s), 1.69 (3 H, s), 1.75 (3 H, s), 1.76 (3 H, s), 1.78 (3 H, s), 1.79 (3 H, s), 1.87 (3 H, s), 2.19 (3 H, s); $\alpha_D$ +112° (*c* 0.18, $CHCl_3$)]. The same sequence of reactions was performed with phosphonium salt **19** (the antipode of **18**), prepared from L-xylose,[9] to yield the C19 and C20 diastereomer of **17**.[13] Upon comparison of the spectroscopic data, synthetic octaacetate **17** was found to be identical with degradation product **17**, establishing the stereochemistry at C19, C20, C45, and C46.

The acetates **20–22** (Chart IV) were known to be more advanced degradation products of **1**.[14] The $^1H$ NMR spectrum of **20** suggested that the relative stereochemistry of the tetrahydropyran ring was as indicated in the structure.[14] The stereochemistry of the acyclic portions remained unknown. Synthesis of **22** [$^1H$ NMR ($CDCl_3$) δ 2.06 (3 H, s), 2.08 (3 H, s), 2.09 (6 H, s); $\alpha_D$ +34.0° (*c* 0.11, $CHCl_3$)] was achieved in six steps from alcohol **23**,[9] which was synthesized from 2,3,4-tribenzyl-1,6-anhydro-D-glucopyranose.[15] Upon comparison of spectroscopic data and optical rotations, synthetic triacetate **22** was found to be identical with degradation product **22**, establishing the absolute configuration at C11 and C15.

Since the stereochemistry of the tetrahydropyran ring was known from the $^1H$ NMR data, only four diastereomers remained as structural possibilities for degradation product **21**. By use of the carbohydrate chain-extension method,[16] all four diastereomeric heptaacetates were synthesized from alcohol **23**.[17] Upon comparison of $^1H$ NMR spectra, synthetic threo heptaacetate **21** [$^1H$ NMR ($C_6D_6$) δ 1.61 (3 H, s), 1.73 (6 H, s), 1.78 (6 H, s), 1.85 (3 H, s), 1.87 (3 H, s)] was found to be identical with degradation product **21**, establishing the stereochemistry at C12, C13, C14, C16, and C17. With use of similar methods, alcohol **24** and its C18 diastereomer were synthesized. The stereochemistry at C18 of **24** was unambiguously established by synthesis of one of the intermediates from L-glyceraldehyde.[17] In order to study the stereochemistry at C8, C9, and C18, we transformed **24** into cis- and trans-α,β-unsaturated ketones **25** and **26** via routine synthetic operations. Osmium tetroxide oxidation of cis-α,β-unsaturated ketone **25**, followed by separation of isomers, borohydride reduction, deacetonization, debenzylation, and acetylation, furnished two pairs of decaacetates with an erythro relationship between C8 and C9. Likewise, two pairs of decaacetates with a threo relationship between C8 and C9 were obtained from trans-α,β-unsaturated ketone **26**. Upon comparison of $^1H$ NMR spectra, one pair of the erythro decaacetates was found to be identical with degradation product **20**,[18] establishing the relative stereochemistry between C8 and C9 and the absolute stereochemistry at C18.

The absolute configuration at C8 was concluded by the following experiments. The erythro diol with the unnatural configuration at C8 and C9, obtained by $OsO_4$ oxidation of **25** (vide supra), was transformed into heptaacetate **27**.[19] The absolute configuration of **27** was determined as follows. Trans-allylic alcohol **28**[20] was subjected to Sharpless' asymmetric epoxidation[21] by using D(−)-diethyl tartrate to yield the expected epoxide **29**,[22] which was then converted to heptaacetate **27**.[23] Heptaacetate **27** thus prepared was found to be identical with heptaacetate **27** derived from **25**, establishing the absolute stereochemistry at C8 and consequently at C9.

Successful assignment of the stereochemistry of degradation products **17** and **20** allows us to define the stereochemistry of degradation product **1** as shown in the structure.[24]

**Acknowledgment.** Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 78-06296) to the Harvard group is gratefully acknowledged. The Nagoya group is grateful to the Foundation for the Promotion of Research on Medical Resources and the Ministry of Education, Japanese Government (Grants-in-Aid 411704 and 56540320), for financial support. Appreciation is also expressed for the use of the 500-MHz NMR instrument at the NMR Facility for Biomolecular Research located at the F. Bitter National Magnet Laboratory, MIT. The NMR facility is supported by Grant RR00995 from the Division of Research Resources of the NIH and by the National Science Foundation under Contract C-670.

**Supplementary Material Available:** Spectroscopic data for compounds **4**, **17**, **21**, **22**, and **27** (two diastereomers) and details of some synthetic sequences (4 pages). Ordering information is given on any current masthead page.

(13) $^1H$ NMR signals due to the C18–C21 portion of **17** were found to correspond exceptionally well to those of *threo*-nonane-1,2,3-triol triacetate but not to those of *erythro*-nonane-1,2,3-triol triacetate.

(14) For acetates **20** and **22**, see ref 2a and 1a, respectively, of part 1 of this series. Acetate **21** was isolated as a minor product of periodate oxidation of **1**.

(15) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(16) See ref 6 in part 1 of this series.

(17) Details of these syntheses will be published elsewhere: Christ, W. J.; Cha, J. K.; Kishi, Y., manuscript in preparation.

(18) This substance was a diastereomeric mixture due to the C7 positon. Separation of the diastereomers was possible by analytical silica gel TLC (Merck HP-TLC silica gel 60F-254 5642; solvent system 1:1 hexane–AcOEt; four developments). $^1H$ NMR of the less polar decaacetate (500 MHz, $C_6D_6$) δ 1.26 (3 H, d, *J* = 6.6 Hz), 1.68 (3 H, s), 1.70 (3 H, s), 1.71 (3 H, s), 1.72 (3 H, s), 1.74 (3 H, s), 1.79 (3 H, s), 1.80 (3 H, s), 1.85 (3 H, s), 1.91 (6 H, s). $^1H$ NMR of the more polar decaacetate (500 MHz, $C_6D_6$) δ 1.09 (3 H, d, *J* = 6.6 Hz), 1.67 (3 H, s), 1.68 (3 H, s), 1.72 (3 H, s), 1.78 (3 H, s), 1.79 (3 H, s), 1.80 (3 H, s), 1.81 (3 H, s), 1.86 (3 H, s), 1.87 (3 H, s), 1.90 (3 H, s).

(19) This transformation was performed in the following six steps: (1) $NaBH_4$; (2) $C_6H_5CH_2Br/NaH$; (3) aqueous AcOH; (4) $NaIO_4$, followed by $NaBH_4$ workup; (5) $H_2/Pd$–C; (6) $Ac_2O$/py.

(20) This substance was prepared from **23** in seven steps: (1) $C_6H_5CH_2Br/NaH$; (2) $O_3$/MeOH/-78 °C; (3) $CH_2{=}CHMgBr/Et_2O$; (4) $C_6H_5CH_2Br/NaH$, followed by TLC separation; (5) $O_3$/MeOH/-78 °C; (6) $(i\text{-}PrO)_2P(O)CH_2CO_2Et/t\text{-}BuOK$/THF; (7) DIBAL/$CH_2Cl_2$–$C_6H_6$. The stereochemistry at C9 of **28** was not determined by this synthesis, but the fact that heptaacetate **27** had an erythro relationship between C8 and C9 permitted the conclusion of the C9 stereochemistry.

(21) See ref 8 in part 1 of this series.

(22) Asymmetric epoxidation using L(+)-diethyl tartrate yielded a diastereomeric epoxide of **29**.

(23) This transformation was performed in the following nine steps: (1) $C_6H_5CH_2OCOCl$/py; (2) $AlCl_3$; (3) $MeOCH_2Br/(i\text{-}Pr)_2(Et)N$; (4) aqueous NaOH; (5) $NaIO_4$; (6) MeMgI, followed by TLC separation; (7) concentrated HCl/MeOH; (8) $H_2/Pd$–C; (9) $Ac_2O$/py.

(24) For the stereochemistry at C47, see part 4 of this series.

## Stereochemistry of Palytoxin. 4.[1] Complete Structure

J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi,* L. L. Klein,† S. S. Ko, J. Leder,‡ W. W. McWhorter, Jr.,§ K.-P. Pfaff,‖ and M. Yonaga

*Department of Chemistry, Harvard University Cambridge, Massachusetts 02138*

D. Uemura

*Faculty of Liberal Arts, Shizuoka University Ohya, Shizuoka 422, Japan*

Y. Hirata

*Faculty of Pharmacy, Meijo University Tempaku, Nagoya 468, Japan*

*Received July 19, 1982*

In the preceding communications we have disclosed the stereochemistry of key degradation products of the marine natural product palytoxin. It is important to note that *all* of the asymmetric centers existing in palytoxin are found intact[2] in these

†National Institutes of Health NRSA Postdoctoral Fellow 1980–1982.

‡National Institutes of Health trainee at Harvard University, 1978 to present.

§National Science Foundation Predoctoral Fellow, 1978–1981; Monsanto Chemical Co. Fellow at Harvard University, 1981–1982.

‖Studienstiftung des Deutschen Volkes Fellow, 1980–1981.

(1) Part 3 of this series: *J. Am. Chem. Soc.*, preceding paper in this issue.

0002-7863/82/1504-7369$01.25/0 

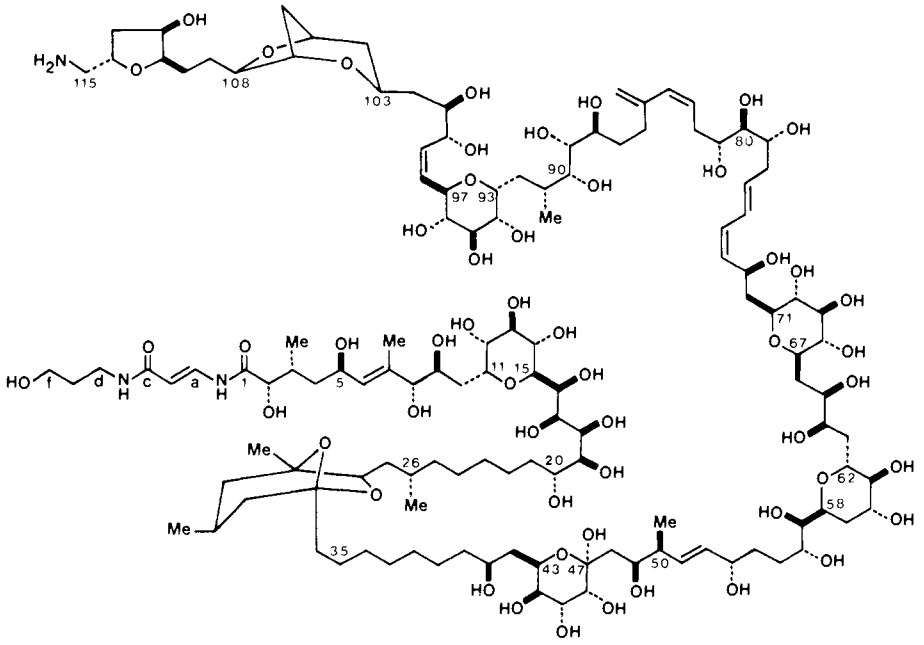


**Figure 1.** Palytoxin (**1**).

degradation products so that we are now in a position to describe the complete structure of the toxin. Owing to extensive investigations by the Nagoya group[3] and by the Hawaii group,[4] no ambiguity remains concerning either the connectivity of these degradation products or the stereochemistry of all of the olefinic bonds. The spin–spin coupling constants in the $^1H$ NMR spectrum of palytoxin itself[5] provided confirmation of the stereochemistry assignment of the double bonds.[6]

The palytoxin used in this study was extracted from Okinawan *Palythoa tuberculosa*,[3] whereas the palytoxin used by the Hawaii group was extracted from Hawaiian *Palythoa toxica* or a Tahitian *Palythoa* species.[4] Although direct comparison of Okinawan palytoxin with Hawaiian or Tahitian palytoxin has not been made, it seems from $^{13}C$ NMR spectra of palytoxin and $^1H$ NMR spectra of degradation products[7] that they are identical. There is, however, one discrepancy between the gross structure assigned to Tahitian palytoxin by the Hawaii group[8] and that assigned to Okinawan palytoxin by the Nagoya group.[9] The latter suggested a hemiketal structure at the C47 position, while the Hawaii group suggested an anhydro structure at the C44 and C47 positions. The $^{13}C$ NMR spectrum of Tahitian palytoxin in $D_2O$ at 25 °C has been reported to show a signal at 100.2 ppm for the C47 ketal carbon, while the $^{13}C$ NMR spectrum of Hawaiian palytoxin has been reported not to show hemiketal carbon signals. The $^{13}C$ NMR spectrum of Okinawan palytoxin in $D_2O$ at room temperature shows an intense signal at 100.3 ppm. The FAB mass spectrum of *this sample* shows an ion at 2678.9 ± 0.2, which corresponds well with the molecular ion of the hemiketal structure (calcd for $C_{129}H_{223}N_3O_{54}$ = 2678.5).[10] The $^{13}C$ chemical shifts of C2 in tagatose, in which the stereochemistry is similar to that at C44, C45, and C46 of palytoxin, and 2,5-anhydrotagatose[11] indicate that it is very unlikely that a hemiketal carbon and a ketal carbon would show identical chemical shifts.[12] The chemical reactivity observed for palytoxin (this includes (1) smooth hydrogen–deuterium exchange at the C48 position in $D_2O$ at room temperature, (2) facile bond cleavage between C46 and C47 upon periodate oxidation at 0 °C, and (3) formation of an $\alpha,\beta$-unsaturated ketone at C47–C49) is easily explained by the hemiketal structure but not by the ketal structure unless hydrolysis of the anhydro form to the corresponding hemiketal is unusually facile. It should be noted that 2,5-anhydrotagatose remained unchanged for 24 h at 55 °C in $D_2O$.

As is known for ketoses,[13] the six-membered hemiketals **1A** must exist in equilibrium with the five-membered hemiketals **1B**. However, the equilibrium of palytoxin is weighted heavily in favor of **1A** for steric reasons—note that four substituents must remain on one face of the tetrahydrofuran ring of **1B**. With regard to the stereochemistry at C47, **1A-a** seems to be preferred over **1A-b** primarily for two reasons: (1) the two bulky side chains can take an equatorial orientation in **1A-a**; (2) **1A-a** has anomeric stabilization.

Palytoxin can now be defined as structure **1**! (See Figure 1.) Thus, a solid foundation has been laid for the next steps in the chemical investigation of the toxin. One final comment on the stereochemistry assignment of palytoxin recently proposed[14] seems

(2) Some degradation products that we have dealt with in the preceding communications were prepared via intermediates with asymmetric centers adjacent to carbonyl groups, e.g., preparation of **17** from **1** in part 3. The possibility that epimerization of these asymmetric centers occurred during preparation and/or isolation of these degradation products was excluded by careful control experiments for each case.

(3) See ref 2a–f in part 1 of this series.

(4) See ref 1a–e in part 1 of this series.

(5) The olefinic region of the $^1H$ NMR spectrum of palytoxin was virtually first order. The following spin–spin coupling constants (Hz) were observed: $J_{a,b}$ = 14.4, $J_{51,52}$ = 15.6, $J_{74,75}$ = 10.9, $J_{76,77}$ = 14.8, $J_{83,84}$ = 10.9, and $J_{98,99}$ = 10.9.

(6) The stereochemistry of the trisubstituted olefin at C6–C7 had been determined by an NOE experiment on the aldehyde, which was obtained by periodate cleavage between C8 and C9 of palytoxin (see ref 2f in part 1 of this series). The possibility that double bond isomerization occurred during preparation and/or isolation of this aldehyde was excluded by the fact that no deuterium was incorporated when the oxidation was carried out in deuterated solvents.

(7) For $^{13}C$ NMR spectra of palytoxin, see ref 1d and 2f in part 1 of this series. For $^1H$ NMR spectra of degradation products from Hawaiian or Tahitian palytoxin, corresponding to **1b** and **10** in part 1, **7** and **11** in part 2, and **4** and acetylated dihydro derivative of **1** in part 3, see ref 1a and 1b in part 1 of this series.

(8) See ref 1a in part 1 of this series.

(9) See ref 2a in part 1 of this series.

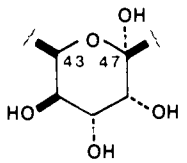
(10) We are indebted to Dr. B. Green at VG/Micromass in Manchester, England, for this experiment. We thank Professor Rinehart, University of Illinois at Urbana–Champaign for arranging to have this measurement taken. Also see ref 2e in part 1 of this series.

(11) Köll, P.; Deyhim, S.; Heyns, K. *Chem. Ber.* **1978**, *111*, 2909.

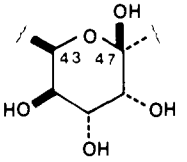
(12) The chemical shift of the ketal carbon of 2,5-anhydrotagatose in $D_2O$ was found to be 109.6 ppm, whereas that of the six-membered hemiketal carbon was 99.2 ppm and that of the five-membered hemiketal carbon was 103.6 ppm. Similar results were observed for fructose (six-membered hemiketal carbon, 98.9 ppm, and five-membered hemiketal carbon, 102.3 ppm) and 2,5-anhydrofructose (108.6 ppm) and for sorbose (six-membered hemiketal carbon, 98.8 ppm, and five-membered hemiketal carbon, 102.8 ppm) and 2,5-anhydrosorbose (111.2 ppm). For $^{13}C$ NMR spectra of ketoses, see ref 13.

(13) Que, L., Jr.; Gray, G. R. *Biochemistry* **1974**, *13*, 146.

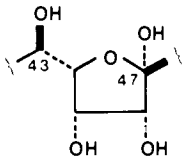
(14) Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.



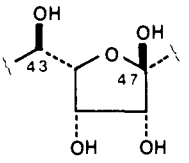
1A-a



1A-b



1B-a



1B-b

warranted here. The misassignment of a large number of stereocenters through primary dependence on NMR methods alone points out the limitation of these types of experiments and the continuing importance of organic synthesis in structure elucidation.

**Acknowledgment.** Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 78-06296) to the Harvard group is gratefully acknowledged. The Nagoya group is grateful to the Foundation for the Promotion of Research on Medical Resources and the Ministry of Education, Japanese Government (Grants-in-Aid 411704 and 56540320), for financial support. Appreciation is also expressed for the use of the 500-MHz NMR instrument at the NMR Facility for Biomolecular Research located at the F. Bitter National Magnet Laboratory, MIT. The NMR facility is supported by Grant RR00995 from the Division of Research Resources of the NIH and by the National Science Foundation under Contract C-670.

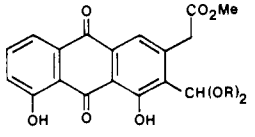
## Practical Asymmetric Synthesis of Aklavinone

J. M. McNamara† and Y. Kishi*

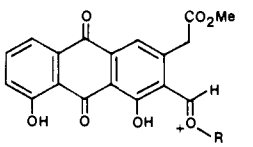
*Department of Chemistry, Harvard University*
*Cambridge, Massachusetts 02138*

*Received August 2, 1982*

We recently reported a practical total synthesis of racemic aklavinone (**1**, Chart I), the aglycone of the aclacinomycin group of medicinally important anthracycline antitumor antibiotics.[1-3] One of the key steps of our synthesis involved a crossed aldol reaction of dimethylacetal **2** with $CH_3CH_2COCH_2Si(CH_3)_3$ in



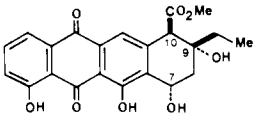
2 : R = Me



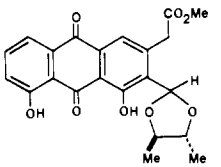
A

$CH_2Cl_2$ containing $SnCl_4$ at −40 °C. The aldol product was then converted to racemic aklavinone in two steps. In this communication we report a practical synthetic route to optically active aklavinone, utilizing an efficient asymmetric crossed aldol reaction.

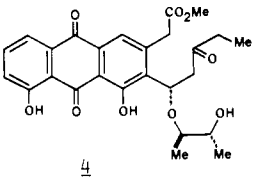
Chart I



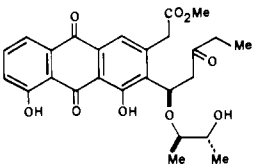
1 : aklavinone



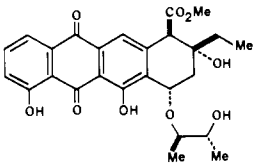
3



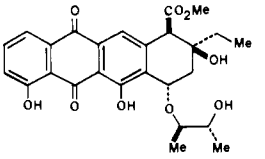
4



5



6



7

It occurred to us that a slight modification of our original synthesis might provide a route to optically active aklavinone.[4] Namely, the acetal corresponding to **2** would allow for generation of chiral oxonium ion A, when the acetal is prepared from an optically active alcohol. The oxonium ion A could, in turn, react with the nucleophile derived from $CH_3CH_2COCH_2Si(CH_3)_3$ from either of its two diastereotopic faces, thereby producing potentially unequal amounts of the two possible diastereomeric aldols.

In order to test this possibility, we synthesized the acetal **3**[5] [mp 192–194 °C; $\alpha_D$ −47.9° (*c* 0.19, $CHCl_3$)] from one of the intermediates used in our previous synthesis.[6] Although **3** was recovered unchanged under the original conditions ($CH_3CH_2COCH_2Si(CH_3)_3/SnCl_4/CH_2Cl_2/-40$ °C),[7] it reacted smoothly and cleanly with $CH_3CH_2COCH_2Si(CH_3)_3$ in $CH_3CN$ ($SnCl_4/CH_3CN/-20$ °C/4 h) to yield a 10:1 mixture of the two possible crossed aldol products **4** [mp 120–124 °C; $\alpha_D$ −155° (*c* 0.19, $CHCl_3$)] and **5** [mp 77–86 °C; $\alpha_D$ −14.2° (*c* 0.45, $CHCl_3$)] in 83% combined yield.[8] It is worth noting that the acetal prepared from l-menthol, i.e., R = l-menthol in **2**, gave lower asymmetric induction (product ratio = 1.5:1.0) on crossed aldol reaction.[9]

The absolute configuration at C7 of **4** was concluded from its successful conversion to natural aklavinone (**1**). Namely, treatment of **4** with excess $K_2CO_3$ in $CH_3OH$ at room temperature for 2 h led to the cyclized products **6** [mp 116 °C and 163–165

† National Institutes of Health Trainee at Harvard University, 1979–1982.

(1) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.

(2) For the synthesis of aklavinone from other groups, see: (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Confalone, P. N.; Pizzolato, G. *Ibid.* **1981**, *103*, 4251. (c) Li, T.-t.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007.

(3) For recent reviews on the chemistry of anthracycline antibiotics, see references given in ref 1, and the following: Arcamone, F. "Doxorubicin"; Academic Press: New York, 1981.

(4) Kende's synthesis provided optically enriched aklavinone. See the paper quoted under ref 2a.

(5) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(6) The acetal **3** was synthesized in 92% yield by acetalization [D(−)-2,3-butanediol/*p*-TSA·py/$C_6H_6$/reflux] of the aldehyde reported as compound **7** in the paper quoted in ref 1. We are indebted to Dr. N. Cohen, Hoffmann-La Roche, Inc., for a generous gift of D(−)-2,3-butanediol.

(7) Under more forcing conditions ($CH_3CH_2COCH_2Si(CH_3)_3/SnCl_4/CH_2Cl_2/-20$ °C → room temperature), **3** did disappear, but many products were observed.

(8) Diastereomers **4** and **5** were easily separated by preparative eluant; gel thin-layer chromatography (12% EtOAc/$C_6H_6$ as eluant; $R_f$(**4**) 0.36; $R_f$(**5**) 0.27).

(9) For use of an optically active acetal derived from D(−)-2,3-butanediol in asymmetric polyene cyclizations, see: Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188.

0002-7863/82/1504-7371$01.25/0 