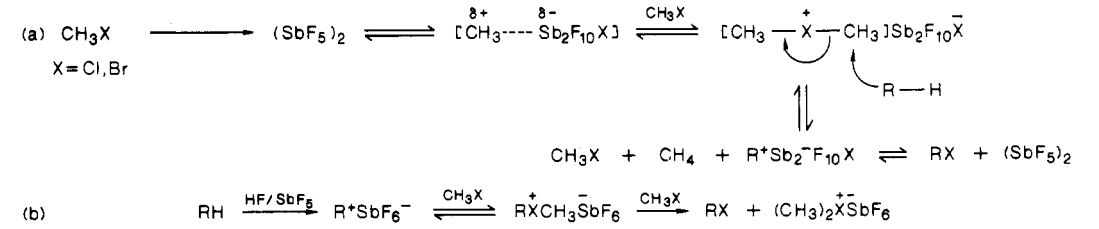
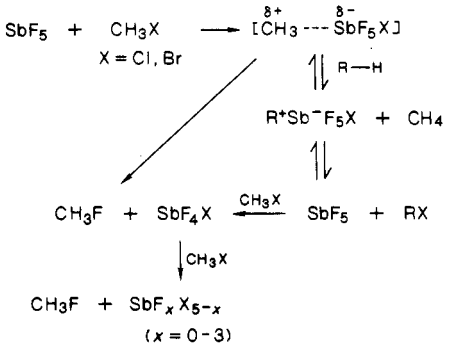
Scheme III



Scheme IV



preparation of stable alkyl carbocation, e.g. 1-adamantyl carbocation, via 1-fluoroadamantane, SbF_5, and SO_2ClF at −78 °C, which was subsequently allowed to react with CH_2X_2 (X = Cl, Br) and CH_3X (X = Cl, Br), respectively, under the similar conditions as previous reactions to afford solely 1-adamantanol after aqueous workup. The present evidence might suggest that Schemes I and III(a) are the likely paths for the title reaction.

Reaction of halomethyl halonium carbocations have not so far been investigated in any system except in the preparation of some other onium ions.[6] A halomethyl halonium ion, as shown in Scheme I, can abstract a hydride from an alkane and generate a carbenium ion responsible for the formation of the observed alkyl halide. formation of carbenium ions may equally be attributed to the reactions of the intermediately formed dimethyl halonium ions and CH_3X–SbF_5 complex with the alkanes via hydride abstractions.

Experimental Section

Antimony pentafluoride (Aldrich), isobutane and propane (Air Product), cyclopentane and adamantane (Aldrich), and neopentane (Alfa) all were commercially available compounds of high purity. Methylene halides (Aldrich) were dried over P_2O_5 under reflux prior to use.

Analysis of liquid products was performed on a Varian Gas Chromatograph (Model 3700) equipped with a quartz silica capillary column coated with DB-1, and that of gaseous products on a Hewlett Packard gas chromatograph (Model 5730A) equipped with a stainless steel column packed with BEEA. GC–MS spectra were recorded on a Finnigan Mat Model 700 GC–MS spectrometer equipped with an ion-trap detector and interfaced with a Varian Associates Model 3500 gas chromatograph. NMR spectra were recorded on a Varian (VXR-200) superconducting NMR spectrometer.

General Procedure for Halogenation of Alkanes. To a well-stirred solution of SbF_5 (fresh distilled; 15 mmol) in methylene chloride or bromide (30 mL) was added 12 mmol of alkane under dry argon at −78 °C. The reaction mixture was stirred for about 2 h at −78 °C and then slowly warmed up to room temperature at which it was allowed to continue for about 24 h. Working up the reaction mixture in ice–bicarbonate followed by extraction in CH_2Cl_2 and removal of the solvent afforded alkyl halides, which were subsequently purified by column chromatography (silica gel, hexane as eluent). The alkyl halides were identified in the GC (by comparing the retention time with authentic compounds), GC–MS, and ^{13}C NMR spectra.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Hydrolysis of Substituted Crown Ether Acetals

Takumi Oshima* and Toshikazu Nagai

Institute of Chemistry, College of General Education, Osaka University, Toyonaka, Osaka 560, Japan

Received September 22, 1988

A number of studies have been made of the hydrolysis of a wide variety of cyclic and acyclic acetals.[1] However, very little is known about the hydrolysis of macrocyclic acetals with the poly(oxyethylene) unit, the so-called crown ether acetals.[2] This is largely attributable to much difficulty in the synthesis of such acetals from carbonyl compounds and oligoethylene glycols by the conventional methods.[3]

Gold et al. prepared a series of 2-methyl-substituted crown ether acetals from acetaldehyde and oligoethylene glycols by using ion-exchange resins[4] and studied the effects of added alkali-metal ions on the acid-catalyzed hydrolysis of these acetals.[2a,b] We recently reported on the effects of ring size on the hydrolysis of 2,2-diphenyl-substituted crown ether acetals,[2c] which were formed by a redoxical acetalization of diphenyldiazomethane with 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of oligoethylene glycols.[5] Successful extension of this redox reaction to other diazoalkanes, providing variously substituted new crown ether acetals,[6] prompted us to investigate the substituent effects in the hydrolysis of these macrocyclic acetals (**1**). Hydrolysis of corresponding dimethyl acetals (**2**) was also made in the same conditions to know the effects of structural change in the alcohol moieties.

Results and Discussion

The rate constants and the activation parameters were collected for the HCl-catalyzed hydrolysis of variously

(1) (a) Cordes, E. H. *Progr. Phys. Org. Chem.* **1967**, *4*, 1. (b) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264. (c) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581. (d) Fife, T. H. *Adv. Phy. Org. Chem.* **1975**, *11*, 1. (e) Bergstrom, R. G. In *The Chemistry of Ethers, Crown Ethers, Hydroxy Groups and Their Sulphur Analogues*; Patai, S., Ed.; Wiley: Chichester, 1980; Chapter 20.

(2) (a) Gold, V.; Sghibartz, C. M. *J. Chem. Soc., Chem. Commun.* **1978**, 507. (b) Baker, D. S.; Gold, V.; Sghibartz, C. M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1121. (c) Ueno, S.; Oshima, T.; Nagai, T. *J. Org. Chem.* **1986**, *51*, 2131.

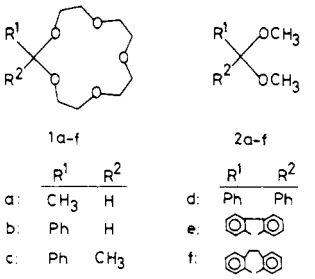
(3) (a) Kawakami, Y.; Suzuki, J.; Yamashita, Y. *Polym. J.* **1977**, *9*, 519. (b) Hill, J. M.; Carothers, W. H. *J. Am. Chem. Soc.* **1935**, *57*, 925.

(4) (a) Astle, M. J.; Zaslowsky, J. A.; Lafyatis, P. G. *Ind. Eng. Chem.* **1954**, *46*, 787. (b) Gold, V.; Sghibartz, C. M. *J. Chem. Soc., Perkin Trans 1* **1983**, 453.

(5) Oshima, T.; Nishioka, R.; Ueno, S.; Nagai, T. *J. Org. Chem.* **1982**, *47*, 2114.

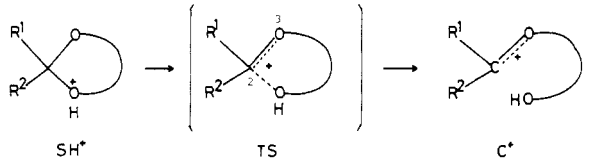
(6) Oshima, T.; Nagai, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3979.

0022-3263/89/1954-1465$01.50/0



substituted 14-membered ring crown ether acetals (**1a–f**) and the corresponding dimethyl acetals (**2a–f**) in 60% dioxane–water (Table I). It was found that the substituents at position 2 of these acetals markedly influence their hydrolysis rates, but quite similar dependence of rates on the substituents was observed for both series of acetals except apparent upper deviations (0.8–1 log units) of methyl- and phenyl-substituted crown ether acetals **1a** and **1b** (Figure 1). Phenyl-substituted crown ether acetal (**1b**) hydrolyzed approximately 30 times faster than methyl-substituted one (**1a**) at 25 °C. The replacement of the hydrogen at position 2 of **1b** by a methyl group produced further increase in rate of about 6 times, leading to the maximum rate among the series. However, substitution of the second phenyl group brought about the sudden decrease in rate; thus, diphenyl-substituted **1d** hydrolyzed only $^1/_{110}$ as fast as monophenyl-substituted **1b**. By comparing **1d** with other diaryl-substituted **1e** and **1f**, it can be noted that the planar arrangement of the two aromatic rings of **1e** turned out to increase the rate by a factor of 16, while the similar twisted structure of the ethylene-bridged two phenyl groups of **1f** resulted in the same order of hydrolysis rate.

According to the generally accepted A-1 mechanism for hydrolysis of simple acetals,[1a,c,e] the rate-determining step is an unimolecular decomposition of the conjugated acid (SH^+), which is given by a preequilibrium protonation of the substrate, to a oxocarbenium ion (C^+), as formulated below. Therefore, 20–30 times higher reactivity of phe-



nyl-substituted **1b** and **2b** than the corresponding methyl-substituted **1a** and **2a** indicates that the resonance effects of the phenyl group contribute much more to the stabilization of a transition state than the inductive and hyperconjugative effects of the methyl group. Similar substituent effects are also known for the hydrolysis of benzaldehyde and acetaldehyde diethyl acetals.[7] The attainment of the maximum rate on replacing the hydrogen of **1b** and **2b** by a methyl group may be attributable to the cooperative affection of phenyl and methyl substituents in the transition state. However, the extent of the rate increment by introducing both the substituents is much smaller than that expected from the assumption of additivity of the intrinsic effects of the individual substituent.[8] Such reducing enhancement of the rate is also known for the hydrolysis of a series of methyl-substituted 1,3-dioxolanes.[9] Salomaa and Kankaanpera[9] explained

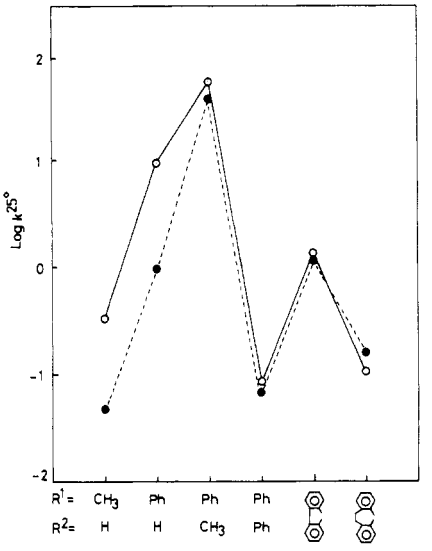


Figure 1. Plots of log $k^{25°}$ vs substituents of crown ether acetals (○) and noncyclic dimethyl acetals (●).

this steric retardation of the rate by assuming that a transition state (TS) has a great deal of oxocarbenium ion character so that the C(2)–O(3) bond has a partial double-bond character. The groups joined by this bond tend to be in the same plane to assist the contribution of the substituents stabilizing the transition state. Such steric requirement would produce much more steric strain in rigid cyclic acetals than in acyclic ones.[10] Consideration of this steric strain nicely explains the failure in the additivity of the substituent effects as mentioned above. Also, it is noticeable that the large rate retardation was caused by the presence of two aromatic substituents in the present acetals. Comparable rate decrease was found in the hydrolysis of benzophenone diethyl acetal[11] and 2,2-diphenyl-1,3-dioxolane[12] compared to propiophenone diethyl acetal and 2-phenyl-2-methyl-1,3-dioxolane, respectively. These results are indicative of a more extreme case of steric inhibition of resonance in the transition state. An alternative explanation for these phenomena observed in the case of diaryl-substituted acetals relied on the transition state resembling the protonated acetals so that resonance effects would become unimportant.[11,13] Higher reactivity of **1e** and **2e** compared to other diaryl-substituted acetals is probably due to the planar structure of the substituent, which will reduce to some extent the steric inhibition of the resonance exerted by the twisted two aromatic rings.

Of special interest is the large upper deviation of monosubstituted crown ether acetals **1a** and **1b** in comparison with the corresponding noncyclic dimethyl acetals (Figure 1). This exceptional behavior may be explained on the basis of the specific interaction between these macrocyclic acetals and a hydronium ion (H_3O^+). It is highly likely that suitable ring-sized crown ether acetals are able to incorporate the H_3O^+ and metal cations in a similar manner as common crown ethers.[14] Indeed, selective cation-binding properties were detected by Gold et al. for the hydrolysis of a series of 2-methyl-substituted crown ether acetals in

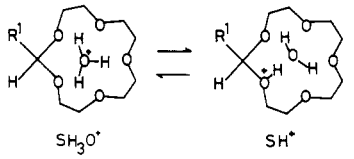
(7) Kreevoy, M. M.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5590.
(8) Acetone diethyl acetal hydrolyzes $10^{3.5}$ times faster than acetaldehyde diethyl acetal, which hydrolyzes $10^{3.8}$ times faster than formaldehyde diethyl acetal; see ref 7.
(9) Salomaa, P.; Kankaanpera, A. *Acta Chem. Scand.* **1961**, *15*, 871.
(10) A typical example is the large rate decrease of 2-phenyl-2-methyl-1,3-dioxolane compared to 2-phenyl-1,3-dioxolane; the former hydrolyzed only one-fifth as fast as the latter: see ref 12.
(11) Kreevoy, M. M.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 4016.
(12) Fife, T. H.; Hagopian, L. *J. Org. Chem.* **1966**, *31*, 1772.
(13) Kreevoy, M. M. *Tetrahedron* **1959**, *5*, 233.
(14) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271 and references cited therein.

Table I. Rate Constants (k) and Activation Parameters for Hydrolysis of Crown Ether Acetals (1a–f) and Noncyclic Dimethyl Acetals (2a–f) in 60% Dioxane–Water (v/v)

	$10k$, dm³/mol·s								
acetals	15 °C	20 °C	25 °C	30 °C	35 °C	40 °C	50 °C	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$,[a] J/mol K
1a			3.28[b]						
1b		56.7	94.8	148	241			68.6	4.61
1c	228	367	556	868				62.0	−3.33
1d			0.855	1.53		4.68	13.2	86.4[c]	24.2[c]
1e		8.26	13.8	23.4	38.1			74.5	7.80
1f			1.00	1.72		4.94	13.2	80.3	5.34
2a				0.909		3.00	8.94	90.7	34.1
2b				16.5		47.8	124	79.5	21.4
2c		257	403	590				59.2	−15.8
2d				1.19		3.63	10.6	86.4	22.3
2e		7.27		19.6		50.3		71.2	0.40
2f				2.82		8.20	21.5	80.3	9.37

[a] Calculated at 30 °C. [b] Datum from ref 2a. [c] Values of $\Delta H^{\ddagger}$ (=89.1 kJ/mol) and $\Delta S^{\ddagger}$ (=32.3 J/mol K) were obtained for the hydrolysis in 80% dioxane–water (v/v).[2c] Variation of the activation parameters with change of medium is known for hydrolysis of 1,3-dioxolanes: Richard, C. N.; et al. *J. Am. Chem. Soc.* **1970**, *92*, 5565.

the presence of added metal chlorides.[2a,b] More noticeable is the fact that this series of acetals showed a maximum hydrolysis rate for the 14-membered ring, namely **1a**, while 2,2-diphenyl-substituted series for one oxyethylene unit longer 17-membered ring.[2c] We interpreted this phenomenon as the results of the formation of hydronium ion complexed acetal like SH_3O^+, which will be in rapid equilibrium with the conjugated acid (SH^+), consequently



playing a role in the stabilization of the transition state. The shift of the maximum rate with the variation of the substituent from methyl to diphenyl can be ascribed to the steric hindrance due to *gem*-diphenyl moiety, which will reduce the effective cavity of the crown rings.

A survey of the activation parameters in Table I shows that the values of $\Delta S^{\ddagger}$ are nearly of the magnitude generally found for unimolecular A-1 reactions,[15] and compensation between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ is roughly operative for each series of acetals regardless of the large variation of the substituents (Figure 2). From the slope (=0.40) of the regression line, it was found that the change of the substituents is much more effective on the enthalpy term than on the entropy one. This result may be rationalized by considering that the increasing stabilization of the transition state by resonance, inductive, and hyperconjugative effects is accompanied by the moderately increasing unfavorable effects on $\Delta S^{\ddagger}$, probably owing to solvation and restriction of rotation in the transition state.[16]

Experimental Section

IR, NMR, and mass spectra were taken on a Perkin-Elmer 983G, a Varian EM390, and a Hitachi RMU 6E spectrometer, respectively.

Materials. Dioxane was refluxed over metal sodium and fractionated. 1,1-Dimethoxyethane (**2a**, Tokyo Kasei Kogyo Co., Ltd.) was dried over potassium hydroxide and fractionated. Syntheses of crown ether acetals **1b–e** and noncyclic dimethyl acetal **2d** were described elsewhere.[6,17] Noncyclic acetals **2b**, **2c**, and **2e** were prepared according to the similar manner described in the previous paper[6] by using 5 equiv of methanol. 2,2-(Bibenzyl-2,2′-diyl)-substituted acetals **1f** and **2f** were provided from equimolar reaction of 5-diazo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene[18] (1.0 g, 4.55 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of tetraethylene glycol (1 equiv) and methanol (5 equiv), respectively, in benzene (10 mL) at 25 °C for 1 h. All acetals were isolated by column chromatography on alumina after usual treatment of the reaction mixtures. Eluents used for the newly prepared acetals were hexane–benzene (9:1 v/v) for **2b,c,e,f** and benzene–ether (3:1) for **1f**. The structures of the new compounds were confirmed by IR, NMR, mass spectra, and elemental analyses as follows.

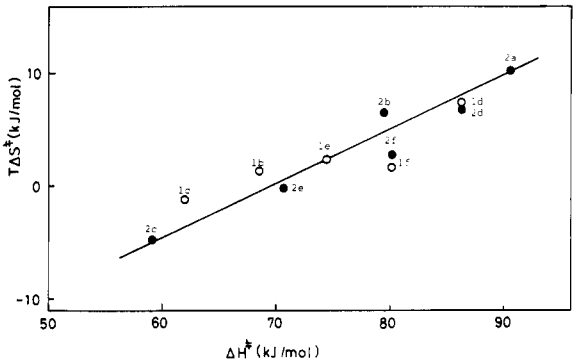


Figure 2. Correlation of $T\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ for hydrolysis of crown ether acetals (○) and noncyclic dimethyl acetals (●).

2,2-(Bibenzyl-2,2′-diyl)-1,3,6,9,12-pentaoxacyclotetradecane (1f): colorless prisms (hexane–ether); mp 102–103 °C; 31% yield; IR (KBr) 2930, 2863, 1119, 1075, 770 cm⁻¹; NMR ($CDCl_3$) δ 3.27 (s, 4 H, CH_2CH_2), 3.5–3.9 (m, 16 H, OCH_2CH_2), 6.9–7.2 and 7.5–7.7 (m, 8 H, aromatic); MS m/e 384 (M^+). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.78; H, 7.31.

Fluorenone dimethyl acetal (2e): colorless prisms; mp 83–84 °C (from hexane–benzene); 35% yield; IR (KBr) 1448, 1215, 1074, 1057, 758 cm⁻¹; NMR ($CDCl_3$) δ 3.30 (s, 6 H, OCH_3), 7.1–7.7 (m, 8 H, aromatic); MS m/e 226 (M^+). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.59; H, 6.27.

Dibenzocycloheptadienone dimethyl acetal (2f): colorless oil; 66% yield; IR (film) 2930, 1482, 1450, 1205, 1080, 767 cm⁻¹; NMR ($CDCl_3$) δ 3.28 (s, 10 H, OCH_3 + ethylene), 7.0–7.2 and 7.4–7.7 (m, 8 H, aromatic); MS m/e 254 (M^+). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.23; H, 7.13. Found: C, 80.22; H, 7.12.

Kinetic Measurements. The rates of hydrolysis of acetals were measured at constant temperature in 60% dioxane–water (v/v) at HCl concentrations of 5.0×10^{-4} mol/dm³ for phenyl- and phenyl methyl-substituted acetals and of 5.0×10^{-3} mol/dm³ for **2a** and diaryl-substituted acetals. The reactions were monitored spectrophotometrically up to 70–80% conversion with a JASCO 505 equipment by following the increase in absorptions

(15) Taft, R. W., Jr.; Purlee, E. L.; Riesz, P.; DeFazio, C. A. *J. Am. Chem. Soc.* **1955**, *77*, 1584.
(16) Long, F. A.; Pritchard, J. G.; Stafford, F. E. *J. Am. Chem. Soc.* **1957**, *79*, 2362.
(17) Oshima, T.; Nishioka, R.; Nagai, T. *Tetrahedron Lett.* **1980**, 3919.
(18) Moritani, I.; Murahashi, S.; Yoshinaga, K.; Ashitaka, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1506.

(A) of the carbonyl products. The pseudo-first-order rate constants (k_{obsd}) were taken from the slopes of plots of ln $[A_\infty - A_t]$ against time. The second-order rate constants (k) were obtained by dividing k_{obsd} by activity of H^+ ($a_{H^+} = 4.39 \times 10^{-4}$ and 3.44×10^{-3} mol/dm^3, respectively, for the low and high HCl solutions) calculated according to Debye-Hückel equation.[19]

Registry No. **1a**, 68375-97-3; **1b**, 110523-60-9; **1c**, 110523-61-0; **1d**, 81194-61-8; **1e**, 110523-62-1; **1f**, 118798-97-3; **2a**, 534-15-6; **2b**, 1125-88-8; **2c**, 4316-35-2; **2d**, 2235-01-0; **2e**, 116143-54-5; **2f**, 118798-98-4.

(19) Debye, P.; Hückel, E. *Phys. Z.* **1923**, *24*, 185.

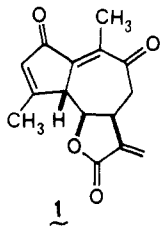
Synthesis of Oxoisodehydroleucodin: A Novel Guaianolide from *Montanoa imbricata*

Andrew E. Greene* and Mark T. Edgar

Université Joseph Fourier de Grenoble, Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité (LEDSS III), Bâtiment 52, Chimie Recherche, BP 53 X, 38041 Grenoble Cedex, France

Received August 12, 1988

α-Santonin, owing to its well-placed functionality and ready availability, is frequently used as the starting material for the synthesis of terpene natural products.[1] We have previously employed this sesquiterpene[2] for the formal total syntheses of naturally occurring (+)-α- and (+)-β-cyperones,[3a] (-)-frullanolide,[3b] (+)-arbusculin B,[3b] (+)-dihydroestafiatone,[3c] (+)-desacetoxymatricarin,[3c] (-)-estafiatin,[3c] (+)-pachydictyol A,[3d] and (-)-dictyolene.[3d] In this paper we report a short, stereoselective synthesis from α-santonin of oxoisodehydroleucodin (**1**), a highly unsaturated guaianolide isolated from *Montanoa imbricata* by Seaman, Fischer, and Mabry.[4] The synthesis serves to corroborate the structure and relative stereochemistry, which were assigned to the natural product solely on the basis of spectroscopic evidence.



Oxoisodehydroleucodin

1

α-Santonin (**2a**, Scheme I) was converted in 61% yield to its 6-epi isomer (**2b**) through treatment with anhydrous hydrogen chloride in hot dimethylformamide. Photolysis of this material under conditions similar to those described by Barton and co-workers[6] then generated 6-*epi*-isophoto-α-santonic lactone (**3**), which has the guaiane skeleton of **1** (31%). This alcohol on dehydration with thionyl chloride in cold tetrahydrofuran-pyridine afforded regioselectively and in good yield the endocyclic olefin **4**. It is interesting to note that isophoto-α-santonic lactone on similar treatment is converted regioselectively to the corresponding exocyclic olefin.[3d,6]

Kabalka's "alkene walk" procedure,[7] a reduction-olefin transposition method that we had previously shown to be useful for the introduction of a ring-fusion hydrogen on the *more* hindered face of a molecule,[3d] when applied to **4** was once again highly stereoselective and provided the required 5β derivative **5a** in 56% yield. Bromination-dehydrobromination[3b,8] of this cis-fused α-methyl-γ-butyrolactone next efficiently served to produce the desired α-methylene-γ-butyrolactone **5c** to the exclusion of the corresponding endocyclic isomer.

The conversion of triene **5c** to the natural product proved to be surprisingly easy. When stirred overnight at room temperature in dichloromethane in the presence of a large excess of Collins' reagent[9] and 4-Å molecular sieves, triene **5c** cleanly afforded the *double* oxidation product, oxoisodehydroleucodin (52% yield, 68% conversion).[10] The identity of the synthetically and naturally derived substances, which was established through comparison of their spectral data, serves to confirm the structure and relative stereochemistry previously proposed for this novel guaianolide.[4]

The approach illustrated in this paper may be useful for the synthesis of several other, structurally related natural products.[11]

Experimental Section

Solvents were generally distilled prior to use: tetrahydrofuran from lithium aluminum hydride; toluene, dimethylformamide, and hexamethylphosphoric triamide from calcium hydride; and dichloromethane from calcium chloride.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70-230 silica gel 60 was employed for column chromatography. A Perkin-Elmer 397 spectrophotometer was used to record IR spectra (as Nujol films). The UV spectra were recorded on a Beckman DB-GT spectrophotometer. A Bruker AM 300 spectrometer was employed for the ^1H and ^{13}C NMR spectra ($CDCl_3$ solutions). Mass spectra were obtained on an AEI MS-30 or VG 30F mass spectrometer (70 eV, direct insert probe) or on a VG Micromass 70 70F instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were obtained with a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS. Santonin was purchased from Sigma.

(3*S*,3a*S*,5a*S*,9b*R*)-3a,5,5a,9b-Tetrahydro-3,5a,9-trimethylnaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione (6-*epi*-α-Santonin, 2b). The procedure described by Piers and Cheng[12]

(1) See: Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1973; Vol. 2. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5.

(2) Previously prepared by total synthesis: Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Proc. Jpn. Acad.* **1952**, *28*, 425-428; **1953**, *29*, 113-114; **1954**, *30*, 116-118, 119-121; *J. Am. Chem. Soc.* **1956**, *78*, 1422-1426. Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1978**, *43*, 1086-1089. Santonin is available from Aldrich, Sigma, and Fluka.

(3) (a) Greene, A. E.; Muller, J.-C.; Ourisson, G. *Tetrahedron Lett.* **1971**, 4147-4149. (b) Greene, A. E.; Muller, J.-C.; Ourisson, G. *J. Org. Chem.* **1974**, *39*, 186-191. (c) Edgar, M. T.; Greene, A. E.; Crabbé, P. *Ibid.* **1979**, *44*, 159-160. (d) Greene, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 5337-5343.

(4) Seaman, F. C.; Fischer, N. H.; Mabry, T. J. *Phytochemistry* **1986**, *25*, 2663-2664. Neither the absolute configuration nor the optical rotation was reported for oxoisodehydroleucodin. However, sesquiterpene lactones from higher plants invariably belong to the same enantiomeric series,[5] and thus the absolute configuration of the natural product is undoubtedly that of α-santonin-derived **1**. A sample of the natural product (or copies of its spectra) could not be obtained from the authors.

(5) See: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2.

(6) Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472-3482. See also: Barton, D. H. R.; de Mayo, P.; Shafiq, M. *Ibid.* **1957**, 929-935.

(7) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574-575. Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *Ibid.* **1977**, *42*, 512-517.

(8) See also: Marco, J. A.; Carda, M. *Tetrahedron* **1987**, *43*, 2523-2532.

(9) Fullerton, D. S.; Chen, C.-M. *Synth. Commun.* **1976**, *6*, 217-220.

(10) At no time during the conversion of **5c** to **1** could more than a possible trace amount of any monoketone be detected by TLC.

(11) See: Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. 2.

(12) Piers, E.; Cheng, K. F. *Can. J. Chem.* **1968**, *46*, 377-383.

0022-3263/89/1954-1468$01.50/0