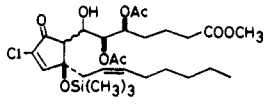
desired allenic condensation product (22%). The stereochemistry of **10** was definitely established by X-ray crystallographic analysis. Hydrogenation of **10** over Lindlar catalyst in methanol afforded the *Z*-olefinic product **11** (98%), $[\alpha]^{21}_D$ −23.0° (*c* 0.13, $CHCl_3$), which in turn was oxidized by pyridinium dichromate in DMF to give the hydroxy enone **12**, $[\alpha]^{25}_D$ −57.6° (*c* 0.25, $CHCl_3$) (91%). Thus in going from **3** to **12**, chirality of the hydroxylated carbon was transferred cleanly in a 1,3 manner. Silylation of **12** with trimethylsilyl triflate and diisopropylethylamine in CH_2Cl_2 gave **13**, $[\alpha]^{23}_D$ −20.9° (*c* 0.31, $CHCl_3$) (86%). Aldol condensation of the enone **13** and the aldehyde **5** (1:3 ratio) was then effected with LDA in THF at −78 °C, leading to **14** in 44% yield (75% yield corrected for recovery of **13**). Dehydration of the aldol product with acetic anhydride and 4-(dimethylamino)pyridine in CH_2Cl_2 and subsequent desilylation in a 6:3:1 mixture of acetic acid, water, and THF gave the desired **1** and **2** (1:4 ratio) (41%) having 5*S*,6*S*,12*S* configuration. However, the 500-MHz ^1H NMR spectra of these products were not identical with those of the naturally occurring (7*E*)- and (7*Z*)-PUG 4, thus dictating revision of the originally postulated structures.[2]

We then prepared all possible diastereomers with respect to C-5, C-6, and C-12 relative configurations similarly from the appropriate chiral cyclopentenones and side-chain units.[16] Of these, only product obtained from **3** and the (2*S*,3*R*)-diacetoxy-aldehyde (enantiomer of **5**) showed consistent ^1H NMR[18] and HPLC behavior (Yamamura Chemical Co., YMC A-003-3 + A-002-3, 1:1 hexane–ether as eluant). However, the CD curves indicated that the synthetic samples were the antipodes of those of the natural specimen: natural (7*E*)-PUG 4 (CH_3OH), $\Delta\epsilon$ −5.0 at 250 nm; natural (7*Z*)-PUG 4 (CH_3OH), $\Delta\epsilon$ −4.8 at 268 nm. The natural (7*E*)- and (7*Z*)-PUG 4 (**15** and **16** respectively 2:5) were synthesized likewise from the enantiomer of **3**,[19] allenyltin **4**, and aldehyde **5**.[20] Irradiation of pure **15** or **16** in benzene (Pyrex, 25-W fluorescent lamp, 25 °C) led to a 7:3 photoequilibrated mixture of **15** and **16**.



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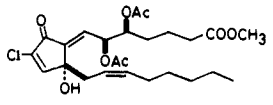
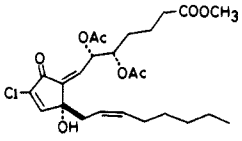


15, 7*E*-PUG 4



16, 7*Z*-PUG 4

We now can conclude that natural (7*E*)- and (7*Z*)-PUG 4 have the 5*S*,6*S*,12*R* configuration. The 17,18-dehydro derivatives, (7*E*)- and (7*Z*)-PUG 3, must have the same stereochemistry.[2] Most significantly, the *R* configuration at C-12 in PUG 3 and 4 is the opposite of the *S* stereochemistry (*ent*-prostanoid structure) of the closely related marine eicosanoids, clavulones[4] or claviridenones.[5] Recently isolated chlorovulones possess also 12*R* configuration.[21] The chlorine atom at C-10 seems to alter the biosynthetic pathway.[22,23]

Acknowledgment. We are grateful to Professor Y. Yamada, Tokyo College of Pharmacy, for providing valuable information prior to publication. Suggestions by Professor N. Harada, Tohoku University, on the CD measurements and valuable comments by Dr. Y. Kobayashi, Tokyo Institute of Technology, on the mechanism of the epoxide ring opening are also appreciated.

Supplementary Material Available: Analytical and spectral data for **1**, **2**, **5**, and **7**–**16**, as well as the C-5, C-6, and C-12 diastereomers (12 pages). Ordering information is given on any current masthead page.

(16) Enantiomer of **5**, $[\alpha]^{22}_D$ +21.8° (*c* 0.97, C_6H_6), was prepared by Scheme I by using D-(−)-diethyl tartrate as the chiral auxiliary in the Sharpless epoxidation. The (2*S*,3*S*)-diacetoxy aldehyde, $[\alpha]^{23}_D$ −0.97° (*c* 0.81, C_6H_6), was obtained from (5*S*,6*R*)-methyl 5,6,7-trihydroxyheptanoate[17] through a four-step sequence: (i) *t*-$C_4H_9(C_6H_5)_2SiCl$, imidazole, 17 °C, 0.5 h, 98%; (ii) $(CH_3CO)_2O$, 4-(dimethylamino)pyridine, 17 °C, 15 min, 91%; (iii) HF–pyridine, CH_3CN, 18 °C, 2.5 h, 94%; (iv) DCC, Me_2SO, CF_3COOH, pyridine, 17 °C, 3 h, 75%.

(17) Corey, E. J.; Marfat, A.; Munroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077.

(18) ^1H NMR chemical shifts of the C-6 and C-7 protons and the H–H coupling constants, $J_{5,6}$ and $J_{6,7}$, of the 7*E* and 7*Z* stereoisomers determined in $CDCl_3$ at 500 MHz as follows: (5*R*,6*R*,12*S*)-7*E* isomer, δ 6.04 and 6.37; 4.4 and 9.2 Hz. (5*S*,6*S*,12*S*)-7*E* isomer **1**, δ 5.69 and 6.32; 4.3 and 10.4 Hz. (5*S*,6*R*,12*S*)-7*E* isomer, δ 6.24 and 6.53; 2.6 and 9.5 Hz. (5*S*,6*R*,12*R*)-7*E* isomer, δ 5.77 and 6.31; 4.9 and 10.3 Hz. (5*R*,6*R*,12*S*)-7*Z* isomer, δ 6.36 and 6.10; 3.7 and 7.8 Hz. (5*S*,6*S*,12*S*)-7*Z* isomer **2**, δ 6.62 and 6.07; 4.4 and 7.9 Hz. (5*S*,6*R*,12*S*)-7*Z* isomer, δ 6.48 and 6.18; 3.5 and 8.9 Hz. (5*S*,6*R*,12*R*)-7*Z* isomer, δ 6.68 and 6.23; 4.0 and 9.2 Hz.

(19) Gill, M.; Rickards, R. W. *Tetrahedron Lett.* **1979**, 1539.

(20) The aldol condensation of the enantiomer of **13** ($[\alpha]^{12}_D$ +23.7° (*c* 1.14, $CHCl_3$)) and **5** was effected in 58% yield (95% yield corrected for the 39% recovery of the starting enone).

(21) Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 223.

(22) Corey, E. J. *Experientia* **1983**, *39*, 1084.

(23) PUG 3 and 4 are derived from PUG 1 and 2, respectively, by elimination of acetic acid.[2] The trans relationship of the two side chains in PUG 1 and 2[2] dictates the *R* configuration at C-8. At present, however, we should refrain from postulating the remaining C-7 configuration by simple NMR analysis.

Total Synthesis of (±)-Fawcettimine (Burnell's Base A)

Clayton H. Heathcock,* Karl M. Smith, and Todd A. Blumenkopf

Department of Chemistry, University of California Berkeley, California 94720

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In 1959, from extracts of alkaloids of *Lycopodium fawcetti* collected in the Blue Mountain Range of Jamaica, Burnell isolated a compound initially referred to as base A[1] and later as fawcettimine.[2] A collaborative effort of three research groups eventually suggested that fawcettimine has the keto carbinolamine structure **1**, and that this structure is in equilibrium with a negligible amount of its ring–chain tautomer **3**, which gives rise to *N*-acetyl, *N*-nitroso, and methiodide derivatives having the nine-membered ring structure.[3]

The gross structure of fawcettimine has been confirmed by chemical correlation of the alkaloid with serratinine[4] and with lycothunine,[5] both of which have been characterized by X-ray crystallography. However, reasonable doubt about the stereostructure of the native alkaloid at C-4 still exists, and there is some confusion about the nature of the keto amine/carbinolamine tautomerization. For example, whereas the infrared spectrum of a CCl_4 solution of fawcettimine has one carbonyl stretch (1730 cm^{-1}), the spectra of the methiodide[2a] and *N*-acetyl[2b] derivatives each contain two ketonic carbonyl bands (1692, 1730 cm^{-1} and 1710, 1735 cm^{-1}, respectively). On the other hand, Burnell has reported that the hydrochloride and perchlorate salts of fawcettimine both have 1690 cm^{-1} carbonyl absorptions, suggesting that these compounds are salts of the tautomeric form **5**.[2] However, it is impossible to construct a molecular model of **5**, although such a model can easily be constructed for the C-4 epimer **6**. The

(1) Burnell, R. H. *J. Chem. Soc.* **1959**, 3091.

(2) (a) Burnell, R. H.; Mootoo, B. S. *Can. J. Chem.* **1961**, *39*, 1090. (b) Burnell, R. H.; Chin, C. G.; Mootoo, B. S.; Taylor, D. R. *Ibid.* **1963**, *41*, 3091.

(3) Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R. H.; Ayer, W. A.; Altenkirk, B. *Tetrahedron Lett.* **1967**, 1069.

(4) Nishio, K.; Fujiwara, T.; Tomita, K.; Ishii, H.; Inubushi, Y.; Harayama, T. *Tetrahedron Lett.* **1969**, 861.

(5) Inubushi, Y.; Harayama, T. *Chem. Pharm. Bull.* **1981**, *29*, 3418.

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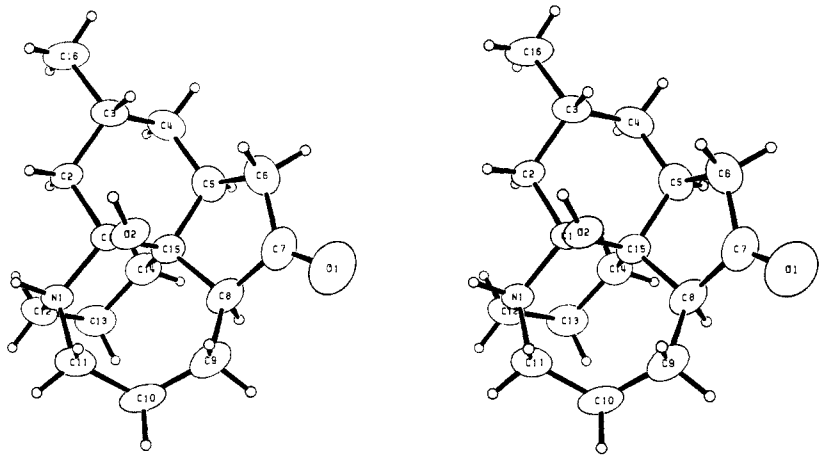
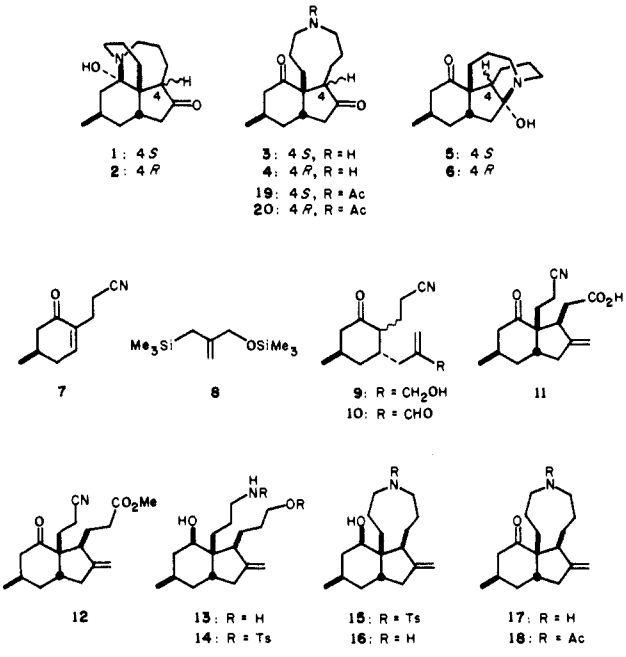


Figure 1. ORTEP representation of (±)-fawcettimine hydrobromide (bromide ion omitted).

reported properties of the hydrochloride and perchlorate salts leave open the question of whether fawcettimine is actually **1** or **2** or whether some epimerization has occurred, either in the isolation process or in formation of derivatives of the alkaloid. A rather lengthy total synthesis (26 steps, 0.1% overall yield)[6] provided additional confirmation of the gross structure but did not give any further information pertaining to the stereochemistry of the alkaloid. In this paper, we report an efficient, stereoselective total synthesis of fawcettimine and its C-4 diastereomer and evidence that the C-4 stereochemistry proposed by Ayer[7] and Inubushi[5] (e.g., **1**) is correct.



Cyano enone **7**[8] is subjected to Sakurai reaction[9] with allylsilane **8**;[10] the product, allylic alcohol **9**, is formed in 94% yield.[11] Oxidation of **9** [$CrO_3(C_5H_5N)_2$;[12] 97%] gives aldehyde **10**, which is treated successively with [(ethoxycarbonyl)methylene]triphenylphosphorane, NaOEt, and NaOH in ethanol to obtain hydrindanone **11** (89%). Arndt–Eistert homologation of **11** [$(COCl)_2$; CH_2N_2; $C_6H_5CO_2^-$ Ag^+, MeOH] provides ester **12** (55%), which is reduced with $LiAlH_4$ (ether, −105 °C to room temperature) to give, in 95% yield, a 9:1 mixture of diastereomeric amino diols. The full stereostructure of the major isomer, amino diol **13**, was ascertained by single-crystal X-ray analysis of a derivative.[13] Amino diol **13** reacts with *p*-toluenesulfonyl chloride in pyridine to give the *N,O*-ditosyl derivative **14** (60%), which is smoothly cyclized by refluxing with KH and 18-crown-6 in toluene (0.005 M in **14**); the yield of the nine-membered heterocycle **15** is 60%.

Removal of the *N*-tosyl activating group is accomplished by treatment of **15** with lithium in ammonia (75%). The product, amino alcohol **16**, is converted into its perchlorate salt, which is oxidized with Jones reagent. The resulting amino ketone **17**, obtained in 90% yield, shows no proclivity for carbinolamine formation, demonstrating that the stereochemistry at C-4 influences the carbinolamine–amino ketone equilibrium position and strongly supporting the original C-4 stereochemical assignment. Ozonolysis of the perchlorate or bisulfate salt of **17** affords in 85% yield amino diketone **4**, which appears to exist predominantly or completely in the form shown. However, **4** is quite unstable and spontaneously isomerizes to **1** at room temperature in a matter of hours. The synthetic (±)-fawcettimine so obtained was found to be identical by proton NMR and IR spectroscopy with Burnell's original sample of base A.[14] A notable feature of the synthesis, which requires 12 steps from cyano enone **7** and proceeds in 9% overall yield, is that no protecting groups are employed.

Treatment of **1** with aqueous hydrobromic acid provides (±)-fawcettimine hydrobromide, identical by proton NMR spectroscopy with an authentic sample.[14] In order to provide a final piece of evidence in favor of the proposed stereochemistry at C-4, the synthetic hydrobromide salt was subjected to single-crystal X-ray analysis.[13] The structure (Figure 1) fully corroborates the Ayer–Inubushi assignment.

Amino alcohol **16** was treated with acetic anhydride in pyridine to obtain an acetamide, which was subjected to Jones oxidation to obtain acetamide **18**. Ozonolysis of this material provided diketo acetamide **20**. Base-catalyzed epimerization of **20** gives (±)-*N*-acetylfawcettimine (**19**) and its C-4 epimer **20** in an equilibrium ratio of 2:1. The two diastereomers are conveniently separable by chromatography, and the equilibrium ratio was determined by starting from both sides. Analysis of two different samples of authentic *N*-acetylfawcettimine kindly provided by Professor W. A. Ayer showed both to be mixtures of **19** and **20**, in ratios of 2.4:1 and 6:1. Thus, it is likely that some C-4 equilibration occurs, either when forming the acetamide derivative or in its long

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(7) Ayer, W. A.; Altenkirk, B.; Fukazawa, Y. *Tetrahedron* **1974**, *30*, 4213.
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(9) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (c) Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354.
(10) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. (b) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.
(11) Although only one enantiomer is depicted in each case, all of the synthetic compounds discussed in this paper are racemates.
(12) Ratcliffe, R. W.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(13) The structure was determined by Dr. Fred Hollander, of the Berkeley College of Chemistry X-Ray Facility; details will be published in a full paper.
(14) This material was kindly provided by W. A. Ayer.

storage (the Ayer samples we obtained had been stored for more than 20 years).

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Generation and Characterization of 2,6-Azulylene

T. Koenig,* K. Rudolf, R. Chadwick, H. Geiselmann, T. Patapoff, and C. E. Klopfenstein

Department of Chemistry, University of Oregon Eugene, Oregon 97403

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Polyenic molecules continue to be important in providing a basis for the discovery of the fundamental features of molecular electronic structures.[1] 2,6-Azulylene (**1**) contains the potential for probing for many electron effects in a nonalternant[2] π system. We wish to report a short synthesis of the [2.2]2,6-azulenophane mixture[3,4] **5** which allowed us a clean method to generate **1** and hence to determine some of the spectral and chemical properties of this reactive polyene.

The synthesis of the cyclophane mixture **5**, in the same syn and anti regioisomer ratio as obtained before,[3,4] is shown in Scheme I. A tetrahydrofuran (THF) solution of sodium cyclopentadienide was treated with 1 equiv of diethyl carbonate, followed by *n*-butyl-4-picolinium bromide (1.0 equiv), giving a 1:1 mixture of 1- and 2-carboethoxy-6-methylazulenes (**2**). Addition of this mixture to an equivalent of sodium hydroxide in aqueous ethanol caused the highly selective hydrolysis of the isomer bearing the carboethoxy group in the 2-position. After neutralization, 2-carboxy-6-methylazulene was isolated in 9.3% overall yield from cyclopentadiene. This application of the Hafner[5] azulene synthesis can easily provide the carboxylic acid precursor to the target [2.2](2,6)-azulenophane mixture **5** in gram quantities in 2 days. The acid produced here is isomeric with that used by Keehn[3] in preparation of **5** and the remainder of our synthesis (Scheme I) is similar to his procedure. The Hofmann elimination, from the present quaternary ammonium hydroxide **4**, proceeded at 85 °C in toluene/H_2O and gave the cyclophane mixture (**5**, syn and anti) in 11% yield. The composition of this mixture (*anti*-**5**:*syn*-**5** = 2:3 by 360-MHz ^{1}H NMR: δ 7.61, doublet, $H_{4,8}$ anti isomer; δ 7.66, doublet, $H_{4,8}$ syn isomer) was nearly the same as that observed by Ito.[4]

Figure 1 shows the proton magnetic resonance (^{1}H NMR, 360 MHz) spectrum of an acetone-d_6 solution of material obtained by passage of **5** through our[6] flash vacuum pyrolysis (FVP) device at 620 °C after collection and transfer below 170 K. The ^{1}H NMR spectrum confirms that dissociation of **5** is clean as expected from previous reports.[7]

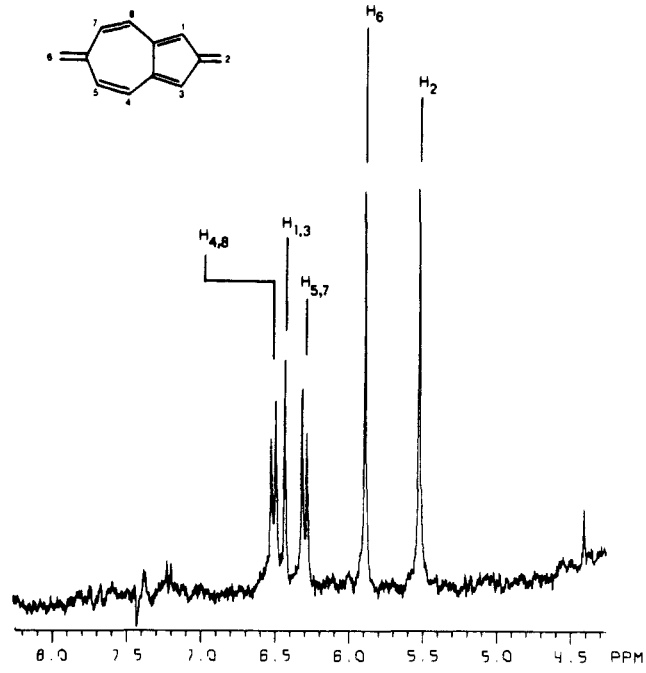

Figure 1. 360-MHz proton magnetic resonance spectrum of 2,6-azulylene (**1**); acetone-d_6, −80 °C. Tentative assignments based on CNDO/S carbon atom charge densities.

Scheme I

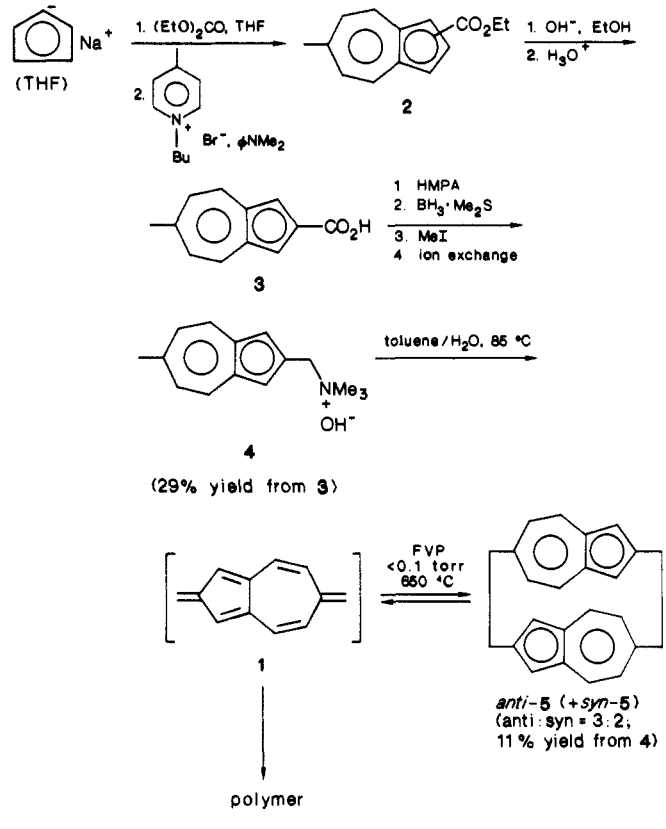

Figure 2 shows the optical absorption, fluorescence, and partial excitation spectra of solutions of the FVP condensate from **5**. The absorption bands between 300 and 420 nm all disappeared at room temperature by phenomenological second-order kinetics.[8] Second-order rates of disappearance of **1** are expected if the polymerization process is self-initiated. Chloroform extraction of the polymeric main product, formed from **1** on warming, yielded a cyclophane mixture **5** of the same composition (syn:anti = 3:2)

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(7) Williams, D. J.; Pearson, J. M.; Levy, M. *J. Am. Chem. Soc.* **1970**, *92*, 1436.

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