Table I. Stereochemistry[a] of the Bromination of R_3Sn-*sec*-butyl

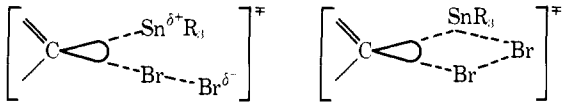
conditions[c]	observed stereochemistry, %			
	i-Pr_3Sn[b]	*i*-Pr_2NpSn[b]	*i*-$PrNp_2Sn$[b]	Np_3Sn[b,d]
CCl_4[e]	70 ret	74 ret	76 ret	89 ret
CH_3OH	22 ret	1 ret	35 inv	40–65 inv[f]
CH_3OH, 0.2 M NaBr	12 ret			~100 inv[g]
CH_3OH, 0.4 M NaBr	9 ret	4 inv		
CH_3OH, 0.91 M $NaClO_4$	10 ret			
CH_3CN	9 inv	60 inv	~100 inv	~100 inv

[a] Defined as optical purity of 2-bromobutane/optical purity of organotin; 15.8° used as maximum rotation of starting *sec*-butyltriphenyltin[13] and 34.2° for *sec*-butyl bromide.[10] ret = retention; inv = inversion. [b] R_3Sn: Np = neopentyl; *i*-Pr = isopropyl. [c] [organotin] = 0.22–0.25 M; reactions performed in dark, in air atmosphere, with dropwise addition of Br_2 over 1–5 h. Reactions not taken to completion. [d] Results from ref 8. [e] With appropriate inhibitor.[8] [f] See notes 9 and 14. [g] [NaBr] = 0.122 M.

as solvent, the amount of inversion increases with neopentyl substitution. If sodium bromide is added to the methanol, a greater amount of inversion is observed. Thus, *sec*-butyltrineopentyltin is brominated in methanol alone with 40% inversion, but the stereospecificity approaches 100% in the presence of bromide ion.[9,14] Similarly, the triisopropyl compound affords *sec*-butyl bromide with 22% retention of configuration in methanol alone; in the presence of 2 equiv of NaBr, 9% retention is realized. This reduction in observed retention is not simply the result of racemization of the product 2-bromobutane by bromide ion: *sec*-butyl bromide is not racemized by Br^- in 48 h in MeOH under reaction concentrations. Also, when *sec*-butyltriisopropyltin was brominated in methanol containing 4.6 equiv of $NaClO_4$, the stereochemistry of the reaction was 10% retention.

Inversion of configuration at carbon is uniformly observed for the bromination reactions in acetonitrile. The amount of inversion again increases with increasing neopentyl substitution at tin.

These results can be interpreted in terms of competing inversion (I) and retention (II or III) transition states.



II III

Carbon tetrachloride cannot support charged-separated species, so that reaction likely occurs via closed retention transition state III, but II may be possible if ions are formed as a close ion pair. In the more polar solvents, acetonitrile, methanol, or methanol–NaBr, competition between inversion transition state I and that for retention (II or III) is possible, and the net stereochemical results are largely governed by solvent polarity.

Acetonitrile favors inversion reactions more than methanol for these S_E2 brominations. The polarizability, dipole moment, and dielectric constant of acetonitrile are greater than the corresponding values for methanol, but methanol is a strong hydrogen bonding solvent and is expected to stabilize the developing bromide ion. Possibly, acetonitrile interacts more strongly than methanol with the leaving trialkylstannyl cation and this strong interaction more than offsets the stabilization (hydrogen bonding) of the leaving bromide ion by methanol. Stereochemical studies must be conducted in a broad range of solvents to understand the role of the solvent.

It is not clear why neopentyl substituents favor inversion more than isopropyl groups. In part, three neopentyl groups effectively block the front-side approach of the electrophile, thus favoring a back-face attack upon the carbon–tin bond. Yet, an examination of space-filling models reveals considerable crowding about the carbon–*tin* bond in triisopropyl-*sec*-butyltin which is brominated with predominant retention. The relative electron-donating capacities of neopentyl and 2-propyl groups may also govern the amount of inversion in these S_E2 reactions. Possibly, the immediate product of inversion, R_3Sn^+, is more stable when R = neopentyl than for isopropyl. Perhaps, also, assistance by relief of steric strain promotes inversion in the neopentyl compound, as is observed in solvolysis reactions on carbon.[15]

There are insufficient data presently available to answer these questions. Current efforts are directed toward elucidating the relative importance of these and other effects in determining the net S_E2 stereochemistry.

Acknowledgment. Grateful acknowledgement is made to the National Science Foundation (GP-33669) and the National Institutes of Health (GM-15373) for support of this research.

References and Notes

(1) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials", McGraw-Hill, New York, 1968.
(2) K. Sisido, S. Kozima, and K. T. Takizawa, *Tetrahedron Lett.*, 33 (1967).
(3) K. Sisido, T. Miyanisi, and T. Isida, *J. Organomet. Chem.*, **23**, 117 (1970).
(4) K. Sisido, K. Ban, and T. Isida, *J. Organomet. Chem.*, **29**, C7 (1971).
(5) M. Gielen, P. Baekelmans, and J. Nasielski, *J. Organomet. Chem.*, **34**, 329 (1972).
(6) D. D. Davis, Ph.D. Thesis, University of California, Berkeley, Calif., 1966.
(7) F. R. Jensen and D. D. Davis, *J. Am. Chem. Soc.*, **93**, 4048 (1971).
(8) F. R. Jensen and R. L. Chambers, "Aspects of Mechanism and Organometallic Chemistry", James Brewster, Ed., Plenum Press, New York, 1978.
(9) Incomplete stereospecificity should never be assumed to result from partial inversion and partial retention since the result may come from partial racemization. This is especially true in S_E2 studies with alkyl organometallic compounds and has largely been ignored by other workers. In previous work we have found that alkyl–metal bonds are usually cleaved as easily or more easily by radical than S_E2 reactions, e.g., ref 1, p 77, and many other citations therein.
(10) A. Rahm and M. Pereyre, *J. Am. Chem. Soc.*, **99**, 1672 (1977).
(11) F. R. Jensen and D. D. Davis, *J. Am. Chem. Soc.*, **93**, 4047 (1971). In this work, *sec*-butylmethanesulfonate was used.
(12) Y. Barrans, M. Pereyre, and A. Rahm, *J. Organomet. Chem.*, **125**, 173 (1977).
(13) Thomas J. Stark, Ph.D. Thesis, University of California, Berkeley, Calif., 1977; A. Rahm and M. Pereyre, *J. Organomet. Chem.*, **88**, 79 (1975).
(14) Added bromide ion suppresses the radical component which could contribute to the low stereospecificity sometimes observed in its absence.
(15) H. C. Brown and H. L. Berneis, *J. Am. Chem. Soc.*, **75**, 10 (1953); P. D. Bartlett and M. Stiles, *ibid.*, **77**, 2806 (1955).

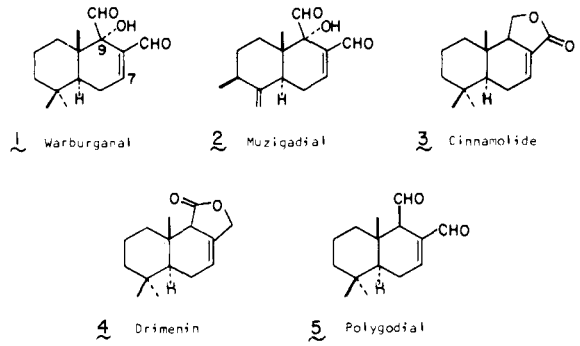
Lawrence F. McGahey, Frederick R. Jensen*
Department of Chemistry, University of California
Berkeley, California 94720
Received February 23, 1979

Stereospecific Total Synthesis of (±)-Warburganal and Related Compounds

Sir:

Three new drimane sesquiterpenoids, warburganal (**1**), 3β-hydroxywarburganal, and muzigadial (**2**), were isolated

0002-7863/79/1501-4398$01.00/0 © 1979 American Chemical Society

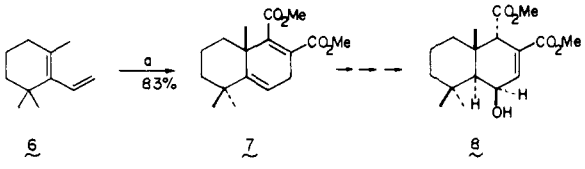


from the East African medicinal trees *Warburgia ugandensis* and *W. stuhlmanii* (Canellacae)[1] together with the known cinnamolide **3**,[2,3] drimenin (**4**),[4,5] and polygodial (**5**).[6,7] Unlike other congenors, warburganal and muzigadial exhibit extremely potent biological activities, including the irreversible and species-specific insect antifeedant activity against the African army-worm *Spodoptera exempta*,[1c,8] cytotoxicity (KB test, 0.01 μg/mL), molluscicidal activity against the schistosome transmitting snail *Biomphalaria glabaratus*,[1c] and a broad antimicrobial spectrum. This paper describes an efficient stereospecific synthesis of (±)-warburganal (and congenors **3–5**) which is characterized by congested functionalities on C-7, -8, and -9.

The Diels–Alder reaction of dimethyl acetylenedicarboxylate with 1-vinyl-2,6,6-trimethyl-1-cyclohexene (**6**)[9,10] (neat, 110 °C, 16 h) provided diester **7**[9b,11] in 83% yield, mp 50.5–51 °C (Scheme I). Reduction of **7** under various catalytic hydrogenation conditions[2,9a,c,12] provided only the cis-fused di- and tetrahydro diesters suggesting that **7** exists with ring A in the boat form.[13] Hydroboration and oxidation (H_2O_2, OH^-)[14] of **7** provided the cis-fused 6β-ol, which upon Jones oxidation, equilibration (NaOMe, MeOH, Δ), and reduction with sodium borohydride gave the trans-fused 6β-ol **8**. However, since it was not possible to remove the unwanted 6-hydroxyl function owing to severe steric hindrance, the following approach was adopted.

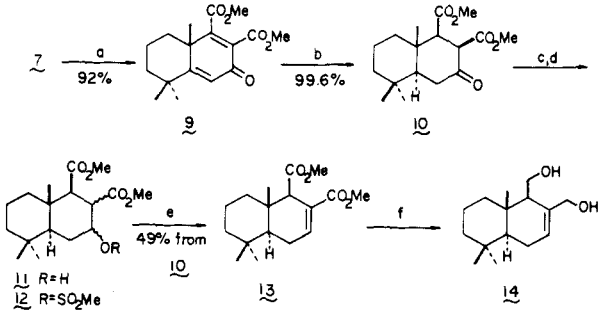
Allylic oxidation of **7** with the chromium trioxide–pyridine complex[15] provided cyclohexadienone (**9**)[11] in 92% yield (Scheme II). Compound **9** was hydrogenated at 3 atm over Pd/C to give the desired trans-fused ketone **10**[11] in 99.6% yield.

Scheme I[a]



[a] (a) Dimethyl acetylenedicarboxylate, neat, 110 °C, 16 h.

Scheme II[a]



[a] (a) $CrO_3 \cdot (pyr)_2$; (b) H_2–Pd/C; (c) $NaBH_4$, MeOH; (d) MsCl, Et_3N, Et_2O; (e) DBU; (f) $LiAlH_4$.

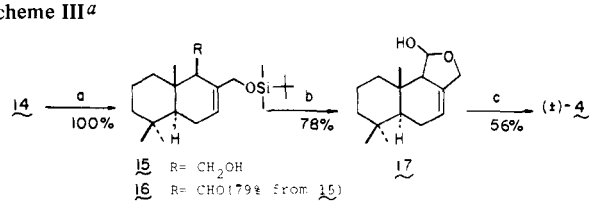
The unwanted, but necessary, oxygen was now situated at the more accessible 7 position. Removal of the 7-one and introduction of the 7,8 double bond was accomplished in a three-step sequence. The reduction of ketone **10** with sodium borohydride (MeOH, 0 °C) and treatment of the resulting free alcohols **11**[11] with methanesulfonyl chloride (2 equiv of MsCl, 7 equiv of Et_3N, Et_2O, room temperature, 2 h) provided mesylates **12**.[11] Refluxing of the mesylates **12** in benzene with 5 equiv of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[16] gave compound **13**[11] in 49% yield from ketone **10**. Lithium aluminum hydride reduction of **13** provided diol **14**,[11,17] mp 73–74 °C (lit.[3] 75.5–77 °C), the key intermediate in the syntheses of **1–5**, in 87% yield.

Inspection of a molecular model of diol **14** suggests that the exposed 8-CH_2OH should react more readily than the hindered 9-CH_2OH. This was indeed the case since Collins oxidation of diol **14** gave a single lactone[11] in 55% yield, mp 85–85.5 °C (lit.[3] mp 88 °C), which was identical in all respects with natural cinnamolide (**3**).[17]

To utilize diol **14** in the synthesis of **1**, **4**, and **5**, the selectivity realized in the oxidation of **14** had to be transferred to selective protection and deprotection of C-11 and C-12 to obtain the desired oxidation patterns. Exclusive monoprotection at C-11 resulted upon treatment of **14** with *tert*-butyldimethylsilyl chloride and imidazole in DMF[18] which gave monosilyl ether **15**[11] in quantitative yield (Scheme III). Oxidation of **15** with pyridinium chlorochromate (PCC)[19] provided aldehyde **16**.[11] Liberation of the 11-OH with tetra-*n*-butylammonium fluoride[18] yielded lactol **17**[11] which, upon oxidation with PCC, gave (±)-drimenin (**4**),[11,17] mp 95–96 °C (lit.[3] mp 97–98 °C), 35% yield, from monosilyl ether **15**.

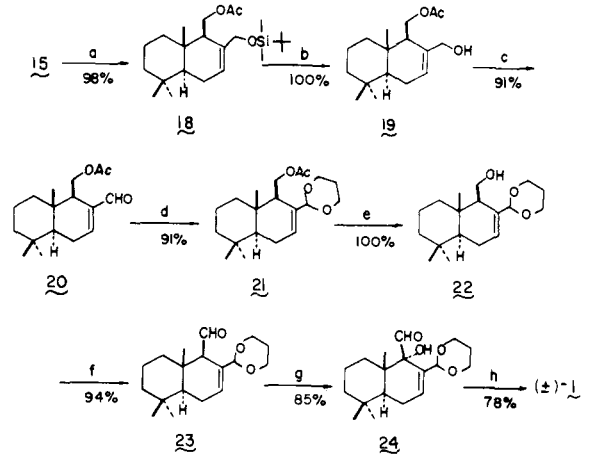
Acetylation of **15** with acetic anhydride and pyridine in refluxing benzene gave acetate **18**[11] which was hydrolyzed (1:3:1 THF, HOAc, H_2O)[18] to the hydroxyacetate **19**[11] in 98% overall yield (Scheme IV). Manganese dioxide oxidation of the allylic hydroxyl function of **19** afforded the crystalline aldehyde **20**:[11] mp 89–90 °C; IR ($CHCl_3$) 1735, 1695, 1645 cm^{-1}; ^{1}H NMR δ 6.89 (m, 7-H), 9.42 (s, CHO); 91% yield. Treatment of **20** with 10 equiv of 1,3-propanediol and a trace of *p*-toluenesulfonic acid in benzene at room temperature gave the

Scheme III[a]



[a] (a) *t*-Bu(Me)$_2$SiCl, imidazole, DMF; (b) (*n*-Bu)$_4$NF, THF; (c) PCC.

Scheme IV



acetoxy acetal **21**,[11] colorless oil, in 91% yield. Saponification of **21** with 10 equiv of methanolic potassium hydroxide (room temperature, 12 h) provided alcohol **22**,[11] which upon Collins oxidation gave the desired monoprotected dialdehyde **23**[11,20] (oil, ^{1}H NMR δ 9.70 (d, J = 5 Hz, CHO)) in 94% yield from **21**. Hydrolysis of the acetal with 2.5% aqueous hydrochloric acid in acetone (room temperature, 20 min) gave (±)-polygodial (**5**)[11,17] (mp 93–94 °C; IR ($CHCl_3$) 1720, 1680, 1640 cm^{-1}; ^{1}H NMR δ 7.12 (m, 7-H), 9.44 (s, 8-CHO), 9.51 (d, J = 4.5 Hz, 9-CHO)) in 83% yield.

Attention was now directed to the introduction of the axial-9-hydroxyl group. The enolate hydroxylation method of Vedejs[21] ($LiN(i\text{-}Pr)_2$, MoO_5·pyridine·HMPA) seemed to be well suited for this task, although, to the best of our knowledge, aldehyde-enolate hydroxylations utilizing this method have not been reported. Formation of the enolate of aldehyde **23** (1.2 equiv of $LiN(i\text{-}Pr)_2$, THF, −78 °C) and treatment with 1.5 equiv of MoO_5·pyridine·HMPA provided hydroxy aldehyde **24**:[11] IR (CCl_4) 3470, 1710 cm^{-1}; ^{1}H NMR δ 9.82 (d, J = 1.5 Hz, 9-CHO); 85% yield. Hydrolysis of the acetal with 2.5% aqueous hydrochloric acid in acetone (room temperature, 20 min) gave crystalline (±)-warburganal (**1**),[11,17] mp 98–99 °C, identical in TLC behavior and spectral (IR, ^{1}H NMR, CI-MS, and UV) properties with natural warburganal. The stereospecific total synthesis of warburganal was thus completed in 15.7% overall yield from diene **6** (see ref 22).

Acknowledgment. The authors are grateful to Dr. Isao Kubo for stimulating discussions and to NIH Grant AI 10187 for financial support.

References and Notes

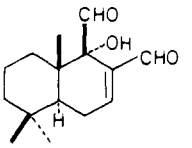
(1) I. Kubo, Y.-W. Lee, M. J. Pettei, F. Pilkiewicz, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 1013–1014 (1976); (b) I. Kubo, I. Miura, M. J. Pettei, Y.-W. Lee, F. Pilkiewicz, and K. Nakanishi, *Tetrahedron Lett.*, 4553 (1977); (c) K. Nakanishi and I. Kubo, *Isr. J. Chem.*, **16**, 28 (1977).
(2) L. Caronica, A. Corbella, G. Jommi, J. Krepinsky, G. Ferrari, and C. Casagrande, *Tetrahedron Lett.*, 2137 (1967); L. Canonica, A. Corbella, P. Gariboldi, G. Jommi, J. Krepinsky, G. Ferrari, and C. Casagrande, *Tetrahedron*, **25**, 3895 (1969).
(3) H. Yanagawa, T. Kato, and Y. Kitahara, *Synthesis*, 257 (1970); T. Suzuki, M. Tanemura, T. Kato, and Y. Kitahara, *Bull. Chem. Soc. Jpn.*, **43**, 1268 (1970).
(4) H. H. Appel, J. D. Connolly, K. H. Overton, and (in part) R. P. M. Bond, *J. Chem. Soc.*, 4685 (1960).
(5) E. Wenkert and D. P. Strike, *J. Am. Chem. Soc.*, **86**, 2044 (1964); Y. Kitahara, T. Kato, T. Suzuki, S. Kanno, and M. Taneumura, *Chem. Commun.*, 342 (1969).
(6) C. S. Barnes and J. W. Loder, *Aust. J. Chem.*, **15**, 322 (1962); see also A. Ohsuka, *Nippon Kagaku Zasshi*, 83, 757 (1962).
(7) Synthesis: T. Kato, T. Suzuki, M. Tanemura, H. S. Kumanireng, N. Ototani, and Y. Kitahara, *Tetrahedron Lett.*, 1961 (1971).
(8) The antifeedant activity is in turn blocked by L-cysteine. This aspect and the irreversibility of antifeedant action was shown by electrophysiological studies also (see ref 1c): W. C. Ma and I. Kubo, *Entomol. Exp. Appl.*, **22**, 107 (1977).
(9) (a) G. Brieger, *Tetrahedron Lett.*, 4429–4431 (1965); (b) J. C. Loperfido, *J. Org. Chem.*, **38**, 399 (1973); (c) J. A. Campos and F. Garcia Jimenez, *Rev. Soc. Quim. Mex.*, **19**, 93 (1975).
(10) Prepared in 92% yield by the addition of methylene triphenylphosphorane to β-cyclocitral.
(11) The structure assignment is supported by IR, NMR, and mass spectral measurements.
(12) G. Stork and H. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); K. Raman and P. N. Rao, *Tetrahedron*, **4**, 294 (1958); D. A. H. Taylor, *J. Chem. Soc.*, 3319 (1961); G. Stork, A. Meisels, and J. E. Davies, *J. Am. Chem. Soc.*, **85**, 3419–3425 (1963); N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **23**, 509 (1971); N. Ototani, T. Kato, and Y. Kitahara, *Bull. Chem. Soc. Jpn.*, **40**, 1730 (1967).
(13) B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *Chem. Ind. (London)*, 1667 (1961); E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964); E. Wenkert, A. Afonso, P. Beak, R. W. J. Corney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).
(14) H. C. Porown and R. M. Gallivan, Jr., *J. Am. Chem. Soc.*, **90**, 2906 (1968), and references cited therein.
(15) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
(16) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972), and references cited therein.
(17) Compared with an authentic natural sample provided by Dr. I. Kubo, Columbia University.
(18) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(19) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(20) Identical (UV, IR, ^{1}H NMR, TLC, and CI-MS) with a monoacetal prepared from natural polygodial under similar conditions.
(21) E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.*, **43**, 188 (1978), and references cited therein.
(22) Dr. T. Oishi and co-workers have also completed a total synthesis of (±)-warburganal: T. Nakata, H. Akita, T. Naito, and T. Oishi, *J. Am. Chem. Soc.*, following paper in this issue.

Steven P. Tanis, Koji Nakanishi*
Department of Chemistry, Columbia University
New York, New York 10027
Received April 4, 1979

A Total Synthesis of (±)-Warburganal

Sir:

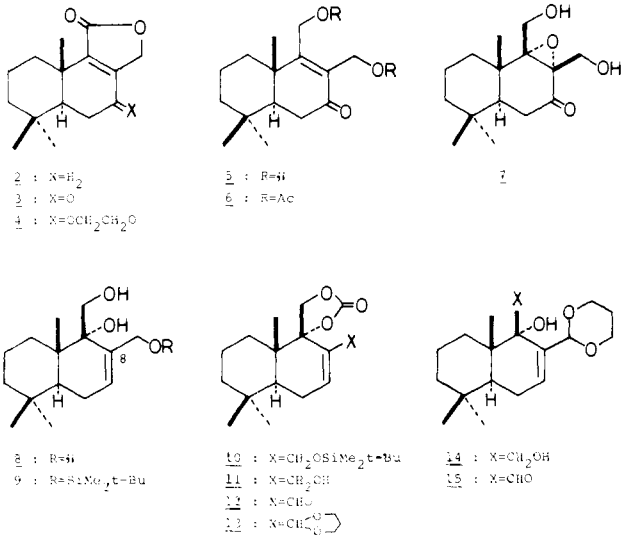
Warburganal (**1**), isolated from the bark of *Warburgia* (Canellaceae) (*W. stuhlmannii* and *W. ugandensis*) by Kubo, Nakanishi, and co-workers,[1] is a unique member of drimanic sesquiterpenes possessing both α-hydroxy aldehyde and enal units in the same ring and is reported to be an extremely effective antifeedant against the African army worms, *Spodoptera littoralis* and *S. exempta*. We report here the total synthesis of (±)-warburganal (**1**)[2] starting from readily available (±)-isodrimenin (**2**). The present work was under-



1

taken in the course of searching for biologically active compounds from drimanic sesquiterpenes and the related synthetic compounds.[3]

A large-scale preparation of (±)-isodrimenin (**2**) from β-ionone has recently been developed in this laboratory.[4a] Oxidation of **2** with CrO_3 in AcOH afforded the ketone **3**,[4c,5] which under the standard conditions (ethylene glycol, p-TsOH, benzene, reflux) was converted into the ketal **4**:[6] 94% yield; mp 89–90 °C; IR (CCl_4) 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84–4.17 (4 H, m), 4.68 (2 H, s). Reductive opening of the lactone ring of **4** with $LiAlH_4$ afforded, after the addition of 10% HCl, the keto dialcohol **5**: oil; IR (CCl_4) 3400, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.21–4.54 (4 H, m). Acetylation of **5** (Ac_2O, Py) gave the diacetate **6**: mp 87–88 °C; IR (CCl_4) 1745, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (3 H, s), 2.05 (3 H, s). The overall yield of **6** from **4** was 67%. Epoxidation of



0002-7863/79/1501-4400$01.00/0 © 1979 American Chemical Society