filtered, and the filtrate was diluted with 15 mL of toluene and evaporated to dryness. The crude product was purified CH_2Cl_2/AcOEt (2:1): yield 37 mg (61%); DCI-MS, m/e 264 [M + H]$^+$; NMR (C_6D_6) δ 0.88 (1 H, br d), 1.15–1.65 (5 H, m), 1.55 (3 H, s), 3.12 (2 H, m), 3.40 (1 H, dddd), 3.52 (1 H, dt), 3.98 (1 H, dd), 4.65 (1 H, br s), 5.38 (1 H, s), 7.05–7.25 (3 H, m), 7.65 (2 H, m); $[\alpha]_d$ +32° (c 1, MeOH).

1 (10 mg) was derivatized to **1a** by procedure f and purified as described above: yield 9 mg (60%); 1 $[\alpha]_D$ +31.6°; other spectral data, identical with those of **13**.

Compound 3c. **3** (10 mg) was acylated by procedure a, acetonized by procedure b, deprotected by procedure c, and purified with hex/AcOEt (5:2): yield 7 mg of **3c**; CI-MS, m/e 319 [M + H]$^+$.

Compounds 3f and 3g. **3** (10 mg) was subjected to periodate oxidation by procedure d. The product obtained was dissolved in 1 mL of dry pyridine, and 6 mg of $PhB(OH)_2$ and molecular sieves type 4A were added. After 1 h molecular sieves were removed, and 20 mg of *p*-BrBzCl was added. After 2 h 0.5 mL of MeOH and 5 mL of heptane were added, and the reaction mixture was evaporated to dryness. The residue was dissolved in 5 mL of Et_2O and passed through a short column packed with basic Al_2O_3. The column was eluted sequentialy with 8 mL of Et_2O and 5 mL of MeOH, and the MeOH eluent was evaporated to dryness. The residue was purified by HPLC with CH_2Cl_2/AcOEt (3:1): yield 4 mg of **3f** and 0.1 mg of **3g** (estimated from UV); DCI-MS for **3f** and **3g**, m/e 575 (50%), 573 (100%), 571 (50%) [M + H]$^+$.

Compound 6c. **6** (10 mg) was acrylated by procedure a, acetonized by procedure b, deprotected by procedure c, and purified with hex/AcOEt (2:1): yield 6 mg; CI-MS, m/e 179 [M + H]$^+$.

Compound 6d. **6** (10 mg) was oxidized by procedure d, acylated by procedure e, and purified by HPLC with hex/AcOEt (10:1): yield 4 mg; DCI-MS, m/e 515 (50%), 513 (100%), 511 (50%) [M + H]$^+$.

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Relative Stabilities of the Desmotroposantonins

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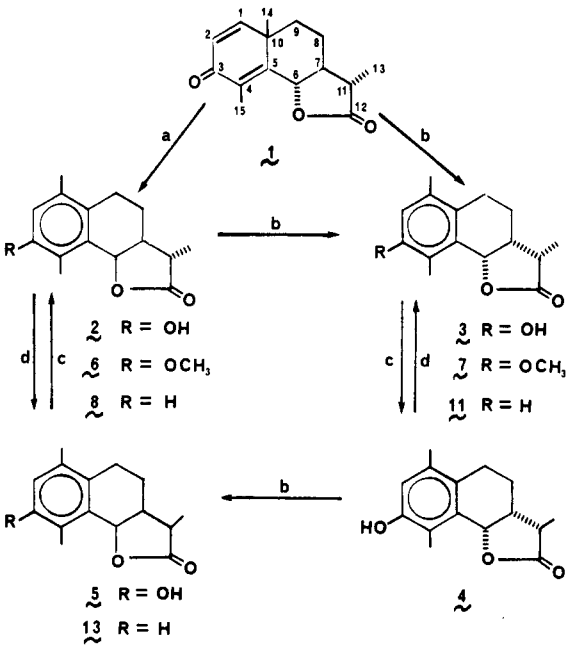
Equilibration of (−)-α-desmotroposantonin methyl ether (**6**), (+)-β-desmotroposantonin methyl ether (**7**), and isohyposantonin (**8**) with K_2CO_3 in xylene gives the same 56:44 mixture of isomers at C-11. Although acid-catalyzed isomerization of (−)-α-desmotroposantonin (**2**) affords (+)-β-desmotroposantonin (**3**) in good yield, the deoxy analogue of **2**, isohyposantonin (**8**), gives an approximately 1 to 1 mixture of **8** and the β-desmotroposantonin analogue (**11**) with acid **10** as the major product. These results indicate that the published data which indicate that the β-isomers are significantly more stable than their α-epimers are based on reactions in which equilibrium was not reached. NMR studies at 200 MHz show that the conformation of the lactone ring in the α- and β-isomers is not the same. A conformation is suggested for α-desmotroposantonin on the basis of the NMR data, and an explanation is offered for the stability relationships in the desmotroposantonin series.

The gross structure of the well-known and readily available sesquiterpene lactone α-santonin (**1**, no stereochemistry implied) was determined many years ago by Clemo, Haworth, and Walton.[1] Just over 30 years ago, in nearly simultaneous publications, Woodward and Corey presented reasonable arguments which strongly suggested that the stereochemistry of santonin is that depicted in **1** but with the configuration at C-11 reversed.[2] A few years later on the basis of crystallographic and degradative work the stereochemistry at C-11 was corrected and structure **1** was established for this historically important natural product.[3]

The incorrect stereochemical assignments were based on the unique cycle in which (−)-α-desmotroposantonin (**2**)[4] and (+)-β-DTS (**3**), dienone phenol rearrangement products of santonin, undergo further isomerizations under the conditions outlined in Scheme I (**2** to **5**).[5,6] Woodward and

Scheme I[a]



[a] (a) Ac_2O/H_2SO_4, 30 min, 90 °C, and then 10% aqueous NaOH/EtOH, 5 h, reflux; (b) 40% aqueous H_2SO_4, 12 h, 85 °C; (c) KOH, 1 h, 210 °C and then acidify; (d) K_2CO_3/xylene, 24 h, reflux.

Corey assumed that the vigorous acid treatment which affords the β-isomers is thermodynamically controlled and

(1) Clemo, G. R.; Haworth, R. D.; Walton, E. J. *J. Chem. Soc.* **1930**, 1110.

(2) (a) Woodward, R. B.; Yates, P. *Chem. Ind. (London)* **1954**, 1391. (b) Corey, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1044. (c) For a summarization of the arguments, see: Cocker, W.; McMurry, T. B. H. *Tetrahedron*, **1960**, *8*, 181.

(3) (a) Nakazaki, M.; Arakawa, H. *Proc. Chem. Soc.* **1962**, 151. (b) Asher, J. D. M.; Sim, G. A. *Ibid.* **1962**, 111. (c) Barton, D. H. R.; Miki, T.; Pinhey, J. T.; Wells, R. J. *Ibid.* **1962**, 112.

(4) The abbreviation DTS will be used to denote desmotroposantonin. The terms α and β refer to the relative stereochemistry at C-7 and C-11.

(5) Huang-Minlon (Huang-Minlon. *J. Am. Chem. Soc.* **1948**, 70, 611) summarizes these conversions in detail, and Barton (Barton, D. H. R. *J. Org. Chem.* **1950**, 15, 467) provides additional mechanistic rationalizations.

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affords the isomer in which C-13 does not eclipse C-8. This leads logically to the conclusion that (+)-β-DTS has structure **4** and (−)-α-DTS structure **5** and that santonin has a configuration at C-11 epimeric to that depicted in **1**.

On the basis of work from our laboratory, it was suggested that the apparent equilibration of (−)-α- (**2**) to (−)-β-DTS (**5**) with potassium carbonate in xylene was actually a kinetic isomerization caused by the extreme insolubility of β-DTS in hot xylene.[7] We found that equilibration of either α- or β-DTS with potassium *tert*-butoxide gave an 8.7 to 1 ratio of α- to β-isomer; however, heat of combustion data indicated that β-DTS is the more stable isomer.[8] Our work was subsequently criticized by Cocker[9] who succintly described the present state of this problem: "No reasons can be advanced at this stage for the greater stability of the β-desmotropo compounds."[9]

A key point in the Woodward–Corey conformational analysis was the assumption that the acid-catalyzed conversion of (−)-α-DTS (**2**) to (+)-β-DTS (**3**) indicated that the β-isomer was more stable. However, in the course of preparing (+)-β-DTS (**3**) by using a modification of Huang-Minlon's procedure,[10] we observed that nearly pure **3** precipitated from the hot reaction mixture. Purification gave **3** in 70% yield, accompanied by 7% of the α-isomer **2**. Although these results may be explained in terms of a thermodynamic isomerization they are equally consistent with the irreversible formation of the insoluble β-isomer.

Cocker's group carried out acid-catalyzed isomerizations on the methyl ethers of (−)-α-DTS (**6**) and (+)-β-DTS (**7**), presumably to avoid solubility problems,[9] but there is the added complication of possible ether cleavage on prolonged heating of **6** and **7** with strong acid. A suitable alternative substrate for studying these isomerizations is isohyposantonin (**8**), which differs from (−)-α-DTS only in the lack of the phenolic hydroxyl group.

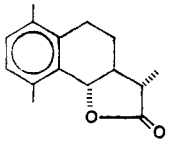
Isohyposantonin is formally the product of the dienol–benzene rearrangement of the doubly allylic alcohol obtained by reduction of santonin accompanied by inversion at C-6. This compound was obtained many years ago by basic hydrolysis of hyposantonin (**9**), followed by reacidification.[13] We have now developed an improved preparation of hyposantonin in which the key step is the reduction of santonin with 2.0–2.4 equiv of sodium borohydride at 0 °C in the presence of 1.5–2.4 equivalents of $CeCl_3 \cdot 7H_2O$.[13]

Reaction of isohyposantonin with sulfuric acid under the conditions used for the conversion of α- to β-DTS gives acid **10** as the major product. The neutral fraction is a mixture of lactone **8** and the β-DTS analogue **11** with isomer **8** always present to the extent of at least 50%.[14]

Table I. Potassium Carbonate Catalyzed Isomerizations[a]

compd	yield, %	product ratio (α/β)[b]
6	100	68/32
6	90	56/44
7	61	52/48
7	76	56/44
8	92	56/44
8[c]	90	78/32

[a] Isomerizations were carried out at reflux (140 °C) by using anhydrous K_2CO_3 in dry xylene for 72 h. [b] The product ratios were obtained by integration of the NMR signals due to H-7. [c] 24 h.



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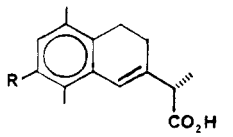


10 R = H
12 R = OH

The suggested mechanism for the acid-catalyzed rearrangement of (−)-α-DTS to the (+)-β-isomer proposes that acid **12** is an intermediate in the isomerization.[5] Supporting evidence was obtained when it was found that acid **12** and its methyl ether were converted by acid, although in poor yield, to mixtures of lactones which were apparently rich in the β-DTS isomers.[9] In order to obtain additional evidence concerning the course of this isomerization, (−)-α-DTS was treated with D_2SO_4–D_2O to give (+)-β-DTS, deuteriated at C-2 and C-7, as predicted by the suggested mechanism. However, isohyposantonin under the same conditions affords acid **10**, deuteriated not only at C-2 and C-3 but also at C-6. Lactones **8** and **11**, obtained in a 1:1 ratio, are deuteriated not only at C-2, C-3, and C-7 but also at C-6. These data indicate that β-DTS is formed irreversibly, presumably via acid **12**. The isomerization of isohyposantonin (**8**), however, appears to be an equilibrium process involving **8**, acid **10** and lactone **11**. The difference in behavior again may be attributed to the extreme insolubility of β-DTS.

A principal argument in support of the relative stability of the desmotroposantonins and one which we have criticized previously[7] is the isomerization of (−)-α-DTS (**2**) to the (−)-β-isomer (**5**) with potassium carbonate in xylene at reflux.[6] These experiments were repeated using as substrates (−)-α-DTS methyl ether (**6**), (+)-β-DTS methyl ether (**7**), and isohyposantonin (**8**), all of which are readily soluble in xylene. The results of these isomerizations are summarized in Table I. These data indicate that the equilibrium mixtures contain approximately equal amounts of the α- and β-isomers and *that α- and β-DTS are of approximately equal stability.*

Although the conclusion that β-DTS is more stable than the α-isomer appears to have had its origins in the insolubility of the β-isomers in common solvents, an explanation we presented some years ago,[7] the conformational factors responsible for the observed similar stability of the isomers are not immediately obvious.[15] The arguments presented

(6) Chopra, N. M.; Cocker, W.; Edward, J. T. *Chem. Ind. (London)* **1955**, 41.
(7) Huffman, J. W. *J. Org. Chem.* **1963**, *28*, 601.
(8) Cocker, W.; McMurry, T. B. H.; Frisch, M. A.; McAllister, T.; Mackle, H. *Tetrahedron Lett.* **1964**, 2233.
(9) Bolt, A. J. N.; Carson, M. S.; Cocker, W.; Hopkins, L. O.; McMurry, T. B. H.; Nisbet, M. A.; Shaw, S. J. *J. Chem. Soc. C* **1967**, 261. The product mixtures described in this paper were analyzed by product isolation and/or calculations based on specific rotations. Woodward (ref 2a) had previously pointed out that the conversion of β- to α-DTS by strong base probably occurs via the salts of hydroxy acids.
(10) Huang-Minlon; Lo, C. P.; Chu, J. J. Y. *J. Chin. Chem. Soc. (Peking)* **1943**, *10*, 126.
(11) The bulk of the early work on the chemistry of santonin and the desmotroposantonins was carried out by various Italian workers and has been summarized by: Simonsen, J.; Barton, D. H. R. *The Terpenes*; University: Cambridge, **1951**: Vol. III, pp 246–322.
(12) (a) Nakazaki (Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1387) reports 61% yield of impure lactone **9** from the zinc–sulfuric acid reduction of santonin oxime. (b) In our hands reduction of the oxime under similar conditions gave 33% yield of pure **9** (see ref 7).
(13) (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) Luche, J. L.; Gemal A. L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 60. The use of less $NaBH_4$ gives incomplete reduction, while more than 2.5 equiv gives evidence of much overreduction.
(14) The mixtures of lactones obtained from apparently identical runs contained 50–80% of **8**. Although lactone **11** was not isolated from the acid-catalyzed isomerizations, its presence is obvious from the NMR spectra of these mixtures. The absolute stereochemistry of this lactone and its enantiomer **13** are assigned by analogy with the β-DTS isomers prepared under similar conditions.

Table II. NMR Chemical Shifts and Coupling Constants for the Acetates of α-DTS (2) and β-DTS (5)[a]

H	compd 2	compd 5
2	6.86	6.89
6	5.58	5.33
7	2.4[b]	2.52
$J_{6,7}$	6.24	4.59
8β	1.75	1.30
8α	1.93	1.90
9β	2.75	2.91
9α	2.45	2.42
$J_{9_{gem}}$	17.26	17.11
$J_{8\alpha,9\beta}$	5.59	2.30
$J_{8\beta,9\beta}$	5.59	4.41
11	2.57	3.05
$J_{7,11}$	5.69	7.08
13	1.39	1.28
$J_{11,13}$	7.28	7.26
14	2.22	2.20[c]
15	2.22	2.23[c]
CH_3CO	2.33	2.33

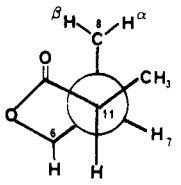
[a] All chemical shifts were determined at 200 MHz as $CDCl_3$ solutions and are reported in ppm relative to Me_4Si (δ). All coupling constants are in Hz. Decoupling experiments with irradiation at δ 1.37 (α-DTS) and 1.27 (β-DTS) were used in determining chemical shifts and coupling constants. [b] Multiplet, buried beneath other signals. [c] Values are interchangeable.

by Woodward and Corey appear to be sound and unoptimized MM2[16] data indicate that α-DTS should be at least 0.9 kcal/mol more stable than β-DTS.[17]

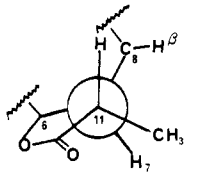
The 200-MHz NMR spectra of the acetates of (−)-α-DTS (**2**) and (−)-β-DTS (**5**), summarized in Table II,[18] indicate that these isomers must have somewhat different conformations. In particular, the 8β proton in **5** is quite shielded (δ 1.30) relative to that in the α-isomer (δ 1.75). Also, the vicinal coupling constants between the protons at C-6 and C-7 are significantly different for the isomeric lactones.

Examination of a Dreiding model of β-DTS constructed such that the bond angles agree with those calculated by MM2 from the X-ray coordinates[17] indicates that the only steric interaction of any apparent consequence is an enhanced gauche interaction between C-8 and C-13 (dihedral angle of 45°).

In addition, the conformation of the lactone ring is such that the 8β proton lies in the shielding cone of the lactonic carbonyl group as depicted in **14**. The geometry of α-DTS may be approximated from the NMR data summarized in Table II. For β-DTS the dihedral angle between H-6 and H-7 is 37.5°, corresponding to a coupling constant of 4.6 Hz leading to a value of J° in the Karplus relationship of 7.3. Using this value for J° and the coupling constants for the same protons in α-DTS the dihedral angle between H-6 and H-7 in **2** is approximately 23°.[19]



14



15

All reasonable conformations for α-DTS have a dihedral angle in excess of 90% between H-7 and H-11 (vs. 30° in the β-isomer) for which the conventional value of J° in the Karplus relationship is 9.5–16,[20] giving a dihedral angle between these protons of 130–140°. The conformation which best fits these calculated angles has a geometry for ring B similar to that determined by crystallography for β-DTS.[17] However, the conformation of the lactone ring has C-6 displaced from the plane made by C-7, C-11, C-12, and the oxygen atom, rather than C-7 as it is in β-DTS.[17] This conformation of the lactone ring in α-DTS removes the 8β proton from the shielding cone of the lactone carbonyl as depicted in **15** and accounts for the difference in chemical shift of this proton in the DTS isomers.

Although it is apparent that there are conformational differences in the lactone ring of the epimeric desmotroposantonins, these differences are not predicted by simple conformational considerations. Simply exchanging the position of the secondary methyl group and the hydrogen at C-11 of β-DTS as was done for the molecular mechanics calculations relieves a gauche butane interaction and appears to introduce no apparent new deleterious steric effect, as indicated by the calculated energy difference.[17] A possible explanation lies in the fact that in β-DTS, the lactone ring is in an envelope conformation with C-7 out of the plane, which places C-13 in the favored quasi-equatorial conformation (**14**).[17,21] If α-DTS has this conformation, C-13 would be quasi-axial. The actual conformation of the lactone ring in α-DTS appears to be an envelope in which C-13 nearly eclipses the hydrogen at C-7 (**15**), which may introduce sufficient strain to offset that relieved by the removal of the gauche interaction present in β-DTS.

Although the exact origin of the steric interactions which cause α-DTS to adopt a conformation different from that of the β-isomer is uncertain, the NMR data leave little doubt that the conformation of the lactone ring in these epimers is different, and the equilibration data indicate that they are of approximately equal stability.

Experimental Section

Melting points were determined with a Kofler hot stage and are uncorrected. NMR spectra were obtained on a JEOL FX-90Q, Hitachi-Perkin-Elmer Model R-24, or IBM-NR-200 spectrometer with deuteriochloroform as solvent. NMR data are reported in parts per million relative to tetramethylsilane (δ). Mass spectra were obtained at 70 eV by using a Hewlett-Packard 5985 mass

(15) The apparent absence of published experimental data makes it difficult to reconcile the equilibrium results we report with the heat of combustion data presented in ref 8.

(16) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127; (b) *QCPE 395*.

(17) The MM2 program is not parameterized for π-delocalized systems. The calculations were carried out with the atomic coordinates found by X-ray crystallography for 2-bromo-(−)-β-DTS by McPhail et al. (McPhail, A. T.; Rimmer, B.; Robertson, J. M.; Sim, G. A. *J. Chem. Soc. B* **1967**, 101), deleting the bromine and the hydroxyl and adding the requisite hydrogens to each carbon atom. For the α-isomer the same coordinates were used for all the carbons except the secondary methyl group, which was given the appropriate geometry by using one of the subroutines of the program. Neither geometry was optimized due to the limitations of the MM2 program. The structure for the α-isomer does not necessarily represent an energy minimum and consequently the calculated energy difference of 0.9 kcal/mol would be expected to increase with optimization. For another recent example in which MM2 does not provide accurate stability data, see: Peterson, P. E.; Leffew, R. L. B.; Jensen, B. L. *J. Org. Chem.* **1986**, *51*, 1948.

(18) The spectra were determined by using the acetates due to the insolubility of the phenols in $CDCl_3$. For convenience the data are reported for the acetate of **5**; however, the spectrum was actually determined by using the acetate of (+)-β-DTS (**3**).

(19) Jackman and Sternhell (Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969; pp 281–284) summarize the use of variable values of J° in the Karplus relationship.

(20) Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964; pp 49–51.

(21) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965; pp 200–206.

spectrometer. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

(−)-α-Desmotroposantonin Methyl Ether (6). The conversion of santonin (**1**) to the acetate of (−)-α-DTS, mp 152–154 °C (lit. mp 157 °C[10]) was carried out by the method of Huang-Minlon.[10] The NMR data for the acetate are summarized in Table II. Hydrolysis of the acetate gave (−)-α-DTS (**2**), mp 192–194 °C (lit. mp 195 °C[10]).

(−)-α-DTS methyl ether (**6**) was prepared by dissolving 0.783 g of (−)-α-DTS in a solution of 0.170 g of sodium in 30 mL of dry methanol at 0 °C. The solution was stirred at 0 °C for 10 min, and 2 mL of methyl iodide was added in one portion. The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to ambient temperature, and stirred for 18 h. The reaction mixture was concentrated at reduced pressure and 40 °C, the residue was taken up in CH_2Cl_2, the CH_2Cl_2 extracts were washed with water and dried, and the solvent was removed to give a viscous oil. Recrystallization from aqueous alcohol gave 0.399 g (48%) of **6**: mp 103–105 °C (lit. mp 111–112 °C[11]); NMR δ 1.36 (d, J = 6.5 Hz, 3 H), 2.24 (s, 6 H), 3.75 (s, 3 H), 5.58 (d, J = 6.3 Hz, 1 H), 6.74 (s, 1 H).[22]

(+)-β-Desmotroposantonin Methyl Ether (7). (−)-α-DTS (**2**) was converted to (+)-β-DTS (**3**) by the following modification of the method of Huang-Minlon.[10] To a stirred solution of 18 mL of water and 12 mL of concentrated H_2SO_4 was added 1.239 g (−)-α-DTS, and the suspension was stirred at 85–90 °C for 12 h. The resulting slurry was poured into water, and the precipitated solid was collected. Recrystallization from ethanol gave 0.864 g (70%) of (+)-β-DTS (**3**): mp 257–259 °C (lit. mp 260 °C[10]); MS, m/e (relative intensity) 247 (6), 246 (39), 187 (17), 174 (12), 173 (100), 172 (13), 158 (11), 145 (10). In another run, carried out on 0.519 g of (−)-α-DTS, concentration of the mother liquors gave 0.040 g of a mixture containing a 2:1 ratio of α/β-DTS in addition to 0.340 g (66%) of (+)-β-DTS. The acetate of (+)-β-DTS, mp 151–153 °C (lit. mp 154 °C[10]), was formed in the usual manner. The NMR data for the acetate are reported in Table II. MS, m/e (relative intensity) 289 (3), 288 (21), 247 (13), 246 (100), 202 (11), 187 (11), 173 (78), 172 (10).

The methyl ether **7** was prepared as described above for methyl ether **6**. From 0.864 g of (+)-β-DTS there was obtained 0.697 (76%) of **7**, mp 141–143 °C, after recrystallization from ethanol (lit. mp 152–153 °C[11]): NMR δ 1.23 (d, J = 7.3 Hz, 3 H), 2.24 (s, 3 H), 2.78 (s, 3 H), 3.80 (s, 3 H), 5.32 (d, J = 4.4 Hz, 1 H), 6.73 (s, 1 H).[22]

Reaction of 0.516 g of (−)-α-DTS (**2**) with a mixture of 6 mL of D_2SO_4 and 9 mL of D_2O under the conditions described above gave, after recrystallization from ethanol, 0.182 g (35%) of deuteriated (+)-β-DTS: mp 259–261 °C; MS, m/e (relative intensity) 2.51 (9), 250 (22), 249 (40), 248 (87), 189 (20), 178 (9), 177 (27), 176 (52), 175 (100), 174 (44).

The acetate of this material, mp 154–155 °C, was prepared in the usual manner: NMR (200 MHz) δ 1.28 (d, J = 7.26, 3 H), 1.30 (m, 1 H), 1.90 (m, 1 H), 2.20, 2.22 (s, 3 H each), 2.33 (s, 3 H), 2.42 (d of t, 1 H), 2.91 (m, 1 H), 3.05 (q, 1 H), 5.32 (s, 1 H); MS, m/e (relative intensity) 292 (5), 291 (8), 290 (18), 251 (10), 250 (23), 249 (44), 248 (100), 204 (11), 189 (11), 177 (17), 176 (33), 175 (66), 174 (26).

Hyposantonin (9). To a strired solution of 2.80 g (11.4 mmol) of santonin and 6.38 g (17.2 mmol) of $CeCl_3 \cdot 7H_2O$ (Aldrich, 99%) in 125 mL of methanol at 0 °C (ice bath) was added as rapidly as practical 0.911 g of $NaBH_4$.[23] The reaction mixture was stirred at 0 °C for 40 min, quenched with acetone, and allowed to warm to room temperature. After acidification, the reaction mixture was concentrated to a small volume (rotary evaporator), the crude product was taken up in CH_2Cl_2, and the solution was washed with water. After the mixture was dried, the solvent was removed at reduced pressure to give 2.53 g of a mixture of hyposantonin (**9**) (ca. 60%), **1** (ca. 20%), and small quantities of four other products, presumably the result of overreduction (total 20%, analysis by NMR). One recrystallization from ethanol gave 1.55 g (59%) of impure **9**, mp 135–150 °C, the NMR spectrum of which was identical with that of pure **9**. A second recrystallization of a small quantity of this material from ethanol gave white crystals, mp 151–153 °C, undepressed as an admixture with a sample prepared from santonin oxime:[7] NMR δ 1.25 (d, J = 6 Hz, 3 H), 2.15, 2.42 (s, 3 H each), 4.97 (d, J = 9 Hz, 1 H), 6.92 (s, 2 H).

Isohyposantonin (8). A solution of 1.55 g of once-recrystallized **9** in a mixture of 40 mL of ethanol and 80 mL of 10% aqueous KOH was heated at reflux for 2.5 h. The solution was cooled, concentrated in vacuo to approximately one-half its volume, cooled, and extracted with two portions of ether. After filtering through Celite,[24] the solution was acidified with concentrated HCl and the solid product collected. Recrystallization from ethanol gave 0.90 g (58%, 35% based on santonin) of white crystals, mp 165–167 °C, undepressed on mixing with a sample prepared previously:[7] NMR ($CDCl_3$) δ 1.35 (d, J = 6 Hz, 3 H), 2.18, 2.38 (s, 3 H each), 5.55 (d, J = 6 Hz, 1 H), 7.01 (s, 2 H); MS, m/e (relative intensity) 231 (5), 230 (28), 171 (14), 158 (13), 157 (100), 156 (17), 142 (16), 141 (15).

When this procedure was carried out with the crude product from the reduction of 2.69 g of santonin there was obtained 0.877 g (35%) of lactone **8** as pale tan crystals, mp 163–165 °C.

Reaction of Isohyposantonin with Acid. Treatment of 0.255 g of lactone **8** with H_2SO_4 as described above for the preparation of (+)-β-DTS but with isolation of the products using CH_2Cl_2 and separation into neutral and acidic fractions with 10% aqueous NaOH gave 0.076 g (30%) of neutral material, the analysis of which by NMR showed that it consisted of 80% of isohyposantonin and 20% of lactone **11**, the enantiomer of which is characterized below. The acid fraction (0.132 g, 52%) on recrystallization from aqueous ethanol gave **10**: mp 114–116 °C; NMR δ 1.36 (d, J = 6 Hz, 3 H), 2.16, 2.24 (s, 3 H each), 6.47 (br s, 1 H), 6.76 (s, 2 H); MS, m/e (relative intensity) 231 (7), 230 (44), 186 (11), 185 (74), 170 (14), 169 (14), 1157 (100), 156 (42).

Reaction of 0.255 g of **8** with a mixture of 3 mL of D_2SO_4 and 4.5 mL of D_2O gave 0.066 g (26%) of an approximately 1:1 mixture of lactones **8** and **11** in which the NMR signals at δ 5.41 (H-7 of **13**), 5.55 (H-7 of **8**), and 7.01 (Ar H) were greatly reduced in intensity. The acid fraction afforded 0.74 g (29%) of **10**, in which the NMR signals at δ 6.47 (H-6) and 6.76 (Ar H) were absent.

Equilibrations. In a typical equilibrium, 0.231 g of isohyposantonin (**8**) in 15 mL of dry xylene was stirred at reflux for 72 h with 0.669 g of K_2CO_3, which had been stored at 120 °C for several days and removed from the oven immediately before use. The hot reaction mixture was filtered and the solvent removed at reduced pressure to give 0.213 g (92%) of a pale yellow oil, the NMR spectrum of which indicated the presence of only lactones **8** and **13** in a ratio of 56 to 44. Two recrystallizations from ethanol gave 0.066 g of isohyposantonin (**8**), mp 162–166 °C, identical with the material described above. The mother liquors were concentrated and diluted with water to give 0.035 g of lactone **13**, mp 108–118 °C.[25] Recrystallization from aqueous ethanol gave the analytical sample: mp 110–113 °C; NMR δ 1.26 (d, J = 7 Hz, 3 H), 2.21, 2.41 (s, 3 H each), 5.41 (d, J = 4.5 Hz, 1 H), 7.00 (s, 2 H); MS, m/e (relative intensity) 231 (4), 230 (27), 171 (20), 158 (14), 157 (100), 156 (22), 143 (12), 142 (19), 141 (19). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.38; H, 7.94. The results of the equilibrations are summarized in Table I.

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(22) Although both methyl ethers melt somewhat lower than reported previously, the NMR spectra of each showed no significant impurities. The melting points did not increase on further recrystallization and/or drying in vacuo.

(23) There is considerable foaming during the addition, which is carried out over a period of 1–2 min.

(24) Filtration through Celite is necessary to remove suspended material which coprecipitates with the product.

(25) This material is contaminated with approximately 10% of lactone **8**, which is much less soluble in ethanol. The mixture of lactones **8** and **13** is homogeneous to TLC on silica gel using several solvent systems. It should be noted that in the isohyposantonin series the solubility behavior of the isomers is the reverse of that in the desmotroposantonins.