Tetrahedron Letters No.18, pp. 2235-2240, 1968. Pergamon Press. Printed in Great Britain.

SESQUITERPENES, V. THE STEREOSPECIFIC SYNTHESIS OF PSEUDOGUAIANOLIDE SESQUITERPENES

J. B. Hendrickson, Camille Ganter, Douglas Dorman, and Helmut Link

Department of Chemistry, Brandeis University,
Waltham, Massachusetts 02154

(Received in USA 26 January 1968)

The pseudoguaianolides constitute a major family of sesquiterpenes, over thirty having been recorded to date. (1) They also afford a singular synthetic challenge in that most members (I) have six asymmetric centers, all grouped on a cycloheptane ring, with both cis- and trans-lactones being represented and C-5 and C-7 bearing identical configurations throughout the family. Furthermore, the study of epimerizations of these asymmetric centers on the cycloheptane ring can go far toward clarifying the subtleties of conformational analysis in seven-membered rings. (2) With these goals in mind we undertook the synthesis of some pseudoguaianolides from santonin, a previously synthesized natural sesquiterpene lactone which is of known absolute configuration and readily available in optically active form to obviate a final resolution of synthetic products.

The synthetic conception which we applied required rearrangement of the 4-methyl to C-5 and of the central bond from C-10 to C-1, both reactions to be applied on molecules with stereoelectronically favorable trans antiparallel orientation of migrating and leaving atoms. The first of these rearrangements is so favored in the structure (II) of santonin epoxide, (3) release of the 1,3-diaxial methyl strain assisting rearrangement of the 4-methyl group on acid-catalyzed opening of the epoxide from C-5. In fact solution of the epoxide in sulfuric acid for a half hour afforded the yellow diketone (IIIa) in 35% yield (m.p. 196-7°, λ_{max} 5.63, 5.77, 5.90, 6.19 μ and 259 mμ (log ε = 3.80), with methyl singlets at τ 8.57 and 8.63, a methyl doublet at 8.73 (J = 6.5), two vinyl proton doublets at 3.11 and 3.69 (J = 10.5), and a C-6 proton doublet at 6.02 (J = 11). Conversion of the diketone to the diazoketone (IIIb) was effected in 80% yield by the action of p-toluenesulfonylhydrazide (4) and triethylamine on the less hindered C-3 carbonyl. The orange diazoketone, m.p. ~ 140° (dec.) showed the expected spectral characteristics: λ_{max} = 4.80, 5.64, 6.07, 6.16 μ and 253, 324 mμ (log ε = 4.17, 3.70); NMR signals as before at 8.69, 8.79, 8.77 (J=6), 3.90, 4.91 (J=10), and 6.03 (J=10).

The unsaturated ketone characteristic of most pseudoguaianolides was created next by controlled reduction of IIIb with hydriodic acid, yielding IVa (≡Va) m.p. 113-113.5°, in 60% conversion; the structure is supported spectrally by these data: λ_{max} = 5.66, 5.97 μ, 229 mμ (log ε = 4.02) and NMR signals as tabulated below. Since the molecule is a conformationally rigid <u>cis</u>-decalin, it may be anticipated that introduction of a leaving group at C-1 for the subsequent rearrangement of the central bond will proceed from the convex face (5) affording an axial substituent (R_a) instead of the required <u>trans</u>-antiparallel R_e in stereostructure V of compounds IV. However, the unsaturated ketone activates epimerization of the C-1 proton via enolization and offers the opportunity of converting R_a to the more stable equatorial R_e position. In the event N-bromosuccinimide acted on IVa to provide in high overall yield a mixture containing 25% IVb (≡Vb) and 75% IVc (≡Vc) and epimerization with dilute sodium methoxide in methanol enriched the mixture to 75% IVb. Although these epimers were not chromotographically separable, pure samples of IVc (m.p. 176-177°) could be crystallized from the initial bromination product and pure IVb (m.p. 151-152°) obtained by the methanolysis of IVc described below, a reaction not affecting IVb, which could then be separated later. Both compounds exhibited IR and UV spectra akin to those of IVa, but differed significantly in the NMR in that each showed only a single proton at C-1, shifted downfield from the C-1 signals of IVa and coupled with the vinyl protons:

	H_1	H_2	H_3	H_6	CH_3:C_5,C_{10}	CH_3:C_{11}
IVa	τ 7.52dd (J=3,2.5) 7.76d (J=5.5)	3.22ddd (J=10.5,5.5, 2.5)	4.05dd (J=10,5.3)	6.00d (J=10)	8.67s,8.83s	8.77d (J=6.5)
IVb	4.89dd (J=2.2,2.6)	2.89 (J=10.5,2.2)	4.15dd (J=10.5,2.6)	6.00d (J=10)	8.65s,8.69s	8.79d (J=6)
IVc	5.45d (J=5.5)	3.10dd (J=10,5.5)	4.12d (J=10,	6.02d (J=10)	8.55s,8.46s	8.77d (J=6)

The couplings of C-1 proton to the C-2 proton are indicative of dihedral angles of approximately 90° in IVb and 30° in IVc, (6) consistent with equatorial bromine in IVb and axial in IVc as also implied by the equilibration experiments with methoxide (the 75:25 = IVb:IVc equilibrium mixture is obtainable from either isomer).

Attempts to rearrange these bromides with silver salts in alcohol or acetonitrile led in most cases to no reaction at all, but under the more vigorous conditions of $AgSO_4/H_2SO_4$ (room temperature, 3 hours) IVb was in fact converted (in 75% yield) to VI, m.p. 188-9°, while IVc was recovered largely unchanged and yielded no VI. The rearrangement product (VI) was characterized by these spectral data: λ_{max} 5.63, 5.87, 6.10, 6.25 μ, and 219 mμ (log ε = 3.95); NMR: 1H peaks for H-2, τ2.49dd (J=6.3); H-3, 3.90dd (J=6,1.5); H-6, 5.52d (J=915); methylene, 4.20s 4.48s; 3H peaks for C_5-CH_3, 8.60s; C_{11}-CH_3, 8.76d (J=6). The reluctance of IVb to rearrange may arise from the introduction of angle strain as the unsaturated ketone ring contracts to the more strained cyclopentenone; consistent with this interpretation is the fact that hydrogenation of VI yields first a dihydro-compound (m.p. 127.5-128°) retaining the exocyclic methylene (NMR = τ 4.15s, 4.53s) and exhibiting a saturated cyclopentanone (λ_{max} 5.76 μ). Two tetrahydro derivatives are formed on further hydrogenation.

At present the only known natural pseudoguaianolides without substitution at C-8 have a cis-lactone, being epimeric with VI at C-6. The cis-lactone series is also available synthetically since acidic methanolysis slowly but essentially quantitatively converts IVc to the cyclic ether VII, m.p. 91-92°, by internal displacement of the axial bromine; IVb is unaffected under these conditions. The spectral data for VII [λ_{max} 5.78, 5.88 μ: no absorption in the ultraviolet; NMR: 1H peaks for H-1, τ5.72s; H-2, 6.4m; H-3, 7.26d (J=4.5), 7.39d (J=6); C-6, 5.95d (J=3); 3H peaks for O-CH_3, 6.38s, 6.67s; C_5-CH_3 and C_{10}-CH_3, 8.88s, 9.22s; C_{11}-CH_3, 8.82d (J=5.5)] allow its formulation as does its conversion in hot aqueous trifluoroacetic acid to VIIIa, m.p. 177-178°, which is converted to an easily separable mixture of crystalline chlorides VIIIb, VIIIc, by thionyl chloride at reflux. These two chlorides are completely analogous to the bromides IVb and IVc in behavior and spectra except in having a different C-6 signal in the NMR (τ4.88d, J=4.5) as expected for the cis-lactone.

The typical conformational flexibility of cis-decalins is frozen in compounds IV (cf., V) by the fusion of the trans-lactone ring but is uninhibited in the cis-lactones VIII so that the rigid and favorable stereochemistry of IVb for rearrangement does not characterize VIII. Accordingly the reaction with $AgSO_4/H_2SO_4$ gives other products as well as a lower yield (10%) of rearrangement to the pseudoguaianolide (VI with cis-lactone, i.e., epimeric at C-6), spectrally comparable with VI. One of the interesting by-products produced in this reaction is the cis-lactone which is an epimer of santonin at both C-6 and C-10; this is also the product of treating VIIIa with sulfuric acid!

Since this synthesis was undertaken, the stereochemistry of most of the natural pseudoguaianolides has been determined. In every compound to date the ring junction is found to be trans (epimeric at C-1 with VI) and the most stable configuration, by equilibration of the cyclopentenone, to be cis, as in VI. (7) Methods of converting VI to the various natural terpenes are in progress as well as studies on the introduction of the common

C-8 oxygen function (I).

Acknowledgement. We wish to thank the National Institutes of Health (Grant GM 10714) for their generous support of this work, and to acknowledge generous gifts of natural pseudoguaianolides from Prof. Werner Herz and Dr. Romo de Vivar.

References

(1) F. Sorm and L. Dolejs, Guaianolides and Germacranolides, Hermann, Paris, 1965, pages 40-60.

(2) J. B. Hendrickson, Tetrahedron, **27**, 1387 (1963).

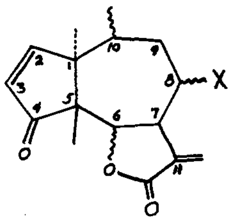
(3) J. B. Hendrickson and T. L. Bogard, J. Chem. Soc., 1962, 1678.

(4) M. P. Cava, R. L. Little, and D. R. Napier, J. Am. Chem. Soc., **80**, 2257 (1958).

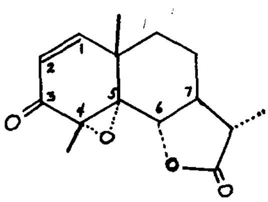
(5) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, Tetrahedron, **2**, 1 (1958).

(6) J. W. Emsley, J. Feeney, L. H. Sutcliffe, High Resolution Nuclear Mag-Resonance Spectroscopy, Pergamon Press, New York, 1966, page 678.

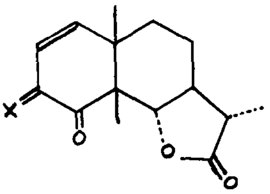
(7) A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan and W. Herz, Tetrahedron, **22**, 3279 (1966), and preceding papers.



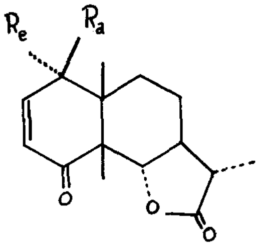
I (X=H or O)



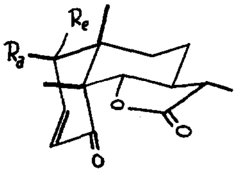
II



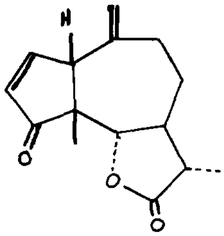
III a, X=O
b, $X=N_2$



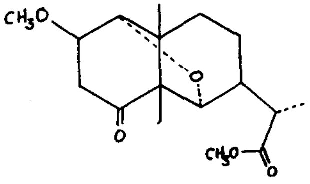
IV a, $R_e=R_a=H$
b, $R_e=Br$; $R_a=H$
c, $R_e=H$; $R_a=Br$



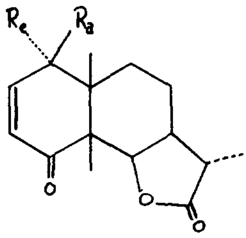
V a, $R_e=R_a=H$
b, $R_e=Br$; $R_a=H$
c, $R_e=H$; $R_a=Br$



VI



VII



VIII a, $R_e=OH$; $R_a=H$
b, $R_e=Cl$; $R_a=H$
c, $R_e=H$; $R_a=Cl$