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TOTAL SYNTHESIS OF dl-MEXICANIN I AND dl-LINIFOLIN A

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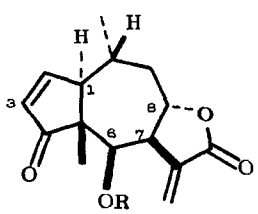
Summary: The helenanolides mexicanin I(1) and linifolin A(4) have been synthesized from hydroazulenol 5, thereby confirming the original structural assignments.

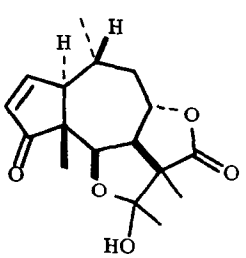
The pseudoguaianolide mexicanin I, isolated from Helenium mexicanum, has been shown by Dominquez and Romo[1] to possess structure 1 based on IR, NMR, and chemical degradative studies, and by correlation with tenulin(2), whose structure was previously correlated with helenalin(3) by Herz and Mitra.[2] Mexicanin I, like tenulin, differs from helenalin at carbon atoms C(6) and C(8) on the seven-membered ring.

Despite extensive structural studies on helenanolides over the past twenty years, synthetic efforts in this area have been thwarted by the inability to control chirality on the non-rigid seven-membered ring.[3,4] We wish to report the total synthesis of mexicanin I(1) and linifolin A(4)[6] from hydroazulenol 5.[7] The synthesis of mexicanin I and linifolin A(acetylmexicanin I) confirms the structural assignments of these long sought after sesquiterpene lactones.



1 R = H

4 R = Ac



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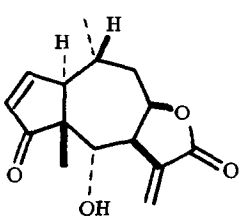

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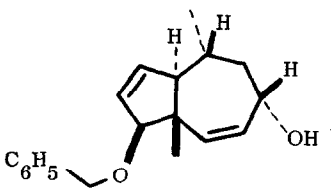
Having previously established the configuration at C(1), C(5), C(8) and C(10) in the key intermediate hydroazulenol 5, we concentrated on elaborating the remaining two chiral centers, C(6) and C(7), of mexicanin I. Epoxidation (m-chloroperbenzoic acid, methylene chloride) of allylic alcohol 5 proceeded as anticipated, giving rise (65%) to pure crystalline syn-epoxy alcohol 6, mp 99-100°C. Treatment of epoxide 6 with the dianion[8] (excess) of acetic acid in dimethoxyethane at 55°C for 16 h followed by workup with 10% hydrochloric acid (pH 3) gave rise exclusively to an 82% yield of tricyclic lactone 7, mp 141-143°C [IR ($CHCl_3$) 3590, 1770 cm^{-1}; NMR



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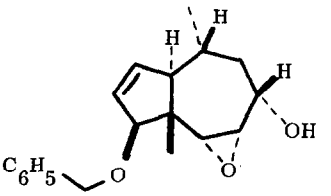

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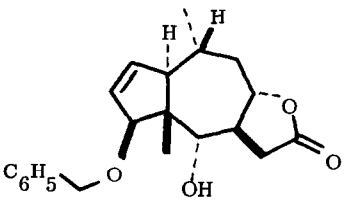

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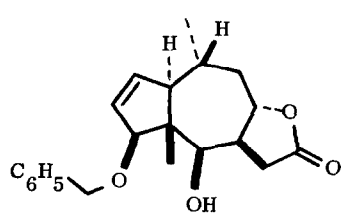
(250 MHz) (CCl_4) δ 3.46 (d, 1H, J = 8.3 Hz, H-6), 4.34 (ddd, 1H, J = 2.2, 10.5, 11.5 Hz, H-8)]. Oxidation of alcohol 7 with Jones reagent at -10°C (20 min) and subsequent reduction (sodium borohydride, ethanol, 0°, 15 min) of the resultant tricyclic ketone produced (70% overall), as the sole product, a new lactone (amorphous solid) which was assigned structure 8. The exclusive formation of the C(6) β-oriented alcohol was not surprising in view of the bulky C(5) methyl group which blocks β-hydride attack.

With the configuration at C(6) and C(7) assured and, more importantly, with the γ-butyrolactone trans-fused we proceeded with cleavage of the benzyl ether for elaboration of intermediate 8 into mexicanin I. Hydrolysis of lactone 8 with potassium hydroxide (1.5 equiv) in dimethoxyethane followed by direct treatment with lithium in liquid ammonia (1 min) and acidic (pH 3) workup generated none of the desired tricyclic diol 9. A 70% yield of the unwanted, cis-fused lactone 10, mp 169-171°C [NMR (250 MHz) (DMSO-d_6) δ 3.80 (m, 1H, H-8), 4.7 (d, 1H, J = 7.5 Hz, H-6)] was isolated.



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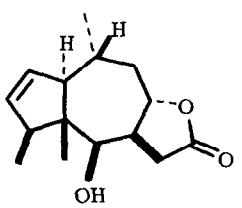

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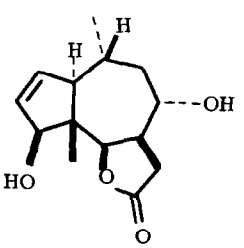

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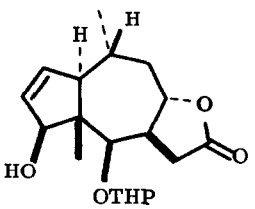
Exclusive generation of the unwanted lactone 10 necessitated prior protection of the C(6) hydroxyl as its tetrahydropyranyl ether (DHP, CH_2Cl_2, TsOH, 0°C, 30 min, 87%). The corresponding tetrahydropyranylated derivative of 8 was smoothly transformed into the tricyclic compound 11 in 75% overall yield via a four step sequence: (1) KOH (1.2 equiv), DME, 5h; (2) Li, NH_3, 1 min; (3) 1N HCl, pH 5; (4) DCC, CH_2Cl_2, 15 min. Tetrahydropyranylation of 11 gave the bis-tetrahydropyranylated derivative 12 in near quantitative yield which was subjected to α-methylenation (56% overall yield) [(1) LDA, THF, -20°C, HCHO; (2) MsCl, Py 0°C (1h), 25°C (30 min); (3) DBU, benzene, 30 min].

Cleavage (60% HOAc, 45°C, 1.5 h) of the protecting groups yielded (86%) the crystalline tricyclic α-methylene lactone 13, mp 144 - 145°C [IR ($CHCl_3$) 3605, 3400, 1760 cm^{-1}; NMR (250 MHz)($CDCl_3$) δ 6.41 (d, 1H, J=3.3 Hz, exocyclic methylene), 5.83 (m, 1H, H-2 or H-3), 5.68 (m, 1H, H-2 or H-3), 5.61(d, 1H, J=3.3 Hz, exocyclic methylene)]. Oxidation of allylic alcohol 13 using manganese dioxide in methylene chloride-benzene (2:1) produced (78%) pure crystalline dl-mexicanin I(1), mp 246 - 248°C, whose spectral properties were identical with those of the natural product.[9,10] Transformation of synthetic dl-mexicanin I into dl-linifolin A(4) was achieved in 86% yield using acetic anhydride in pyridine containing a catalytic amount of 4-dimethylaminopyridine.[11] The crystalline dl-linifolin A(4), mp 182.0 - 182.5°C, obtained was identical in all respects with an authentic sample of linifolin A by comparison of spectral properties (IR, NMR, mass spectrometry) and thin-layer mobility in several solvent systems.[12,13]



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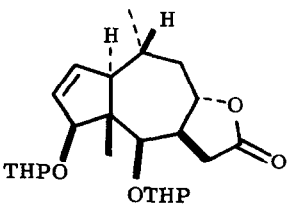

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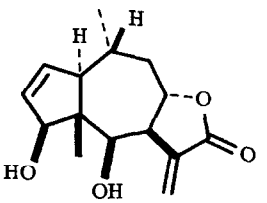

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References and Notes

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2. W. Herz and R. B. Mitra, J. Am. Chem. Soc., 80, 4876 (1958).
3. Whereas the ambrosanolides have received considerable attention during the past few years,[5] only one report has appeared in the literature detailing a total synthesis of a helenanolide.[4]
4. For the total synthesis of dl-helenalin see Y. Ohfune, P. A. Grieco, C.-L. J. Wang, and G. Majetich, J. Am. Chem. Soc., 100, 5946 (1978).

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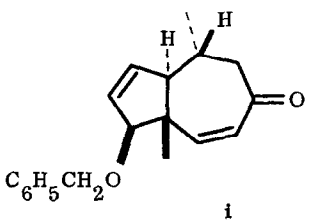
6. For the isolation and structure elucidation of linifolin A, see W. Herz, J. Org. Chem., 27, 4043 (1962); W. Herz, C. M. Gast, and P. S. Subramanian, J. Org. Chem., 33, 2780 (1968).

7. Hydroazulenol 5, mp 62 - 64°C, has been prepared in a completely stereospecific fashion from the known hydroazulenone i,[4] mp 79 - 80°C, by reduction ($LiAlH_4$, THF, 0°) [P. A. Grieco, Y. Ohfune, and G. Majetich, J. Org. Chem., 44, 0000 (1979)].



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8. P. L. Creger, J. Org. Chem., 37, 1907 (1972); cf. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, J. Am. Chem. Soc., 99, 6066 (1977); also see reference #4 above.

9. Mexicanin I: IR (KBr) 3490, 1750, 1690, 1580 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 7.67 (d, 1H, J=1.8, 6.1 Hz, H-2), 6.41 (d, 1H, J=3.5 Hz), 6.16 (dd, 1H, J=2.5, 6.1 Hz, H-3), 5.67 (d, 1H, J=3.5 Hz), 4.81 (m, 1H, H-8), 4.54 (dd, 1H, J=5.2, 2.7 Hz, H-6), 3.11 (m, 1H, H-7), 2.68 (m, 1H, H-1), 2.57 (m, 1H, H-9), 2.42 (d, 1H, J=2.7 Hz, OH), 2.22 (m, 1H, H-10), 1.39 (m, 1H, H-9), 1.25 (d, 3H, J=6.5, C(10) Me), 1.24 (s, 3H, C(5) Me).

10. We thank Professor T. J. Mabry (Austin) for the NMR spectrum of natural mexicanin I.

11. G. Höfle, W. Steglich, and H. Vorbrüggen, Angew. Chem. Int. Ed., 17, 569 (1978).

12. Linifolin A: IR ($CHCl_3$) 1755 (γ-lactone and acetate), 1710, 1660, 1590 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 7.59 (dd, 1H, J=1.8, 6.0 Hz, H-2), 6.27 (d, 1H, J=3.5 Hz), 6.12 (dd, 1H, J=3.0, 6.0 Hz, H-3), 5.96 (d, 1H, J=4.7 Hz, H-6), 5.70 (d, 1H, J=3.5 Hz), 4.81 (ddd, 1H, J=2.9, 9.2, 11.6 Hz, H-8), 3.26 (m, 1H, H-7), 2.78 (dt, 1H, J=2.2, 10.4 Hz, H-1), 2.58 (ddd, 1H, J=2.9, 4.5, 13.3 Hz, H-9), 2.23 (m, 1H, H-10), 2.08 (s, 3H), 1.42 (m, 1H, H-9), 1.26 (d, 3H, J=6.5 Hz), 1.23 (s, 3H).

13. We are indebted to Dr. Alfonso Romo de Vivar (Instituto de Quimica, Universidad Nacional Autonoma de Mexico) for a generous sample of linifolin A (acetyl mexicanin I).

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