Acknowledgment. This research was supported in part by a grant (GM 13956) from the National Institutes of Health. High-field NMR spectra and GC/MS analyses were obtained with the aid of the University of Illinois NSF Regional Instrumentation Facility (NSF CHE 79-16100) and a grant from the National Cancer Institute (CA 11388), respectively. We are grateful to Professor Charles A. West, Department of Chemistry, University of California, Los Angeles, CA, for his advice and encouragement throughout this work and to Dr. H. Meier, Hofmann-La Roche, Basel, Switzerland, for a generous gift of (*E,E*)-farnesylacetone.

Registry No. 1a, 24286-51-9; **1b**, 81408-84-6; **4**, 73175-23-2; *cis*-**4**-d_3, 81408-85-7; *trans*-**4**-d_3, 81445-46-7; (−)-**4**, 81408-86-8; 6-methyl-5-hepten-2-one ethylene ketal, 3695-38-3.

Stereoselective Induction of Biomimetic Polyene Cyclizations[1] by Remote Chiral Centers. Effect of a Pro-C-7 Substituent in a Substrate Leading to Steroidal Products

William S. Johnson,* Daniel Berner, Donald J. Dumas, Pieter J. R. Nederlof, and John Welch

Department of Chemistry, Stanford University Stanford, California 94305

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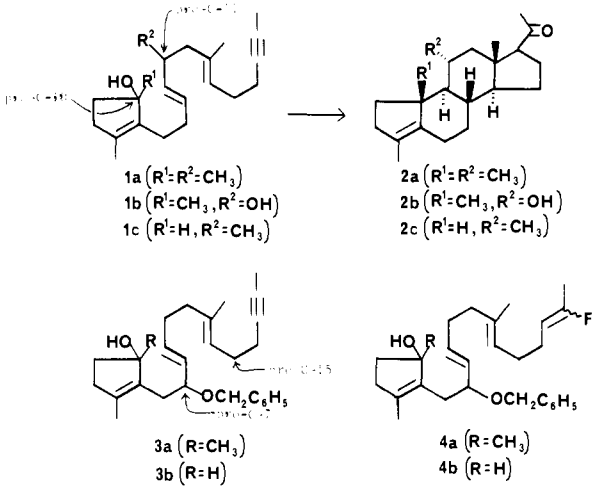
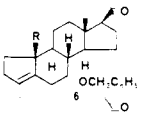
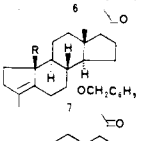
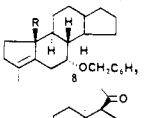
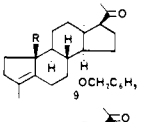
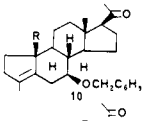
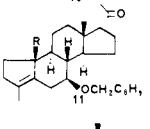
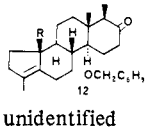
Ever since it was discovered that in the biomimetic cyclization of the substrates **1a** and **1b** the chiral center at *pro-C*-11 induced



ring closure so as to give preferentially the 11α-substituted products **2a** and **2b**, respectively[2]—a results that has led to the total asymmetric synthesis of a corticoid[3]—we have been intrigued by the possibility that a chiral center, even further removed from the initiating site of reaction might mediate diastereoselective cyclization. The case with a chiral center at *pro-C*-7, as in substrate **3a**, is particularly interesting for theoretical reasons (see below), and it also offered the potential of leading to some important steroids, e.g., spironolactone.

The diastereoselectivity previously observed in the cyclization **1a** → **2a** as well as **1b** → **2b** is easily understood because the transition state required for production of the (undetected) 11β epimer involves a destabilizing 1,3-diaxial interaction between the C-19-methyl group at *pro-C*-10 and the substituent (R^2) at *pro-C*-11. This contention was confirmed by the fact that cyclization of substrate **1c**, lacking such a 1,3-diaxial interaction (no C-19 methyl) was not diastereoselective, forming ca. equal amounts of **2c** and its 11β epimer.[4]

Table I. Distribution (%) of Cyclization Products[a]

tetracyclic product	from 3a (R = CH_3)	from 4a (R = CH_3)	from 3b (R = H)	from 4b (R = H)
	61.5	49	59	48
	1.5	27.5	1	26
	12.5	5	17	6
	2	6.5	3.5	6
	9	4.5	2	2
	2	3.5	1	1
	8	0	8	0
unidentified products	3.5	4	8.5	11

[a] By GC on a 14-m SE 54 capillary column. Values are uncorrected for any differences in detector response.

In the cyclization of **3** and **4**, however, there are no obvious steric interactions that might lead to diastereoselectivity.[5] One possibility that comes to mind is that, if there were extensive coiling of the acyclic chain in the transition state (as for a totally concerted process), then the *pro*-equatorial β-substituent at *pro-C*-7 could have nonbonded interactions with the *pro-C*-15 methylene group. Such a hypothesis, however, seemed to be divergent with van Tamelen's evidence[6] that epoxide-initiated polyene cyclizations are not concerted beyond the stage of the formation of the first ring.[7] Indeed we were not optimistic about the *pro-C*-7 substituent problem until the emergence of some encouraging, although preliminary, results on the cyclization of **3b**.[8]

(1) For a recent paper in the series on biomimetic polyene cyclizations, see: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513.

(2) (a) Johnson, W. S.; DuBois, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 1038–1039. (b) Johnson, W. S.; Escher, S.; Metcalf, B. W. *Ibid.* **1976**, *98*, 1039–1041. (c) Compare: Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161–163.

(3) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341–8343.

(4) Johnson, W. S.; Yarnell, T. M., unpublished work. See: T. M. Yarnell, Ph.D. Thesis, Stanford University, Stanford, CA, 1975.

(5) Note that the chiral center in the cyclopentenol moiety of **3** is expected to be lost, by dehydration, prior to cyclization; therefore, it may be ignored as a factor influencing the stereochemical course of the reaction (cf. footnote 6, ref 2a).

(6) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950–952.

(7) The concerted cyclization observed for formation of two rings (Bartlett, P. A.; Brauman, J. I.; Johnson, W. S.; Volkmann, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 7502–7504) is a special case involving participation of an aromatic ring. It is not so surprising, therefore, that remote substituents in such systems have resulted in diastereoselective cyclizations: Broess, A. I. A.; van Vliet, N. P.; Zeelen, F. J. *J. Chem. Res., Synop.* **1981**, 20–21 and ref 1 cited therein. Macco, A. A.; Buck, H. M. *J. Org. Chem.* **1981**, *46*, 2655–2660 and ref 1 cited therein.

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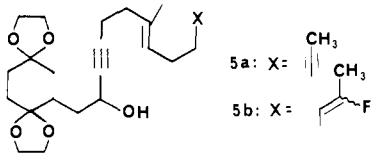
The present paper discloses the results of a study of the cyclization of the substrates **3a** and **3b**, as well as of **4a** and **4b**,[2c] which establish beyond doubt that there is indeed a strong diastereoselection induced in these ring closures by the substituent at *pro-C*-7.

For the synthesis of the cyclization substrates, a strategy was employed that is related, in principle, to that previously used for producing the *pro-C*-11-oxy substrates.[2b,c] The scheme involved, as the key intermediates, the propargylic alcohols **5a**[9a,10a] and



5b,[9a,10a,b] which were prepared, in the convergent step, by addition of the lithio salts of appropriately substituted acetylenic compounds to the 4,7-diketal of 4,7-diketooctanal.[11]

A solution of substrate **3a** (obtained by reaction of 265 mg of the enone precursor[11] with methyllithium) in 10 mL of ethylene dichloride was added over a 25-min period to a stirred mixture (under argon) of 33 mL of trifluoroacetic acid, 33 mL of trifluoroethanol, and 150 mL of ethylene dichloride at 0 °C. After 3 h at 0 °C, the mixture was treated with excess 20% potassium hydroxide in methanol. The crude product (see Table I for results of GC analysis on a 14-m SE 54 capillary column) was chromatographed on 20 g of Florisil to give 160 mg (60% yield) of fractions consisting of tetracyclic material. Similar procedures were used for the cyclization of substrates **3b**, **4a**, and **4b**, and the yields were 64, 66%, and 59%, respectively. The identification of the various products shown in Table I was carried out as summarized below.

Products from Substrates 3a and 4a. A specimen of the major product **6** (R = CH_3),[10a,b] mp 82–84 °C,[10d] was readily isolated in the case of the product from **3a** by crystallization of appropriate chromatographic fractions. The 7α (axial) configuration of the benzyloxy group was shown by the ^{1}H NMR coupling pattern for the 7β (equatorial) proton, which appeared as a complex multiplet at δ 3.45–3.60. This is to be compared with the broad diffuse pattern due to the axial 7α proton in the 7β-benzyloxy epimer **10** (R = CH_3) (see below). The remaining constitution of **6** (R = CH_3) was unequivocally established by its conversion[12] into known compounds including spironolactone. The identity of the 17α epimer **7** (R = CH_3),[9f,10a,b] mp 117–118 °C,[10d] was established by base-catalyzed interconversion experiments, **6** (R = CH_3) $\rightleftarrows$ **7** (R = CH_3) (**6**:**7** ratio at equilibrium = 85:15). Note that the mixture of these two epimers from cyclization of **4a**, readily isolated by chromatography, could be used directly for further synthetic work.[12] The interconvertible (at C-17) 13α (C/D cis) isomers **8** (R = CH_3)[10a,c] and **9** (R = CH_3)[10a,c] (**8**:**9** ratio at equilibrium ca. 97:3), are tentative assignments based on the coincidence of the ^{1}H NMR signals at δ 0.81 and 1.20, respectively, for the C-18 methyl with those of established cases.[2a,13,14] These are expected products from the cyclization of **3a**, although it was surprising to find as much as 11% arising from **4a**.[2c,13] The interconvertible (at C-17) 7β-benzyloxy isomers **10** (R = CH_3),[10a,b] mp 105–107 °C,[10d] and **11** (R = CH_3) (**10**:**11** ratio at equilibrium ca. 83:17) were identified by the ^{1}H NMR broad diffuse coupling pattern for the 7α (axial) proton and by the conversion of **10** (R = CH_3) (via hydrgenolysis of the benzyl group over Pd–C followed by oxidation of the alcohol with Jones reagent) into the 7-keto compound,[10a,c] (R = CH_3) identical (by GC, IR, NMR, MS) with an authentic sample of the ketone similarly prepared from **6** (R = CH_3). The D-homo isomer **12**[10a,b] (R = CH_3), mp 137–139 °C,[10d] is a tentative assignment.[2c,13] Its absence in the product derived from **4a** is consistent with previous observations.[2c,13]

Products from Substrates 3b and 4b. The interconvertible isomers **6** (R = H),[10a,b] mp 125–129 °C[10d] and **7** (R = H) were transformed[12] into known substances including 19-norspironolactone. The 7α-configuration for the benzyloxy group was shown by the ^{1}H NMR (see above). The structures of the interconvertible (at C-17) 13α isomers **8** (R = H)[10a,c] and **9** (R = H)[10a,c] are tentative assignments (see above). The interconvertible (at C-17) 7β-benzyloxy compounds **10** (R = H)[10a,c] and **11** (R = H) were identified by the ^{1}H NMR coupling patterns and the oxidation of each isomer to the same (by GC, MS) 7-keto compound (R = H) as in the normal series (R = CH_3) described above. The constitution of the D-homo isomer **12** (R = H),[10a,c] mp 150–152 °C, is tentative as in the case of **12** (R = CH_3).

Conclusions. The chiral center with the benzyloxy group at *pro-C*-7 in substrates **3a**–**4b** has a profound influence on the stereochemical course of the ring closure, inducing strong diastereoselection in the development of the first new bond between C-9 and C-10, which in turn determines the diastereoselectivity of the rest of the process. The degree of diastereoselection is reflected by the ratios of 7α and 7β epimers in the tetracyclic products, which were calculated from the data in Table I. Thus the 7α:7β ratio for the products derived from substrate **3a** was 6:1, that from **3b**, 10:1, that from **4a**, 20:1, and that from **4b**, 25:1. It is surprising that the ratios for the 19-nor series are significantly higher than in the normal series.

As an alternative to the coiling hypothesis (see introduction), the diastereoselectivity in these ring closures can be rationalized by postulating the intermediacy of a furano oxonium ion species (resulting from reaction of the *pro-C*-7 oxygen with the cyclopentenyl cation), which is opened by an S_N2' attack by the *pro-C*-8 olefinic bond. Experiments designed to distinguish between these two possibilities are in progress.

Finally, since the methodology is available[15] for converting the propargylic alcohol **5** (via asymmetric reduction of the corresponding ketone) into enantiomerically rich forms of **5**, the asymmetric synthesis of the cyclization products, described above, seemingly is close at hand.

Acknowledgment. We thank the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. D.B. is indebted to the Swiss National Science Foundation (ZWO) and P.J.R.N. to the Netherlands Organization for the Advancement of Pure Research for financial aid. D.J.D. was the recipient of an NIH Postdoctoral Fellowship. We also thank Dr. F. J. Zeelen for helpful discussions.

Registry No. 3a, 81740-42-3; **3b**, 81740-43-4; **4a**, 81740-44-5; **4b**, 81740-45-6; (±)-**5a**, 81740-46-7; (±)-**5b**, 81740-47-8; (±)-**6** (R = CH_3), 81740-48-9; (±)-**6** (R = H), 81740-49-0; (±)-**7** (R = CH_3), 81767-83-1;

(8) Groen, M. B.; van Vliet, N. P.; Zeelen, F. J. Symposium Papers, IUPAC International Symposium on Chemistry of Natural Products, 11th ed.; Marikov, N.; Ognyavov, I.; Orahovats, A. Eds.; 1978; Vol. 3, pp 29–31. This abstract describes the treatment of **3b** with CF_3CO_2H in $(CH_3)_2CHNO_2$ to give a mixture of epimeric (at 7 and 17) forms of *O*-(7-benzyloxy-3-methyl-*A*-nor-19-norpregn-3-en-17-yl)acetone oxime (compare: Morton, D. R.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4419–4420). The 7α:7β ratio was estimated (NMR) to be 9:1. This information was available to us, prior to publication, through a collaborative arrangement between Organon and one of us (W.S.J.).

(9) The product was purified by (a) chromatography on Florisil, (b) chromatography on silica gel, (c) distillation at reduced pressure through a short Vigreux column, (d) (for high-boiling compounds and/or small amounts of material) evaporative distillation (e.g., through a Kugelrohr), (e) chromatography on alumina, and (f) HPLC on DuPont Zorbax ODS.

(10) (a) The NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound. (c) The mass spectrum exhibited the correct molecular ion peak. (d) Recrystallized material was used for determining the melting point.

(11) A summary of the complete scheme involving a number of new compounds is given in the supplementary material.

(12) Johnson, W. S.; Dumas, D. J.; Berner, D. *J. Am. Chem. Soc.*, following communication in this issue.

(13) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802.

(14) Peters, J. A. M.; Posthumus, T. A. P.; van Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *J. Org. Chem.* **1980**, *45*, 2208–2214 and references cited therein.

(15) Brinkmeyer, R. S.; Kapoor, V. *J. Am. Chem. Soc.* 1977, *99*, 8339–8341.

(±)-7 (R = H), 81799-94-2; (±)-8 (R = CH_3), 81767-84-2; (±)-8 (R = H), 81767-85-3; (±)-9 (R = CH_3), 81767-86-4; (±)-9 (R = H), 81800-03-5; (±)-10 (R = CH_3), 81740-50-3; (±)-10 (R = H), 81740-51-4; (±)-11 (R = CH_3), 81767-87-5; (±)-11 (R = H), 81767-88-6; (±)-12 (R = CH_3), 81753-04-0; (±)-12 (R = H), 81768-76-5; I, 5312-85-6; II, 81740-52-5; III, 81740-53-6; Va, 81740-54-7; Vb, 81740-55-8; (±)-VIa, 81740-56-9; (±)-VIb, 81740-57-0; (±)-VIIa, 81740-58-1; (±)-VIIb, 81740-59-2; (±)-VIIIa, 81740-60-5; (±)-VIIIb, 81740-61-6; (±)-IXa, 81740-62-7; (±)-IXb, 81753-05-1.

Supplementary Material Available: A summary of the complete scheme for the preparation of the cyclization substrates **3a**, **3b**, **4a**, and **4b** involving a number of new compounds (3 pages). Ordering information is given on any current masthead page.

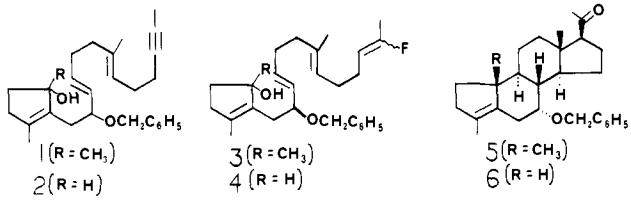
Total Synthesis of *dl*-Spironolactone and *dl*-19-Norspironolactone by Biomimetic Polyene Cyclization Methodology[1]

William S. Johnson,* Donald J. Dumas, and Daniel Berner

Department of Chemistry, Stanford University
Stanford, California 94305

Received February 8, 1982

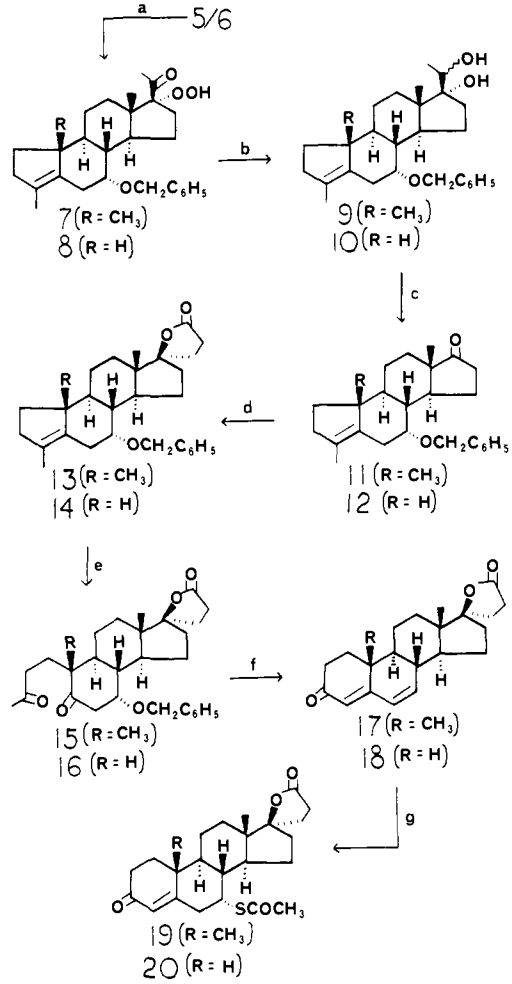
The cyclization of the substrates **1**, **2**, **3** and **4** is described in



the preceding communication.[2] The major product derived from **1** as well as from **3** was presumed to be the 7α-benzyloxy steroidal substance **5**. Similarly the principal product from either **2** or **4** was thought to be the 19-nor material **6**. We decided to try to obtain unequivocal proof of the constitution of **5** and **6** by transforming them into substances of established structure, in particular the well-known[3b] spironolactone types and intermediates leading thereto. The present communication discloses an account of these structure-proving experiments that have led also to the realization of one of the major aims of the original study, namely, the total synthesis of the racemic form of the aldosterone blocking agent, spironolactone (**19**), an important diuretic for treating severe cases of hypertension.

The synthetic transformations that were developed for conversion of **5** and **6** into the spironolactones **19** and **20**, respectively, are summarized in Scheme I. Thus **5** was submitted to base-catalyzed oxygenation,[4] giving the 17α-hydroperoxy compound **7**. Attempts to effect cleavage of this latter substance directly to the 17-keto compound[5] resulted in formation of highly impure specimens of **11**. Better results were obtained by sodium borohydride reduction of **7** to give the diol **9** as a mixture of C-20 epimers, followed by lead tetraacetate oxidation. Thus, without any purification of the intermediates **7**[7a] and **9**,[7a] the ketone **11**,[6a,7a,b] mp 77–80 °C,[7d] was produced in 58% yield from **5**.

Scheme I



[a] Excess *t*-BuOK, 4:4:1 *t*-BuOH/THF/DMF, O_2, 1 h, 0 °C. [b] Excess $NaBH_4$, EtOH, 2 h, 20 °C. [c] Excess $Pb(OAc)_4$, HOAc, 1 h, 20 °C. [d] 3 mol equiv of $(Me_2N)_2P(O)OCH_2CH{=}CH_2$, 5 mol equiv of 1.5 M *n*-BuLi/hexane, THF, 10 min, −60 °C; 30 m, −20 °C, then 5 mol equiv of TMEDA; 11 or 12, 10 min, −60 °C; NH_4Cl. [e] Excess O_3, 1 mol equiv of MeOH, 0.5% C_5H_5N in CH_2Cl_2, 20 min, −78 °C; excess Zn, HOAc. [f] 40:4:1 HOAc/concentrated HCl/H_2O, 65 h, 22 °C. [g] HSAc, 4 h, 29 °C.

Similarly **6** was converted via the intermediates **8**[7a] and **10**[7a] into **12**,[6a,7a,b] mp 98–102 °C[7d] (73% yield from **6**). Ketone **11** was transformed, by the elegant one-step method of Sturtz et al.,[8] into the lactone **13**,[6a,7a,b] mp 101–103 °C[7d] (68% conversion, 79% yield). Similarly **12** was converted into **14**,[6a,7a,b] mp 116–119 °C[7d] (79% yield). Lactone **13** was ozonolyzed, and the resulting crude diketo compound **15**[7a] was treated with hydrochloric acid/acetic acid at 22 °C, which effected concomitant cyclodehydration of the 1,5-diketo system and elimination of the benzyloxy group, giving the dienone lactone **17**,[7a,c] mp 210–212 °C,[7d] in 47% yield. This material was identified by comparison[9] with authentic, naturally derived canrenone (**17**).[3b] Similarly lactone **14** was converted via **16**[7a] into the dienone lactone **18**,[6b,7a,b] mp 191–192 °C[7d] (65% yield), which was identified by comparison[9] with authentic 19-

(1) For a recent paper in the series on biomimetic polyene cyclizations, see: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513.
(2) Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J., *J. Am. Chem. Soc.* preceding communication in this issue.
(3) (a) Cella, J. A.; Brown, E. A.; Burtner, R. R. *J. Org. Chem.* **1959**, *24*, 743–748. (b) Cella, J. A.; Tweit, R. C. *Ibid.* **1959**, *24*, 1109–1110.
(4) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578–1591. The procedure employed was that of Gardner et al. (Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 1566–1570).
(5) Siddall, J. B.; Baddeley, G. V.; Edwards, J. A. *Chem. Ind. (London)* **1966**, 25–26.
(6) The product was purified by (a) chromatography on Florisil, (b) chromatography on silica gel.
(7) (a) The NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound. (c) The mass spectrum exhibited the correct molecular ion peak. (d) The melting point was determined on recrystallized material.
(8) Sturtz, G.; Yaouanc, J.-J.; Krausz, F.; Labeeuw, B. *Synthesis* **1980**, 289–291.
(9) The two substances were identical with respect to the following properties: ^1H NMR spectra, solution IR spectra, GC (coinjection) retention times.

0002-7863/82/1504-3510$01.25/0