Studies in the Total Synthesis of Mono- and Sesquiterpenes. 3.[1] Genipic Acid

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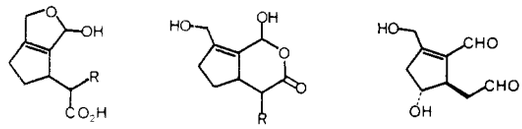
Several pathways for the synthesis of genipic acid (**1a**) were explored. Specifically, the epoxyolefin **7** was converted to the penultimate intermediates **6**, **11**, and **12** by short sequences. In no case were conditions found that could be used to transform these compounds into the novel, unsaturated bicyclo[3.3.0]lactol system evident in genipic acid.

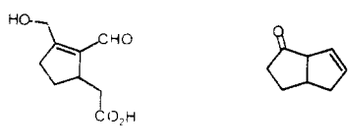
A period of 13 years has passed since W. H. Tallent proposed structures **1a** and **1b** for genipic acid and genipinic acid, respectively.[2] It is curious that during that period no communications have appeared detailing synthetic efforts directed at this fascinating pair, since, in addition to significant antibiotic activity, these iridoid terpenes are endowed with a highly unusual unsaturated lactol moiety.[3] Though the information obtained for these molecules seems consistent only with the suggested structures, it is troublesome that those factors favoring lactol formation from γ-hydroxyaldehydes are here more than sufficient to compensate for what must be considerable strain in the lactol form.[4] It is conceivable that these acids exist in the alternative, lactol–lactone forms **2a** and **2b**, which would be consistent with the lack of aldehydic absorption observed in the ^1H NMR of the natural products. However, genipic acid was converted with diazomethane to a methyl derivative that exhibited methyl absorption at δ 3.70, but still lacked aldehydic absorption. It thus appears that, at least in methyl genipate, the unsaturated lactol function does exist. A recent communication detailing some of the chemistry of the acubin aglycone only casts more confusion on the matter as the dialdehyde **3** refused to be converted into any lactol form.[5]



1a: R = H; **b**: R = CO_2CH_3 **2a**: R = H; **b**: R = CO_2CH_3 **3**

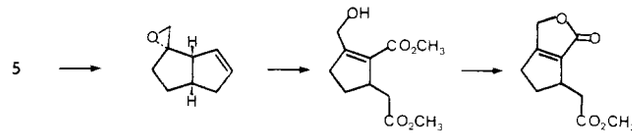
For some time, we have been developing methods for synthesizing cyclopentanoid terpenes of the iridoid class from the more readily available bicyclo[3.3.0]octane derivatives. A glance at the ring opened form of genipic acid (**4**) reveals that the cyclopentene ring bears three consecutive side chains, each at a progressively higher oxidation state. Thus, the major synthetic challenge is the assemblage of these chains at the correct levels of oxidation, either by unique introduction of each or by appropriate differentiation.

The propitious unsaturated ketone **5**[6] is a natural starting point for elaboration to genipic acid, since cleavage of the alkene linkage would afford the adjacent two and one carbon side chains, and conversion of the carbonyl functionality to a hydroxymethyl substituent would complete the carbon skeleton. In the event, the ketone **5** was transformed into the lactone ester **6** by the sequence illustrated in Scheme I. The



4 **5**

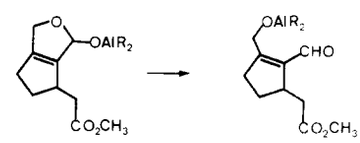
Scheme I



7 **8** **6**

epoxide **7**[7] was prepared in 60% yield using Corey's dimethylsulfonium methylide reagent,[8] though varying quantities of the starting ketone **5** tenaciously failed to react even with large excesses of the ylide, rapid stirring during addition, or dilution of the ketone in dimethyl sulfoxide prior to addition.[9] Ozonolytic cleavage of epoxide **7** followed by alkaline silver oxide oxidation[10] of the ozonide to the diacid followed by diazomethane esterification produced the diester alcohol **8** in 40% overall yield. Lactonization of **8** using Amberlyst-15[11] as an acid catalyst in refluxing benzene afforded in moderate yield the lactone **6** in which the central, lactone carboxyl carbon would appear to be ideally situated for selective, partial reduction to the aldehyde stage.

However, we were totally thwarted in our efforts to form methyl genipate from lactone **6**. Diisobutylaluminum hydride reduction[12] failed to produce any detectable quantity of methyl genipate over many attempts under a variety of conditions. Changing the solvent from toluene to methylene chloride or THF, varying the temperature from −100 to −78 to −30 to +25 to +110 °C, and adjusting the ratio of hydride to lactone from the desired 1:1 to a large deficiency of reducing agent all failed to alter the apparent course of the reaction–overreduction. This failure can perhaps be rationalized by assuming that the intermediate from addition of the first hydride does indeed possess considerable strain and thus opens to the aldehyde **9** at a rate considerably faster than the initial reduction.



9

Other reducing agents, including 9-BBN,[13] diborane,[14] sodium borohydride,[15] and Red-Al,[16] were tried, all with equally dismal results. An attempted in situ methylation with Magic Methyl (CH_3OSO_2F)[17] followed by Red-Al reduction failed to produce any of the anticipated methyl lactolide.

Our inability to accomplish a controlled reduction of the lactone **6** prompted us to turn to the alternative approach wherein the olefin would be cleaved with ozone as before, but left at the dialdehyde stage with a subsequent selective oxidation of the two-carbon aldehyde providing the carboxyl carbon of genipic acid. In fact, zinc and acetic acid reduction of the ozonide from epoxyolefin **7** served to open the epoxide

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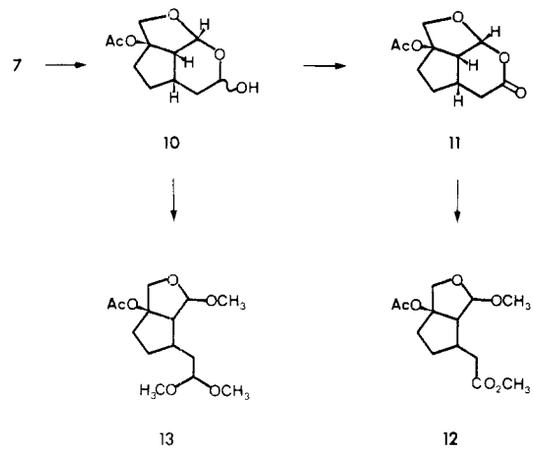
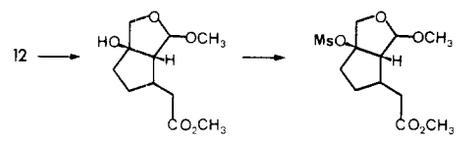


10 11 13 12

function as well, affording the cyclic form of the dialdehyde (**10**) in moderate yield. The selective oxidation now became a trivial matter; pyridinium chlorochromate[18] produced the crystalline lactone acetate **11** in good yield. Having now assembled the three chains each at the appropriate oxidation level, we had only the apparently simple tasks of removing acetic acid and opening the lactone ring.

Unfortunately, elimination of the elements of acetic acid could be effected neither thermally (450–600 °C) nor with acid catalysis (aprotic boron trifloride etherate or trifluoroacetic acid, or aqueous acid) without concomitant destruction of the product(s) thus formed. The only identifiable material obtained from reactions run under any of these conditions was the starting lactone acetate. On the other hand, the lactone ring in **11** was smoothly cleaved with *p*-toluenesulfonic acid in methanol, providing the acetate–lactolide ester **12.** Alternatively, a similar array (**13**) was obtained from lactol **10** under the same conditions. As before, neither of these acetates produced volatile products from vapor phase thermolysis in the range 350–600 °C.

In order to obtain a functionality which might serve as a precursor to the double bond under more gentle conditions than those required for the acetates **11–13,** the tertiary alcohol **14** was prepared in 70% overall yield by the sequence potassium carbonate–methanol and then diazomethane. Here again, no identifiable products were obtained from the treatment of **14** with phosphorus oxychloride or thionyl chloride in pyridine,[19] or with aqueous acid. Though the xanthate of **14** could not be obtained, the mesylate **15** was



14 15

formed smoothly.[20] No identifiable products were obtained from reaction of **15** with either 1,5-diazabicycloundecene or potassium *tert*-butoxide under conditions sufficiently vigorous to cause disappearance of the starting material.

Still seeking a more labile leaving group, we rationalized that the acetoxy function in the lactol acetate **10** had resulted from a first-order-like opening of the epoxide to the cation and subsequent trapping. Hence, the iodide **16** might be obtainable if potassium iodide, fortuitously present as the reductant for the ozonide,[21] would compete successfully for the cation. In fact, a tricyclic iodide was produced as the result of potassium iodide–acetic acid reduction of the ozonide of olefin **5,** and subsequent oxidation afforded a lactone with ^{1}H NMR spectra quite similar to that of the acetate lactone **11.** However, the presence in the ^{13}C NMR of a triplet at δ 10.1, consistent with the presence of a $-CH_2-I$ structural unit, suggested the alternative lactone **17,** which would be the ultimate result of a second-order-like nucleophilic opening by iodide at the less hindered position of the epoxide. The suggested arrangement in **17** was firmly established by a three-dimensional x-ray analysis on a single crystal.[22] It is clear that the tricyclic lactol precursor to iodolactone **17** exposes the wrong aldehyde to further oxidation and thus in the lactone the oxidation levels of the carboxylic and aldehydic carbons are the reverse of those in genipic acid.

16 17

The repeated failure of several penultimate intermediates to suffer conversion to genipic acid led us to direct our synthetic efforts elsewhere.

Experimental Section

Procedure. Dry tetrahydrofuran (THF) was distilled immediately before use from a deep red mixture containing lithium aluminum hydride and triphenylmethane, while dry ether was distilled from a deep blue solution resulting from benzophenone and sodium. Dimethyl sulfoxide was dried by extended contact (several days) with molecular sieves. Drying of organic layers resulting from aqueous extractions was accomplished with 4A sieves. All reactions were routinely run under a nitrogen atmosphere.

Proton spectra were recorded on a Varian HA-100 using deuteriochloroform solutions and are reported on the δ scale relative to internal tetramethylsilane. Infrared spectra were obtained using a Perkin-Elmer 237B.

Elemental microanalyses were done by Chemalytics, Inc., Tempe, Ariz.

Methyl (2-Keto-3-oxabicyclo[3.3.0]oct-$\Delta^{1,5}$-en-8-yl)acetate (6). A solution of 0.662 g (2.90 mmol) of diester **8** and 0.60 g of dry Amberlyst-15 in 30 mL of benzene was refluxed for 45 min, cooled, and then the resin was removed by filtration. Concentration of the yellow solution followed by purification by preparative thin layer chromatography on silica gel with 1:1 ethyl acetate–cyclohexane afforded 0.36 g (63%) of lactone: IR (CH_2Cl_2) 1755, 1735 cm^{-1}; NMR δ 1.6–3.3 (m, 7 H), 2.45 (s, 3 H), 4.08–4.18 (m, 2 H); HRMS Calcd for $C_{10}H_{12}O_4$: 196.0736. Found: 196.0733.

8-Methyl-8a,9-oxidobicyclo[3.3.0]oct-2-ene (7). A solution of 144 mmol of dimsyl anion prepared from 0.607 g of 57% sodium hydride dispersion (twice pentane washed) in 72 mL of dry DMSO was diluted with an equal volume of dry THF and cooled in an ice–salt bath. A solution of 2.94 g (144 mmol) of trimethylsulfonium iodide in 12 mL of DMSO was then added rapidly with stirring followed after 1 min by 1.5 g (123 mmol) of ketone added neat over 1 min. After 5 min the cooling bath was removed and stirring was continued for 1 h. The reaction was diluted with three volumes of water and the product extracted with three 50-mL portions of pentane. The combined organic layers were dried and concentrated, affording 1.4 g of crude product containing from 10 to 40% of the starting ketone. Recycling this mixture using a 20% excess of the ylide necessary for the remaining ketone afforded essentially pure epoxide after distillation (bp 82–85 °C (20 mmHg)): NMR δ 1.72 (d, 2 H, J = 6 Hz), 1.2–2.1 (m, 3 H), 2.85 (s, 2 H), 2.5–3.2 (m, 3 H), 5.5 (m, 1 H), 5.75 (m, 1 H). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.12; H, 8.97.

Methyl (2-Carbomethoxyl-3-hydroxymethylcyclopent-2-enyl)acetate (8). One equivalent of ozone was passed into a solution of 0.564 g (4.15 mmol) of epoxide **7** in 40 mL of dichloromethane at −78 °C. This solution was then concentrated and the resulting white foam (0.79 g) was taken up in 21 mL of ethanol. With stirring, first a solution of 3.04 g (17.9 mmol) of silver nitrate in 4 mL of water and then 2.48 g (30 mmol) of 87% potassium hydroxide in 42 mL of water was added. After 2 h the silver salts were removed by filtration and washed with 65 mL of water. The combined aqueous solutions were extracted twice with 50-mL portions of ether and then acidified to pH 2 with 2.0 N hydrochloric acid. Extraction with ten 25-mL portions of ethyl acetate followed by drying and concentration of the combined organic layers afforded 0.644 g of crude diacid. This material was dissolved in ether and treated with excess diazomethane. Concentration of the ether solution and purification of the resulting material

by preparative layer chromatography on silica gel with 1:1 ethyl acetate–cyclohexane afforded 0.378 g (40%) of pure diester: IR (CH_2Cl_2) 1740, 1710; NMR δ 1.5–4.0 (m, 8 H), 3.70 (s, 3 H), 3.79 (s, 3 H), 4.4–4.6 (m, 2 H). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.65; H, 6.79.

4β-Acetoxy-9-hydroxy-2,10-dioxatricyclo[5.3.1.0^{4,11}]undecane (10). The crude ozonide from 0.49 g of epoxide **7** obtained as described above was treated with 0.235 g (2 equiv) of zinc dust in 25 mL of glacial acetic acid for 3 h. with stirring at room temperature. Most of the solvent was then removed on the vacuum pump. The residue was taken up in 25 mL of methylene chloride and extracted with 25 mL of 1.0 N aqueous sodium bicarbonate. The aqueous layer was extracted with three 25-mL portions of methylene chloride which were combined with the original organic layer and concentrated to 0.38 g of crude lactol, purified by preparative layer chromatography on silica gel (1:3 ethyl acetate–cyclohexane) affording 0.14 g of **10:** NMR δ 1.1–2.8 (m, 8 H), 2.05 (s, 3 H), 4.0–4.2 (m, 2 H), 4.3–4.6 (m, 1 H), 5.3–5.7 (m, 2 H); IR (CH_2Cl_2) 3575 (broad), 2950 (broad), 1740, 1357, 1240 cm^{-1}.

4β-Acetoxy-9-keto-2,10-dioxatricyclo[5.3.1.0^{4,11}]undecane (11). A solution of the crude lactol **10** from 3.85 g (23.6 mmol) of epoxide **7** in 100 mL of methylene chloride was added all at once to a stirred suspension of 5 g (24 mmol) of pyridinium chlorochromate in 50 mL of the same solvent. After 2 h the reaction mixture was diluted with 200 mL of ether and filtered through a short column of activity IV alumina. The column was washed with 50 mL of additional ether and the combined organic layers were concentrated to 2.9 g of crude lactone. Column chromatography (silica gel, 3:1 cyclohexane–ethyl acetate) afforded a fraction (1.2 g) which could be crystallized from ethyl acetate to 0.8 g (15% overall) with mp 124–125 °C: IR (CH_2Cl_2) 1745 cm^{-1} (broad); NMR δ 1.2–3.0 (m, 7 H), 2.06 (s, 3 H), 3.25 (d, d, J = 6, 9 Hz, 1 H), 3.97 and 4.4 (AB q, J = 10 Hz, 2 H), 5.88 (d, J = 6 Hz, 1H). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.45; H, 6.04.

Methyl (1β-Acetoxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (12). A mixture of 0.488 g (2.2 mmol) of lactone **11** and 0.100 g of *p*-toluenesulfonic acid in 20 mL of dry methanol was stirred for 2 days. The mixture was then diluted with 100 mL of aqueous 1 N sodium bicarbonate and extracted with three 25-mL portions of dichloromethane. The combined organic layers were dried and concentrated to 0.583 g (100%) of essentially pure ester **12:** IR (CH_2Cl_2) 1745 cm^{-1} (broad); NMR δ 1.2–2.8 (m, 8 H), 2.04 (s, 3 H), 3.34 (s, 3 H), 3.72 (s, 3 H), 4.03 and 4.25 (AB q, J = 10 Hz, 2 H), 4.80 (s, 1 H); MS, no molecular ion, m/e 257 (m − 15), 241 (m − 31 = MeO), 199 (base peak). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.32; H, 7.21.

Methyl (1β-Hydroxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (14). Acetate **12** (0.583 g, 2.14 mmol) was stirred in 25 mL of 4:1 methanol–water containing 0.592 g (4.3 mmol) of potassium carbonate for 12 h. The solution was then diluted with water, acidified with 2 N hydrochloric acid, and extracted with three 50-mL portions of ethyl acetate. The combined organic layers were dried and concentrated, and the residue was taken up in ether and treated with excess diazomethane. Removal of the solvent afforded 386 mg (78%) of essentially pure alcohol **14:** IR (CH_2Cl_2) 3560 (broad), 2940 (broad), 1735, 1190, 1090, 1025 cm^{-1}; NMR ($CDCl_3$) 1.2–3.0 (m, 8 H), 3.45 (s, 3 H), 3.70 (s, 3 H), 3.80 and 3.95 (AB q, J = 9 Hz, 2 H), 4.80 (s, 1 H).

Methyl (1β-Methanesulfonyloxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (15). To a stirred solution of 180 mg (0.78 mmol) of alcohol **14** and 0.83 mL (6.0 mmol) of triethylamine in 15 mL of dichloromethane at −5 °C was added dropwise 0.33 mL of methanesulfonyl chloride in 10 mL of the same solvent. After 15 min, the solution was extracted with 10 mL of water, 10 mL of 2 N hydrochloric acid, and then 10 mL of 1 N aqueous sodium bicarbonate. Concentration afforded 250 mg (100%) of essentially pure mesylate **15,** used without further purification: NMR δ 1.2–3.4 (m, 8 H), 3.05 (s, 3 H), 3.35 (s, 3 H), 3.70 (s, 3 H), 4.05 and 4.35 (AB q, J = 10 Hz, 2 H), 4.8 (bs, 1 H).

3-Iodomethyl-8-keto-2,9-dioxatricyclo[4.3.1.0^{3,7}]decane (17). A solution of 0.760 g (4.1 mmol) of the crude ozonide from epoxide **7** in 10 mL of glacial acetic acid was treated with 1.37 g (8.2 mmol) of potassium iodide. The resulting dark red solution was stirred 1 h, and then the color was discharged with 10% aqueous sodium bisulfite. The solvents were removed with the vacuum pump, and the residue was partitioned between dichloromethane and 1 N sodium bicarbonate. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic layers were concentrated to yield 0.808 g of crude lactol: IR (CH_2Cl_2) 3550 (broad), 2925 (broad), 1115, 1060, 1035, 960 cm^{-1}. All of the above was oxidized with pyridinium chlorochromate as described above for the conversion of lactol **10** to lactone **11.** The crude material (0.60 g, 50% overall) was quite pure and could be crystallized from ethyl acetate–hexane to afford an analytical sample with mp 61–61.5 °C: IR (CH_2Cl_2) 1760 cm^{-1}; NMR δ 1.6–2.5 (m, 6 H), 2.6–3.92 (m, 2 H) 3.28 and 3.39 (ABq, J = 10 Hz, 2 H), 5.65–5.75 (m, 1 H). Anal. Calcd for $C_9H_{11}O_3I$: C, 36.76; H, 3.77; I, 43.15. Found: C, 36.66; H, 3.67; I, 42.95.

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Registry No.—**1a,** 6902-76-7; **5,** 56138-05-7; **6,** 65276-79-1; **7,** 65276-80-4; **8,** 65276-81-5; **10,** 65276-82-6; **11,** 65276-83-7; **12,** 65276-84-8; **14,** 65276-85-9; **15,** 65276-86-0; **16** lactol derivative, 65276-87-1; **17,** 65276-88-2; methanesulfonyl chloride, 124-63-0.

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(22) We are grateful to Professor R. E. Davis, University of Texas at Austin, for the execution of this structure determination.