propenylepioxazoline (**25**) from 6-epipenicillin sulfoxide (**24**) was reported from our laboratories.[11] Since treatment of **25** with Et_3N gave isopropylideneepioxazoline (**7**) in quantitative yield and epimerization of penicillin sulfoxides at position 6 is more facile than that of penicillins,[5] the overall yield of epioxazoline **7** from penicillin G ester **4** has now become ~60% making the present synthetic route advantageous.

The last crucial problem in our synthesis is transformation of compound **2** having the fundamental skeleton of antibiotic **1a** to the methoxy amine nucleus **3** without epimerization at C-7; it is well known that the side-chain cleavage of a thia analogue (cephamycin-type compound) gives an undesired, thermodynamically stable 7α-amino-7β-methoxy epimer as a major product.[12] With the expectation that probable hydrogen bonding between the oxygen atom at position 1 and the 7β-amino group would stabilize the 1-oxa product **3**, compound **2** was subjected to side-chain cleavage (PCl_5, pyridine, CH_2Cl_2; MeOH; Et_2NH;[13] 3–10 °C) to give the 7α-methoxy amine **3**, mp 164–165.5 °C (from CH_2Cl_2–MeOH), in 54% yield, accompanied by an unappreciable amount of the 7β-methoxy epimer.

Conversion of **3** into the antibiotic **1** can be easily achieved, as reported in our previous paper,[3] by acylation with 2-[4-[(4-methoxybenzyl)oxy]phenyl]-2-[[(4-methoxybenzyl)-oxy]carbonyl]acetyl chloride and pyridine, deprotection of diester **1c** with trifluoroacetic acid or $AlCl_3$ in the presence of anisole, and treatment of the resulting diacid **1b** with sodium hexanoate.[14]

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(6) For a recent development of azetidinone–oxazoline chemistry in the "normal" series, see Stoodley, R. T. in ref 4f, p 189, and references cited herein.

(7) Use of cosolvents (CH_2Cl_2, benzene, etc.) and/or other acids (BF_3-ether, TsOH, MsOH, etc.) gave less satisfactory results.

(8) Corbett, D. F.; Stoodley, R. T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 185.

(9) A minor amount (~5%) of the "cis" isomer of **8** was detected by NMR spectroscopy of the crude product.

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(13) Other organic bases such as Et_3N, pyridine, piperidine, etc., were also effective. Without addition of a base, phosphoramidation of **3** could not be avoided.

(14) The structure assignments of new compounds were supported by their IR and NMR data. Correct combustion analyses were obtained for all the crystalline compounds whose melting points (uncorrected) were given.

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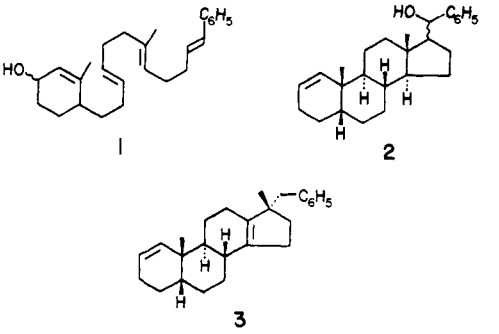
Received February 13, 1979

Biomimetic Polyene Cyclizations.[1] Trapping of the Resultant Carbocation by an Internal Nucleophile

Sir:

The idea expressed in the title, besides having possible biogenetic implications,[2] is attractive because good control of cyclizations may be expected with substrates containing built-in nucleophiles that can be intramolecularly delivered only to that site destined for termination of the process.[3] The present paper discloses the results of our first study along these lines, involving the use of an internal nucleophile in conjunction with a styryl terminator.

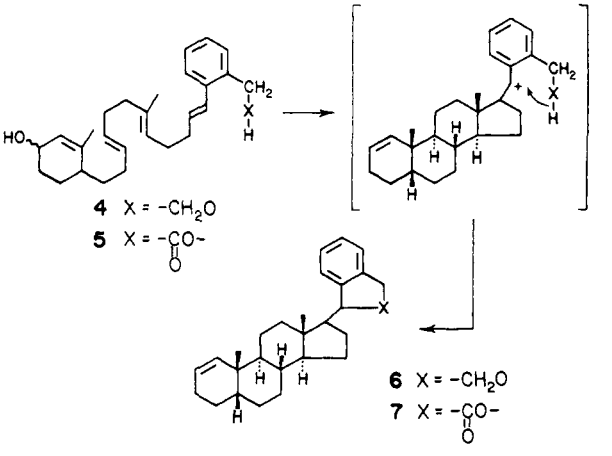
An appropriately positioned styryl group has certain advantages as a terminator of polyene cyclizations because it not only participates regiospecifically to form directly the five-membered D ring of the steroid nucleus,[4] but it reacts in a highly stereoselective manner to give the C/D trans (natural) configuration,[5] as illustrated in the conversion **1** → **2**.[4] On the



other hand, the tetracyclic benzylic cation (formula **2** with a plus charge in place of OH) is highly susceptible to both polymerization and backbone rearrangement (to form **3**) which are the major reactions observed except under carefully controlled conditions.[6] The problem is exacerbated in cyclizations conducted in nonnucleophilic media, which provide no readily accessible means of trapping the aforementioned benzylic cation. Thus treatment of **1** with stannic chloride in methylene chloride gives mainly polymers, while, under conditions of high dilution, up to 50% yields of **3** can be isolated from the mixture. We were therefore prompted to explore the use of an internal nucleophile with this system, anticipating the transformation suggested in Scheme I.

Substrate **4** was prepared by a convergent synthesis as depicted in Scheme II. Thus the alcohol **10**[11a,12,13] was derived from the isochroman **8** in eight steps in an overall yield of 36%.[14] Collins oxidation of **10** afforded the aldehyde **11** in 86% yield.[12,13] The polyenic thioketal **13** was obtained by a Wittig–Schlosser condensation[15,16] of **11** and the known phos-

Scheme I



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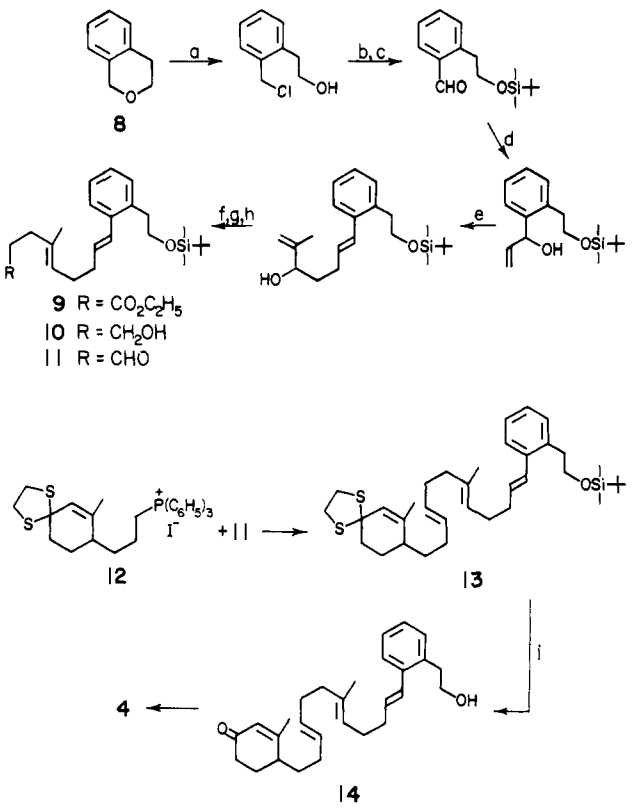
Scheme II[a]



[a] (a) Excess BCl_3 in CH_2Cl_2; aqueous $NaHCO_3$; (b) 1 equiv of *tert*-butyldimethylsilyl chloride and 1 equiv of imidazole in DMF; (c) 1.1 equiv of NaOMe, 1.1 equiv of 2-nitropropane;[7] (d) 1.1 equiv of CH_2=$CHMgBr$ in THF; (e) 2 equiv of 2-methyl-3,3-dimethoxy-1-butene, 0.5 equiv of 2,4-dinitrophenol,[8] $LiAlH_4$ in THF; (f) to give **9**, excess triethyl orthoacetate, propionic acid;[9] (g) to give **10**, $LiAlH_4$ in THF; (h) to give **11**, 6 equiv of CrO_3–pyridine in CH_2Cl_2;[10] (i) CH_3I, H_2O in CH_3CN.[15]

phonium salt **12**[15] in 85% yield.[11a,13] Finally the substrate **4**[13a,b] was obtained in 82% yield from **13** by removal of the dithioketal and *tert*-butyldimethylsilyl protecting groups, followed by reduction of the resulting enone **14**[11a,12,13] with lithium aluminum hydride.

The substrate **4**, upon treatment with stannic chloride in dichloromethane,[17] cyclized to give a mixture, isolated[11a] in 73% yield, consisting of three of the four possible diastereomeric (at C-17 and C-20) isochromans (**15**).[18] The isomers were separated[11b] and recrystallized from methanol–isopropyl ether by a slow evaporation technique giving samples melting at 148–150,[13b,c] 128–129.5,[13b,c] and 118–120 °C.[13b,c] Analysis of the aforementioned mixture by VPC showed these isomers to be present in the ratio of 50:6:44, respectively. Single-crystal X-ray diffraction analysis of the 150 °C isomer by Ulrich Schubert[19] at the Anorganish Chemisches Institut, Technischen Universitat, Munchen, showed it to have the constitution **16** (17α, C-20(*S*)) (see Figure 1). X-ray analyses of the 129 and 120 °C isomers have not yet been completed. However, in view of the spectroscopic similarities of the four isomers (including the liquid isomer described below), as well as the established stereoselectivity of the styryl terminator to give almost exclusively C/D-trans steroidal products,[5] we feel that these four isomers are all diastereomers of the type **15**.

Substrate **5** was prepared as follows. The keto alcohol **14** was oxidized first with Collins reagent (to give the keto aldehyde[13a,b]) and then with Jones reagent to give the keto acid[13a,b] which was converted, with diazomethane, into the keto methyl ester (formula **14** with $-CO_2CH_3$ in place of $-CH_2OH$)[11a,12,13] in 67% yield from **14**. Reduction of the keto ester with sodium

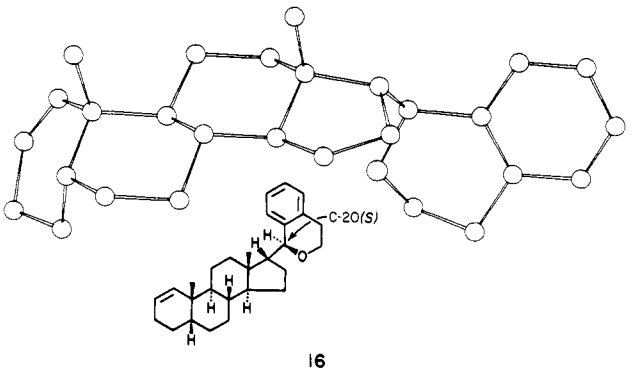
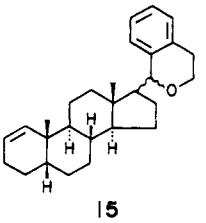


Figure 1. Computer structure plot from X-ray analysis of 150 °C isomer.

borohydride followed by saponification and careful acidification gave in 66% yield the hydroxy acid **5**,[13a] which was used without purification in the cyclization.

Upon treatment with stannic chloride in dichloromethane,[20] the substrate **5** was converted (68% yield) into an isomeric mixture of oxygen-sensitive lactones, **7**[11a,12,13b,c] which could not be readily separated into its components. Instead, the lactone mixture was reduced with lithium aluminum hydride and the resulting mixture of diols[13a,b] (obtained in 95% yield) was treated with *p*-toluenesulfonic acid in dichloromethane to afford a mixture of the isochromans **6**[13b] (69% yield), separation of which[11b] gave, in addition to the aforementioned 150, 129, and 120 °C isomers of **15**, the fourth (noncrystalline



isomer.[13b] The ratios of these isomers in the mixture was shown by VPC to be 30:32:23:15.

The efficacy of an internal nucleophile to terminate polyene cyclizations has been demonstrated. Thus, whereas treatment of the substrate **1** with stannic chloride in methylene chloride gave no detectable amount of product having the steroidal nucleus, similar treatment of **4** and **5**, containing an internal nucleophile, gave unrearranged steroidal products in yields that were close to some of the best we have yet seen for producing three new carbocyclic rings.[1b] These results portend well for future studies in this area.

Acknowledgment. We are indebted to the National Institutes of Health and to the National Science Foundation for support of this research. We also express our thanks to Dr. Ulrich Schubert for performing the X-ray analysis.

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(12) The product was evaporatively distilled (using a Büchi Kugelrohroffen) at temperatures ranging between 150 and 220 °C and pressures of 10–50 μ.
(13) (a) The product was of adequate purity for proceeding to the next step. (b) The NMR and IR spectra were consistent with the assigned structure. (c) Satisfactory C, H analyses were obtained on an appropriately purified specimen.
(14) Except for *o*-chloromethyl-2-phenylethanol,[13a,b] all of the other intermediates between **8** and **10** were fully characterized.[13]
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(17) Compound **4** (0.12 mmol) in 1 mL of dichloromethane was added dropwise to 1.2 mL of 0.1 M stannic chloride in dichloromethane at −25 °C over a period of 3 min. After another 3 min at −25 °C, the reaction was quenched with 0.1 mL of pyridine.
(18) The chromatography of the reaction mixture also afforded a polar fraction (12% yield), consisting of what appeared to be (by NMR) the product of backbone rearrangement, i.e., formula **3** with an *o*-hydroxyethyl substituent on the phenyl group.
(19) Details of the X-ray analyses will be reported elsewhere.
(20) A solution of 0.4 mL of 0.1 M stannic chloride in dichloromethane was added to 0.3 mmol of **5** in 3 mL of dichloromethane at −21 °C over a period of 0.5 min. The reaction was quenched with 1 mL of 33% pyridine in dichloromethane.

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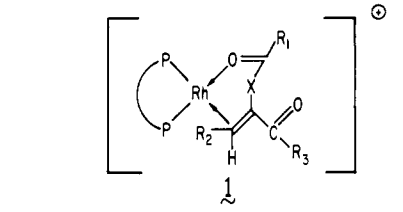
Catalytic Asymmetric Hydrogenation with a Rhodium(I) Chiral Bisphosphine System. A Study of Itaconic Acid and Some of Its Derivatives and Homologues

Sir:

The catalytic asymmetric hydrogenation of prochiral olefins with rhodium(I) chiral bisphosphine complexes is especially successful (i.e., fast rates and high enantiomeric excesses (ee)) when the olefins are (*Z*)-α-acylaminoacrylic acids[1] or (*Z*)-α-acyloxyacrylic esters.[1f,h] This is presumably because of their ability to form chelates of the type **1a** and **1b**.[1f,2] Chelation is important because it generates a low-energy complex in the transition state, which results in a fast rate, and because it produces a rigid complex which maximizes the substrate–ligand interactions and consequently the enantioface discriminating ability of the catalyst. Itaconic acid **2**, which should form a similar type of chelate **1c**, has met with low asymmetric induction when hydrogenated with most catalyst systems.[3a,b] A recent exception affords an 84% ee as the free acid[3c] which is increased to 92% ee as the anion,[3a] an inexplicably high induction considering that this chiral ligand **8** is very similar to the rest.

An explanation for the anomalous behavior of itaconic acid in its asymmetric hydrogenations with rhodium(I) chiral bisphosphines has not been proposed. Such an explanation, however, may be useful in designing both ligands and substrates for asymmetric reduction. In particular (a) why does itaconic acid hydrogenate poorly with most catalyst systems and (b) why does it hydrogenate efficiently when the ligand is **8**?



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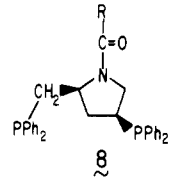
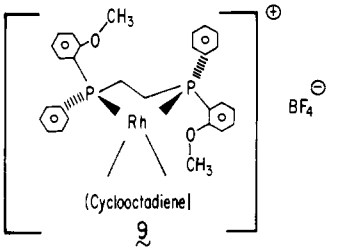
	R_1	R_2	R_3	X
a.	CH_3, Ph	H, alkyl, aryl	OH, OCH_3, NH_2	NH
b.	CH_3	H, Ph	OCH_3	O
c.	OH	H	OH	CH_2



8



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In this communication, these questions are addressed by studying the asymmetric hydrogenation behavior of **2** and some of its derivatives **3–7** with the [Rh(1,5-COD)(DiPAMP)]$^+$-BF_4^- catalyst precursor **9**. Then, as an additional probe of substrate requirements, the hydrogenation properties of the α-methyleneglutaric acid derivatives **13** and **14** (homologues of itaconic acid derivatives **3** and **4**) are briefly explored with the same catalyst system. The results are summarized in Table I.

All of the data can be explained in terms of the substrates ability to form a bidentate complex in the transition state with the rhodium(I) phosphine system. For itaconic acid and its derivatives, this chelating ability appears to be influenced by the H-bonding properties of the substrate, as explained below.

Itaconic acid **2** hydrogenates slowly with a poor 38% ee at a 0.4 M concentration in alcohol. Interestingly, a very dilute 0.002 M solution of **2** is hydrogenated in a respectable 77% ee, suggesting that intermolecular H-bonding interactions are affecting the transition state and, consequently, the optical discrimination of the catalyst. This result can be explained by supposing that **2** exists exclusively as an intermolecular H-bonded species, either dimeric or polymeric, at the higher concentration. (Itaconic acid has been shown by X-ray analysis to exist as a polymer in the crystal.[4]) This dimeric and/or polymeric species is not a good substrate, presumably because its H-bonded nature prevents the necessary chelate formation, probably because of unavailability of the 4-carbonyl function. In a very dilute solution, **2** is monomeric (with the 4-carbonyl group free in at least one conformation) and can form a chelate of the type **1c** which hydrogenates with good stereoselectivity. Itaconic acid dianion **3** and dimethyl itaconate **4**, in which H-bonded interactions cannot interfere with chelate formation, hydrogenate rapidly with high optical bias, 78 and 88%, respectively.

The half-ester **5** reduces with the same low optical bias (55% ee) and slower rates at both 0.4 and 0.002 M concentrations! A possible explanation is that, at both high and low concentrations, **5** exists entirely as the intramolecular H-bonded

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