Vitamin C in Organic Synthesis: Reaction with *p*-Hydroxybenzyl Alcohol Derivatives

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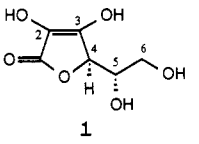
The reaction of L-ascorbic acid (1) with *p*-hydroxybenzyl alcohol (9) yields 2-(*p*-hydroxybenzyl)-3-ketohexulosonic acid lactone (10). This reaction proceeds by the addition of the conjugate base of ascorbic acid to the protonated quinone methide derived from 9. The total synthesis of delesserine (2), methylrhodomelol (6), and rhodomelol (8) was accomplished by this methodology. Treatment of ascorbic acid with methyl 3-hydroxy-3-(*p*-hydroxyphenyl)propionate (21) affords a mixture of dilaspirolactone aglycon (3) and ester lactone 22. This result is explained by the existence of an equilibrium between 22 and starting materials; 3 is the result of irreversible lactonization. These observations led to the preparation of leucodrin (4), leudrin (5), and reflexin (7).

Introduction

Over the past 10 years, considerable attention has been focused on the chemistry and application of vitamin C (1) to organic synthesis.[1] Fodor has investigated the conjugate addition of ascorbic acid to unsaturated carbonyl compounds. His investigations have shown that unsaturated ketones and aldehydes yield Michael adducts;[2,3] whereas, unsaturated 4-keto aldehydes or 1,4-dialdehydes afforded aldol derived products.[4] The Michael addition of vitamin C to geraniin has been used to biomimetically synthesize the tannin elaeocurpusin.[5] Recently, we have reported the conjugate addition of ascorbic acid to unsaturated acyl nitriles culminating in the synthesis of piptosidin.[6]

Reexamination of the carbon alkylation of vitamin C has demonstrated its ability to react at C-2 with unsaturated alkyl halides.[7] The hydrogenation of the ascorbic acid nucleus has been the subject of various reports by Godefroi in the preparation of 4,5,6-trihydroxylated norleucins.[8] Studies directed toward the construction of the avermectins and melbemycins have utilized the molecular framework of this unique tetronic acid[9] and vitamin C has been used as a chiral starting material for the construction of R-GABOB.[10]

In this paper, we describe our research focused on the addition of ascorbic acid to protonated quinone methides generated from *p*-hydroxybenzyl alcohol derivatives.[11] The results of this investigation have led to stereospecific construction of delesserine (2), dilaspirolactone aglycon, (3), leucodrin (4), leudrin (5), methylrhodomelol (6), reflexin (7), and rhodomelol (8).



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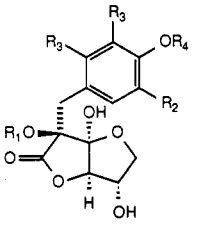
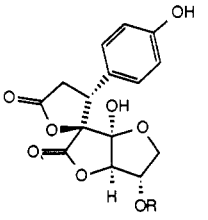
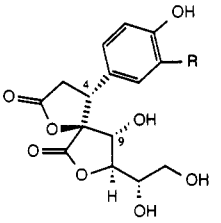
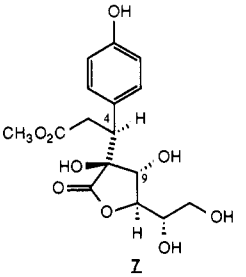




2 $R_1 = CH_3$, $R_2 = R_3 = H$, $R_4 = H$
6 $R_1 = CH_3$, $R_2 = OH$, $R_3 = Br$, $R_4 = H$
8 $R_1 = H$, $R_2 = OH$, $R_3 = Br$, $R_4 = H$
19 $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = Br$, $R_4 = CH_3$

3 R = H
20 R = Glu





4 R = H
5 R = OH

7

Results and Discussion

Delesserine, Rhodomelol, and Methylrhodomelol.

The aqueous extract from marine algae belonging to the *Delesseriaceae* family has long been known to exhibit powerful anticoagulent properties.[12] The ether soluble material of the water–ethanol extract of the marine alga *Delesseria sanguinea*, a member of this family, was found to contain the secondary sugar metabolite delesserine (2); the configuration of which was determined by X-ray crystallographic analysis.[13] Seebach and co-workers have succeeded in preparing delesserine by an aldol approach.[14] A recent study of the red alga *Polysiphonia lanosa* (*L.*) revealed two bromophenols structurally similar to 2, namely, rhodomelol (8) and methylrhodomelol (6).[15]

Vitamin C is an excellent template from which to craft these unusual sugar-derived natural products. Retrosynthetic analysis suggests that C-2 benzylation of the ascorbic

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(11) Poss, A. J.; Belter, R. K. *Tetrahedron Lett.* **1987**, *28*, 2555.

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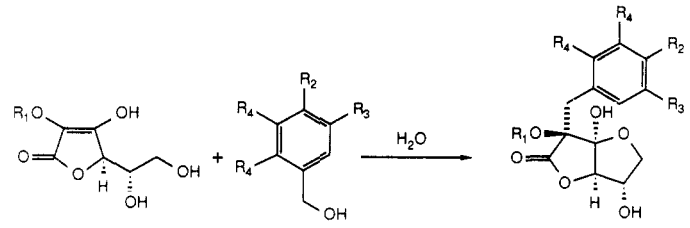
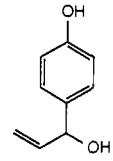
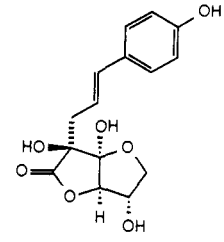
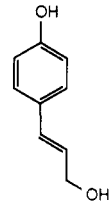
(15) Glombitza, K.-W.; Sukopp, I.; Wiedenfeld, H. *Planta Med.* **1985**, 437.

0022-3263/88/1953-1535$01.50/0

Table I



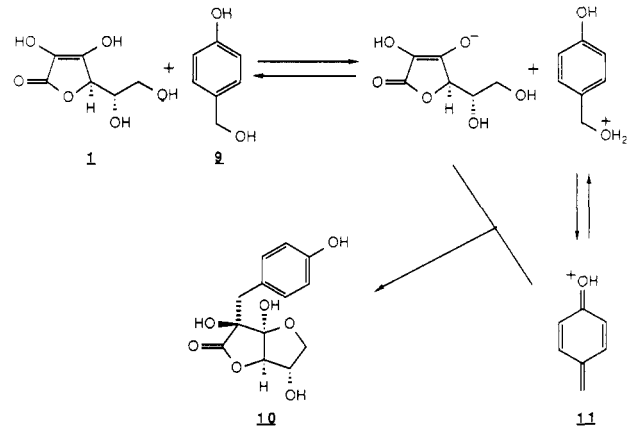
substrates		product	% yield
1: R_1 = H	R_2 = NMe_2, R_3 = R_4 = H	12: R_1 = R_3 = R_4 = H, R_2 = NMe_2	62
1: R_1 = H	R_2 = OMe, R_3 = R_4 = H	13: R_1 = R_3 = R_4 = H, R_2 = OMe	20
1: R_1 = H	9: R_2 = OH, R_3 = R_4 = H	10: R_1 = R_3 = R_4 = H, R_2 = OH	87
1: R_1 = H	17: R_2 = R_3 = OH, R_4 = Br	8: R_1 = H, R_2 = R_3 = OH, R_4 = Br	54
18: R_1 = OMe	9: R_2 = OH, R_3 = R_4 = H	2: R_1 = OMe, R_2 = OH, R_3 = R_4 = H	80
18: R_1 = OMe	17: R_2 = R_3 = OH, R_4 = Br	6: R_1 = OMe, R_2 = R_3 = OH, R_4 = Br	25
1: R_1 = H	 14	 15	70
1: R_1 = H	 16	15	32

acid nucleus should give the desired skeletal framework. Toward this end, Jackson and Jones have reported the alkylation of sodium ascorbate with benzyl chloride to yield 2-benzyl-3-ketohexulosonic acid lactone.[16] However, all attempts to add *p*-hydroxybenzyl halide derivatives to ascorbate anion led to reaction on oxygen rather than the desired carbon addition.

Having determined that standard basic alkylation was an unacceptable course to follow, we pursued carbon–carbon bond formation under acidic conditions. Treatment of an aqueous solution of vitamin C (1), with *p*-hydroxybenzyl alcohol (9) at room temperature for 3 days gave an 87% yield of adduct 10 (Scheme I). This reaction proceeds by ascorbic acid protonation of the benzylic alcohol moiety. The phenol next initiates the elimination of water. The resulting protonated quinone methide 11 adds to the conjugate base of 1 to yield 10. The alkylation occurs from the less hindered α face of 1 as dictated by the C-5,6 side chain.

As suggested by the quinone methide intermediate, this reaction is dependent upon the presence of an electron-donating substituent in the para position of the benzyl alcohol moiety. Reaction of 1 with *o*- or *m*-hydroxybenzyl alcohol or benzyl alcohol gave no addition products; whereas, reaction of an aqueous solution of ascorbic acid (1) with *p*-(dimethylamino)- and *p*-methoxybenzyl alcohol afforded 12 and 13, respectively (Table I). Olefinic extension of the quinone methide intermediate led to reaction only at the terminus of the ensuing conjugated system. Benzyl alcohol 14, upon treatment with ascorbic acid in water at room temperature for 4 days, gave addition product 15. Similarly, the only product observed from the reaction of 16 with 1 was 15.

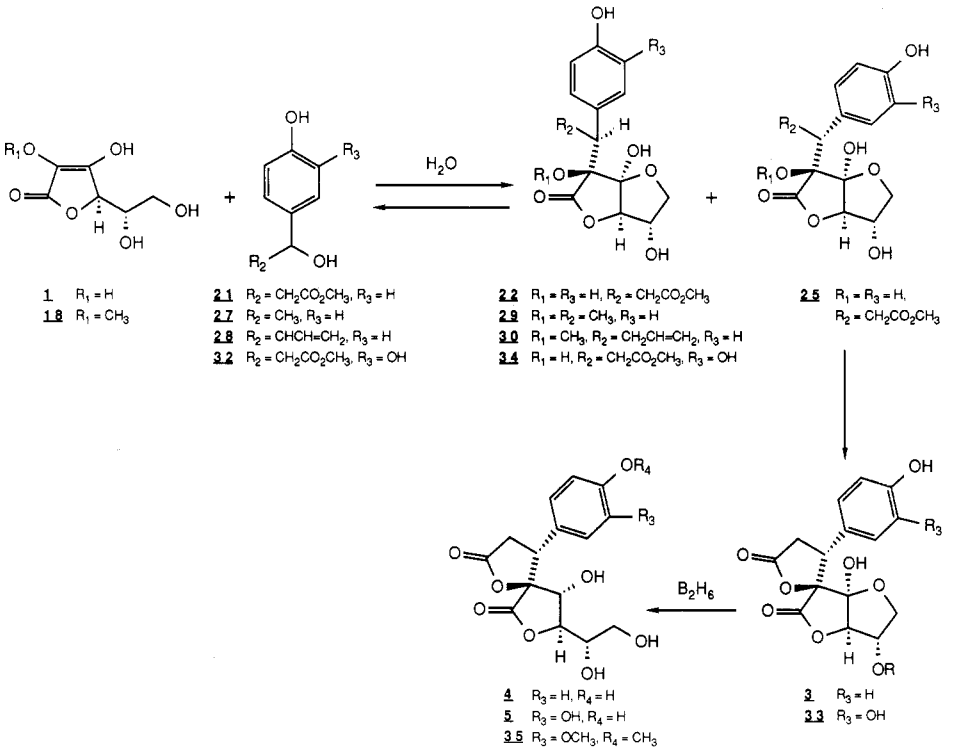
Scheme I



Having successfully devised a method for C-2 benzylation of vitamin C, we embarked upon the synthesis of delesserine, methylrhodomelol, and rhodomelol. Rhodomelol (8) was prepared in 54% yield by reacting ascorbic acid (1) with 2,3-dibromo-4,5-dihydroxybenzyl alcohol (17) in water for 3 days at 50 °C. The presence of additional substituents on the aromatic nucleus did not retard quinone methide formation. Delesserine (2) and methylrhodomelol (6) both require 2-*O*-methylascorbic acid (18) as the reactive acidic species. Compound 18 was conveniently prepared by methylation of the dianion of vitamin C under the conditions described by Seib and co-workers.[17]

(16) Jackson, K. G.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 450.

Scheme II

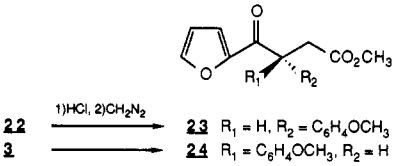


Treatment of an aqueous solution of 18 with *p*-hydroxybenzyl alcohol (9) gave delesserine (2) in 80% yield. The ^{13}C NMR of 2 contained 28 carbons, indicating that, in solution, delesserine exists as a mixture of open and closed hemiketal forms.[13] Similarly, methylrhodomelol (6) was prepared by the reaction of 2-*O*-methylascorbic acid with 17 (36% yield). To confirm our synthesis of 17, methylrhodomelol was converted to its dimethyl ether 19 by treatment with diazomethane and compared with the same compound prepared by Glombitza and co-workers.[15]

Dilaspirolactone Aglycon, Leucodrin, Leudrin, and Reflexin. The phenolic constituents of the leucadendron species were first reported by Meiring-Beck in 1886 in his probe for a quinine substitute.[18] The investigation was later pursued by Rapson,[19] and more recently, Perold has reported the structures of these unusual glycosides. Leucodrin (4) occurs in most of the species of the genus *Leucadendron* (Proteaceae) and is often accompanied by its catechol analogue leudrin 5.[20] In the same family, the genus *Leucospermum* has proven a source of reflexin (7), the analogous B-ring diastereoisomeric opened methyl ester of 4.[21] The structures of these metabolites has been determined by extensive chemical degradation and spectrographic analysis.[22] The deciduous shrub *Viburnum dilatatum* is the source of the structurally related glycoside dilaspirolactone 20. The fruits of this plant have been used as a seasoning in pickles and wine.[23]

These bislactone natural products offer the combined synthetic challenge of constructing a 1,7-dioxa-2,6-dioxospiro[4.4]nonane skeleton while controlling the stereochemistry of the C-4 phenolic residue. The bislactone framework was envisaged to derive from lactonization of the adduct derived for vitamin C addition to ester alcohol 21. The spatial configuration at C-4 was anticipated to arise from electronic and steric considerations along the reaction pathway.

Scheme III



Since leucodrin (4) represents the C-9 reduction product of dilaspirolactone aglycon (3), compound 3 was chosen as the penultimate target (Scheme II). Treatment of ascorbic acid (1) with 21 in water for 14 days led to a 4:1 mixture of 22 to 3 (82% yield).[24] The ratio of products could be shifted to a 1:1 mixture by conducting the experiment at 50 °C for 3 days (94% yield). ^{13}C NMR analysis of these products, indicated that C-4 in ester lactone 22 was shifted 3.5 ppm downfield from that of 3. Comparison of these shifts with similar observations by Perold, led to the conclusion that C-4 in dilactone 3 was of the *R* configuration and 22 contained an *S* configuration at the same center.[22]

To chemically confirm these assignments, the methyl glycoside of 3 was prepared by the action of acidic methanol and found identical with that derived from 20. To verify compound 22, 3 and 22 were degraded into furano ketones 23 and 24, respectively, by treatment with dilute acid followed by diazomethane (Scheme III). Polarimetric

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(18) Meiring-Beck *Pharm. J.* **1886**, *17*, 327, 408.
(19) Rapson, W. S. *J. Chem. Soc.* **1938**, 282. (b) Rapson, W. S. *J. Chem. Soc.* **1939**, 1085. (c) Rapson, W. S. *J. Chem. Soc.* **1940**, 1271.
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(21) Perold, G. W.; Hodgkinson, A. J.; Howard, A. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2450. (b) Perold, G. W.; Hodgkinson, A. J.; Howard, A. S.; Kruger, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2457.
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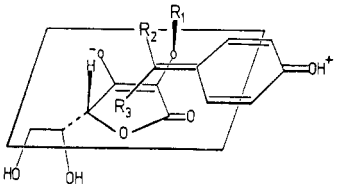
(23) Iwagawa, T.; Hase, T. *Phytochemistry* **1984**, *23*, 2299.
(24) All substituted *p*-hydroxybenzyl alcohol derivatives were prepared by reacting *p*-[(trimethylsilyl)oxy]benzaldehyde with the appropriate Grignard reagent or lithium anion. Wolf, F.; Hoffmann, M. *Z. Chem.* **1964**, *4*, 30.

analysis of **23** and **24** showed they had opposite rotations, indicating the contrary stereochemistry of **22** relative to **3** at C-4.

Mechanistically, the reaction of ascorbic acid (**1**) with benzyl alcohol **21** follows a course similar to that outlined previously (Scheme II).[25] The conjugate base of **1** adds to the quinone methide derived from **21**, yielding esters **22** and **25**. Intermediate **25** irreversibly lactonizes by acid-catalyzed loss of methanol to dilaspirolactone aglycon (**3**). The steric congestion that would arise between the hemiketal functionality and the C-4 phenolic residue prevents the formation of the B-ring in **22**. The acidic reaction media also provides a reversible pathway in which ester lactone **22** can exude the quinone methide and regenerate starting materials. The product ratios indicate that the equilibrium can be shifted toward **3** with increased temperature.

To definitively prove the existence of an equilibrium between ester lactone **22** and starting materials, compound **22** was exposed to a 0.3 M aqueous solution of vitamin C at 50 °C for 2 days. The reaction afforded at 70% yield of a 1:1 mixture of **3** and **22**, as well as 5% of benzyl alcohol **21**. Further experimentation revealed that by either treating **21** with 10 equiv of vitamin C at 50 °C for 16 days or by reacting **22** with **1** for the extended period of time, the equilibrium was forced completely toward **3** (37% yield).

Insight as to the predominance of ester lactone **22** at low temperature can be discerned by assuming the transition state depicted in structure **26a**. Here, the methyl acetate



26a $R_1 = R_2 = H$, $R_3 = CH_2CO_2CH_3$

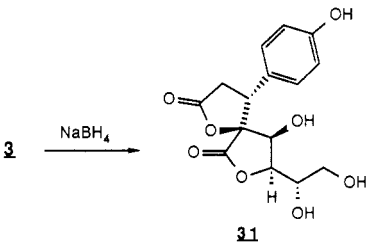
b $R_1 = R_3 = H$, $R_2 = CH_2CO_2CH_3$

c $R_1 = R_3 = CH_3$, $R_2 = H$

moiety occupies a position opposite the O-2 proton of ascorbic acid. This spatial relationship can be argued based on either steric or electrostatic repulsions present in the opposite orientation. To test the steric argument, benzyl alcohols **27** and **28** were reacted with vitamin C and no partiality in the product ratio was observed. When the steric bulk at O-2 was increased, as in the case of 2-*O*-methylascorbic acid (**18**), the quinone methide is forced into configuration **26c** in our transition-state model. This was supported by the observation that the reaction of **27** with **18** (3 days, 50 °C, 73% yield) gave exclusively **29**. Analogously, only **30** was obtained from the reaction of **28** with **18**. These observations indicate that the O-2 proton is not large enough to control the orientation of the quinone methide with respect to **1**. Therefore, the controlling element in the transition-state model is the electrostatic repulsion (alkoxide ester hydroxyl) present in conformation **26a** versus **26b**.[26]

All that remained to complete the synthesis of leucodrin (**4**) was reduction of the hemiketal moiety of dilaspirolactone aglycon (**3**). This was accomplished in 69% yield

Scheme IV



by the action of diborane in THF on **3**. The basic borane opens the hemiketal to its corresponding keto alcohol and complexes to the C-10 and C-11 hydroxyls. The hydride is then delivered from the sterically congested β face.[27] Treatment of **3** with sodium borohydride gave diasteroisomer **31**, by uncomplexed reduction from the less hindered α face (Scheme IV).[28] Similarly, ester lactone **22** was exposed to a solution of diborane in THF and workup under neutral conditions afforded reflexin (**7**) in 70% yield.

In a parallel fashion, leudrin (**5**) was prepared from vitamin C. Treatment of an aqueous solution of **1** with benzyl alcohol **32** at 50 °C for 2 days gave a 1:1 mixture of **33** to **34** in 72% yield. After chromatographic separation, isomer **33** was reduced with diborane in THF to afford a 38% yield of leudrin (**5**). To confirm our synthesis of **5**, the natural product was converted to its dimethyl ether **35** by reaction with diazomethane and compared with the same compound isolated by Perold.[22]

In summary, the reaction of an aqueous solution of ascorbic acid (**1**) with *p*-hydroxybenzyl alcohol (**9**) affords 2-(*p*-hydroxybenzyl)-3-ketohexulosonic acid lactone (**10**). This observation is the result of the addition of the conjugate base of vitamin C to protonated quinone methide **11**. Delesserine (**2**), methylrhodomelol (**6**), and rhodomelol (**8**) have been prepared by similar reactions. Extension of this methodology to the construction of dilaspirolactone aglycon (**3**), leucodrin (**4**), and reflexin (**7**) showed that treatment of ascorbic acid (**1**) with benzyl alcohol **21** yields ester lactone **22** and dilaspirolactone aglycon (**3**). The ratio of these products is dependent upon the reaction conditions, with **3** being the result of irreversible lactonization. Other studies into the synthetic utility of vitamin C are currently under way.

Experimental Section

The ^{13}C and ^{1}H NMR spectra were recorded on a JEOL FX-90Q and Varian EM-390. Chemical shifts are expressed in parts per million downfield from Me_4Si. The infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Mass spectra (70 eV) were measured on a VG MM70-SE high-resolution mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 automatic polarimeter, using a 10-cm cell. Thin-layer chromatography utilized precoated Analtech medium hard silica gel GHLF glass plates of 0.25-mm thickness. Column chromatography were carried out on silica gel G/HR (Baker TLC grade) as described by Schlessinger.[29] Melting points were determined on a Fisher-Johns melting point block and reported uncorrected.

All reactions were run in flame-dried vessels under an atmosphere of nitrogen except those in which water was present. All additions wherever possible, were made via syringe through a septum and all reactions were stirred with magnetic stirrers. Dry THF was obtained by distillation from sodium benzophenone

(25) Neither lactonization nor β-elimination precede carbon–carbon bond formation, as demonstrated by Brimacombe, J. S.; Murry, A. W.; Haque, Z. *Carbohydr. Res.* **1975**, *45*, 45.

(26) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.

(27) For a similar directing effect, see: Isobe, M.; Iio, H.; Kwai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940.

(28) Lowry, J. B.; McAlpine, J. B.; Riggs, N. V. *Aust. J. Chem.* **1975**, *28*, 109.

(29) Kieczykowski, G. R.; Quesada, M. L.; Schlesisnger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.

(30) Rotation value obtained from a sample provided by Professor G. W. Perold, University of Witwatersrand, Johannesburg, South Africa.

ketyl. All other reagents and solvents were obtained from commercial sources and purified by standard methods.

Rhodomelol (8). To 2,3-dibromo-4,5-dihydroxybenzyl alcohol (**17**) (298 mg, 1 mmol) in water (10 mL) was added L-ascorbic acid (**1**) (529 mg, 3 mmol) and the solution stirred at 75 °C for 12 h. The reaction was evaporated and the residue chromatographed (5:1, EtOAc/hexanes) to give 235 mg (54%) of rhodomelol (**8**): mp 178–181 °C (EtOAc/hexanes); $[\alpha]_D$ +17.4° (*c* 0.5, 95% EtOH). IR ($CHCl_3$) ν 1770, 1740, 1705 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 173.9, 144.4, 143.5, 126.9, 118.2, 116.0, 112.3, 107.5, 86.8, 77.6, 74.7, 74.0, 40.4. MS (FAB), *m/e* (relative intensity): 457 (0.7), 397 (1.1), 364 (3.1), 335 (1.3), 303 (3.0), 239 (4.8).

Delesserine (2). To 2-*O*-methylascorbic acid (**18**) (198 mg, 1.04 mmol) in water (2 mL) was added *p*-hydroxybenzyl alcohol (**19**) (43 mg, 0.34 mmol) and the solution stirred at 50 °C for 3 days. The reaction was evaporated and the residue chromatographed (4:1, EtOAc/hexanes) to afford 80 mg (80%) of delesserine (**2**): $[\alpha]_D$ +41 (*c* 0.56, MeOH) (lit.[14] $[\alpha]_D$ +44° (*c* 0.72, MeOH), lit.[13] $[\alpha]_D$ +36° (*c* 0.72, MeOH). IR ($CHCl_3$): ν 1792, 1768, 1735 cm^{-1}. ^{13}C NMR (D_2O): (open form) δ 210.8, 177.4, 158.6, 134.8, 125.4, 118.6, 87.2, 85.6, 72.8, 64.1, 58.8, 44.2; (closed form) δ 177.5, 157.9, 135.1, 128.1, 118.2, 111.2, 90.2, 87.6, 78.2, 75.7, 55.8, 38.3. MS (70 eV), *m/e* (relative intensity): 296 (2.1), 278 (0.9), 236 (1.6), 220 (2.5), 202 (2.2), 190 (1.9), 172 (3.1), 130 (18.1), 107 (100).

Methylrhodomelol (6). To 2,3-dibromo-4,5-dihydroxybenzyl alcohol (**17**) (317 mg, 1.06 mmol) in water (10 mL) was added 2-*O*-methylascorbic acid (**18**) (500 mg, 1.06 mmol) and the solution stirred at 70 °C for 12 h. The reaction was evaporated and the residue chromatographed (5:1, EtOAc/hexanes) to afford 178 mg (36%) of methylrhodomelol (**6**): mp 86–88 °C (EtOAc/hexanes); $[\alpha]_D$ +19.2 (*c* 0.25, 95% EtOH). IR ($CHCl_3$): ν 1770, 1740 cm^{-1}. ^{13}C NMR DMSO-d_6) δ 170.8, 144.7, 143.7, 126.6, 117.8, 116.2, 112.3, 108.8, 87.7, 82.2, 75.3, 73.2, 53.4, 37.1.

Compound 19. To methylrhodomelol (**6**) (37 mg, 0.08 mmol) in MeOH (0.35 mL) at 0 °C was added an ethereal solution of CH_2N_2 until a yellow color persisted. The reaction was stirred over solid $MgSO_4$ for 1 h, filtered, evaporated, and chromatographed (2:1, EtOAc/hexanes) to give 40 mg (99%) of **19**: mp 172–172.5 °C (EtOAc/hexanes) (lit.[15] mp 172 °C); $[\alpha]_D$ +37.6° (*c* 0.39, 95% EtOH) (lit.[15] $[\alpha]_D$ +38.3° (EtOH)). ^{13}C NMR (DMSO-d_6): δ 170.5, 151.3, 149.4, 132.4, 115.7, 108.5, 87.5, 81.8, 75.0, 73.0, 59.5, 55.9, 53.4, 36.9.

Compound 21. To a solution of diisopropylamine (5 mL, 42.7 mmol) in THF (43 mL) at −78 °C was added *n*-butyllithium (35.6 mmol, 16.8 mL of 2.12 M in hexane) and stirred for 15 min. Methyl acetate (3.1 mL, 39.1 mmol) was added, the reaction stirred for 1 h at −78 °C, and *p*-(trimethylsiloxy)benzaldehyde[24] (6.9 g, 35.6 mmol) added. After 1 h at −78 °C, the reaction was quenched with saturated NH_4Cl (50 mL), warmed to room temperature, and stirred for an additional 6 h. The solution was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to give 5.6 g (80%) of **21**: mp 93–94 °C (Et_2O/hexanes). IR ($CHCl_3$): ν 3750–3100, 1742, 1622, 1524 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (m, 2 H), 3.55 (s, 3 H), 4.9 (dd, J = 5.4, 9.0 Hz, 1 H), 5.4 (br s, 2 H), 6.7 (d, J = 9.0 Hz, 2 H), 7.1 (d, J = 9.0 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 171.3, 156.5, 135.1, 127.0, 114.9, 69.2, 51.3, 44.4. MS (70 eV), *m/e* (relative intensity): 196 (10.1), 178 (19.9), 147 (29.4), 123 (100).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.27; H, 6.22.

Reaction of L-Ascorbic Acid (1) with 21. To L-ascorbic acid (**1**) (135 mg, 0.77 mmol) in water (1.5 mL) was added compound **21** (50 mg, 0.26 mmol) and the solution stirred at 50 °C for 3 days. The reaction was evaporated and the residue chromatographed (2:1, EtOAc/hexanes) to afford 39 mg (46%) of dilaspirolactone aglycon (**3**) and 43 mg (47%) of **22**.

Dilaspirolactone aglycon (**3**): mp 210–214 °C (EtOAc/hexanes); $[\alpha]_D$ −1.5 (*c* 0.33, MeOH), −2.7° (*c* 1, 95% EtOH). IR ($CHCl_3$): ν 3610–3060, 1809, 1617, 1521 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 174.2, 157.6, 131.3, 129.7, 122.5, 115.5, 105.0, 89.2, 88.4, 74.6, 73.5, 44.1, 32.8. MS (70 eV), *m/e* (relative intensity): 322 (1.1), 304 (1.2), 260 (2.6), 147 (17.3), 120 (45.9), 91 (12).

Anal. Calcd for $C_{15}H_{14}O_8$: C, 55.73; H, 4.68. Found: C, 55.33; H, 5.07.

Compound **22**; mp 102–114 °C (EtOAc/hexanes); $[\alpha]_D$ +28.8° (*c* 0.33, MeOH), +27.0° (*c* 1, 95% EtOH). IR ($CHCl_3$): ν 3600–3160, 1796, 1735, 1618, 1519 cm^{-1}. ^{13}C NMR (DMSO-d_6): (open form) δ 210.1, 176.8, 173.0, 156.9, 131.5, 126.1, 115.7, 80.8, 75.2, 73.9, 61.1, 51.6, 47.6, 33.6; (closed form) δ 174.2, 171.9, 157.8, 129.8, 124.9, 114.9, 107.9, 86.0, 83.3, 74.3, 70.2, 51.2, 47.9, 32.4. MS (70 eV), *m/e* (relative intensity): 322 (2.3), 304 (3.5), 281 (1.5), 255 (3.6), 207 (4.2), 178 (3.9), 147 (84.8), 120 (100).

Anal. Calcd for $C_{16}H_{18}O_9$: C, 54.24; H, 5.12. Found: C, 53.84; H, 5.45.

Methyl Glycoside of Dilaspirolactone Aglycon (3). To a solution of MeOH (5 mL) saturated with hydrogen chloride gas at 0 °C was added **3** (100 mg, 0.31 mmol) in MeOH (5 mL). The reaction was warmed to room temperature, stirred for 48 h, evaporated, and chromatographed (4:1 EtOAc/hexanes) to afford 104 mg (99%) of the methyl glycoside of dilaspirolactone aglycon: mp 261–265 °C (lit.[23] mp 261–262 °C); $[\alpha]_D$ −17.5° (*c* 0.08, MeOH) (lit.[23] $[\alpha]_D$ −33.3° (*c* 0.33, MeOH)). IR ($CHCl_3$): ν 3600–3100, 1816, 1621, 1525 cm^{-1}. ^1H NMR (270 MHz, C_5D_5N): δ 3.05 (dd, J = 8.5, 17.3 Hz, 1 H), 3.5 (dd, J = 13.4, 17.2 Hz, 1 H), 3.6 (s, 3 H), 4.15 (dd, J = 3.9, 9.6 Hz, 1 H), 4.3–4.4 (m, 3 H), 4.55 (dd, J = 3.9, 6.5 Hz, 1 H), 4.8 (br s, 2 H), 6.98 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.6 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 173.8, 171.1, 159.0, 130.1, 122.3, 115.8, 107.4, 89.3, 88.5, 75.7, 73.4, 50.9, 44.4, 33.0. MS (70 eV), *m/e* (relative intensity): 336 (4.3), 318 (8.1), 290 (2.7), 203 (10.5), 179 (14.4), 147 (14.7), 137 (27.4), 120 (72.3).

Degradation of Dilaspirolactone Aglycon (3) to (−)-Methyl 3-α-Furoyl-3-(*p*-methoxyphenyl)propionate (24). Dilaspirolactone aglycon (**3**) (536 mg, 1.59 mmol) was dissolved in 1 N HCl (32 mL) and refluxed for 2 h. After cooling to room temperature, the reaction was extracted with $CHCl_3$ (3 × 25 mL), and the combined organic layers were dried through $MgSO_4$ and evaporated to give 273 mg (67%) of 3-α-furoyl-3-(*p*-hydroxyphenyl)-propionic acid. The crude product was dissolved in MeOH (5 mL) and treated at 0 °C with an ethereal solution of CH_2N_2 until a yellow color persisted. The reaction was stirred over $MgSO_4$ for 1 h, evaporated, and chromatographed (1:1, EtOAc/hexanes) to afford 275 mg (91%) of (−)-methyl 3-α-furoyl-3-(*p*-methoxyphenyl)propionate (**24**): $[\alpha]_D$ −30.4° (*c* 0.5, MeOH) (lit.[23] $[\alpha]_D$ −35.4 (*c* 0.24, MeOH). ^1H NMR ($CDCl_3$): δ 2.8 (dd, J = 6.1, 17.2 Hz, 1 H), 3.35 (dd, J = 8.7, 17.2 Hz, 1 H), 3.74 (s, 3 H), 3.86 (s, 3 H), 4.83 (dd, J = 6.1, 8.7 Hz, 1 H), 6.3–8.0 (m, 7 H).

Degradation of 22 to (+)-Methyl 3-α-Furoyl-3-(*p*-methoxyphenyl)propionate (23). Compound **22** (298 mg, 0.81 mmol) was dissolved in 1 N HCl (16 mL) and refluxed for 2 h. After cooling to room temperature, the reaction was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were dried through $MgSO_4$ and evaporated to give 84 mg (40%) of 3-α-furoyl-3-(*p*-hydroxyphenyl)propionic acid. The crude product was dissolved in MeOH (5 mL) and treated at 0 °C with an ethereal solution of CH_2N_2 until a yellow color persisted. The reaction was stirred over $MgSO_4$ for 1 h, evaporated, and chromatographed (1:1, EtOAc/hexanes) to afford 90 mg (98%) of (+)-methyl 3-α-furoyl-3-(*p*-methoxyphenyl)propionate (**23**): $[\alpha]_D$ +4.0° (*c* 1, MeOH); considerable racemization occurred during degradation. ^1H NMR ($CDCl_3$): δ 2.8 (dd, J = 6.1, 17.2 Hz, 1 H), 3.35 (dd, J = 8.7, 17.2 Hz, 1 H), 3.74 (s, 3 H), 3.86 (s, 3 H), 4.83 (dd, J = 6.1, 8.7 Hz, 1 H), 6.3–8.0 (m, 7 H).

Leucodrin (4). To **3** (50 mg, 0.16 mmol) in THF (1.5 mL) was added B_2H_6 (0.16 mL, 1 M in THF) and the solution refluxed for 1 h. The reaction was diluted with water (0.5 mL), evaporated, and chromatographed (4:1, EtOAc/hexanes) to afford 12 mg of **3** and 34 mg (69%) of leucodrin (**4**): mp 214–215 °C (lit.[20] mp 216 °C); $[\alpha]_D$ −17.6° (*c* 1.7, 50% EtOH), −11.2° (*c* 1, 95% EtOH) (lit.[20] $[\alpha]_D$ −15.4 (*c* 0.92, 95% EtOH)). IR ($CHCl_3$): ν 3600–3100, 1800, 1640 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 174.6, 171.9, 157.1, 129.9, 123.4, 115.4, 89.9, 79.7, 69.1, 67.9, 61.2, 40.9, 33.1. MS (70 eV), *m/e* (relative intensity): 324 (23.9), 306 (3.1), 247 (3.0), 220 (8.4), 147 (37.3), 120 (100).

Anal. Calcd for $C_{15}H_{16}O_8$: C, 55.56; H, 4.97. Found: C, 55.57; H, 5.01.

Reflexin (7). To **22** (35 mg, 0.1 mmol) in THF (2 mL) was added B_2H_6 (0.1 mL, 1 M in THF) and the solution refluxed for 1 h. The reaction was diluted with water (0.5 mL), evaporated, and chromatographed (4:1, EtOAc/hexanes) to afford 10 mg of **22** and 25 mg (70%) of reflexin (**7**): mp 110–114 °C (EtOAc/hexanes) (lit.[21] mp 110–114 °C); $[\alpha]_D$ +39.8 (*c* 0.95, 95% EtOH)

(lit.[21] $[\alpha]_D$ +36 (c 0.95)). IR ($CHCl_3$): ν 3600–3100, 1780, 1736, 1619, 1521 cm^{-1}. ^{13}C NMR (DMSO-d_6) δ 177.7, 173.2, 156.6, 131.4, 127.8, 115.0, 80.3, 79.7, 75.9, 69.1, 62.3, 51.5, 47.6, 32.7. MS (70 eV), m/e (relative intensity): 324 (14.4), 296 (1.6), 265 (0.6), 220 (7.8), 165 (6.9), 147 (16.4), 120 (100).

Anal. Calcd for $C_{16}H_{20}O_9$: C, 53.93; H, 5.66. Found: C, 53.83; H, 5.98.

Compound 32. To a solution of diisopropylamine (1.7 mL, 12 mmol) in THF (12 mL) at −78 °C was added n-butyllithium (10 mmol, 4.7 mL of 2.12 M in hexane) and stirred for 15 min. Methyl acetate (0.88 mL, 11 mmol) was added, the reaction stirred for 1 h at −78 °C, and 3,4-bis(trimethylsiloxy)benzaldehyde (1.4 g, 5 mmol) added. After 1 h at −78 °C, the reaction was quenched with saturated NH_4Cl (10 mL), warmed to room temperature, and stirred for an additional 6 h. The solution was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried with Na_2SO_4, and evaporated to give 0.42 g (41%) of **32**: mp 101–102 °C. IR ($CHCl_3$): ν 3700–3100, 1742, 1640, 1528 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.63 (d, J = 6.8 Hz, 2 H), 3.65 (s, 3 H), 4.9 (t, J = 6.9 Hz, 1 H), 6.6–6.8 (m, 3 H), 7.1–7.6 (br s, 3 H). ^{13}C NMR (DMSO-d_6) δ 171.3, 145.0, 144.4, 135.8, 116.6, 115.7, 113.3, 69.3, 51.2, 44.5. MS (70 eV), m/e (relative intensity): 212 (28.7), 194 (44.1), 163 (46.9), 139 (100).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.70; H, 5.78.

Reaction of L-Ascorbic Acid (1) with 32. To compound **32** (102 mg, 0.5 mmol) in water (5 mL) was added L-ascorbic acid (**1**) (264 mg, 1.5 mmol) and the solution stirred at 50 °C for 3 days. The reaction was evaporated and the residue chromatographed (4:1, EtOAc/hexanes) to afford 64 mg (34%) of bislactone **33** and 76 mg (38%) of lactone ester **34**.

Bislactone **33**: $[\alpha]_D$ −10.3° (c 1.0, 95% EtOH). IR ($CHCl_3$): ν 3600–3100, 1806, 1610, 1529 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 174.8, 171.3, 145.6, 145.3, 128.3, 123.2, 119.4, 115.8, 105.1, 89.2, 88.5, 74.7, 73.5, 44.3, 33.0. MS (70 eV), m/e (relative intensity): 313 (1.1), 283 (7.3), 255 (94.3), 213 (22.7), 171 (100).

Lactone ester **34**: $[\alpha]_D$ +20.2° (c 1.0, 95% EtOH). IR ($CHCl_3$): ν 3600–3100, 1795, 1768, 1742, 1610, 1540 cm^{-1}. ^{13}C NMR (DMSO-d_6): (open form) δ 210.2, 176.3, 172.8, 145.1, 144.6, 126.7, 120.6, 117.3, 115.0, 80.4, 74.6, 73.3, 60.7, 51.6, 47.2, 32.7; (closed form) δ 174.1, 171.6, 145.1, 144.4, 128.3, 125.0, 119.0, 115.8, 107.8, 86.8, 83.1, 73.9, 69.9, 51.2, 47.6, 31.9. MS (70 eV), m/e (relative intensity): 355 (0.1), 303 (0.1), 284 (0.8), 255 (3.8), 220 (6.8), 194 (91.1), 163 (100).

Leudrin (5). To **33** (102 mg, 0.28 mmol) in THF (3 mL) was added B_2H_6 (0.55 mL, 1 M in THF) and the solution refluxed for 1 h. The reaction was diluted with water (1 mL), evaporated, and chromatographed (3:1, EtOAc/hexanes) to afford 39 mg (38%) of leudrin (**5**): $[\alpha]_D$ −16.7° (c 0.88, 95% EtOH). IR ($CHCl_3$): ν 3650–3100, 1802, 1716, 1640 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 174.6, 171.9, 145.1, 124.0, 121.7, 119.8, 115.8, 89.9, 79.8, 69.1, 67.9, 61.3, 41.8, 33.4. MS (70 eV), m/e (relative intensity): 340 (17.3), 220 (7.2), 163 (20.3), 136 (100).

Compound 35. Leudrin (**5**) (39 mg, 0.1 mmol) was dissolved in MeOH (0.2 mL) and treated at 0 °C with an ethereal solution of CH_2N_2 until a yellow color persisted. The reaction was stirred over $MgSO_4$ for 1 h, evaporated, and chromatographed (1:1, EtOAc/hexanes) to afford 40 mg (96%) of compound **35**: $[\alpha]_D$ −18.0° (c 1, 95% EtOH) (lit.[30] $[\alpha]_D$ −19.2° (c 0.92, 95% EtOH). IR ($CDCl_3$): ν 3700–3000, 1799, 1522 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ 174.7, 172.0, 147.4, 146.4, 125.9, 121.5, 112.9, 112.0, 89.9, 79.9, 69.1, 68.0, 61.2, 55.6, 41.2, 33.4. MS (70 eV), m/e (relative intensity): 368 (3.0), 354 (33.5), 336 (3.7), 250 (4.3), 177 (22.8), 150 (100).

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Kinetics and Mechanism of the Ketonization of a Conjugated Trienol

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The steroidal trienol 3-hydroxy-3,5,7-estratrien-17-one (**1**) decomposes in aqueous solution to yield 5,7-estradiene-3,17-dione (**2**), 4,7-estradiene-3,17-dione (**3**), and an unidentified oxidation product (**5**). The relative amounts of the products vary, with **3** predominant at pH ~1 and **2** the major product at pH values between 2 and 8. The oxidation product **5** is formed in significant amounts only in relatively basic solutions (pH >6) and increases as the pH is increased. The rate constant for the overall reaction may be expressed as k^{obsd} (s^{-1}) = (1.24 ± 0.07) × 10^{-2} + (2.54 ± 0.13)[H^+] + (1.78 ± 0.06) × 10^5[OH^-]. The rate constant for protonation of **1** in acidic solution is ca. 200-fold smaller than that for 1-cyclohexenol, presumably due to the extended conjugation of the enol system in **1**. Although the hydroxide-catalyzed rate constant for ketonization of **1** is comparable to the rate constants for conjugated dienols, the uncatalyzed ketonization rate constant for **1** is ca. 10^3-fold slower than that for most dienols. The much slower uncatalyzed rate constant for **1** is due to its inability to undergo the characteristic 1,5-sigmatropic shift of other conjugated enols.

The kinetics and mechanism of the interconversion of simple aldehydes and ketones with their enols has been the subject of active investigation for a long time.[1] Although rate constants for enolization of carbonyl compounds are relatively straightforward to measure by a variety of techniques, it has only recently been possible to monitor this reaction in the thermodynamically favorable direction of enol to aldehyde or ketone. Primarily

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