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UNAMBIGUOUS TRANSFORMATION OF EREMANTHIN INTO (-)-ESTAFIATIN[1a,b]

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Summary: A stereoselective synthesis of (-)-estafiatin (2a) from eremanthin (1) has been achieved. The α configuration of the epoxide in the former is confirmed by chemical shift correlation with related oxides.

We have already reported on several stereoselective transformations of eremanthin (1) leading to other naturally occuring guaianolides[2] including estafiatin (2a)†[3]. This latter compound was made by epoxidation of the triene 3 obtained by BF_3 catalized isomerization of dehydrocostus lactone[2]. The synthesis of 2a from the key intermediate 3 has also been recently described by Crabbé and coworkers starting with α-santonin[4].

Analysis of the ^{1}H NMR spectrum of the mixture of epoxides obtained in the reaction of 3 with m-chloroperbenzoic acid showed the presence of 2a (~80%) and 2b (~20%)[1a,4]. The major isomer does in fact show identical properties with the naturally occuring 2a but the NMR characteristics of both isomers are so similar that a simple argument based on the assumption that the major product in the epoxidation of 3 would be produced by approach of the peracid from the less hindered α face did not seem to us a conclusive argument in favor of the proposed correlation (vide infra). It seemed therefore desirable to design a new synthetic strategy in which the epoxide could be introduced at an early stage thus allowing a more definite correlation along the pairs of possible isomeric epoxide intermediates.

Reaction of isoeremanthin (4)[2] with equimolar amount of m-chloroperbenzoic acid resulted in the almost exclusive formation of the epoxide 5[5] which upon reaction with HCl in THF gave a mixture of the chlorohydrins 6 (~30%) and 7 (~70%)[6]. Surprisingly, epoxidation of 6 led to a nearly equimolar mixture of 8a (~55%) and 8b (~45%) showing that steric hindrance to the approach of the epoxidating agent cannot always be used as a safe argument to predict the orientation of the resulting oxide. Dehydration of 8a and 8b with a mixture of $SOCl_2$/pyridine[2] under identical conditions led to the chloroderivatives 9a and 9b in 85% and 82% yield respectively. While 9a underwent facile dechlorination reaction with Zn[2] to yield 2a (~18 hr at rt), compound 9b took ~120 hr to yield a mixture of starting material and two dihydroderivatives tentatively identified (^{1}H NMR) as 10 and 11.

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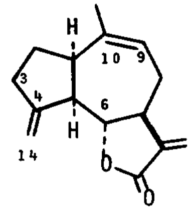
† Compounds assigned an arabic number followed by the letters a or b refer to the α-oriented or β-oriented 3,4-epoxides respectively.



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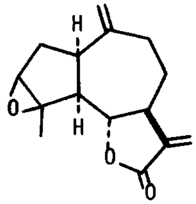
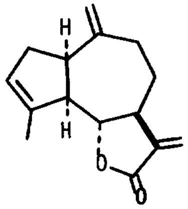


2a,b



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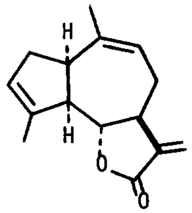

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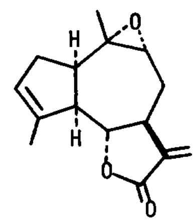

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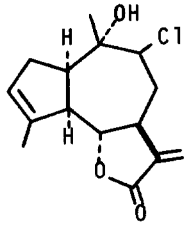

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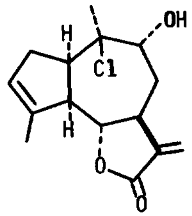

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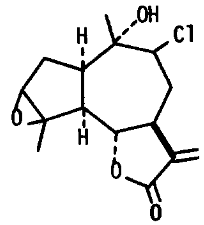
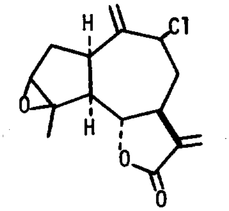
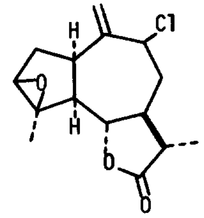


8a,b



9a,b



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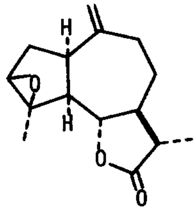

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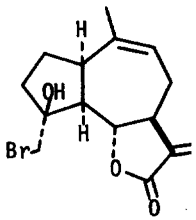

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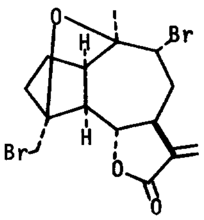

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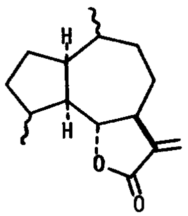

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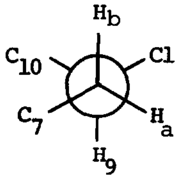
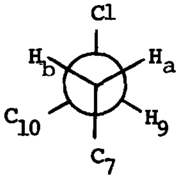
We have described so far a new synthesis of 2a but we have not yet provided a more definite argument in favor of its stereochemistry as depicted. To this end it is relevant to consider the downfield shift that a sterically related β-oriented electronegative substituent causes on H-6[7]. This effect was first observed in compound 12 (H-6 at 4.42 δ as compared with 4.03 δ in 4) unequivocally obtained by reaction of the dibromoether 13[8] with Zn[2].

For this effect to be of diagnostic value for the assignement of configuration of isomeric 3,4-epoxides, the preferred conformation of the molecules under discussion will have to be defined. In the case of 9,10-disubstituted derivatives of 4, a parameter which could serve this purpose is the coupling constant between H-9 and the C-8 protons. Thus for compound 6 the observed values are $J_{8a,9} = 4$ Hz and $J_{8b,9} = 12$ Hz. These values are best accomodated by a chair or a distorted chair conformation as implicit in the Newman projection formulas A and B respectively.



A



B

Inspection of a Dreiding model of 6 shows that intermediate conformations between A and B will be easily detected by measuring the coupling constants between H-9 and the protons at C-8. Further, it may also be noted that many of these intermediate conformers are such that the Cl at C-9 will be in close proximity with H-6 thus shifting this latter proton to lower field.

For the pair 8a and 8b the corresponding J values are 4.6 and 11 Hz and 4 and 12 Hz respectively, thus suggesting that the preferred conformation (as implicit in A or B) of 6 is to a large extent preserved in both isomeric epoxides. On the other hand, while 8a displays H-6 at 4.24 δ, 8b shows the same signal at 4.36 δ suggesting that in 8b the oxygen atom of the epoxide is in closer proximity (β-oriented) with H-6 than in 8a[9].

Analogously, the ^{1}H NMR spectrum of both 9a and that of 9b shows H-9 as a doublet of doublets with $J_{8a,9} = 4$ Hz and $J_{8b,9} = 12$ Hz. While the conformer implicit in A readily explains the relatively high chemical shift of H-6 (3.88 δ) in 9a (H-6 lies near the center of the exocyclic double bond at C-10), the conformer implicit in B (double bond at C-10 away from H-6 and the 3,4-β-epoxide) seems to fit the properties of 9b better. In this latter compound too, the oxygen of the epoxide is closer to H-6 and this is reflected in its relatively low chemical shift (4.26 δ). This change in conformation might be the main responsible for the observed difference in reactivity between 9a and 9b towards zinc (vide supra).

It is interesting to note that 2b displays its H-6 at an almost identical chemical shift (4.25 δ) as that of 9b from which it was derived. This coincidence suggests that both are conformationally related (closer to B). Further, 2a shows its H-6 at 4.06 δ (0.18 ppm at lower field than in 9a) indicating that it also exists in a conformation as defined in B in which the exocyclic double bond at C-10 away from H-6 does not cause any appreciable effect on this proton. Support for this conclusion comes from the observation that in tetrahydrodehydrocostus lactone (14), a compound lacking an exocyclic double bond at C-10, H-6 appears at 4.07 δ.[10] Thus for the anisotropic effect of that double bond to be felt by H-6, the molecule will have to be in (or close to) conformation as implicit in A (9a for example) only. It follows that in the absence of other contributing factors, the difference in chemical shift of H-6 between 2a and 2b may only be attributed to the presence, in the latter, of the 3,4-β-oriented epoxide.

Concluding, (-)-estafiatin has the absolute stereochemistry as depicted in 2a as previously suggested[4].

References and Notes

1. (a) Taken in part from the MSc. Theses of M. Garcia, NPPN-UFRJ, 1975; F.W.L. Machado, NPPN-UFRJ, 1977, and L. A. Maçaira, NPPN-UFRJ, 1978.

   (b) Part 7 in the series "Chemical Transformations of Abundant Natural Products". Part 6 is An. Acad. Brasil. Ciênc., 49, 563 (1977).

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3. J. Romo and F. Sanchez-Viesca, Tetrahedron, 19, 1285 (1963).

4. M.T. Edgar, A.E. Greene and P. Crabbé, J. Org. Chem., 44, 159 (1979).

5. All new compounds reported gave analytical and spectral data in complete agreement with the proposed structures.

6. It is of interest to note that the corresponding 9,10-α-epoxide derived from 1 gave, under similar conditions, a mixture of chlorohydrins containing ~55% of the product resulting from the attack of the Cl^- at C_9.

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9. A recent reference concerning long range deshielding of epoxides is L.A. Paquette, W. E. Fristed, C.A. Schuman, M. A. Beno, and G.G. Christoph., J. Am. Chem. Soc., 101, 4645 (1979).

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