Acknowledgment. We thank Professor D. F. Shriver, Northwestern University, and Professor E. L. Muetterties, University of California, Berkeley, for information on their studies in this area prior to publication.

Supplementary Material Available: A list of atomic coordinates and thermal parameters for $Fe_4(CO)_{13}C$ (2 pages). Ordering information is given on any current masthead page.

Novel Bay-Region Diol Epoxides from Benzo[*c*]phenanthrene

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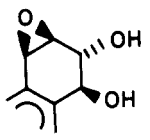
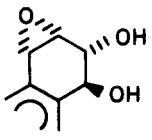
Diol epoxides in which the epoxide group forms part of a sterically hindered bay region of the molecule have been identified as ultimate carcinogenic metabolites of a number of polycyclic aromatic hydrocarbons.[1] Two diastereomers are possible in which the benzylic hydroxyl group is either cis (series **1**) or trans (series **2**) to the epoxide oxygen. In the absence of unusual steric effects, the diol epoxide **1** diastereomers prefer the conformation in which their hydroxyl groups are quasi-diaxial, whereas the diol epoxide **2** diastereomers prefer the quasi-diequatorial conformation.[2] Only the quasi-diequatorial diol epoxide **2** diastereomers have shown high tumorigenic activity.[3] In the case of benzo[*e*]pyrene, whose bay-region diol epoxide **1** and **2** diastereomers prefer the quasi-



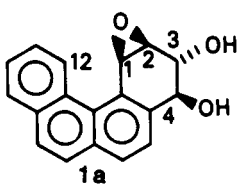
series 1



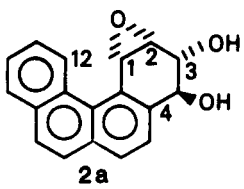
series 2

a, benzo[*c*]phenanthrene
b, chrysene
c, benzo[*a*]pyrene
d, phenanthrene

diaxial conformation for steric reasons,[4] neither diastereomer displayed strong tumorigenic activity.[5] The 3,4-diol 1,2-epoxides **1a** and **2a** derived from benzo[*c*]phenanthrene were synthesized

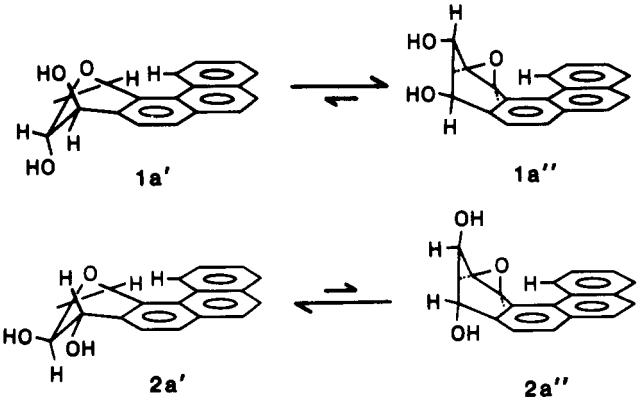


1a



2a

Scheme I



1a' **1a''** **2a'** **2a''**

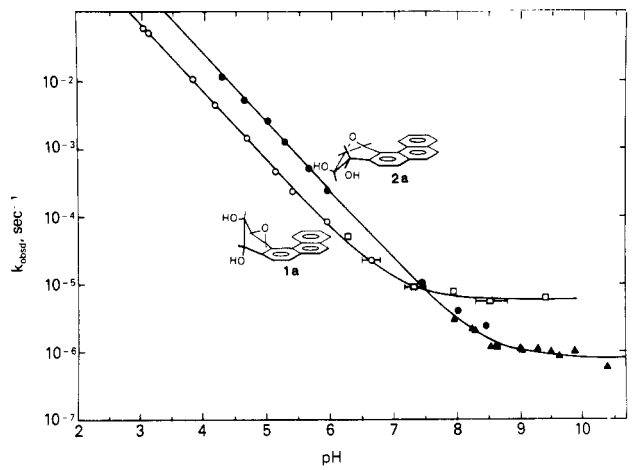


Figure 1. Dependence of pseudo-first-order rate constants for hydrolysis of **1a** and **2a** on pH in 10:90 (v/v) dioxane–water, ionic strength 0.1 M ($NaClO_4$) at 25 °C. Circles designate rate constants determined spectrophotometrically (271 nm) under pseudo-first-order conditions, triangles, rate constants determined from measurement at 271 nm of initial rate, and squares, rate constants determined by HPLC assay of reactant (as the mercaptoethanol adduct) in aliquots of the reaction mixture (see supplementary material for details).

for the present study in the hope that the highly hindered bay region between carbons 1 and 12 (referred to as a fjord region[6]) would cause **1a** to adopt the presently unknown quasi-diequatorial conformation for a diol epoxide **1** diastereomer.

Conformation and Activity. Procedures used with other dihydrodiols[2,7] cleanly converted *trans*-3,4-dihydroxy-3,4-dihydrobenzo[*c*]phenanthrene[8] into diol epoxide **1a** via an intermediate bromohydrin and into **2a** via direct epoxidation. The large values of the coupling constant $J_{3,4}$ (J_{diol}) of 9.0 Hz for **1a** and of 8.0 Hz for **2a** in the ^1H NMR spectra of the diol epoxides[9] indicate that the predominant conformation is that in which the hydroxyl groups are quasi-diequatorial for both diastereomers (**1a''** and **2a'**, Scheme I). Thus **1a** is the first example in the diastereomer-**1** series in which the quasi-diequatorial conformation is preferred. Relief of steric hindrance between H_1 and H_{12} in **1a'** and a possible intramolecular H bond between the hydroxyl groups in **1a''** favor **1a''**. Although the adverse interaction between H_1 and H_{12} is

(1) For a recent review and leading references, see: Nordqvist, M.; Thakker, D. R.; Yagi, H.; Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. in "Molecular Basis of Environmental Toxicity"; Bhatnagar, R. S., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 329–357.
(2) (a) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881–6883. (b) Lehr, R. E.; Schaefer-Ridder, M.; Jerina, D. M. *Tetrahedron Lett.* **1977**, 539–542. (c) Whalen, D. L.; Ross, A. M.; Yagi, H.; Karle, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1978**, *100*, 5218–5221.
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(4) Yagi, H.; Thakker, D. R.; Lehr, R. E.; Jerina, D. M. *J. Org. Chem.* **1979**, *44*, 3439–3442.
(5) Chang, R. L.; Levin, W.; Wood, A. W.; Lehr, R. E.; Kumar, S.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1981**, *41*, 915–918.
(6) Bartle, K. D.; Jones, D. W. *Adv. Org. Chem.* **1972**, *8*, 317–423.
(7) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 1604–1611.
(8) Croisy-Delcey, M.; Ittah, Y.; Jerina, D. M. *Tetrahedron Lett.* **1979**, 2849–2852.
(9) The 100-MHz ^1H NMR spectra (Me_2SO) are as follows. **1a**: δ 4.32 (H_1), 3.87 (H_2), 3.60 (H_3), 4.64 (H_4), 5.82 (C–OH_3 and C–OH_4), 7.50–8.10 (aromatic protons H_5–H_{11}), 9.05 (H_{12}), (J_{12} = 4.0, $J_{2,3} \sim$ 1.0, $J_{3,4}$ = 9.0, and $J_{OH_3,H_3} = J_{OH_4,H_4}$ = 6.3 Hz). **2a**: δ 4.71 (H_1), 3.69 (H_2), 3.76 (H_3), 4.60 (H_4), 5.59 (C–OH_3), 5.78 (C–OH_4), 7.50–8.10 (aromatic protons H_5–H_{11}), and 8.60 (H_{12}), ($J_{1,2}$ = 4.2, $J_{2,3}$ = 2.0, $J_{3,4}$ = 8.0, J_{OH_3,H_3} = 6.3, and J_{OH_4,H_4} = 4.9 Hz).

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Table I. Rate Constants for Hydrolysis of Diol Epoxides in 10:90 Dioxane-Water[a]

compd	$\Delta E_{deloc}/\beta$[b]	k_{H^+}, M^{-1} s^{-1}	k_0, s^{-1}
benzo[*c*]phenanthrene	0.600		
1a		65	$(6 \pm 1)10^{-6}$
2a		230	$(8 \pm 2)10^{-7}$
chrysene	0.639		
1b		31	2.5×10^{-5}
2b		113	7.5×10^{-6}
benzo[*a*]pyrene[c]	0.794		
1c		510	4.2×10^{-3}
2c		1400	1.3×10^{-4}

[a] At 25 °C, ionic strength 0.1 M ($NaClO_4$). Constant pH was maintained by the use of 10^{-3} M amine or carboxylic acid buffers. No detectable effect of buffer concentration on the rate of reaction of **2a** is observed with concentrations of 2-(*N*-cyclohexylamino)ethanesulfonic acid buffer, pH 9.27, up to 10^{-2} M, and rate constants measured at similar pH values with different buffers agree within experimental error. [b] For bay-region benzylic carbonium ion formation from the hydrocarbon.[11] [c] Reference 12.

present in the preferred conformation **2a′**, the possibility for an intramolecular H bond in this conformation and an adverse eclipsing interaction between the epoxide C–O bond and the nonbenzylic hydroxyl group in **2a″** result in **2a′** being the favored conformation.

Both diastereomers (**1a**, **2a**) display exceptionally high biological activity.[10] Mutagenicity experiments with Chinese hamster V79 cells have shown that these diol epoxides have activity comparable to that of the potent benzo[*a*]pyrene-7,8-diol 9,10-epoxides. In initiation-promotion experiments on mouse skin, both diastereomers had similar tumorigenic activity.[10,11] This is the first example of a diol epoxide **1** isomer with high tumorigenic activity. Even more interesting is the fact that these diol epoxides are about 15-fold more tumorigenic than benzo[*a*]anthracene-3,4-diol 1,2-epoxide **2**, previously the most tumorigenic diol epoxide tested on mouse skin (cf. ref 11). The present study sought to identify chemical factors responsible for this remarkable biological activity.

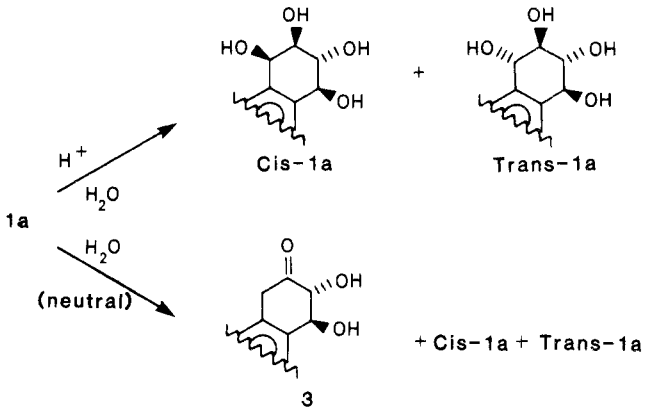
Hydrolysis. The pH–rate profiles (Figure 1) for hydrolysis of **1a** and **2a** in 10:90 (v/v) dioxane–water, ionic strength 0.1 M ($NaClO_4$), correspond to the rate law,

$$k_{obsd} = k_{H^+}a_{H^+} + k_0$$

with values of k_{H^+} and k_0 given in Table I. In contrast to their high mutagenic and tumorigenic activity, the solvolytic reactivity of **1a** and **2a** is low, consistent with estimates ($\Delta E_{deloc}/\beta$)[11] of the ease with which bay-region benzylic carbonium ions can be formed from these compounds. For the benzo[*c*]phenanthrene derivatives, k_0 is more than 100-fold smaller than for the corresponding benzo[*a*]pyrene derivatives,[12] and is even smaller than k_0 for the very weakly mutagenic and tumorigenic chrysene diol epoxides. The variation in k_{H^+} with structure among these bay-region diol epoxides is much smaller than that in k_0.

There is no significant difference between the comparative kinetics of hydrolysis (pH-rate profiles) of the two diastereomeric benzo[*c*]phenanthrene diol epoxides and that of the diastereomers derived from benzo[*a*]pyrene, phenanthrene, or chrysene, despite the novel conformation of the saturated ring in **1a**. For these sets of diastereomers, k_{H^+} is 3- to 4-fold smaller, whereas k_0 is 3- to

Scheme II



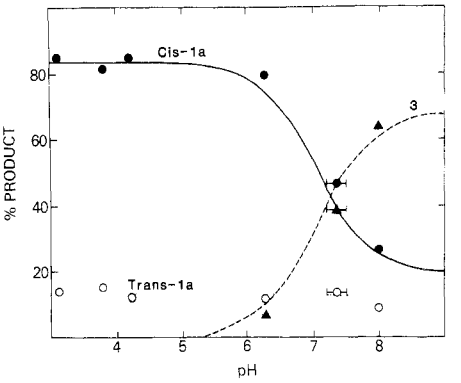
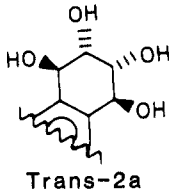


Figure 2. Dependence on pH of product distribution from the solvolysis of **1a** in 10:90 (v/v) dioxane–water, ionic strength 0.1 M ($NaClO_4$) at 25 °C. The curves show the expected product distribution at intermediate pH values based on the distribution at high and low pH, assuming identical pH dependences for rate and product determination. The limiting product distribution at high pH was extrapolated from the observed value at pH 8.0 where ~90% of the reaction occurs via the k_0 pathway.

30-fold larger for the isomer-**1** series than for the isomer-**2** series. In the k_0 reaction, **1a** reacts approximately seven times faster than **2a**, even though the preferred conformation, **1a″**, has its benzylic hydroxyl group quasi-equatorial and unfavorable for hydrogen bonding to the epoxide oxygen. For the corresponding chrysene and phenanthene[2c] derivatives **1b** and **2b** and **1d** and **2d**, in which no unusual steric factors are present, $k_0^{(1)}$ is only 3.3–3.7 times larger than $k_0^{(2)}$. Since hydrogen bonding of the benzylic hydroxyl group to the epoxide oxygen[2a] would require that an unfavorable steric interaction be overcome in the transition state for **1a** but not for **1b** or **1d**, these results are inconsistent with such hydrogen bonding as a major determinant of the enhanced reactivity of **1a** relative to **2a** toward neutral solvolysis in predominantly aqueous solution.

Acid-catalyzed and neutral hydrolyses of **2a** yield exclusively *trans*-**2a** whereas hydrolysis of **1a**, like that of other isomer-**1** diol



epoxides, gives a distribution of products that is pH dependent[2c,12,13] (Scheme II and Figure 2). Compared to **1b** and **1d**,[2c] which

(10) Wood, A. W.; Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Croisy-Delcey, M.; Ittah, Y.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 2876–2883. Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Jerina, D. M.; Conney, A. H., *Ibid.* **1980**, *40*, 3910–3914.

(11) Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R.; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H. in "Biological Reactive Intermediates, Vol. 2. Chemical Mechanisms and Biological Effects"; Snyder, R., Parke, D. V., Koesis, J., Jollow, D. J., Gibson, G. G., Eds.; Plenum Press: New York, in press.

(12) Whalen, D. L.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5522–5524.

(13) The observation that the pH dependences for rate and product determination are identical within experimental error is most consistent with either the rate-determining reaction of a carbonium ion formed in a rapid equilibrium step or the absence of a *common* intermediate for the k_{H^+} and k_0 pathways that is in protonic equilibrium with the solvent.

Table II. Reactions of Nucleophiles with Diol Epoxides from Benzo[c]phenanthrene and Phenanthrene[a]

Morpholine

compd	solvent	k_{morph}, M^{-1} s^{-1}
2a	10% dioxane[b]	1.04×10^{-3}
2d		3.4×10^{-3}

Mercaptoethanol Anion

compd	solvent	k_{RS^-}, M^{-1} s^{-1}	$k_{RS^-}{}^{(1)}/k_{RS^-}{}^{(2)}$
1a	10% dioxane[b]	0.23	
2a		0.21	1.10
1d	10% dioxane[b]	2.28	
2d		1.49	1.53
1a	50% dioxane[c]	0.036	
2a		0.012	3.00
1d	50% dioxane[c]	1.53	
2d		0.178	8.60

[a] At 25 °C. [b] Ionic strength 0.2 M ($NaClO_4$). [c] Ionic strength 0.1 M ($NaClO_4$).

exhibit similar reactivity (k_{H^+}) toward acid-catalyzed hydrolysis, **1a** undergoes substantially more cis hydration at acid pH (~85% as opposed to 50-60% for **1b** and **1d**).

The hydrolysis of **2a** is also subject to general acid catalysis, according to the rate law, $k_{obsd} = k_0 + k_{H^+}a_{H^+} + k_{HA}[HA]$. Catalytic constants, k_{HA}, measured in 10% dioxane, ionic strength 0.2 M, for phosphoric acid (pK_a = 2.1),[14] dichloromethylphosphonate monoanion[15] (pK_a = 5.4),[14] and dihydrogen phosphate monoanion (pK_a = 6.9)[14] are 13.3, 3.2×10^{-2}, and 1.6×10^{-3} M^{-1} s^{-1}, respectively, corresponding to a Brønsted α value of approximately 0.85 for these three acids. For **2a**, catalysis by phosphoric acid is observable in Na_2HPO_4/NaH_2PO_4 buffers at pH 5.9-6.9, a finding similar to that of Bruice and co-workers for the 1,2- and 3,4-epoxides of 1,2,3,4-tetrahydrophenanthrene[16] and the diol epoxides of naphthalene.[17,18]

Reactions with Nucleophiles. Morpholine and mercaptoethanol anion react with benzo[c]phenanthrene and phenanthrene diol epoxides according to the rate laws $k_{obsd} = k_{morph}$[morpholine free base] or $k_{obsd} = k_{RS^-}[HOCH_2CH_2S^-]$. Values of k_{morph} and k_{RS^-} in 10% dioxane (Table II) are 3- to 10-fold smaller for the benzo[c]phenanthrene diol epoxides than for the corresponding phenanthrene derivatives. In 50% dioxane, where hydrogen bonding to the cis benzylic hydroxyl group may significantly stabilize the transition state for nucleophilic cleavage of some isomer-**1** diol epoxides,[17,20] there is an even greater difference in reactivity (43-fold) for **1a** relative to the phenanthrene derivative **1d**. The very low reactivity of **1a** relative to **1d** under conditions where hydrogen bonding is important probably results from the unfavorable conformational requirement for such hydrogen bonding in **1a** but not in **1d**.

Our results for both S_N2 and solvolysis reactions indicate that the benzo[c]phenanthrene diol epoxides are the most chemically unreactive bay-region diol epoxides studied to date. *Hence, their high mutagenic and tumorigenic activity is not dependent upon high chemical reactivity* in simple "model" reactions and must result from more specific aspects of their reactivity, possibly involving binding phenomena with cellular macromolecules.

Supplementary Material Available: Details of the syntheses of **1a** and **2a** and of kinetic experiments, kinetic data for determination of general acid catalytic constants and S_N2 rate constants, details of HPLC analyses of hydrolysis products, and listing of the ^1H NMR spectra for acetylated hydrolysis products and thioethers of **1a** and **2a** (12 pages). Ordering information is given on any current masthead page.

(14) These are apparent pK_a values determined in 10% dioxane, ionic strength 0.2 M ($NaClO_4$), from the observed pH of buffer solutions or by titration.

(15) For preparation of the conjugate acid, see: Kinnear, A. M.; Perren, E. A. *J. Chem. Soc.* **1952**, 3437-3445. Crofts, P. C.; Kosolapoff, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 5738-5740.

(16) Rogers, D. Z.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4713-4719.

(17) Becker, A. R.; Janusz, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5679-5687.

(18) The ability to observe catalysis by phosphoric acid at pH values well above its pK_a for the phenanthrene, naphthalene, and benzo[c]phenanthrene derivatives but not for the benzo[a]pyrene diol epoxides[19] may result from decreased sensitivity to catalyst acidity for the more reactive benzo[a]pyrene derivatives. An upper limit of 800 M^{-1} s^{-1} is estimated for $k_{H_3PO_4}$ for **2c**, based on the lack of any observable pH dependence[19] of the quantity, $k_{obsd}/[H_2PO_4^-]$, at pH 6.34-7.60 and the assumption that a 10% increase at pH 6.34 would have been detectable. This corresponds to a value of $k_{H_3PO_4}/k_{H_2PO_4^-} \leq 1.6 \times 10^3$ for **2c**, which is smaller than the observed values of 8.3×10^3 for **2a** and 4.1×10^4 for 3,4-epoxy-1,2,3,4-tetrahydrophenanthrene.[16] Thus, for the benzo[a]pyrene diol epoxide **2c**, catalysis by the weakly acidic dihydrogen phosphate monoanion is able to swamp out any catalysis by phosphoric acid at neutral pH, where the concentration of phosphoric acid is extremely low.

(19) Whalen, D. L.; Ross, A. M.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 5086-5088.

(20) The effect of solvent composition on the relative rates ($k_{RS^-}{}^{(1)}/k_{RS^-}{}^{(2)}$) for isomers **1** and **2** of a given diol epoxide is consistent with a role for intramolecular hydrogen bonding in 50% dioxane. In 10% dioxane, where such hydrogen bonding should be relatively unimportant, there is no significant difference between the reactivity of diastereomers **1** and **2** in either the phenanthrene or the benzo[c]phenanthrene series ($k_{RS^-}{}^{(1)}/k_{RS^-}{}^{(2)}$ = 1.1-1.5). In 50% dioxane, $k_{RS^-}{}^{(1)}/k_{RS^-}{}^{(2)}$ for the phenanthrene diol epoxides is 8.6, consistent with greater stabilization, in the less aqueous solvent, of the transition state for opening of **1d**, in which intramolecular hydrogen bonding is possible, relative to **2d**. A similar value of $k_{RS^-}{}^{(1)}/k_{RS^-}{}^{(2)}$ of 7.9 was observed in 50% dioxane for the diol epoxides of naphthalene.[17] For the benzo[c]phenanthrene derivative, **1a**, whose preferred conformation (**1a''**) has the cis benzylic hydroxyl group unfavorably located for hydrogen bonding to the epoxide, $k_{RS^-}{}^{(1)}$ is only three times larger than $k_{RS^-}{}^{(2)}$ in 50% dioxane. This is the effect that would be expected if hydrogen bonding in the transition state for reaction of **1a** cannot occur without first overcoming an unfavorable steric interaction, with the result that the net stabilization of the transition state for **1a** relative to **2a** is decreased.

Acyclic Stereoselection. 14. *O*-Alkyllactic Acid Esters: Reagents for the Stereoselective Construction of *erythro*- and *threo*-α-Methyl-α,β-dihydroxy Carbonyl Compounds[1]

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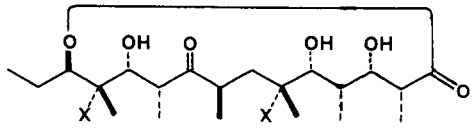
In their recent total synthesis of 6-deoxyerythronolide B (**1**),[2] Masamune and co-workers have impressively demonstrated the power of the aldol condensation for construction of the polypropionate framework characteristic of the macrolide antibiotics.[3]



1: X = H
2: X = OH

For the application of such a strategy to the synthesis of eryth-

(1) For part 13, see C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, in press.

(2) S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981).

(3) For a complete discussion of the problem, see C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

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