K_2CO_3, $CaCO_3$, CH_2Cl_2) which was pyrolyzed in situ (*o*-dichlorobenzene, 150 °C) to give *trans*-dihydroaustamide **18**[4,15] (mp 110–115 °C) in 50% overall yield. This material was identical in all respects (NMR, UV, MS, TLC) with an authentic sample of (12*R*)-dihydroaustamide prepared by hydrogenation of austamide.[1]

The dianion of **18** was formed with lithium diisopropylamide (2 equiv) in tetrahydrofuran at −78 °C, which in turn was quenched with 2 equiv of diphenyl disulfide at −78 °C to room temperature. In this manner the tertiary alcohol **19**[4,16] as a mixture of stereoisomers (amorphous solid) was formed as the major product after aqueous workup. This alcohol was treated with excess triethylamine and mesyl chloride in methylene chloride at room temperature to give *dl*-austamide (**1**) in 40% overall yield. The synthetic material was identical in all respects (NMR, UV, MS, TLC) with an authentic sample.

Acknowledgment. We thank Dr. Steyn for a sample of austamide. Financial assistance from the National Science Foundation is gratefully acknowledged.

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(1) Steyn, P. S. *Tetrahedron Lett.* **1971**, 331–3334; *Tetrahedron* **1973**, *29*, 107–120.
(2) Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, 539–542.
(3) See for example, Sames, P. G. *Fortschr. Chem Org. Naturst.* **1975**, *32*, 51–117.
(4) Satisfactory spectroscopic data were obtained for this susbtance.
(5) NMR ($CDCl_3$): δ 1.50 (6 H, s), 2.01 (2 H, t, J = 7 Hz); MS *m/e* 369 (M^+, 9%), 216 (100), 172 (51).
(6) Harrison, I. T. *Proc. Chem. Soc.* **1964**, 110.
(7) NMR ($CDCl_3$): δ 1.28 (6 H, s); MS *m/e* 349 (M^+ − 18, 15%), 196 (100).
(8) NMR ($CDCl_3$): δ 1.61 (6 H, s), 2.25 (2 H, t, J = 7 Hz), MS *m/e* 607 (M^+, 4%), 320 (100), 198 (75).
(9) A paper describing the use of this protecting group is presently in preparation.
(10) Salmi, E. J ; Leimu, R.; Kallio, H. *Suom. Kemistil. B* **1944**, *17*, 17–19.
(11) NMR ($CDCl_3$): δ 1.55 (3 H, s), 1.62 (3 H, s); MS *m/e* 381 (M^+ − 80, 12%), 228 (100), 198 (63).
(12) NMR ($CDCl_3$): δ 1.43 (3 H, s), 1.80 (3 H, s); MS *m/e* 461 (M^+, 9%), 459 (M^+, 21), 73 (100).
(13) NMR ($CDCl_3$): δ 1.31 (3 H, s), 1.61 (3 H, s), 2.44 (3 H, s); MS *m/e* 564 (M^+ − 197, 19%), 196 (100).
(14) NMR ($CDCl_3$): δ .85 (3 H, s), 1.03 (3 H, s), 3.25 (3 H, s); UV (MeOH) λ 392 nm (log ε 3.46), 256 (3.86), 232 (4.40); MS *m/e* 397 (M^+, 10%), 365 (74), 309 (100).
(15) Note Added in Proof. Subsequent investigations have uncovered a new method to effect the conversion of **18** into austamide which is superior to that described in the text both in terms of overall yield and reproducibility. A solution of **18** in tetrahydrofuran was stirred under oxygen atmosphere in the presence of benzoyl peroxide at 50 °C for 24 h, after which the reaction mixture was treated with excess methyl sulfide at room temperature. In this manner a 72% yield of 12,13-dihydro-12-hydroxyaustamide, the stereoisomer with respect to X of **19**, was obtained which was found to be identical with the authentic sample by comparison of their NMR spectra. Treatment of this substance with methanesulfonyl chloride and triethylamine in methylene chloride as described in the text gave a 63% yield of *dl*-austamide (**1**). We are indebted to Dr. Steyn for the NMR spectrum of natural 12,13-dihydro-12-hydroxyaustamide.
(16) The gross structure **19** corresponds to that of one of the minor metabolites isolated from *A. ustus:* Steyn, P. S.; Vleggaar, R. *Phytochemistry* **1956**, *15*, 355–356.

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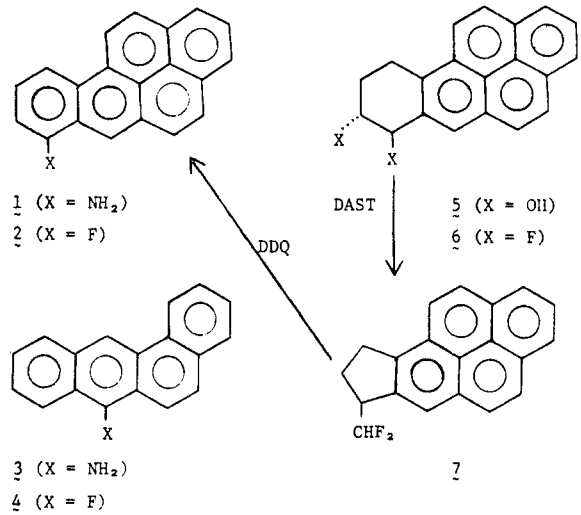
Received May 29, 1979

A Novel Synthesis of 7-Fluorobenzo[*a*]pyrene Involving Two New Molecular Rearrangements[1]

Sir:

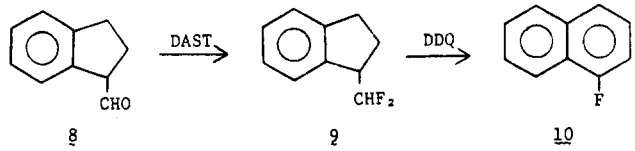
Because of our interest in the possible metabolic pathways by which benzo[*a*]pyrene produces cancer we sought to convert 7-aminobenzo[*a*]pyrene (**1**) into 7-fluorobenzo[*a*]pyrene (**2**) desired for testing. However, only very small amounts of **2** could be produced from **1** by conventional diazotization via the diazonium fluoroborate[2,3] and none at all using the modified procedure recently described for converting 7-aminobenz[*a*]-anthracene (**3**) into 7-fluorobenz[*a*]anthracene[4] (**4**).



We then turned to *trans*-7,8-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene[5] (**5**) in the hope that treatment with diethylaminosulfur trifluoride (DAST)[6,7] would yield the corresponding difluoride (**6**), which might be converted into 7- or 8-fluorobenzo[*a*]pyrene or a mixture of the two.[8] Treatment of **5** with DAST produced a compound which on heating in benzene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded **2** in 60% overall yield from **5**. Examination of the NMR spectra[9] of the intermediate difluoro compound showed that rearrangement into 7-difluoromethyl-8,9-dihydro-7(*H*)-cyclopenta[*a*]pyrene (**7**) had taken place. This rearrangement is surprising, especially since it has been mentioned that the OH group in isobutyl alcohol can be replaced by F without causing extensive rearrangement or dehydration.[7]

Perhaps even more surprising is the rearrangement of **7** into **2** in high yield on heating in benzene with DDQ, a reagent noted mainly for its ability to oxidize by extracting two hydrogens. The formation of **2** from **7** provides an example of what may become a new method for synthesis of fluorinated aromatic compounds as shown in Scheme I.

Scheme I



We are studying the synthesis of nuclear substituted compounds of type **8**, the conversion of these two compounds of type **9** by treatment with DAST,[10] and the effect of DDQ and other reagents on the rearrangement of **9** to **10**. It is also of interest to see if dichlorides, dibromides, and dimethoxy compounds analogous to **9** can be caused to rearrange to compounds of type **10**. Typical experimental procedures follow.

To a stirred suspension of 0.90 g of **5** in 250 mL of CH_2Cl_2 at −78 °C was added 1.5 g of DAST.[6,7] After 30 min the temperature was allowed to rise to 0 °C and the mixture became clear. After water was added, the organic product was isolated and treated at reflux in benzene containing 0.90 g of DDQ for 16 h. Chromatography over basic alumina afforded 0.50 g (60%) of **2**, mp 174–175 °C. Anal.[11] ($C_{20}H_{11}F$) C, H, F.

In another experiment similar to the above, the crude product from the DAST treatment was chromatographed over neutral alumina to yield (40%) pure **7**, mp 112–113 °C. Anal.[11] ($C_{20}H_{14}F_2$) C, H, F. A sample of pure **7** gave **2** in 82% yield on treatment with DDQ as above.

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The ^{19}F NMR spectrum[12,13] showed a doublet of doublets centered at δ 120 ppm (J = 57, 14.5 Hz, with additional smaller couplings of 2.5 Hz). The ^{1}H NMR spectrum showed a triplet of doublets centered at δ 5.9 ppm (1 proton, CHF_2, J_{HF} = 57, J_{HH} = 5 Hz).

The oxime of 7-keto-7,8,9,10-tetrahydrobenzo[*a*]pyrene[4] was converted into its acetate, mp 193–195 °C, which on heating with Pd/C in naphthalene at 200–205 °C for 2 h yielded after dry column chromatography[15] 36% **1**, mp 203–204 °C; NMR showed two exchangeable protons at δ 4.66. Anal.[11] ($C_{20}H_{13}N$) C, H, N.

To a stirred mixture under N_2 of 2.18 g of $NaBF_4$ in 50 mL of dry THF was added 2.6 mL of CF_3COOH followed by 1.07 g of **1**. After 15 min at 25 °C, the mixture was cooled to −20 to −15 °C and 500 mg of $NaNO_2$ was added in small portions. The dark brown suspension of diazonium salt formed was stirred for 15 min and the solid was collected, washed with dry THF, and dried under vacuum. This solid had an IR peak at 2200 cm^{-1} (RN_2^+). The dry salt, mixed with powdered dry KF, was added to 100 mL of boiling dry xylene. The product was chromatographed over basic alumina to give 290 mg of solid, mp 152–156 °C. Analysis showed this to be a mixture of **2** and benzo[*a*]pyrene.[2,3]

The mass spectra[16] agreed with the assigned structures for **1**, **2**, and **7**.

References and Notes

(1) This work was supported by Grant 5 R01CA07394 from the National Cancer Institute of the Department of Health, Education and Welfare.
(2) We thank Dr. Don Jerina, NCI, Bethesda, Md., for purifying by high-pressure liquid chromatography a reaction product from diazotization that we supplied.
(3) A small amount of pure **2**, mp 174–175 °C, was obtained which was identical with that which we prepared by the alternate method.
(4) Newman, M. S.; Lilje, K. C. *J. Org. Chem.*, in press.
(5) McCaustland, D. J.; Engel, J. F. *Tetrahedron Lett.* **1975**, 2549.
(6) We thank Dr. W. J. Middleton of the Du Pont Co., for a generous gift of DAST.
(7) Middleton, W. J.; Bingham, E. M. "Organic Synthesis"; Wiley: New York, 1977; Vol. 57, p 50.
(8) Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D. *J. Med. Chem.* **1978**, *21*, 38. The synthesis of monofluoro-5-methylchrysenes from dihydrodihydroxy-5-methylchrysenes served as a model—except that our compound was a tetrahydrodiol in the benzo[*a*]pyrene series.
(9) We thank Professor John Swenton and Dr. Charles Cottrell for interpretation of the NMR spectra.
(10) Middleton, W. J. (*J. Org. Chem.* **1975**, *40*, 574) records the conversion of trimethylacetaldehyde into 1,1-difluoro-2,2-dimethylpropane by DAST in 88% yield.
(11) Analyses were by the Galbraith Laboratories, Inc., Knoxville, Tenn., and the values agree with calculated values within ±0.4%.
(12) Fuqua, S. A.; Duncan, H. G.; Silverstein, R. M. *J. Org. Chem.* **1965**, *30*, 2543.
(13) The ^{19}F NMR spectrum was obtained in deuteriochloroform on a Bruker Hx 90-MHz instrument. The chemical shift is reported in parts per million relative to $CFCl_3$ using CF_3COOH as external standard. The ^{1}H NMR spectrum was obtained in deuteriochloroform on EM + 360 60-MHz spectrometer using tetramethylsilane as an internal standard.
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(16) We thank Mr. Richard Weisenberger for running the mass spectra.
(17) Postdoctoral Research Associate.

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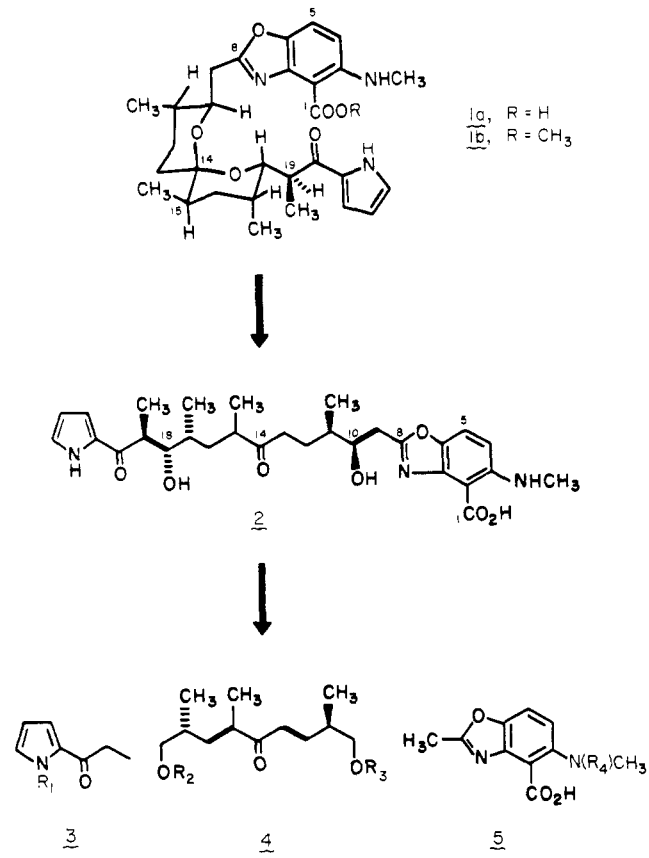
Polyether Antibiotics Synthesis. Total Synthesis and Absolute Configuration of the Ionophore A-23187

Sir:

Over the last few years the general interest in polyether antibiotics has risen dramatically.[1] This rapidly growing class of compounds, produced mainly by *Streptomyces* organisms, characteristically form lipophilic metal ion complexes which are effective in ion transport across lipid barriers.[2] To date, the ionophore antibiotic A-23187 (calcimycin, **1a**)[3] appears to be unique in its divalent cation transport selectivity.[4] Extensive literature is now rapidly accumulating on the application of this ionophore as an effective probe for the involvement of metal ions in the control of numerous physiological processes.[5] This communication describes the first synthesis of A-23187 (**1a**) and defines the absolute configuration of this natural product.

Scheme I



Based upon oxygen anomeric effects and related stereochemical considerations,[6] we projected that the 1,7-dioxaspiro[5.5]undecane skeleton in **1** with the requisite C_{14} stereocenter would be readily attainable from the acyclic keto diol precursor **2** via acid-catalyzed ring closure (Scheme I).[7] This internal ketalization process is undoubtedly a plausible step in the biosynthesis of **1a.** We further assumed that stereochemical control of the C_{15} methyl-bearing stereocenter need *not* be an issue in the enantioselective synthesis of the penultimate precursor **2** since acid-catalyzed equilibration of this center in the target molecule should afford the desired equatorial methyl diastereoisomer.[8] The intermediate **2**, upon aldol disconnection, appeared to be readily accessible from the heterocyclic precursors **3** (R = H)[9] and **5** and the ketone **4** which possesses a C_2 axis of symmetry with respect to skeletal carbons C_{10}–C_{12} and C_{16}–C_{18}.

After several abortive attempts, a practical synthesis of the benzoxazole moiety **5** was developed. Methyl 5-hydroxyanthranilate,[10] upon trifluoroacylation (TFAA, C_5H_5N), afforded **6a,** mp 136–138 °C, in 92% yield.[11] A priori, we had anticipated that mononitration of **6a** would have revealed a greater propensity for electrophilic substitution at C_4 vs. C_6, thereby thwarting attempts to construct the requisite aminophenol **6c.** This concern was unfounded. Nitration (1 equiv of HNO_3, Et_2O, 25 °C) afforded a 2:1 mixture of the desired nitrophenol **6b**[11] (mp 121–124 °C) and the corresponding

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