

carbocyclics. Simple modifications in the above scheme should make it possible, for example, to utilize the INOC reaction in the construction of other cyclopentanoids (e.g., pentenomycin and the methylenomycins¹⁰). By a building of additional oxygen functionality into the nitroalkene, the synthesis of prostaglandins and prostaglandin analogues becomes equally feasible.¹¹

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. HL20579) for support of these investigations.

Registry No. (±)-1, 82065-11-0; (±)-2, 82065-12-1; (±)-3, 82065-13-2; (±)-5, 82065-14-3; (±)-6, 82065-15-4; (±)-7, 82080-50-0; (±)-sarkomycin, 72581-31-8; *p*-ClC₆H₄NCO, 104-12-1.

(10) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233. Haneishi, T.; Kitiyara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393. Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977.

(11) All new compounds reported herein gave satisfactory NMR, IR, and mass spectral data.

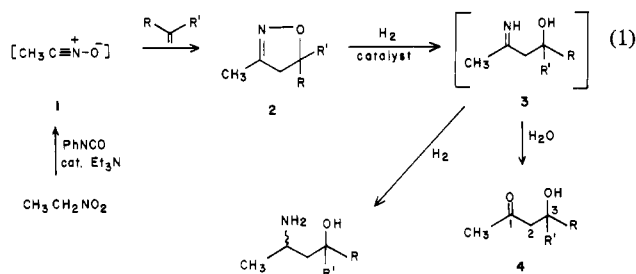
Reduction of Δ²-Isoxazolines: A Conceptually Different Approach to the Formation of Aldol Adducts

Dennis P. Curran¹

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received April 5, 1982

The aldol reaction and related carbonyl condensations continue to be of fundamental importance in organic chemistry.² We now report a conceptually different approach to aldol adducts that involves cycloaddition, rather than carbonyl condensation, in the key carbon-carbon bond-forming reaction. The two-step sequence exploits the potential synthetic equivalency of Δ²-isoxazolines and β-hydroxy ketones as outlined in eq 1. Well-known cycloaddition



of an in situ generated nitrile oxide **1** with a mono- or 1,1-disubstituted olefin typically produces the 5-substituted Δ²-isoxazoline **2** in high yield with complete regioselectivity.³ Although most of the previous conditions used to reduce Δ²-isoxazolines have resulted in complete reduction to the amino alcohol,⁴ we felt that supported metal-type catalysts should reduce the weak N-O bond first. In the presence of water, rapid hydrolysis of the labile hydroxyimine **3** should then occur.⁵

(1) Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1981-1986.

(2) (a) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 629-682. (b) Barco, A.; Bennetti, S.; Baraldi, R.; Guarneri, M.; Pollini, G. P.; Simoni, O. *J. Chem. Soc., Chem. Commun.* **1981**, 599.

(3) For an excellent review of the chemistry of nitrile oxides see: Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971.

(4) Jäger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133. Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101. Jäger, V.; Buss, V.; Schwab, W. *Ibid.* **1980**, 122. Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601. For reduction to aziridines see: Kotera, K.; Takano, Y.; Matsuura, A.; Kotahonoki, K. *Tetrahedron* **1970**, *26*, 539.

Table I

entry	isoxazoline ^a	con- di- tions	pro- duct	yield, ^b %	% epimeri- zation ^c
1	2a R ₁ = R ₂ = H; R ₃ = <i>n</i> -C ₄ H ₉	<i>d</i>	4a	81	
2	2a	<i>e</i>	4a	(90)	
3	2b R ₁ = R ₂ = H; R ₃ = Ph	<i>f</i>	4b	79	
4	2c R ₁ = H; R ₂ = CH ₃ ; R ₃ = <i>n</i> -C ₃ H ₇	<i>g</i>	4c	84	
5	6a R ₁ = R ₃ = CH ₃ ; R ₂ = H	<i>d</i>	8a	(88)	9
6	6a	<i>e</i>	8a	(86)	6
7	6a	<i>f</i>	8a	83	<2
8	R ₁ = R ₃ = <i>n</i> -C ₃ H ₇ ; R ₂ = H	<i>f</i>		79	<2
9	7a R ₁ = R ₂ = CH ₃ ; R ₃ = H	<i>f</i>	9a	77	<2
10	R ₁ , R ₂ = (CH ₂) ₄ ; R ₃ = H	<i>f</i>		87	<2
11	R ₁ , R ₂ = (CH ₂) ₃ ; R ₃ = H	<i>g</i>		(97)	<2
12	6b <i>n</i> = 2; R ₁ = H; R ₂ = CH ₃	<i>f</i>	8b	(92)	4
13	6b	<i>g</i>	8b	85	<2
14	<i>n</i> = 2; R ₁ = H; R ₂ = Ph	<i>g</i>		73	<2
15	6c <i>n</i> = 1; R ₁ = H; R ₂ = CH ₃	<i>g</i>	8c	(84)	<2
16	7b <i>n</i> = 2; R ₁ = CH ₃ ; R ₂ = H	<i>f</i>	9b	(89)	5
17	7b	<i>g</i>	9b	90	<2
18	<i>n</i> = 2; R ₁ = Ph; R ₂ = H	<i>g</i>		74	<2
19	7c <i>n</i> = 1; R ₁ = CH ₃ ; R ₂ = H	<i>f</i>	9c	(81)	15
20	7c	<i>g</i>	9c	(86)	<2
21	10 <i>n</i> = 2; R ₁ = CH ₃ ; R ₂ = CH ₂ OAc	<i>g</i>	11	82	<5 ^h

^a Nitro olefins were prepared intentionally as a mixture of isomers via Wittig reaction. After cycloaddition, the isomers were separated by flash chromatography. ^b Yields refer to isolated yield of product purified by recrystallization or evaporative distillation. Crude yields were generally above 90%. Yields in parentheses refer to crude product. ^c Diastereomeric ratios were determined by integration of the carbinol proton region in the expanded 300-MHz spectra of crude products. In most cases the ratios were confirmed by integration of other appropriate resonances.

^d NaOAc/HOAc buffer. ^e NaH₂PO₄/Na₂HPO₄ buffer. ^f Catalytic Raney nickel, 15:1 MeOH/H₂O, 2 equiv of B(OCH₃)₃, H₂ gas, 0.4-6 h, room temperature. ^g Catalytic Raney nickel, 5:1 MeOH/H₂O, 2-5 equiv of B(OH)₃, H₂ gas, 0.5-6 h, room temperature.

^h Due to absence of a carbinol proton resonance, a more accurate determination was not possible.

A survey of common catalysts⁶ using adduct **2a** indicated that Raney nickel⁷ (catalytic amount, 15:1 MeOH/H₂O, 1 atm of H₂) was most satisfactory. Thus **2a** was reduced to **4a** in 81% yield after evaporative distillation⁸ (see Table I, entry 1). The presence

(5) Most recently, two isolated examples of this type of reduction have been published. (a) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (b) Asoaka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735. (c) The amino alcohol has also been oxidized to the hydroxy ketone. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.

(6) Platinum oxide (MeOH, H₂O, AcOH) produced the amino alcohol. Palladium on carbon (MeOH, H₂O, HOAc) produced variable amounts of the hydroxy ketone and amino alcohol. Subsequently, we have found that reduction of **2a** to **4a** is cleanly accomplished by 10% Pd-C (MeOH, H₂O, B(OH)₃); however, the generality of these conditions has not been determined.

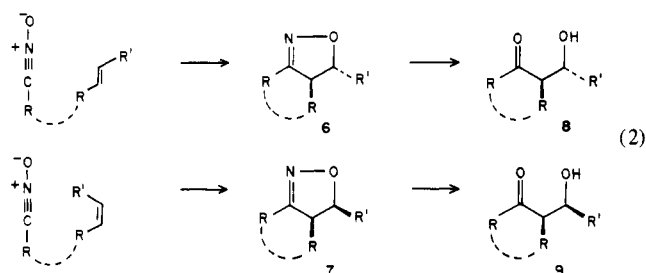
(7) Most of the reductions were performed with commercially available Ra-Ni (Alfa Inorganics), which was carefully washed free of hydroxide by repeated stirring with water and decantation (~20 times) and stored under MeOH. Subsequently, it was found that W-2 Ra-Ni (Mozino, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 181) was effective, with a faster reaction rate. This was also carefully washed free of hydroxide and stored under MeOH.

(8) Known β-hydroxy ketones exhibited spectra and physical data identical with those obtained from literature sources. New β-hydroxy ketones exhibited spectra consistent with proposed structures as well as satisfactory elemental analysis and/or high-resolution mass spectra.

of a buffer is also crucial. Although **2a** was cleanly reduced by using acetate or phosphate buffers (entries 1 and 2), subsequent results showed borate buffers to be far superior. Clean conversion of **2b** to **4b** (entry 3) illustrates the mildness of the reduction conditions. No evidence for competing hydrogenolysis of the benzylic C–O bond or reduction to the amino alcohol was found. 5,5-Disubstituted isoxazoline **2c** was also reduced to **4c** (entry 4) without difficulty.

Thus, in its simplest form, the cycloaddition–reduction sequence outlined in eq 1 allows the rapid, selective formation of directed aldol adducts⁹ between methyl ketones and aldehydes or ketones, bypassing the traditional problems including enolate equilibrium and cross condensation. We emphasize the mildness of the reaction conditions (cycloaddition, catalytic Et₃N; reduction, buffered, pH ~5.5) as opposed to the large range of aldol conditions that typically employ either strong base or strong acid. This sequence also complements the normal aldol reaction in that the new C–C bond in **4** is formed between C₁ and C₂ rather than C₂ and C₃.

In recent years, much attention has been focused on the diastereoselective formation of threo and erythro aldol adducts,¹⁰ and recent advances have been quite spectacular.¹¹ Virtually all of these approaches are based on variations of carbonyl condensation chemistry.¹² Since [3 + 2] dipolar cycloadditions of nitrile oxides are well known to be 100% stereospecific,¹³ our cycloaddition–reduction sequence allows the unique possibility for the *diastereospecific* formation of β -hydroxy ketones. In principle, the relative stereochemistry obtained is governed only by the stereochemistry of the starting olefin. As outlined in eq 2, cy-



cloaddition of a nitrile oxide **1** to a trans olefin selectively produces the adduct **6**, while the use of a cis olefin gives the isomeric adduct **7**. Hydrogenolysis and hydrolysis of **6** should give the threo aldol **8**, whereas the same conditions applied to **7** give the erythro isomer **9**.

The viability of the sequence was examined by using the *cis*- and *trans*-2-butene adducts (entries 5–8). Although the reduction proceeded smoothly, problems were encountered with epimerization. In a typical experiment, Raney nickel catalyzed reduction of the trans-adduct **6a** using an acetate buffer gave the isomers **8a** and **9a** in a ratio of 91:9 (entry 5). Thus, the control over

stereochemistry was significantly lost. While epimerization was noticeably less in the presence of phosphate buffers (entry 6), results using borate additives were much more encouraging. In the presence of 2 equiv of trimethylborate, **6a** was cleanly reduced to **8a**, which was >98% threo diastereomer (entry 7). Similar reduction of **7a** gave **9a**, >98% erythro (entry 9). Thus it is apparent that a judicious choice of additives is critical for the suppression of epimerization. This was confirmed by the reduction of several other adducts (entries 8, 10, 11) in high yield without detectable epimerization.

Limitations exist, however, in applications involving intermolecular nitrile oxide cycloadditions with 1,2-disubstituted olefins due to lower yields of cycloadduct and poor to moderate regioselectivity.³ The useful alkylative chemistry of Δ^2 -isoxazolines developed by Jäger¹⁴ offers potential to overcome these limitations. Intramolecular nitrile oxide olefin cycloadditions,¹⁵ however, are not subject to the aforementioned limitations as regiochemistry is controlled by the length of the intervening chain and yields of cycloadduct are excellent. As such, synthetic applications involving intramolecular cycloaddition and reduction appear particularly promising.¹⁶

The general approach, similar to the intermolecular variant, is outlined in eq 2 (R, R = (CH₂)_n).¹⁷ Initial experiments in the cyclohexyl and cyclopentyl series using trimethyl borate lead to consistently higher amounts of epimerized products (4–15%; entries 12, 16, 19). This can be attributed to the well-known stability of endocyclic olefins (particularly in the cyclopentyl series) relative to their exocyclic counterparts. However, in view of the mildness of the reduction conditions (3 h, 25 °C, ~pH 6) we were surprised at the degree of epimerization. Most interestingly, control experiments readily demonstrated that neither the starting isoxazolines nor the aldol products were significantly epimerized under the reaction conditions. By assumption that the intermediate hydroxyimine **3** is the species suffering epimerization, a vastly improved set of reaction conditions was designed (5:1 MeOH/H₂O; B(OH)₃) to increase the rate of imine hydrolysis by raising the water concentration and making the borate slightly more acidic. Under these conditions, a series of cyclohexyl (entries 13, 14, 17, 18) and cyclopentyl (entries 15, 20) systems were reduced to the corresponding *threo*- and *erythro*- β -hydroxy ketones without significant epimerization (<2%).

Finally, a unique possibility exists in the utilization of the intramolecular cycloaddition with a trisubstituted olefin.¹⁸ This is illustrated by the clean reduction of trisubstituted adduct **10** to β -hydroxy ketone **11** (entry 21), which is formally the product of a diastereoselective aldol condensation between two ketones. A transformation such as this is presumably most difficult by use of existing condensative technology since these methods rely on steric differences between H and R in aldehydes (RCHO) for their diastereoselectivity.

In summary, the two-step sequence of nitrile oxide olefin cycloaddition and reduction of the resulting Δ^2 -isoxazolines offers a unique and attractive alternative to the classical aldol reaction and its many variants. It is anticipated that this will greatly expand the synthetic utility of Δ^2 -isoxazolines.¹⁹

(9) For a selection of methodologies useful for directed aldol reaction see: Wittig, G.; *Fortschr. Chem. Forsch.* **1976**, 67, 1. Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, 39, 3459. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, 96, 7503. Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3. Kuwajima, I.; Sato, T.; Afai, M.; Minami, N. *Ibid.* **1976**, 1817. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, 102, 13248. Mukaiyama, T. *Org. React.*, in press.

(10) For a review of the general problem of acyclic stereoselection including aldol diastereoselection, see: Bartlett, P. A. *Tetrahedron*, **1980**, 36, 2.

(11) Several recent contributions in this rapidly growing area include: Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, 103, 1566. Masamune, S.; Hiram, M.; Mori, S.; Ali, S. K. A.; Garvey, D. S. *Ibid.* **1981**, 103, 1568. Evans, D. A.; Bartroli, J.; Shih, T. *Ibid.* **1981**, 103, 2127. Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, 23, 807. Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, 37, 4087. Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, 103, 4278. Noyori, R.; Nishida, I.; Sakata, J. *Ibid.* **1981**, 103, 2106.

(12) A related approach based on addition of allyl organometallics to aldehydes and subsequent oxidative cleavage of the olefin has been explored by several groups. See: Hoffmann, R. W.; Zeiss, H. *J. Org. Chem.* **1981**, 46, 1309 and references cited therein.

(13) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, 106, 3258.

(14) Jäger, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3129. Grund, H.; Jäger, V. *Liebigs Ann. Chem.* **1980**, 80. For a related alkylation see: Lidor, R.; Shatzmiller, S. *J. Am. Chem. Soc.* **1981**, 103, 5916.

(15) See ref 6a. Also: Garanti, L.; Sala, A.; Zecchi, G. *J. Org. Chem.* **1975**, 40, 2403. Jäger, V.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 246. Confalone, P. N.; Lollar, E. D.; Pizzalato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, 100, 6291. Kozikowski, A. P.; Ishida, H. *Ibid.* **1980**, 102, 4265. Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.*, **1981**, 46, 5248. Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.*, in press.

(16) This sequence has proven effective in a short, efficient synthesis of sarkomycin. See: Kozikowski, A. P.; Stein, P., preceding paper in this issue. See also ref 5b.

(17) The requisite nitro olefins were readily prepared from the corresponding olefins by a sequence of (1) Wittig reaction, (2) NaI exchange, (3) NaNO₂ displacement. Intramolecular cycloaddition under the standard conditions (PhNCO, Et₃N) gave the cycloadducts in uniformly high yield.

(18) To our knowledge, this is the first example of an intramolecular nitrile oxide cycloaddition to a trisubstituted olefin. Although the corresponding intermolecular reaction yields are often poor (ref 3) due to competing dimerization, this is not a factor in the intramolecular case.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. David Singleton is also thanked for valuable technical assistance.

Registry No. **2a**, 72553-35-6; **2b**, 7064-06-4; **2c**, 82149-99-3; **4a**, 82150-00-3; **4b**, 5381-93-1; **4c**, 82150-01-4; **6a**, 82150-02-5; **6a** ($R_1 = R_3 = n\text{-C}_3\text{H}_7$; $R_2 = \text{H}$), 82150-03-6; **6b**, 82150-04-7; **6b** ($n = 2$; $R_1 = \text{H}$; $R_2 = \text{Ph}$), 82150-05-8; **6c**, 82150-06-9; **7a**, 82150-07-0; **7a** [$R_1, R_2 = (\text{C}_2\text{H}_5)_4$; $R_3 = \text{H}$], 82150-08-1; **7a** [$R_1, R_2 = (\text{CH}_2)_3$; $R_3 = \text{H}$], 69423-36-5; **7b**, 26343-65-7; **7b** ($n = 2$; $R_1 = \text{H}$; $R_2 = \text{Ph}$), 42052-56-2; **7c**, 26343-67-9; **8a**, 53538-95-7; **8a** ($R_1 = R_3 = n\text{-C}_3\text{H}_7$; $R_2 = \text{H}$), 82150-09-2; **8b**, 82150-10-5; **8b** ($n = 2$; $R_1 = \text{Ph}$; $R_2 = \text{H}$), 82150-11-6; **8c**, 82150-12-7; **9a**, 53496-45-0; **9a** [$R_1, R_2 = (\text{CH}_2)_4$; $R_3 = \text{H}$], 82150-13-8; **9a** [$R_1, R_2 = (\text{CH}_2)_3$; $R_3 = \text{H}$], 32435-36-2; **9b**, 26343-66-8; **9b** ($n = 2$; $R_1 = \text{Ph}$; $R_2 = \text{H}$), 13161-18-7; **9c**, 26343-68-0; **10**, 82150-14-9; **11**, 82150-15-0.

(19) Other isoxazoline-based synthetic methodologies include conversion to α,β -unsaturated ketones via β elimination and oxime cleavage (Jäger, V.; Grund, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 50), conversion to β,γ -unsaturated oximes (Jäger, V.; Grund, H.; Schwab, W. *Ibid.* **1979**, *18*, 78), opening to β -hydroxy nitriles (Huisgen, R.; Cristl, M. *Chem. Ber.* **1973**, *106*, 3291. Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209. Kalvoda, J.; Kaufman, H. *Ibid.* **1976**, 210. Wade, P. M.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. Kozikowski, A. P.; Adamczyk, M., to be submitted for publication), cycloreversion to enol silyl ethers (Cunico, R. F. *J. Org. Met. Chem.* **1981**, *212*, C51).

Absolute Configuration of the *trans*-9,10-Dihydrodiol Metabolite of the Carcinogen Benzo[*a*]pyrene

Haruhiko Yagi and Donald M. Jerina*

Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
National Institutes of Health, Bethesda, Maryland 20205

Received March 26, 1982

The cytochromes P-450 are the principal enzymes in liver that are responsible for the oxidative detoxification of nonpolar foreign compounds by mammals.¹ Among these enzymes, cytochrome P-450c² is particularly effective in catalyzing the oxidation of polycyclic aromatic hydrocarbons and accounts for 70% of the total cytochromes P-450 in the livers of rats that have been treated with the inducer 3-methylcholanthrene.³ We have recently proposed a stereochemical model for the catalytic binding site of cytochrome P-450c that predicts the absolute configuration of arene oxides of many polycyclic hydrocarbons formed by this enzyme.⁴ So that this model for the binding site of cytochrome P-450c could be tested, the present study assigns absolute configuration to the (+)- and (-)-enantiomers of benzo[*a*]pyrene 9,10-dihydrodiol which are formed by the action of epoxide hydrolase on their benzo[*a*]pyrene 9,10-oxide precursors. Configurational assignment was achieved through chemical correlation of the 9,10-dihydrodiol with the 7,8-dihydrodiol of known absolute configuration based on circular dichroism⁵ as well as X-ray crystallographic studies.⁶

(1) Hathway, D. E. "Foreign Compound Metabolism in Mammals"; The Chemical Society: Burlington House, London, 1975; Vol. 3. White, R. E.; Coon, M. J. *Ann. Rev. Biochem.* **1980**, *49*, 315-356.

(2) Ryan, D. E.; Thomas, P. E.; Korzeniowski, D.; Levin, W. *J. Biol. Chem.* **1979**, *254*, 1365-1374.

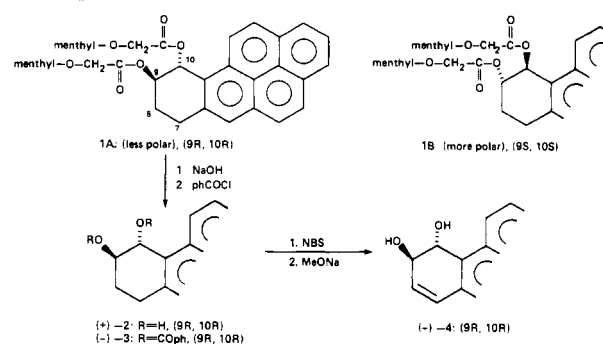
(3) Thomas, P. E.; Reik, L. M.; Ryan, D. E.; Levin, W. *J. Biol. Chem.* **1981**, *256*, 1044-1052. Thomas, P. E.; Korzeniowski, D.; Ryan, D.; Levin, W. *Arch. Biochem. Biophys.* **1979**, *192*, 524-529.

(4) Jerina, D. M.; Michaud, D. P.; Feldmann, R. J.; Armstrong, R. N.; Vyas, K. P.; Thakker, D. R.; Yagi, H.; Thomas, P. E.; Ryan, D. E.; Levin, W. In "Microsomes, Drug Oxidations, and Drug Toxicities", Fifth International Symposium on Microsomes and Drug Oxidations; Sato, R.; Kato, R., Eds.; Japan Scientific Societies Press: Tokyo, Japan, in press.

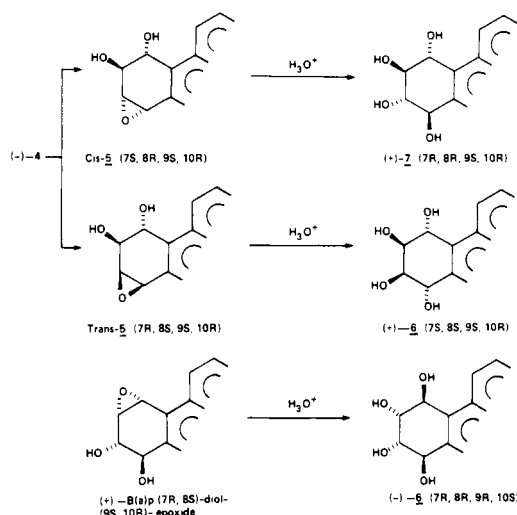
(5) (a) Yagi, H.; Akagi, H.; Thakker, D. R.; Mah, H. D.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 2358-2359. (b) Nakanishi, K.; Kasai, H.; Cho, H.; Harvey, R.; Jeffrey, A.; Jennette, K.; Weinstein, I. *Ibid.* **1977**, *99*, 258-260.

(6) Boyd, D. R.; Gadaginamath, G. S.; Kher, A.; Malone, J. F.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2112-2116. Boyd, D. R.; Gadaginamath, G. S.; Hamilton, R.; Yagi, H.; Jerina, D. M. *Tetrahedron Lett.* **1978**, 2487-2490.

Scheme I



Scheme II



Enantiomers of the 9,10-dihydrodiol were obtained via resolution of *trans*-9,10-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene⁷ as its diastereomeric bisesters (**1**, Scheme I) with (-)-menthoxyacetic acid. The diastereomeric bisesters were obtained in essentially quantitative yield by allowing the tetrahydrodiol to react with menthoxyacetyl chloride in pyridine at 50 °C for 24 h. Separation of the diastereomers was achieved by HPLC on a 2.5 × 120 cm column of 10- μ m silica gel eluted with 12% ether in cyclohexane ($\alpha = 1.34$):

1A: k' (less polar) = 2.00
 $[\alpha]_D -99^\circ$ (11 mg/mL, CHCl_3)

1B: k' (more polar) = 2.75
 $[\alpha]_D -37^\circ$ (12 mg/mL, CHCl_3)

Both diastereomers were colorless oils. Preliminary indication of the absolute configuration of these diastereomers was obtained from examination of their NMR spectra (100 MHz, C_6D_6). Previous studies⁸ of the bis(menthoxy) esters of several *trans*-diol derivatives of polycyclic hydrocarbons have shown that the diastereotopic CH_2 hydrogens in the pair of COCH_2O groups of the less polar bisester with the more negative $[\alpha]_D$ generally appear as a pair of singlets and have an *R,R* configuration whereas the

(7) Gibson, D. T.; Mahadevan, V.; Jerina, D. M.; Yagi, H.; Yeh, H. J. C. *Science Washington, D.C.* **1975**, *189*, 295-297. McCaustland, D. J.; Fischer, D. L.; Kolwyck, K. C.; Duncan, W. P.; Wiley Jr., J. C.; Menon, C. S.; Engel, J. F.; Selkirk, J. K.; Roller, P. P. In "Carcinogenesis", Freudenthal, R. I., Jones, P. W., Eds.; Raven Press: New York, 1976; Vol. 1, pp 349-411.

(8) Kedzierski, B.; Thakker, D. R.; Armstrong, R. N.; Jerina, D. M. *Tetrahedron Lett.* **1980**, *22*, 405-408. Yagi, H.; Vyas, K. P.; Tada, M.; Thakker, D. R.; Jerina, D. M. *J. Org. Chem.* **1982**, *47*, 1110-1117. Halpin, R. A.; El-Naggar, S. F.; McCombe, K. M.; Vyas, K. P.; Boyd, D. R.; Jerina, D. M. *Tetrahedron Lett.* **1982**, *23*, 1655-1658. In some instances, the NMR signal of one of the OCOCH_2O groups in the early eluting diastereomer is split. This splitting pattern was first noted by Boyd and co-workers in menthoxyacetic acid esters of bromohydrins: Akhtar, M. N.; Boyd, D. R.; Hamilton, J. G. *J. Chem. Soc. Perkins Trans. 1* **1979**, 2437-2440.