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THE TOTAL SYNTHESIS OF DELESSERINE, LEUCODRIN, AND DILASPIROLACTONE AGLYCONE[1]

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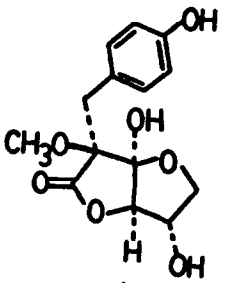
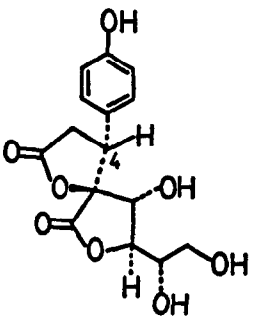
Abstract: The synthesis of delesserine, 1, leucodrin, 2, and dilaspirolactone aglycone, 3, are reported. The preparation of these ascorbigens was implemented by the addition of ascorbic acid to a p-hydroxy benzyl alcohol derived quinone methide.

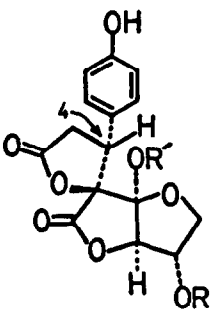
Vitamin C has been the subject of vigorous biochemical investigation, however its synthetic utility has remained virtually unnoticed.[2] Herein, we describe a novel method for the benzylation of ascorbic acid at C-2 that permits the stereospecific construction of delesserine, leucodrin, and the aglycone of dilaspirolactone.



1



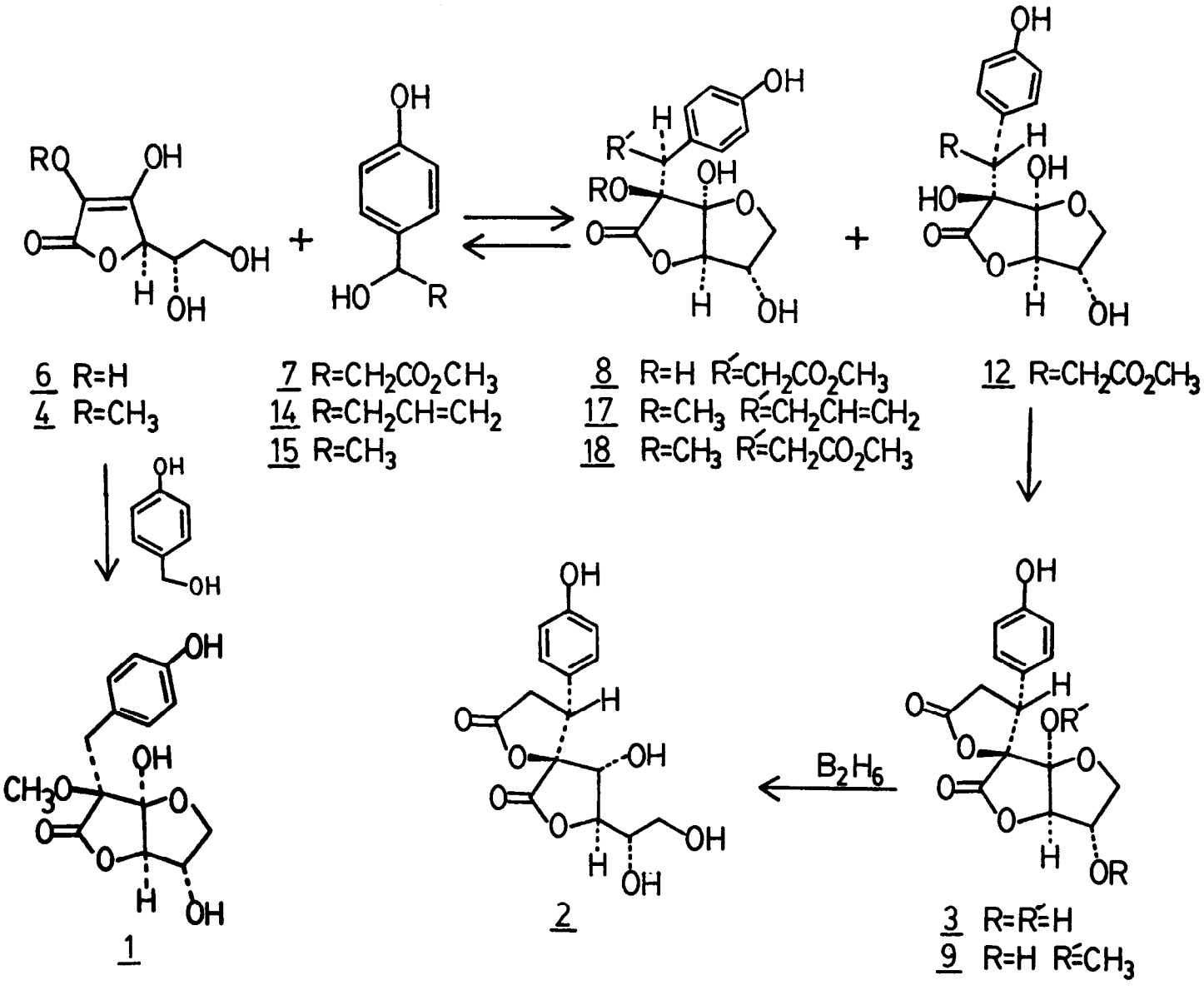
2



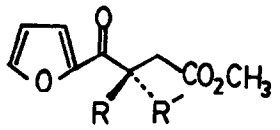
3 R=R'=H
5 R=Glu R'=H

The secondary sugar metabolite, delesserine, 1, was isolated from the marine alga Delesseria sanguinea and thought to have anticoagulant properties.[3] Compound 1 was prepared in 80% yield by reacting 2-O-methyl ascorbic acid, 4,[4] (3 equ) with 4-hydroxy benzyl alcohol (1 equ) in water (0.5M) for 3 days at 50°C.[5] The reaction proceeds by 2-O-methyl ascorbic acid initiated protonation of the benzylic alcohol moiety. The phenol next initiates the elimination of water and the resulting protonated quinone methide adds to the conjugate base of 4 from the less hindered alpha face, to yield 1.[6]

The next synthetic challenge was to construct the 1,7-dioxa-2,6-dioxospiro[4,4]nonane skeleton of 2 and 3 while controling the stereochemistry of the C-4 phenolic residue. Leucodrin, 2, is a phenolic constituent of various species of the genus Leucadendron (Proteaceae).[7] The deciduous shrub Viburnum dilatatum is the source of the glucoside dilaspirolactone, 5.[8] Treatment of ascorbic acid, 6, (3 equ.) with 7 (1 equ.) in water (0.5M) at 22°C for 14 days led to a 4:1 mixture of 8 to 3 (82% yield).[5,9] Compounds 3 and 8 were chromatographically separated (EtOAc/hexanes, 1:1) and the stereochemistry at C-4 in 3 established by comparison of its methyl hemiketal 9 (MeOH, HCl gas, 48 hr., reflux) with that derived from 5. To confirm our assignment of 8, 3 and 8 were converted into furanoketones 10 and 11 (respectively), by the action of dilute


RO
OH
O
O
H
OH
OH
+
OH
HO
R
OH
R'
H
RO
OH
O
O
O
H
OH
+
OH
R
H
HO
OH
O
O
O
H
OH
6 R=H
4 R=CH3
7 R=CH2CO2CH3
14 R=CH2CH=CH2
15 R=CH3
8 R=H R'=CH2CO2CH3
17 R=CH3 R'=CH2CH=CH2
18 R=CH3 R'=CH2CO2CH3
12 R=CH2CO2CH3
OH
OH
CH3O
OH
O
O
O
H
OH
1
OH
OH
O
O
O
H
OH
H
OH
2
B2H6
OH
H
OR'
O
O
O
O
H
OR
3 R=R'=H
9 R=H R'=CH3

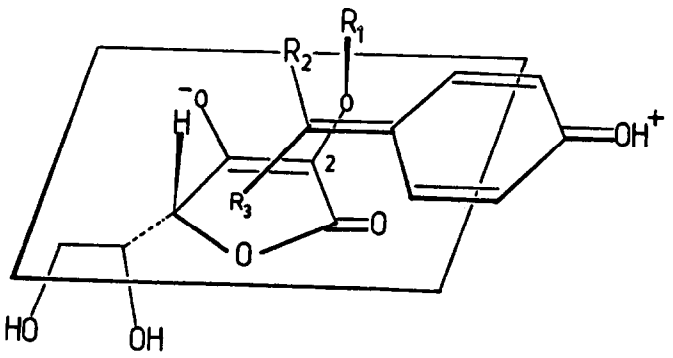
HCl (2 hr., reflux) followed by CH_2N_2, and found to have opposite rotations.[5] The reaction of 6 with 7 at 50°C (3 days) gave a 1:1 ratio of 8 to 3 in 94% yield.



3 → 10 R=H R'=$C_6H_4OCH_3$
8 → 11 R=$C_6H_4OCH_3$ R'=H

The reaction proceeds by addition of the conjugate base of 6 to the quinone methide derived from 7, yielding esters 8 and 12. Compound 12 undergoes acid catalyzed loss of MeOH affording 3, whereas lactonization of 8 would lead to steric congestion of the C-4 phenolic residue and the hemi-ketal functionality. Under the reaction conditions, ester-lactone 8 can exude the quinone methide to regenerate starting materials. The product ratios observed indicate that higher temperatures increase the reversibility of 8 to ascorbic acid. As a definitive proof of this mechanism, ester-lactone 8 was exposed to a 0.3M solution of Vitamin C (50°C) for 2 days and a 1:1 mixture of 3 and 8 (70% yield) was isolated along with 5% of benzyl alcohol 7. The equilibrium could be forced to yield only 3 by either treating 8 with 10 equ. of ascorbic acid at 50°C for 16 days (37% yield) or by reacting 7 (1 equ.) with 6 (3 equ.) under similar conditions (37% yield).

The stereochemistry exhibited in the formation of 8 can be rationalized by assuming a transition state as depicted in structure 13a, where the methyl acetate moiety occupies a position opposite the C-2 hydroxyl group of ascorbic acid. This spatial relationship is preferred due to the electrostatic repulsion (alkoxide-ester-hydroxyl) that would be present with the opposite orientation, 13b.[10] When the reaction was conducted with benzyl alcohol substrates 14 and 15, no preference was observed in the product ratio. Therefore, the O-2 proton does not act as a sterically congesting group. Compound 14 (1 equ.) was reacted with 2-O-methyl ascorbic acid, 4,



13a 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=CH_3 R_2=H R_3=$CH_2CH{=}CH_2$

(3 equ., 3 days, 50°C, 73% yield) and found to yield exclusively 17. When the steric bulk at O-2 is increased, the propenyl group assumes configuration 13c in our transition state model. Similarly, only 18 (45% yield) was obtained from the reaction of 7 with 4.

Leucodrin, 2, was prepared in 69% yield by the action of B_2H_6 in THF (1 equ., reflux, 1 hr.) on aglycone 3.[5,11] The basic borane opens the hemi-ketal to its corresponding keto-diol form and complexes to the C-10 and C-11 hydroxyls, thus, delivering hydride from the sterically congested beta face.[8]

References

1. We are indebted to the Donors of The Petroleum Research Fund, adminstered by the American Chemical Society, for the support of this research. We also thank Professor Chevolet for a sample of delesserine, Professor Perold for a sample of leucodrin, and Hoffman-LaRoche for ascorbic acid.
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4. Lu, PW.; Lillard, D.W.; Seib, P.A.; Kramer, K.J.; Liang, YT. J. Agric. Food Chem. 1984, 32, 21.
5. Satifactory spectral data were obtained for all compounds reported herein. For compound 1: $[\alpha]_D$= +41 (c=0.56, MeOH); lit.[3b]: $[\alpha]_D$= +44 (c=).72, MeOH); lit.[3a]: $[\alpha]_D$= +36 (c=0.72, MeOH). The C^{13} NMR for C-4 in compounds 3 (44 ppm, d_6-DMSO) and 8 (47.5 ppm, d_6-DMSO) correspond to similar stereochemical changes as observed by Highet, R.J.; Perold, G.W.; Sokoloski, E.A. J. Org. Chem. 1976, 41, 3860. Compound 2: mp 214-215, lit.[7a] 212-212.5, lit.[7b] 216; $[\alpha]_D$=-17.6 (c=0.9, 50% EtOH), lit.[7a] $[\alpha]_D$= -15.45, lit.[7b] $[\alpha]_D$= -21 (c=1.7, 50% EtOH). Compound 9: mp 261-265, lit.[8] 261-262; $[\alpha]_D$= -17.5 (c=2.3, MeOH), lit.[8] $[\alpha]_D$=-33.3 (c=0.33, MeOH). Compound 10: $[\alpha]_D$= -30.4 (c=0.5, MeOH); lit.[8] $[\alpha]_D$= -35.4 (c=0.24, MeOH). Compound 11: $[\alpha]_D$= +4.0 (c=1.0, MeOH); considerable racemization occured during degradation.
6. The alkylation of ascorbic acid with benzyl chloride has been reported (Jackson, K.G.H.; Jones, J.K.N. Can. J. Chem. 1965, 43, 450), however, all attempts to add p-hydroxy benzyl halide derivatives to vitamin C under basic conditions led to reaction at O3. For the preparation and reactions of quinone methides, see: Becker, H.D.; Gustafson, K. J. Org. Chem. 1976, 41, 214 and references therein.
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