matography. Since these compounds are also air sensitive,[9] they were stored under argon in frozen benzene containing 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical as antioxidant.
(25) These studies which will be published separately show (from ^{1}H NMR data) that the cis double bond in conjugation with the ylide retains its configuration during ylide generation and coupling, an important finding for this and other applications.
(26) The *N*-trifluoroacetyl derivative of glutathione dimethyl ester was obtained by reaction of the tetramethyl ester of the disulfide form of glutathione (Watanabe, T.; Kohno, K.; Noda, K.; Hayashi, K. Japanese Patent 6 820 166, 1968; *Chem. Abstr.* **1969**, *70*, 58286j) with trifluoroacetic anhydride and powdered sodium carbonate in methylene chloride with stirring at 0 °C for 30 min, followed by isolation and disulfide cleavage using triphenylphosphine in 2:1 dimethoxyethane–water at 23 °C for 3 h.
(27) In contrast four stereoisomeric products were obtained (as expected) by reaction of *N*-trifluoroacetylglutathione methyl ester with the mixture of 5,6-cis and 5,6-trans isomers of (±)-**2** synthesized as described earlier;[9] these were readily separated by HPLC with one component corresponding to the product from (−)-**2**.
(28) Hydrolysis of the mixture of stereoisomeric[27] *N*-trifluoroacetyl trimethyl esters afforded a mixture of **1** and 3 stereoisomers which was readily resolved by reversed-phase HPLC.
(29) Superimposible lines were obtained in extensive dose-response studies using synthetic **1** and leukotriene C-1 with guinea pig ileum as test tissue.[2,5]
(30) Reversed-phase HPLC retention times were in the order cys analogue ≫ cys gly analogue > **1**, as expected.
(31) The attachment of a glutathione moiety at C-6 in leukotriene C-1 rather than cys or cys gly units has also been demonstrated by amino acid determination.[4]
(32) The research at Harvard was assisted by a grant from the National Science Foundation, NIH postdoctoral fellowships to D.C. and A.M., a research fellowship to G.G. from the Takeda Chem. Ind. Ltd., and a NATO fellowship to C.M. The work in Stockholm was supported by a grant from the Swedish Medical Research Council (Project 03X-217).

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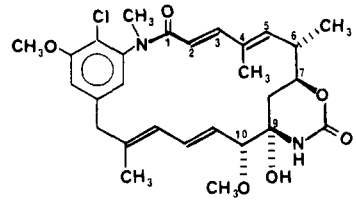
Received November 30, 1979

Total Synthesis of (−)-*N*-Methylmaysenine

Sir:

The first total synthesis of a maytansenoid, (±)-*N*-methylmaysenine, (±)-**1**, was recently reported from these labo-



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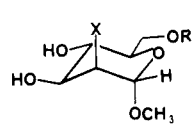
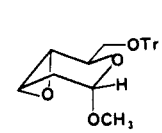
ratories.[1,2] We now describe a synthetic route to *N*-methylmaysenine which yields this substance in the natural optically active (levo) form without the need of resolution. The individual steps in the synthesis proceed in very good yields and the various chiral centers are established with high stereochemical efficiency.

Commercially available tri-*O*-acetyl-D-glucal (Pfanstiehl Laboratories, Inc.) was transformed into the epoxy trityl (Tr) ether **5** in 62% overall yield by a sequence of steps which were readily conducted on a 0.5-mol scale. The acetyl groups of tri-*O*-acetyl-D-glucal were cleaved by methanolysis (2 M solution of triacetate in dry methanol containing as catalyst 0.05 mol of sodium methoxide at 23 °C for 1.5 h), and the resulting solution of unsaturated triol was treated with 1.05 equiv of mercuric acetate for 2.5 h at 23 °C to effect methoxy mercuration. The mercuration product **2** was obtained as a crystalline solid by filtration through Celite, concentration under reduced pressure to ~25% of the original volume, and filtration; further concentration of the filtrate afforded a second crop of crystals (total yield 75%).[3] Reaction of a solution of **2** in methanol (1.3



2, X = HgOAc, R = H
3, X = R = H
4, X = H, R = Tr



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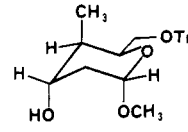

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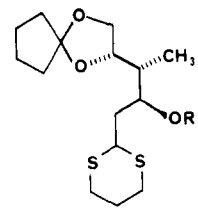
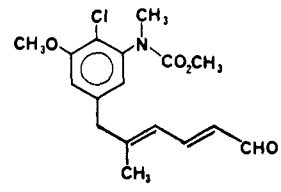


7, R = H
8, R = MEM



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M) with 1.5 equiv of sodium chloride (15 min at 23 °C) produced a solution of the corresponding chloromercurial which was cooled to 0 °C and treated with a slight excess (1.05 equiv) of sodium borohydride in isopropyl alcohol. After 30 min at 0 °C, methanol was removed under reduced pressure, the residue was suspended in ethyl acetate with rapid stirring, treated with a slight excess of 12 *N* hydrochloric acid and then with excess solid sodium bicarbonate to neutralize the slightly acidic mixture, dried over molecular sieve (4 Å), filtered through Celite, and evaporated in vacuo to afford triol **3** (99%) after drying over P_2O_5 at 23 °C for 48 h, at 55 °C for 16 h, and at 100 °C for 1 h. The thoroughly dried triol **3** upon treatment with 1.1 equiv of trityl chloride in dry pyridine (1.25 mL/g of **3** at 23 °C for 16 h) afforded, after recrystallization of crude product from ether–methylene chloride–pentane (40 to −20 °C), the trityl ether diol **4**, mp 142–144 °C, $[\alpha]^{25}_D$ +43° (*c* 3.04, $CHCl_3$).[4] A solution of the diol **4** in hexamethylphosphoric triamide (HMPT, 4.7 mL/g of **4**) was added to a suspension of sodium hydride (4 equiv) in HMPT (4 mL/g of **4**) at 5 °C and the mixture was brought to 23 °C for 30 min and diluted with 0.5 vol. of tetrahydrofuran (THF). After cooling to −25 °C, the disodium derivative of **4** was treated with triisopropylbenzenesulfonylimidazole (1.1 equiv based on **4**) in THF (3 mL/g of sulfonyl reagent) with stirring at −25 °C for 1 h and −25 to −5 °C for 3 h. Filtration of the reaction mixture through Celite after dilution with ether, concentration under reduced pressure, and extractive isolation (Darco treatment) afforded a crude product which yielded 75% epoxide **5**, mp 101–102 °C, $[\alpha]^{25}_D$ +40° (*c* 4.22, $CHCl_3$), by crystallization from ether–pentane and an additional 15% by chromatography of the mother liquors (90% total yield of **5**). Reaction of the epoxide **5** with 2.8 equiv of methyllithium and 0.57 equiv of cuprous iodide in 2:1 ether–toluene at −78 °C for 48 h and −45 °C for 48 h afforded 95% **6**, mp 125–126 °C (from ether–pentane), $[\alpha]^{25}_D$ +36° (*c* 4.2, $CHCl_3$).[6] Treatment of **6** with 5 equiv of propane-1,3-dithiol in 1:6 chloroform–12 N hydrochloric acid at 0 °C for 15 min resulted in cleavage of the pyranose ring and the trityl ether to give 96% trihydroxyalkyl-1,3-dithiane, mp 107–108 °C, $[\alpha]^{25}_D$ −16.9° (*c* 3.0, $CHCl_3$), which was selectively protected by reaction with 1.6 equiv of 1-ethoxycyclopentene and 0.04 equiv of boron trifluoride etherate in THF (15 mL/g of triol) at −30 °C for 30 min to give the ketal dithiane **7**, mp 62–63 °C (from ether–hexane), $[\alpha]^{25}_D$ −28.8 °C (*c* 1.0, $CHCl_3$), in 86% yield. For complete protection **7** was treated with 3 equiv of β-methox-

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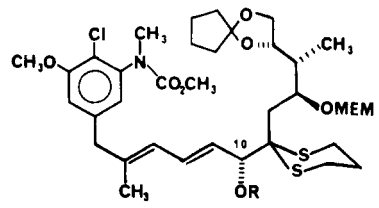
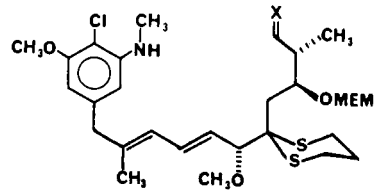
yethoxymethyl chloride (MEM chloride)[7] and 6 equiv of diisopropylethylamine in methylene chloride (2 mL/g of **7**) at 20 °C for 20 h to give the MEM ether **8**, $[\alpha]^{20}_D$ −16.8° (*c* 1.2, $CHCl_3$), as a colorless oil, yield 99%.

The protected dithiane **8** was lithiated using 1 equiv of *n*-butyllithium-tetramethyethylenediamine in THF (3.8 mL/g of **8**) at −25 °C for 3 h, cooled to −78 °C, and allowed to react with the dienal **9**[8] (0.81 equiv) in THF at −78 °C for 30 s to afford ~90% yield of a 1:1 mixture of **10** and its C-10 epimer. These were readily separated by short column chromatography[9] on silica gel (pentane–ether, 1:4) to give 44% **10** and an equal amount of the C-10 epimer which was efficiently converted into **10** (~85% yield; total yield of **10** from **8**, 80%) by oxidation to the **10** ketone (fourfold weight of activated manganese dioxide in methylene chloride at 0 °C for ~4 h), followed by reduction with a large excess of lithium *n*-butylborohydride[10] in toluene at −78 °C for 26 h and chromatographic separation from a small amount (8–9%) of epimer at C-10.[11] Treatment of **10** with an excess of sodium hydride and methyl iodide in THF (20 mL/g of **10**) at 20 °C for 15 min produced the methyl ether **11** as a colorless oil (91% yield), $[\alpha]^{20}_D$



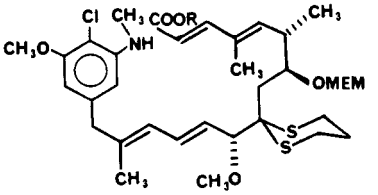
10, R=H
11, R=CH_3



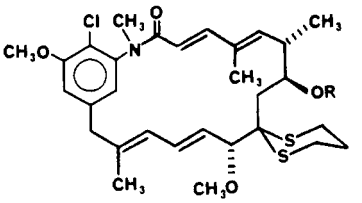
12, X= O
13, X= C(CHO)CH_3

+28.8° (*c* 1.0, $CHCl_3$), TLC R_f 0.42 (silica gel, ether). Deprotection of the amino function in **11** was effected in 90% total yield by reaction with 5 equiv of lithium thiomethoxide[12] in dimethylformamide (DMF) at 0 °C for 40 h; a small amount of phenolic byproduct resulting from cleavage of the aromatic methoxy group could be recycled (CH_3I, K_2CO_3, acetone, 23 °C). The ketal group protecting the 1,2-diol unit was then removed (0.3 M perchloric acid in 50% aqueous acetonitrile at 0 °C for 40 min), and the resulting 1,2-diol (87% yield) was cleaved by reaction with 1 equiv of lead tetraacetate in acetonitrile (0.17 M) in the presence of excess potassium acetate at −25 °C for a few minutes to give the unstable aldehyde **12** (95% yield). The aldehyde is isolated by removal of most of the acetonitrile in vacuo in the cold, passage in ether at 0 °C through a short column of Florisil, and removal of ether in vacuo.

The conversion of the aldehyde **12** into the (*E*)-enal **13** was carried out using the α-lithio derivative of α-trimethylsilylpropionaldehyde *N*-*tert*-butylimine[1,13] at −110 °C for 5 min and −78 °C for 10 min, followed by ether extraction, concentration of the wet extract in the presence of silica gel (to effect conversion of imine into enal), and finally treatment with pyridinium chloride in methylene chloride (25 mL/g) at 20 °C for 2 h (to effect *Z* → *E* isomerization of any (*Z*)-enal present), and the enal **13** was purified by chromatography on silica gel, 82% yield, TLC R_f 0.53 (silica gel, ether). Chain extension of **13** to form the conjugated α,β-*E*,γ,δ-*E*-unsaturated ester **14** was accomplished in 96% yield by reaction with 5 equiv of the lithio derivative of dimethyl methoxycarbonylmethanephosphonate in THF (30 mL/g of **13**) at 20 °C for 6 h.[1] The methyl ester **14** was saponified to the corresponding acid **15** (90% yield) by treatment with 0.2 *M* tetra-*n*-butyl-



14, R = CH_3
15, R = H



16, R= MEM
17, R= H

ammonium hydroxide in 1:1 aqueous THF at 20 °C for 6 h; TLC R_f 0.32 (silica gel, ether). Lactamization of the amino acid **15** to form the macrocyclic lactam **16** was accomplished in 90% yield using the mixed anhydride with mesitylenesulfonic acid for carboxyl activation.[1] A solution of the tetra-*n*-butylammonium salt of **15** (thoroughly dried by azeotropic distillation of toluene) in benzene (~1 mg/mL) was slowly added to a large excess of mesitylenesulfonyl chloride and diisopropylethylamine in benzene at 40 °C (syringe drive over 20 h). Extractive isolation and chromatography on silica gel yielded 90% pure **16**, $[\alpha]^{25}_D$ −76.5° (*c* 0.2, in ethanol), λ_{max} (ethanol) 212 (21 500), 246 (51 500), 276 (30 900) nm. The MEM group in **16** was removed by exposure to 10% aqueous sulfuric acid–toluene (10:1) at 40 °C for 5 h (rapid stirring) to afford after chromatography 92% free alcohol **16**, $[\alpha]^{25}_D$ −94.1° (*c* 0.15 in ethanol), purity 100% by high pressure liquid chromatographic (HPLC) analysis, spectroscopically and chromatographically identical with racemic material previously synthesized.[1,14]

The completion of the synthesis of (−)-*N*-methylmaysenine followed the path previously described for the racemic series.[1] Carbamoylation of the hydroxyl group in **17** was effected (80% yield) by reaction with excess *p*-nitrophenylchloroformate and pyridine at 27 °C for 5 hr followed by treatment with an excess of 15 N ammonium hydroxide in *tert*-butyl alcohol (1:1) at 27 °C for 8 h using extractive isolation and chromatography on silica gel (R_f 0.24 using 3% methanol in ether). The carbomate was then converted into **1** (76% yield) by reaction with 5 equiv of mercuric chloride and excess calcium carbonate in 5:1 acetonitrile–water at 30 °C for 17.5 h followed by chromatography on silica gel (R_f 0.25 using ethyl acetate): $[\alpha]^{25}_D$ −224° (*c* 0.04 in ethanol); λ_{max} in ethanol 234 (43 000), 247 (51 000), 271 (28 000), 254 (42 200); infrared max in $CDCl_3$ (cm^{-1}) 3420 (sharp), 3340 (broad), 1710, 1660, 1620, 1580, 1350, 1255, 1090, 1050, 980, 910, 735, 700; CD (in ethanol) $\Delta\epsilon_{289}$ −16.5°, $\Delta\epsilon_{259}$ −46.1° $\Delta\epsilon_{240}$ +28.7°, $\Delta\epsilon_{220}$ −6.0°.[15] Synthetic and naturally derived *N*-methylmaysenine were identical in all spectroscopic, chromatographic (including HPLC) and optical rotatory measurements. In addition the synthetic and

natural compounds were indistinguishable after conversion into the 9-methyl ether as previously described (0.5% tosic acid in methanol at 25 °C for 20 min).[1]

With the completion of the first total synthesis of an optically active maytansenoid in natural form by a sequence of highly selective and efficient steps, the stage is now set for the synthesis of maytansine and related active anti-tumor agents.[16]

References and Notes

(1) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978,** *100,* 2916.
(2) A second synthetic route to (±)-**1** has been described by Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *Ibid.* **1979,** *101,* 4734.
(3) The crystalline methoxy mercuration product **2** possesses the axial (α) orientation of methoxy at C-1, in consonance with a previous report. See Inglis, G. R.; Schwarz, J. C. P.; McLaren, L. *J. Chem. Soc.* **1962,** 1014. Methoxy mercuration of tri-*O*-acetyl-D-glucal under the same conditions affords a mixture of α- and β-anomeric methoxy triacetates in a ratio of 55:45. Although the mixture of anomeric methoxy triacetates was obtained in high yield (>95%) and in principle can be used for the synthesis, in practice the β anomer was found to be unsatisfactory in a later step of the synthesis (epoxide opening by methylcopper reagent). See also, Manolopoulos, P. T.; Mednick, M.; Lichtin, N. N. *J. Am. Chem. Soc.* **1962,** *84,* 2203 for the mercuration step.
(4) Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained using chromatographically homogeneous samples of each synthetic intermediate. All reactions involving air or moisture sensitive components were performed under an atmosphere of dry argon.
(5) This procedure represents a modification of the method described by Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974,** 203, which uses tosyl imidazole as reagent. The reaction of trityl ether diol **4** with this reagent was found to produce not only the desired α-oxide **5** but also (in approximately equal amount) the corresponding β-oxide.
(6) Interestingly, the reaction of **5** with lithium dimethylcuprate in ether–THF at −50 °C afforded in high yield the allylic alcohol which results from elimination of a proton from C-2 and oxygen from C-3 if halide-free CH_3Li was used.
(7) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976,** 809.
(8) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipschutz, B. *Ibid.* **1978,** 1051.
(9) Rigby, W.; Hunt, B. J. *Chem. Ind. (London)* **1967,** 1868.
(10) For the original use of this reagent see: Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S. Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978,** *100,* 4620. The reagent was prepared form equimolar amounts of borane-dimethyl sulfide complex in toluene and *n*-butyllithium in hexane (under Argon). The solvent and dimethyl sulfide were removed in vacuo and dry toluene added to give a 0.25 M solution of reagent.
(11) The R_f values found for **10** and the C-10 epimer using silica gel plates with ether as solvent were 0.37 and 0.32, respectively; rotations for **10** and the C-10 epimer were $[\alpha]^{20}_D$ +39.6° and −3.3° (*c* 0.7 in $CHCl_3$), respectively.
(12) Kelley, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977,** 3859. Lithium thiopropoxide in DMF or HMPT was found to be less satisfactory.
(13) Corey, E. J.; Enders, D.; Bock, M. G. *Tetradedron Lett.* **1976,** 7.
(14) Circular dichroism data (CD) in ethanol for **16:** $\Delta\epsilon_{293}$ −2.1°, $\Delta\epsilon_{278}$ −7°, $\Delta\epsilon_{265}$ −23°, $\Delta\epsilon_{238}$ +13°, $\Delta\epsilon_{223}$ −7°; λ_{max} (ethanol) 210 (30 000), 247 (51 000), 275 (25 000) nm; ^{1}H NMR in (deuterioacetone) 3.90 (s, 3 H), 3.25 (s, 3 H), 320 (s, 3 H), 1.35 (s, 3 H), 1.30 (s, 3 H), 1.05 (d, 3 H) ppm and other peaks as expected.
(15) ^{1}H NMR data for **1** (at 80 MHz in $CDCl_3$, ppm): 1.27 (d, 3 H), 1.48 (br s, 3 H), 1.70 (br s, 3 H), 3.25 (s, 3 H), 3.30 (s, 3 H), 3.51 (d, 1 H), 4.00 (s, 3 H), 4.18 (m, 1 H), 5.33 (dd, 1 H), 5.40 (d, 1 H), 5.60 (br d, 1 H), 6.03 (d, 1 H), 6.32 (br s, 1 H), 6.38 (dd, 1 H), 6.61 (d, 1 H), 6.79 (d, 1 H), 7.23 (d, 1 H).

(16) This research was assisted financially by a grant from the Cancer Institute of the National Institutes of Health to whom we are grateful. We thank Dr. John Douros of NIH for his advice and help at various stages of the project.

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Aromatic Hydroxylation by O(^{3}P) Atoms

Sir:

Oxidations of aromatic compounds yielding phenols can be considered as important biological reactions. As a typical example, oxidations induced by monooxygenase can be mentioned which are accompanied by characteristic intramolecular migrations and retentions of substituents of the aromatic ring, commonly referred to as NIH shift.[1,2] An oxygen-transfer mechanism involving cationoid or arene oxide intermediates has been proposed by several investigations for hydroxylations induced by microsome and nonenzymatic model systems.[3-5] However, the elementary reactions of this mechanism are not known with certainty.

Table I. Retention of Deuterium in Cresols Formed by the Hydroxylation of Deuterated Toluenes with O(^{3}P) Atoms

substrate[a]	products[b]	*G* value[c]	distribution of D, % d_3	d_2	d_1
toluene-*3,5*-d_2 (**1**)	*o*-cresol	1.89		90	10
	m-cresol	0.14	*d*	*d*	*d*
	p-cresol	0.68		75	25
toluene-*2,4,6*-d_3 (**2**)	*o*-cresol	1.86	33	67	*e*
	m-cresol	0.14	*d*	*d*	*d*
	p-cresol	0.70	52	48	*e*

[a] Toluene-*3,5*-d_2 and -*2,4,6*-d_3 were prepared by the method of Howe et al.: Howe, I.; McLafferty, F. W. *J. Am. Chem. Soc.,* **1971,** *99,* 93. Best, A. P.; Wilson, C. L. *J. Chem. Soc.,* **1946,** 239. The deuterium contents of the substrates were determined by mass spectrometry and NMR spectrometry. The mole fraction of two deuterium atoms in the substituted positions of **1** was >0.95 and the mole fraction of three deuterium atoms in the substituted positions of **2** was >0.93. [b] Trace amounts of phenol was also observed as the products. Cresols were analyzed by GLC (UCON LB 550X and silicon DC 550 after trimethylsilylation) and mass spectrometer (Hitachi RMU-4). [c] Molecules per 100 eV absorbed. The conversion was kept lower than 10% to prevent the further reactions. [d] The measurement of a mass spectrum of *m*-cresol was not successful because the yield was low and the separation from *p*-cresol was not complete. [e] Negligibly small.

During our investigations, oxidations were achieved via O(^{3}P) atoms produced during the γ radiolysis of liquid carbon dioxide.[6] Upon the oxidation of toluene-*2,4,6*-d_3, cresol is formed.[7] In this case we observed a pronounced retention of deuterium atoms on the aromatic ring. This result resembled that obtained during oxidations induced by microsomes.[4,8] These observations prompted us to investigate the mechanism of oxidations initiated by O(^{3}P) atoms. These results are considered being of a model character with respect to the understanding of NIH shift in compounds of biological importance.

The γ radiolysis of liquid CO_2 (1.4 mol) in the presence of toluene-*3,5*-d_2 (**1**) and -*2,4,6*-d_3 (**2**) (5 mmol, respectively) was carried out at 0 °C for 1 h in a stainless steel autoclave (65 mL) using a ^{60}Co source. Product cresols were analyzed by GLC and mass spectrometry after treatment with water to exchange the phenolic deuterium completely by hydrogen. The results are shown in Table I.

The rather high retention of deuterium indicates that in these cases the hydroxylation does not proceed via direct insertion of oxygen atoms into the aromatic C–H bonds and that intramolecular migration takes place to a significant extent. It becomes, therefore, very probable that a mechanism is operative involving a 2,4-cyclohexadienone intermediate which undergoes aromatization to cresol. By Jerina et al.[9] and Bruice et al.[10] it has been assumed that such an intermediate is formed during the aromatization of arene oxides to phenols. Scheme I shows the formation of *p*-cresol from toluene-*2,4,6*-d_3 (**2**), as a typical example.

On the basis of the two sets of data, i.e., the deuterium retentions in *p*-cresol formed from **1** and **2,** the isotope effect for the aromatization of 2,4-cyclohexadienone (**4**) to *p*-cresol was calculated to be k_H/k_D = 2.1. Thus, for the relative ratio of path a to path b one obtains 77:23. It is clear that the main course of the hydroxylation by O(^{3}P) atoms is path a which causes a significant NIH shift, although the direct path (path b) is contributing to the oxidation process to a small extent.

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