4$ requires 348.2300). Keto ester **6**: $(\alpha)_D$ −88.1 (*c* 0.7, $CHCl_3$) (lit.[3] $(\alpha)_D$ −84.4); IR 3000–2860, 1745, 1665, 1650, 1445, 1380, 1350, 1200, 1170, 1100, 900 cm^{-1}; ^{1}H NMR δ 0.94, 1.12, 1.18 (C-4 and C-10 Me), 1.41 (C-13

(22) Stahl, E. "Thin-Layer Chromatography, A Laboratory Handbook", 2nd ed.; Springer-Verlag: West Berlin, Heidelberg, New York, 1969; p 857.
(23) Mangoni, L.; Belardini, M. *Gazz. Chim. Ital.* **1962**, *92*, 995.
(24) Frimer, A. A; Bartlett, P. O.; Boschung, A. F.; Jewett, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 7977.

Me), 1.96 (C-8 Me), 2.70 (ABq, J = 6.4, H-14), 2.60 (s, H-5), 3.66 (OMe), 5.66 (br s, H-7); mass spectrum, m/e (relative intensity) 348 (M^+, 6), 333 (3), 320 (6), 275 (4), 224 (100), 192 (14), 164 (16), 150 (40), 123 (22), 109 (37), 95 (34), 69 (19).

Keto Ester 6 from 11. Basic alumina (500 mg) was added to a stirred solution of **11** (84.1 mg) in CH_2Cl_2 (15 mL). After 3 h of heating at reflux the mixture was filtered and the solvent evaporated. The residue (80.5 mg, 96.5%) was shown to be pure **6** by TLC analysis.

Methyl 6β-Hydroxygrindelate (7b). To a solution of **6** (163 mg, 0.47 mmol) in dry Et_2O (20 mL) was added an ethereal solution of $Zn(BH_4)_2$. The mixture was stirred for 4 days at room temperature and under N_2. After the addition of a HOAc (2 mL)–Et_2O (10 mL) solution and H_2O under ice cooling, the mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Chromatography of the residue (151 mg) over silica gel (10 g) with hexane and with mixtures of hexane and increasing amounts of EtOAc resulted in the recovery of starting material **6** (30.6 mg) and the isolation of **7b** (49 mg) and traces of **7a** (TLC). The oily hydroxy ester **7b**: $(\alpha)_D$ −136.7 (c 0.7 $CHCl_3$); IR ($CHCl_3$) 3690, 3615, 3000–2860, 1735, 1610, 1450, 1380, 1350, 1320, 1150, 1035, 1020, 980, 950, 880 cm^{-1}; ^1H NMR δ 1.07, 1.30, 1.32 (C-4, C-10 and C-13 Me), 1.83 (C-8 Me), 2.63 (ABq, J = 14.5, H-14), 3.65 (OMe), 4.37 (m, H-6), 5.50 (br dd, H-7); MS, m/e (relative intensity) 332 ($M^+ - H_2O$, 39), 317 (5), 299 (4), 247 (4), 200 (13), 197 (10), 187 (100), 171 (10), 145 (18), 105 (10), 91 (7); found for M^+, 350.2423 ($C_{21}H_{34}O_4$ requires 350.2457) and found for $M^+ - H_2O$, 332.2387 ($C_{21}H_{32}O_3$ requires 332.2351).

Acknowledgment. This work was carried out with financial support from CONICET (Consejo Nacional de Investigaciones Científicas y Tēcnicas) and UNR (Universidad Nacional de Rosario). We thank Drs. O. S. Giordano and E. Guerreio (Universidad Nacional de San Luis) for a generous supply of grindelic acid and for the high-resolution mass spectra determination and also Dr. J. C. Oberti (Universidad Nacional de Cōrdoba) for the low-resolution mass spectral data. A.C.O. thanks CONICET for a fellowship.

Registry No. **1a**, 1438-57-9; **1b**, 1438-58-0; **2a**, 92471-20-0; **3a**, 79491-96-6; **4**, 79491-99-9; **5**, 92420-60-5; **6**, 80865-71-0; **7a**, 80931-20-0; **7b**, 80952-80-3; **8**, 92420-61-6; **10** (isomer 1), 92420-62-7; **10** (isomer 2), 92471-21-1; **11**, 92420-63-8; **12**, 92456-15-0.

A Novel Method for Stereoselective Glucuronidation

Bilha Fischer, Abraham Nudelman,* Margareta Ruse, Jacob Herzig, and Hugo E. Gottlieb

Chemistry Department, Bar Ilan University, Ramat Gan, Israel

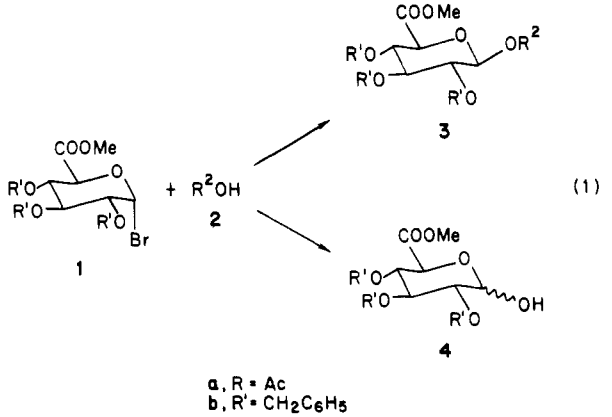
Ehud Keinan*

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Received March 28, 1984

A variety of hydroxylic aglycones can be glucuronidated directly with methyl 2,3,4-tri-*O*-acetylglucopyranuronate (**4a**), activated with trimethylsilyl trifluoromethanesulfonate (Me_3Si–OTf). This reaction provides mostly β, and sometimes α, glucopyranosiduronic acid derivatives (referred to as glucuronides) rapidly and at low temperatures. The epimeric ratio depends on the relative aglycone nucleophilicity vs. its tendency to form a stabilized carbocation by the formal loss of –OH. Glucuronides of various aromatic and aliphatic aglycones as well as those of a number of cyanohydrins were prepared. The characteristic features of the ^1H NMR spectra of α and β derivatives which are presented are useful in the assignment of product stereochemistry and determination of epimeric ratios in those reactions where mixtures are obtained.

The synthesis of glucopyranosiduronic acid derivatives (referred to as glucuronides) is most frequently carried out via the Koenigs–Knorr reaction or its modifications (eq 1)[1] in which the electrophilic character of the anomeric bromide **1** is enhanced by a halophilic agent (such as silver carbonate, mercuric oxide, cadmium carbonate, etc.) that facilitates nucleophilic substitution by the aglycon **2**, leading to glucuronide **3**. The main drawbacks of these procedures are the instability of the bromo derivatives **1**[2] (which have a rather limited shelf life even at 0 °C), the need for elevated reaction temperatures and frequently prolonged reaction times, and the ubiquitous formation of hemiacetals **4** as hydrolysis side products of **1**. Some of these difficulties have been elegantly circumvented by modifying the leaving group. For example, the conversion of **4b** into the imidate **5b**, followed by activation with boron trifluoride allowed stereospecific reactions with various aglycones to give the corresponding β-glucuronides (eq 2).[3] However, this procedure also suffers from the necessity of preparing the reactive starting material, which has a limited stability and hydrolyzes quite readily to **4b**. Obviously, it would be highly desirable to carry out the glucuronidation directly on the stable free hydroxy derivatives **4**.



(1)

(1) (a) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957. (b) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243. (c) Keglevič, D. *Adv. Carbohydr. Chem. Biochem.* **1979**, *36*, 57.

(2) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310.

(3) (a) Schmidt, R. R.; Grundler, G. *Synthesis* **1981**, 885. (b) Schmidt, R. R.; Stumpp, M.; Michel, J. *Tetrahedron Lett.* **1982**, *23*, 405.

0022-3263/84/1949-4988$01.50/0