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# Preparation, Decarboxylation and Absolute Configuration of (+)-11α-Carboxy- and (+)-11β-Carboxy-3α,4β,5α,6βH-hexahydrosantonin, and (−)-11β-Carboxysantonin

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A simple and stereoselective preparation of (−)-11β-carboxysantonin (**8a**) was achieved by carboxylation of *l*-α-santonin (**5b**), based on the non-stereoselective two-step method described earlier. (+)-11β-Carboxy- (**3a**) and (+)-11α-carboxy-3α,4β,5α,6βH-hexahydrosantonin (**3b**) were prepared in a ratio of 3: 1 by alkoxycarbonylation of 3α,4β,5α,6β,11βH-hexahydrosantonin (HHS) (**1a**), followed by hydrolysis.

The absolute configurations at C-11 in the three optically active 11-carboxysantonins have now been confirmed on the basis of the stereochemistry of the fourth new stereoisomer, (−)-11β-carboxysantonin (**8a**). The complete structure of **8a** was established by its transformation to (+)-11β-carboxy-4β,5α,6βH-tetrahydrosantonin (**7a**), correlating with **3a**. The proton magnetic resonance (PMR) signals of 6β-hydrogens in 11β-carboxy- or 11β-methoxycarbonyl-HHS (**2a**—**4a**) are anisotropically shifted further downfield compared to those in the 11α-oriented epimers (**2b**—**4b**). A similar result was obtained for the pairs of epimers in the 4β,5α,6β,11βH-tetrahydrosantonin (THS) series (**6a**, **7a** and **6b**, **7b**).

The stereospecific decarboxylation of the 11β- and 11α-carboxylactone derivatives (**3a**, **7a**, **8a**, and **3b**, **7b**, **8b**) afforded the thermodynamically more stable 11α-methyl lactone analogs (**1a**, **5a**, **5b**), and not the 11β-methyl epimers (**1c**, **5c**, **5d**). The rate of decarboxylation of the former lactone acids was faster than that of the latter, supporting the foregoing assignments, based on spectral data, for the configurations of the 11β- and 11α-carboxyl groups.

**Keywords**——(−)-11β-carboxysantonin; (+)-11β-carboxysantonin; (−)-11α-carboxysantonin; (+)-11α-carboxysantonin; (±)-11β-carboxysantonin; (±)-11α-carboxysantonin; (+)-11β-carboxy-3α,4β,5αH-hexahydrosantonin; (+)-11α-carboxy-3α,4β,5αH-hexahydrosantonin; stereoselective preparation; stereospecific decarboxylation

Our preceding paper[2a,2b,2c] reported a new synthetic pathway to α-methyl-$\Delta^{\alpha,\beta}$-butenolides from simple α-methyl-γ-butyrolactones by sequential carboxylation–bromination–dehydrobromination.[2a,2b] With a view to its extention to various kinds of naturally occurring lactones, another new approach has recently been developed in our laboratory for the regiospecific preparation of α-methyl-$\Delta^{\alpha,\beta}$-butenolides and α-methylene-γ-butyrolactones by the electrolysis of α-carboxy-α-methylbutanolides and by the oxidation of α-dimethylamino-α-methyl-butanolides in a fused lactone system such as that of santanolide.[2c]

The present paper describes a study on the alkoxycarbonylation of 3α,4β,5α,6β,11βH-hexahydrosantonin (HHS) (**1a**) and the stereoselective carboxylation of *l*-α-santonin (**5b**) as well as stereospecific decarboxylation of the lactone acids thus obtained by the introduction of a carboxyl group at the α-position of the starting α-methylbutanolides, *i.e.*, at the C-11 position of santanolides. The absolute configurations of three of the four optically active isomers of *dl*-11β- and *dl*-11α-carboxy-6α-hydroxy-3-keto-eudesm-1,4-dien-6,12-olide [(±)-**8a**

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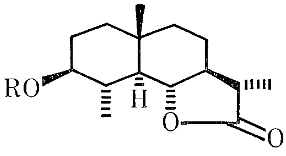
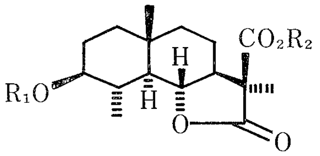
[2] This paper constitutes part IV of a series entitled "Studies on New Synthetic Pathways to $\Delta^{\alpha,\beta}$-Butenolides from α-Methylbutanolides." *a*) Part I: S. Inayama and T. Kawamata, *Chem. Pharm. Bull.*, **21**, 461 (1973); *b*) Part II: T. Kawamata, S. Inayama, and K. Sata, *ibid.* **28**, 277 (1980); *c*) Part III: S. Ianayama, T. Kawamata, and N. Shimizu, *ibid.* **28**, 282 (1980).

and ($\pm$)-**8b**] reported by Abe *et al.*3) have been confirmed by the correlation of the fourth isomer ($-$)-11$\beta$-carboxysantonin (**8a**) obtained from **5b** with its tetrahydro derivative (**7a**) prepared from **1a** by an independent route, as will be described later.

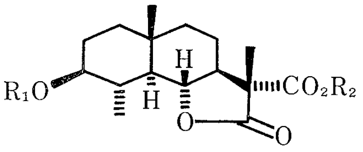
Methoxycarbonylation not at the C-11 position of **1a**, but at the C-3 hydroxyl group was observed when dimethyl carbonate and sodium hydride were used in benzene or tetrahydrofuran (THF). This might lead to the desired introduction of a methoxycarbonyl group in the presence of hexamethylphosphoramide (HMPA), as described in our previous paper.2a) In practice, refluxing the enolate of **1a** in dimethyl carbonate containing HMPA (25%) afforded an epimeric mixture of 11$\beta$- (**2a**) and 11$\alpha$-methoxycarbonyllactone cathylate (**2b**), whose proton nuclear magnetic resonance (PMR) spectrum showed two tertiary methyl singlets at 1.46 and 1.38 ppm, with disappearance of the secondary methyl doublet at 1.19 in **1a**. This indicates that the methoxycarbonyl group was introduced into the desired $\alpha$-position of the lactone-carbonyl with 11$\beta$ and 11$\alpha$ configuration, as depicted in formulae **2a** and **2b**, respectively. The ratio of the epimers was estimated to be approximately 3:1 by integration of the PMR signals of the C-11 methyl groups, but an attempt to separate each isomer failed at this stage. Treatment of the reaction product with concentrated hydrochloric acid in dioxane (2:1) afforded, in moderate yield, a mixture of the corresponding



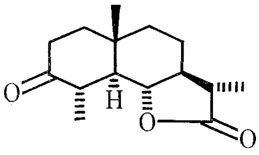
**1a**: R=H
**1b**: R=$COOCH_3$
**1c**: **1a** (11$\alpha$H)
**1d**: **1a** (3$\beta$H)



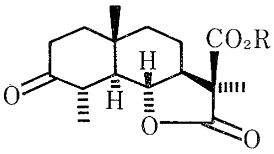
**2a**: $R_1$=$COOCH_3$, $R_2$=$CH_3$
**3a**: $R_1$=$R_2$=H
**4a**: $R_1$=H, $R_2$=$CH_3$



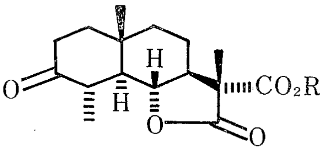
**2b**: $R_1$=$COOCH_3$, $R_2$=$CH_3$
**3b**: $R_1$=$R_2$=H
**4b**: $R_1$=H, $R_2$=$CH_3$



**5a**
**5b**: **5a** ($\Delta^{1,4}$)
**5c**: **5a** (11$\alpha$H)
**5d**: **5b** (11$\alpha$H)



**6a**: R=$CH_3$
**7a**: R=H
**8a**: **7a** ($\Delta^{1,4}$)



**6b**: R=$CH_3$
**7b**: R=H
**8b**: **7b** ($\Delta^{1,4}$)

Chart 1

TABLE I. PMR Chemical Shifts of 6$\beta$-Hydrogens in 11-Substituted Santan-6$\alpha$,12-olides

| Compound No. (Group) | Chemical shifts (in $CDCl_3$) | | |
|---|---|---|---|
| | a-Series (11$\beta$) | b-Series (11a) | $\Delta$ |
| 2 (COOMe) | 4.23 | 4.04 | 0.19 |
| 3 (COOH) | 4.74a)<br>(0.0%)b) | 4.15a)<br>(8.3%)c) | 0.59 |
| 4 (COOMe) | 4.24 | 4.02 | 0.22 |
| 6 (COOMe) | 4.43 | 4.08 | 0.35 |
| 7 (COOH) | 4.42 | 4.10 | 0.32 |
| 8 (COOH) | 5.20 | — | — |

*a*) in $C_5D_5N$, *b*) NOE (6$\beta$H/11$\alpha$Me), *c*) NOE (6$\beta$H/11$\beta$Me).

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3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).

carboxylactones together with the decarboxylation product (**1a**). Careful recrystallization from methanol provided the major lactone acid (**3a**) as plates, mp 213—215° (dec.). Repeated recrystallization of the crystalline powder obtained from the mother liquor gave the other acid (**3b**) as needles, mp 249—250° (dec.). The ratio of the acids (3:1) thus obtained was consistent with that estimated from the PMR spectrum of the original ester mixture.

The stereochemistry of the lactone acids (**3a** and **3b**) was confirmed on the basis of a detailed examination of the corresponding methyl esters (**4a**, mp 194—196.5°, and **4b**, mp 172—174°) which were readily obtained by reaction of each acid with diazomethane. The PMR signal of the C-6 ether proton of **4a** appeared at 4.24 ppm, whereas the signal of the epimer (**4b**) was at somewhat higher field, at 4.02 ppm. Similarly, the signals of 11$\beta$-methoxycarbonyllactones (**2a**, **4a**, and **6a**) and 11$\beta$-carboxylactones (**3a** and **7a**) all appear at lower field than those of the corresponding 11$\alpha$-epimers (**2b**, **4b**, **6b**, **3b**, and **7b**) (see Table I). These spectral data suggest that the electron-attracting substituent at C-11 in the a-series of lactone derivatives is $\beta$-oriented, in *cis* relationship to the C-6$\beta$ proton. In contrast, that of the epimeric b-series is $\alpha$-oriented in a *trans* relationship to the C-6 hydrogen, because the anisotropic effect on this proton in the a-series is stronger than that in the b-series. This was confirmed by determination of the nuclear Overhauser effect (NOE) between the C-6 hydrogen and C-11 methyl group; NOE enhancement was 8.3% in **3b** but was absent in **3a**. In addition, **3a** showed positive plain curves of both optical rotatory dispersion (ORD)[4] and circular dichroism (CD),[5] while **3b** exhibited a strong negative Cotton effect in both ORD and CD. These spectroscopic data, being in accordance with the prediction from the lactone sector rule,[4] also support the conclusion that the configuration of the C-11 carboxyl group is $\beta$ and $\alpha$, respectively, in **3a** and **3b**. Each hydroxylactone acid (**3a** and **4b**) was converted *via* the ketolactone acid (**7a** and **7b**) to the ketolactone ester (**6a** and **6b**) by Jones oxidation followed by esterification as before. In order to find an alternative method for the direct introduction of a carboxyl group at the C-11 position of *l*-$\alpha$-santonin (**5b**), a solution of **5b** in tetrahydrofuran was treated with gaseous carbon dioxide in the presence of lithium diisopropylamide[6] (LDA). The sole product, obtained in high yield, was found to be (—)-11$\beta$-carboxysantonin (**8a**) as will be described below. A solution of **8a** in methanol was hydrogenated in the presence of 5% palladium on charcoal with a drop of concentrated hydrochloric acid. Recrystallization of the product gave (+)-11$\beta$-carboxy-4$\beta$,5$\alpha$,6$\beta$H-tetrahydrosantonin[7] (**7a**), which had also been derived from **1a** through the well-defined pathway mentioned above. Thus, the absolute structures of the other three optically active stereoisomers of 11-carboxysantonin can be assigned on the basis of the following considerations.

Abe *et al.*[3] reported that the two stereoisomers [mp 210° (dec.) (A) and mp 186° (B)] of synthetic 11-carboxysantonin could be separated by fractional recrystallization from aqueous methanol. The insoluble brucine salt (mp 134—138°), obtained when the former racemate (A) was treated with brucine, yielded an optically active 11-carboxysantonin [(—)-Al], mp 213° (dec.), $[\alpha]^{18}_{D}$ —75.1°. Decarboxylation of (—)-Al was found to afford pure *l*-$\alpha$-santonin (**5b**). Furthermore, the less soluble quinine salt (mp 170°) obtained from A on treatment with quinine reverted to a second optically active lactone acid [(+)-A2], mp 200°

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4) J.P. Jennings, W. Kleyne, and P.M. Scopes, *J. Chem. Soc.*, **1965**, 7211; W. Kleyne, P.M. Scopes, R.C. Sheppard, and S. Turner, *ibid.*, **1968**, 1954.

5) A.F. Beecham, *Tetrahedron Lett.*, **1968**, 2355, 3591.

6) P.A. Grieco and K. Hiroi, *J. Chem. Soc. Chem. Commun.*, **1973**, 500.

7) The other component of the hydrogenation products is presumably 11$\beta$-carboxy-4$\alpha$,5$\beta$,6$\beta$H-tetrahydrosantonin, by analogy with the hydrogenation of *l*-$\alpha$-santonin (**5b**) under similar conditions, which gave the 4$\beta$,5$\alpha$,6$\beta$H-tetrahydro derivative ("$\alpha$"-THS, **5a**) as the major product together with the 4$\alpha$,5$\beta$,6$\beta$H-tetrahydro isomer ("$\gamma$"-THS) as a minor one.[8]

8) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955); cf. B. Riniker, Ph. D. Thesis, E.T.H., Zürich (1955).

(dec.), $[\alpha]_D^{20}$ +140.7°, yielding exclusively *d*-$\alpha$-santonin [(+)-**5b**] on decarboxylation. On the other hand, the quinine salt (mp 182°) prepared from the latter racemate (B) led to a third optically active 11-carboxysantonin [(+)-B1], mp 213° (dec.), $[\alpha]_D^{18}$ +75.4°, giving *d*-$\alpha$-santonin as above.

However, the stereochemistry of these three lactone acids has so far been obscure, though the absolute structure of the new dienone lactone acid (**8a**) [mp 207—208° (dec.), $[\alpha]_D^{24}$ −138.0°] has been independently defined as mentioned above.[9] Decarboxylation of **8a** provided, in a stereospecific manner, the thermodynamically more stable *l*-$\alpha$-santonin[10] (**5b**). Thus, this isomer (**8a**) must be the fourth optically active lactone acid [(−)-B2], since its specific rotation (−138°) is identical within experimental error with that (+140°) of the second isomer [(+)-A2] except in sign, even though its melting point (207—208°, dec.) is somewhat higher than that (200°, dec.) of (+)-A2.

On the basis of the absolute configuration of **8a** established as above, the stereochemistry at the C-11 position in the foregoing three isomers could be established. Both the new lactone acid (**8a**) [(−)-B2], prepared by the stereoselective carboxylation of *l*-$\alpha$-santonin (**5b**), and the first isomer (**8b**) [(−)-A1], obtained by optical resolution of the brucine salt of one of the epimeric 11-carboxysantonins [mp 210° (dec.) (A)], afforded **5b** on decarboxylation. Since all the configurations in these isomers except that at C-11 are identical, **8a** and **8b** must be a pair of diastereomers at C-11. Similarly, both the second lactone acid [(+)-**8a**] [(+)-A2] obtained by resolution of the quinine salt of the same epimer, and the third one [(+)-**8b**][(+)-B1] obtained by resolution of the quinine salt of the other epimeric 11-carboxysantonin [mp 186° (B)] provided *d*-$\alpha$-santonin [(+)-**5b**] on decarboxylation. (+)-**8a** and (+)-**8b** are therefore the other pair of diastereomers at C-11. On the other hand, since (+)-**8a** [(+)-A2] has identical physical constants (mp and $[\alpha]_D$), except for the opposite sign of rotation, with **8a**, compound (+)-A2 is clearly the enantiomer of **8a**. By the same token, **8b** [(−)-A1] and (+)-**8b** [(+)-B1] must be in enantiomeric relation based on their physical constants.

Careful examination of the decarboxylation reaction of 11-carboxy-HHS (**3a** and **3b**) mentioned above indicated that both acids stereoselectively afforded, in reasonable yields, the same thermodynamically more stable isomer (**1a**) having an $\alpha$-oriented methyl group at C-11, and not the stable $\beta$-methyl epimer (**1c**).[10,11] The product in each case was identical, in terms of mixed melting point, rotation and infrared (IR) and PMR spectra, with an authentic sample of **1a**. These results are in agreement with the finding that the dienone lactone acids (**8a** and **8b**) both afforded, on decarboxylation, *l*-$\alpha$-santonin (**5b**) with the more stable $\alpha$-oriented C-11 methyl group.[10,11] The similar tetrahydro derivatives (**7a** and **7b**) were decarboxylated to $\alpha$-tetrahydro-*l*-$\alpha$-santonin (THS) (**5a**), having an 11$\alpha$-methyl group;[8] this is more stable than the 11$\beta$-methyl epimer, *i.e.*, $\alpha$-tetrahydro-*l*-$\beta$-santonin[11] (11-epi-THS) (**5c**). It is of interest to note that the decarboxylation of **3a** proceeds more rapidly (1.4 min) than that of **3b** (3.2 min). The rates of decarboxylation of **7a** and **7b** were almost equal to those of **3a** and **3b**, respectively. The apparent difference in these reaction rates may be due to steric assistance due to the *trans* 1,3-diaxial interaction between the $\beta$-carboxy group at C-11 and $\beta$-hydrogens at C-6 and C-8 in 11$\beta$-carboxy analogs such as **3a**, **7a**, and **8a**, when compared with the corresponding 11$\alpha$-carboxy epimers such as **3b**, **7b**, and **8b**. These data also support the foregoing assignment of the stereochemistry at C-11 in the two series of lactone acids.

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[9] Since authentic samples of the three known optical isomers[3] are unfortunately not available at present, direct comparison of **8a** has been impossible.

[10] W. Cocker and T.B.H. McMurry, *J. Chem. Soc.*, **1955**, 4430.

[11] 4$\beta$,5$\alpha$,6$\beta$,11$\alpha$H-6$\alpha$-hydroxy-eudesman-6,12-olide (3-deoxy-11-epi-HHS) was converted to its 11$\beta$H epimer (3-deoxy-HHS) by treatment with sodium methoxide. M. Yanagita and H. Ogura, *J. Org. Chem.*, 23, 1268 (1958).

## Experimental

The melting points were determined with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G3 instrument. PMR spectra (60 and 100 MHz) were taken on Hitachi R-22 and JEOL JMN MH-100 spectrometers in $CDCl_3$ unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants are given in ppm and Hz, respectively, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and c=complex. Optical rotations were measured on a Jasco DIP-180 automatic polarimeter. Thin-layer chromatography (TLC) was performed on silica gel G (Merck) plates with AcOEt–benzene (1:4). Mass spectra (MS) were measured on a Hitachi RMS-4 spectrometer. Gas–liquid chromatography (GLC) was conducted with a Shimadzu GC-5A (FID) gas chromatograph, using a glass column ($0.4\phi \times 50$ cm) of 1.5% OV-17 on Chromosorb W (80—100 mesh) with a column temperature of 250° and injection temperature of 290°. $t_R$ refers to the retention time in GLC.

**3α,4β,5αH- and 3β,4β,5αH-Hexahydro-*l*-α-santonin (1a and 1d)**——A solution of $NaBH_4$ (1.5 g) in $H_2O$ (7.5 ml) was added slowly to a solution of 4β,5αH-tetrahydro-*l*-α-santonin (THS) (**5a**) (7.35 g) in MeOH (200 ml) under ice-cooling with stirring over a period of 3 hr. The solution was acidified with 10% HCl, concentrated under reduced pressure, and extracted with benzene containing a small amount of $CHCl_3$. The organic layer was washed with satd. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave, in almost quantitative yield, a crystalline residue, which consisted of **1a** ($t_R$ 0.8 min) and **1d** ($t_R$ 0.6 min) in a 3:1 ratio as determined by GLC. Recrystallization from benzene and petr. ether gave 3α,4β,5α,6β,11βH-hexahydrosantonin (HHS) (**1a**) as crystals (6 g, 82%), mp 171—173° [mp 171—172°,[12a] mp 168—169°[12b]], $[\alpha]_D^{31}$ +51.5° ($c$=1.06, $CHCl_3$), $[\alpha]_D^{15}$ +50.7° ($c$=0.56, $CHCl_3$[12a]). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3525, 1756. GLC: $t_R$ 0.8 min. PMR $\delta$: 0.99 (3H, s, $C_{10}$–C$\underline{H}_3$), 1.19 (6H, d, $J$=7.0, $C_4$–C$\underline{H}_3$+$C_{11}$–αC$\underline{H}_3$), 3.12 (1H, br. t, $J$=9.5, $C_3$–$\underline{H}$), 3.85 (1H, br. t, $J$=9.0, $C_6$–β$\underline{H}$).[13] Concentration of the mother liquor afforded other crystals, which were recrystallized several times from benzene–petr. ether to give 3-epi-HHS (**1d**) as prisms (1 g, 13%), mp 143—145° [mp 142—143°[12a]]; this material was found to be an epimeric mixture of **1a** and **1d** by GLC [$t_R$ 0.79 and 0.6 min (1:2)].[14]

**Cathylate of 3α,4β,5αH-Hexahydro-*l*-α-santonin (1b)**——NaH (0.3 g), used after washing the oil disperison twice with dry benzene, was added to a solution of **1a** (0.8 g) in $(MeO)_2CO$ (20 ml). After refluxing for 4 hr, the reaction mixture was poured into ice-cooled HCl and extracted with benzene. The extract was washed with satd. NaCl and dried over $MgSO_4$. Concentration of the solvent gave the cathylate (**1b**), mp 164—166.5°. $[\alpha]_D^{32}$ +555.0° ($c$=1.0, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 66.14; H, 8.95. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1784, 1748, 1764, 1742 (sh.), 1268. PMR $\delta$: 1.00 (3H, s, $C_{10}$–C$\underline{H}_3$), 1.12 (3H, d, $J$=6, $C_4$–C$\underline{H}_3$), 1.20 (3H, d, $J$=6, $C_{11}$–αC$\underline{H}_3$), 3.79 (3H, s, COOC$\underline{H}_3$), 4.19 (2H, m, $C_3$–$\underline{H}$+$C_6$–β$\underline{H}$).

**Hydrolysis of 1b**——A solution of **1b** (100 mg) in 5% KOH–MeOH (4 ml) was stirred overnight at room temperature. The reaction mixture was acidified with conc. HCl under ice cooling and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with satd. NaCl and dried over $MgSO_4$. White crystals (mp 169—171°, 64 mg, 80%) obtained upon removal of the solvent were identical with those of HHS (**1a**).

**(+)-11β-Carboxy- and (+)-11α-Carboxy-3α,4β,5α,6βH-hexahydrosantonin (3a and 3b)**——A mixture of $(MeO)_2CO$ (8 ml) and NaH (0.426 g) was added to a stirred solution of **1a** (0.746 g) in HMPA (8 ml). The mixture was heated with stirring in an oil bath at 120° for 4 hr. The reaction mixture was poured into ice-water, and the solution was extracted with benzene. The organic layer was washed with 10% HCl, then satd. NaCl, and dried over $MgSO_4$. Removal of the solvent at reduced pressure gave 1.023 g (93%) of a semisolid [IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1785, 1746], which was found to be a mixture of the cathylates of 11β- and 11α-methoxycarbonyl lactone (**2a** and **2b**) (3:1, as estimated by PMR).

Conc. HCl (50 ml) was added to a solution of this semisolid (4.517 g) in dioxane (25 ml), and the mixture was refluxed in an oil bath at 140° for 4 hr. Removal of the solvent gave a crystalline residue, which was dissolved in $CHCl_3$ and extracted with 5% $Na_2CO_3$. The aqueous layer was acidified with cold HCl, and the crystalline precipitate was collected. The mother liquor was extracted with $CHCl_3$, and the organic layer was washed with satd. NaCl, dried over $MgSO_4$, and concentrated to give additional crystals. The combined crystals (2.142 g, 60.8%) were recrystallized from MeOH to give 11β-carboxy-HHS (**3a**) (0.778 g, 22.4%), mp 207—210°. Further recrystallization afforded an analytical sample of **3a** as white prisms, mp 213—215° (dec.), $[\alpha]_D^{32}$ +2.4° ($c$=1.6, pyridine); $[\alpha]_D^{18}$ +69.7° ($c$=1.0, MeOH). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.89; H, 8.16. Found: C, 64.42; H, 8.53. CD, positive plain curve ($c$=0.24, MeOH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3394, 3000—

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12) *a*) W. Cocker and T.B.H. McMurry, *J. Chem. Soc.*, **1956**, 4549; *b*) H. Ogura, *J. Org. Chem.*, **25**, 679 (1960).

13) The prefix α or β, representing the configuration of a hydrogen or methyl group, is only shown for substituents of C-6 or C-11 in the PMR spectral data.

14) A chromatographically (TLC and GLC) pure sample of **1d**, mp 146—147.5°, was not obtained by this recrystallization procedure;[12] details of **1d** will be published elsewhere.

2500, 1759, 1716, 1251, 1134, 1017. GLC: $t_R$ 2.75 min (TMS derivative). PMR $\delta$ (in $C_5D_5N$): 0.87 (3H, s, $C_{10}-C\underline{H}_3$), 1.56 (3H, d, $J=6$, $C_4-C\underline{H}_3$), 1.05—2.15 (12H, c), 1.69 (3H, s, $C_{11}-\alpha C\underline{H}_3$), 3.29 (1H, m, $C_3-\underline{H}$), 4.74 (1H, t, $J=10$, $C_6-\beta\underline{H}$), 9.83 (1H, s, COO$\underline{H}$).

Repeated recrystallization of the crystals (0.171 g, 5.0%) obtained from the mother liquor gave an analytical sample of 11$\alpha$-carboxy-HHS (**3b**) as colorless needles, mp 249—250°. $[\alpha]_D^{19}$ +69.2° ($c=1.07$, MeOH); $[\alpha]_D^{32}$ +2.37° ($c=1.05$, pyridine). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.89; H, 8.16. Found: C, 64.42; H, 8.53. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3430, 3000—2500, 1769, 1743. PMR $\delta$ (in $C_5D_5N$): 0.91 (3H, s, $C_{10}-C\underline{H}_3$), 1.48 (3H, d, $J=6$, $C_4-C\underline{H}_3$), 1.58 (3H, s, $C_{11}-\beta C\underline{H}_3$), 1.05—2.1 (11H, c), 2.88 (1H, m, $C_{11}-\underline{H}$), 3.25 (1H, m, $C_3-\underline{H}$), 4.15 (1H, t, $J=10$, $C_6-\beta\underline{H}$), 9.75 (1H, s, COO$\underline{H}$). CD $[\theta]_{min}^{217}$: −7736 ($c=0.0835$, MeOH).

The organic layer remaining after separation of the aqueous solution of the sodium carboxylates was washed with satd. NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to afford the starting material (**1a**) (0.833 g, 27.9%).

**Decarboxylation of 3a**——**3a** (50 mg) was heated in an oil bath at 260° until no further evolution of $CO_2$ was observed (1.4 min). Recrystallization of the crystalline product (42 mg, 98.5%) from benzene afforded **1a** (33 mg, 78.5%), mp 169—171°, which was identical with an authentic sample of **1a** as regards physicochemical data.

**Decarboxylation of 3b**——As described above for **3a**, **3b** (50 mg) was heated in an oil bath at 260° until no further evolution of $CO_2$ was observed (3.2 min). Recrystallization of the pyrolysate (41 mg, 96.2%) gave **1a** (28 mg, 69.4%) as prisms, mp 167—170°; the spectral data were identical with those of authentic **1a.**

**(+)-11$\beta$-Methoxycarbonyl-3$\alpha$,4$\beta$,5$\alpha$,6$\beta$H-hexahydrosantonin** (**4a**)——A solution of **3a** (60 mg) in MeOH (50 ml) was treated with a cold ether solution of $CH_2N_2$, and the mixture was kept in a refrigerator overnight. After the addition of 1 drop of AcOH followed by removal of the solvent, the residue was taken up in $CHCl_3$ and the $CHCl_3$ solution was washed successively with 5% KOH, 10% HCl, and satd. NaCl, then dried over $MgSO_4$, and evaporated to dryness. The crystalline residue (60 mg) was recrystallized twice from MeOH to afford the lactone ester (**4a**), mp 194—196.5°. $[\alpha]_D^{32}$ +42.6° ($c=1.03$, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.87; H, 8.79. ORD and CD, positive plain curves ($c=0.124$, MeOH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3535, 1765, 1750, 1249, 1211. PMR $\delta$: 0.93 (3H, s, $C_{10}-C\underline{H}_3$), 1.19 (3H, d, $J=7$, $C_4-C\underline{H}_3$), 1.43 (3H, s, $C_{11}-\alpha C\underline{H}_3$), 1.83 (1H, s, O$\underline{H}$ disappeared on addition of $D_2O$), 1.02—2.0 (14H, m), 3.11 (1H, m, $C_3-\underline{H}$), 3.77 (3H, s, COOC$\underline{H}_3$), 4.24 (1H, t, $J=10$, $C_6-\beta\underline{H}$).

**(+)-11$\alpha$-Methoxycarbonyl-3$\alpha$,4$\beta$,5$\alpha$,6$\beta$H-hexahydrosantonin** (**4b**)——Esterification of **3b** (54 mg) as described above quantitatively provided the lactone ester (**4b**), which gave, on recrystallization from MeOH, a pure sample of **4b** as prisms, mp 171—174°. $[\alpha]_D^{32}$ +26.0° ($c=0.5$, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.79; H, 8.76. ORD ($c=0.084$, MeOH): $\phi$ (nm) +965.3 (267) (peak), −297.0 (240) (trough). ma (molecular amplitude) +126.2. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3502, 1763, 1749. PMR $\delta$: 0.96 (3H, s, $C_{10}-C\underline{H}_3$), 1.18 (3H, d, $J=7.5$, $C_4-C\underline{H}_3$), 1.47 (3H, s, $C_{11}-\beta C\underline{H}_3$), 2.02 (1H, s, O$\underline{H}$), 2.52 (1H, m, $C_7-\underline{H}$), 3.14 (1H, m, $C_3-\underline{H}$), 3.77 (3H, s, COOC$\underline{H}_3$), 4.02 (1H, t, $J=10$, $C_6-\beta\underline{H}$).

**(+)-3$\beta$-Methoxycarbonyloxy-11$\beta$-methoxycarbonyl-4$\beta$,5$\alpha$,6$\beta$H-hexahydrosantonin** (**2a**)—A solution of **4a** (126 mg) in $(MeO)_2CO$ (3 ml) was treated with NaH (36 mg, prepared as mentioned above), and the mixture was refluxed for 1 hr. The solvent was evaporated off under reduced pressure, and the residue was diluted with $H_2O$ and acidified with dil. HCl under ice-cooling; the desired diester (141 mg, 77%) precipitated. Recrystallization from benzene–petr. ether gave the cathylate (**2a**), mp 200—203°. $[\alpha]_D^{32}$ +32.6° ($c=1.22$, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 62.31; H, 7.96. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1784, 1745, 1273, 1263 (sh.). PMR $\delta$: 0.96 (3H, s, $C_{10}-C\underline{H}_3$), 1.15 (3H, d, $J=7$, $C_4-C\underline{H}_3$), 1.45 (3H, s, $C_{11}-\alpha C\underline{H}_3$), 1.15—2.11 (11H, c), 3.77 (6H, s, COOC$\underline{H}_3\times 2$), 4.19 (1H, m, $C_3-\underline{H}$), 4.23 (1H, t, $J=10$, $C_6-\beta\underline{H}$).

**(+)-3$\beta$-Methoxycarbonyloxy-11$\alpha$-methoxycarbonyl-4$\beta$,5$\alpha$,6$\beta$H-hexahydrosantonin** (**2b**)——As described above for **2a** (except that reflux was carried out for 6 hr), **4b** (55 mg) was treated with $(MeO)_2CO$ (3 ml) and NaH (12 mg). The crystalline product (47 mg, 72.0%) was recrystallized from benzene–petr. ether to give the cathylate (**2b**) (22.5 mg), mp 172.5—174°. $[\alpha]_D^{28}$ +64.8° ($c=0.29$, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 62.00; H, 7.93. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1789, 1748, 1273 (sh.), 1265. PMR $\delta$: 0.89 (3H, s, $C_{10}-C\underline{H}_3$), 1.15 (3H, d, $J=7$, $C_4-C\underline{H}_3$), 1.38 (3H, s, $C_{11}-\beta C\underline{H}_3$), 1.18—2.12 (10H, c), 2.58 (1H, c, $C_7-\underline{H}$), 3.78 (6H, s, COOC$\underline{H}_3\times 2$), 4.04 (1H, t, $J=10$, $C_6-\beta\underline{H}$), 4.22 (1H, m, $C_3-\underline{H}$).

**(+)-11$\beta$-Carboxy-4$\beta$,5$\alpha$,6$\beta$H-tetrahydrosantonin** (**7a**)——The Jones reagent (0.3 ml) was added to a solution of **3a** (200 mg) in acetone (25 ml) under ice cooling, and the reaction mixture was stirred at room temperature for several minutes. The reaction mixture was then poured into ice-water, concentrated under reduced pressure (bath temp., 45°) and extracted with ether after addition of NaCl. The ether extract was washed with satd. NaCl and dried over $MgSO_4$. Removal of the solvent left 150 mg (75%) of a crystalline ketone (**7a**), mp 178—179° (dec.). An analytical sample was obtained by passing the AcOEt solution through neutral $Al_2O_3$ followed by recrystallization from AcOEt–petr. ether. mp 187—189° (dec.). $[\alpha]_D^{16}$ +34.3° ($c=1.05$, $CHCl_3$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3425, 3000—2500, 1787, 1735 (sh.), 1725, 1697. MS $m/e$: 294 ($M^+$). *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 67.18; H, 7.67. PMR $\delta$: 1.20 (3H, s, $C_{10}-C\underline{H}_3$), 1.26 (3H, d, $J=7.2$, $C_4-C\underline{H}_3$), 1.48 (3H, s, $C_{11}-\alpha C\underline{H}_3$), 4.42 (1H, t, $J=10$, $C_6-\beta\underline{H}$), 9.70 (1H, s, COO$\underline{H}$).

**Decarboxylation of 7a**——Compound **7a** (37 mg) was heated in an oil bath at 210° for 2.5 min until no further evolution of $CO_2$ was observed. Recrystallization of 26 mg (82.5%) of the pyrolysate from MeOH–AcOEt yielded scales, mp 149—151°. $[\alpha]_D^{24}$ +22.0° ($c$=0.32, $CHCl_3$); this material was identical with an authentic sample of THS (**5a**) on the basis of mixed melting point and comparison of the IR spectra. GC-mass spectroscopy[15] showed no contamination by 11-epi-THS (**5c**).

**(+)-11$\beta$-Methoxycarbonyl-4$\beta$,5$\alpha$,6$\beta$H-tetrahydrosantonin** (**6a**)——A cold ether solution of freshly prepared $CH_2N_2$ was added to a solution of **7a** (200 mg) in MeOH (5 ml) and the mixture was kept in a refrigerator overnight. After the addition of several drops of HOAc, the organic solution was washed with 5% $NaHCO_3$ and satd. NaCl, then dried over $MgSO_4$. Removal of the solvent left crystals (180 mg, 90%). Recrystallization from AcOEt–ether gave the lactone ester (**6a**) as prisms, mp 142.5—145.5°. $[\alpha]_D^{19}$ +23.0° ($c$=1.0, $CHCl_3$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1786, 1721, 1703. *Anal.* Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.38; H, 8.11. PMR $\delta$: 1.15 (3H, s, $C_{10}$–$C\underline{H}_3$), 1.24 (3H, d, $J$=7.2, $C_4$–$C\underline{H}_3$), 1.46 (3H, s, $C_{11}$–$\alpha C\underline{H}_3$), 3.79 (3H, s, $COOC\underline{H}_3$), 4.43 (1H, t, $J$=9.3, $C_6$–$\beta\underline{H}$).

**(+)-11$\alpha$-Carboxy-4$\beta$,5$\alpha$,6$\beta$H-tetrahydrosantonin** (**7b**)——Compound **3b** (150 mg) was treated with the Jones reagent and worked up as described above to afford crude crystals, mp 171—175° (63 mg). Recrystallization from AcOEt–petr. ether gave needles, mp 179.5—181.5° (dec.). $[\alpha]_D^{18}$ +42.9° ($c$=1.0, $CHCl_3$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3425 (br.), 3000—2500, 1783, 1741, 1713, 1674. MS $m/e$: 294 ($M^+$). *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.88; H, 7.58. PMR $\delta$: 1.18 (3H, s, $C_{10}$–$C\underline{H}_3$), 1.24 (3H, d, $J$=7.0, $C_4$–$C\underline{H}_3$), 1.44 (3H, s, $C_{11}$–$\beta C\underline{H}_3$), 4.10 (1H, t, $J$=10, $C_6$–$\beta\underline{H}$), 8.18 (1H, s, $COO\underline{H}$).

**Decarboxylation of 7b**——As described above for **7a**, heating of **7b** (40 mg) in an oil bath at 210° for 5 min resulted in complete decarboxylation. A solution of 31 mg (91%) of the pyrolysate in AcOEt was passed through neutral $Al_2O_3$ to afford 22 mg (65%) of crystals from the whole eluate. Recrystallization from AcOEt–petr. ether afforded scales, mp 147—150°; $[\alpha]_D^{24}$ +23.6° ($c$=0.09, $CHCl_3$). The product was identical with **5a** in all respects, including GC–MS.[15]

**(+)-11$\alpha$-Methoxycarbonyl-4$\beta$,5$\alpha$,6$\beta$H-tetrahydrosantonin** (**6b**)——A cold ether solution of freshly prepared $CH_2N_2$ was added to a solution of **7b** (24 mg) dissolved in MeOH (0.5 ml), and the mixture was kept in a refrigerator overnight. After the addition of a small amount of HOAc, the organic solution was concentrated to leave a crystalline residue. An AcOEt solution of the crystals was passed through a short column of neutral $Al_2O_3$, and the eluate gave, on removal of the solvent, 22 mg (88%) of the lactone ester (**6b**) as crystals (mp 98—101°), which were recrystallized from AcOEt and petr. ether to afford an analytical sample of **6b** as prisms, mp 105—107.5°. $[\alpha]_D^{28}$ +49.1° ($c$=0.35, $CHCl_3$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1779, 1740, 1711. PMR $\delta$: 1.18 (3H, s, $C_{10}$–$C\underline{H}_3$), 1.25 (3H, d, $J$=6.6, $C_4$–$C\underline{H}_3$), 1.42 (3H, s, $C_{11}$–$\beta C\underline{H}_3$), 3.79 (3H, s, $COOC\underline{H}_3$), 4.08 (1H, t, $J$=10.5, $C_6$–$\beta\underline{H}$). High resolution mass MS $m/e$: 308.1660 (Calcd for $C_{17}H_{24}O_5$: 308.3600).

**(−)-11$\beta$-Carboxysantonin (8a)**——A solution of BuLi (5.1 g) in hexane was added dropwise over a period of 0.5 hr to a solution of (iso-Pr)$_2$NH (1.214 g) in dry THF (50 ml) at −71 to −73°. After adding **5b** (2.45 g) to the above solution, $CO_2$ gas was introduced into the mixture for 0.5 hr at *ca.* −40° and then for 1 hr at room temperature. The reaction mixture was quenched by the addition of 10% HCl. After separation of the organic layer, the aqueous layer was saturated with NaCl and extracted with ether. The combined organic solution was washed with satd. NaCl and 10% $Na_2CO_3$. The ether solution was dried over $MgSO_4$ and concentrated to recover the starting material (0.966 g, 39.3%).

On the other hand, the $Na_2CO_3$ solution afforded, on acidification, crystals of the lactone acid (**8a**) (1.472 g, 51%); this material was recrystallized from MeOH to give a pure sample of **8a**, mp 207—208° (dec.). $[\alpha]_D^{24}$ −138.0° ($c$=0.44, EtOH). *Anal.* Calcd for $C_{16}H_{18}G_5$: C, 73.14; H, 7.39. Found: C, 73.04; H, 7.33. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3120—2800, 1741, 1737 (sh.), 1659, 1618, 1603. PMR $\delta$ (in $(CD_3)_2SO$): 1.26 (3H, s, $C_{10}$–$C\underline{H}_3$), 1.35 (3H, s, $C_4$–$C\underline{H}_3$), 2.00 (3H, s, $OCOC\underline{H}_3$), 5.20 (1H, d, $J$=10.5, $C_6$–$\beta\underline{H}$), 6.14 (1H, d, $J$=10, $C_2$–$\underline{H}$), 6.91 (1H, d, $J$=10, $C_1$–$\underline{H}$), 7.33 (1H, s, $COO\underline{H}$).

**Decarboxylation of 8a**——As described for **3a** and **3b**, **8a** (50 mg) was heated in an oil bath at 205—210° for 2 min to give 43 mg (quantitative) of a pyrolysate, $[\alpha]_D^{28}$ −160° ($c$=0.62; EtOH). The AcOEt solution was passed through neutral $Al_2O_3$ to afford crystals on removal of the solvent. Recrystallization from EtOH yielded 36 mg of microprisms, mp 171.5—173.5°; $[\alpha]_D^{30}$ −170.0° ($c$=0.14, EtOH). This product showed no depression of the melting point on admixture with an authentic sample of **5b**, and gave the same IR spectrum as **5b**.

**Hydrogenation of 8a**——Three drops of conc. HCl and 5% Pd–C (30 mg) were added to a solution of **8a** (290 mg) in MeOH (50 ml), and the mixture was hydrogenated under atmospheric pressure at 27° using the Parr apparatus. After removal of the catalyst, the solvent was evaporated off to give a crystalline residue in quantitative yield. Recrystallization from AcOEt–petr. ether gave crystals, mp 177—181° (dec.) (141 mg, 49%). Recrystallization from the same solvent provided a sample of **7a**,[16] mp 179—180° (dec.), unde-

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15) The GC-mass spectrum was determined on a JNS-D-300 GC-mass spectrometer (GC: 220° oven temperature and 250° injection temperature, using 3% OV-1/Gaschrom Q in a 0.4$\phi$ × 100 cm glass column.

16) The possible *cis*-fused isomer (11$\beta$-carboxy-4$\alpha$,5$\beta$H-tetrahydro-*l*-$\alpha$-santonin could not be isolated in satisfactory purity even after several recrystallizations of the crude crystals from the mother liquor.

pressed on admixture with the authentic sample mentioned above [mixed mp 177—179°]. The IR spectrum of the sample was identical with that of **5a.**

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