O_3, treated with glacial AcOH (4 mL), and transferred to a microdistillation apparatus. When the distillation started, the distillate was cautiously collected in a solution of 2,4-dinitrophenylhydrazine in a H_2SO_4–EtOH mixture.[5] The first distillate produced in the collecting tube a precipitate which was filtered while the distillation stopped. The filtered product was washed and dried and turned out to be the 2,4-DNP of acetone: 0.010 g; mp 127–128 °C (lit.[12] mp 128 °C).

The liquid residue of the distillation was diluted with water and extracted with ether. Evaporation of the washed (water, saturated $NaHCO_3$, water) and dried ether extracts gave **6-oxoheptanal dimethyl acetal (9)**: 0.050 g; oil; IR 1718, 1129, 1081, 1052 cm^{-1}; NMR δ 4.30 [m, 1, $CH(OCH_3)_2$], 3.26 [s, 6, $CH(OCH_3)_2$], 2.07 (s, 3, $COCH_3$). The addition of a portion of **9** (0.010 g) to a solution of 2,4-dinitrophenylhydrazine in H_2SO_4–EtOH[5] afforded the bis 2,4-DNP of **9**: mp 187–188 °C. Anal. Calcd for $C_{19}H_{20}N_8O_8$: C, 46.72; H, 4.09; N, 22.95. Found: C, 46.61; H, 4.05; N, 23.22.

Ozonolysis of 1-Methylcyclohexene (10). The ozonolysis of **10**[13] (0.50 g) was performed as described above for **6**. The methanolic solution from the ozonolysis tube, after acidification with glacial AcOH, was gently warmed at 50–60 °C for 5 min, cooled, diluted with water, and extracted with ether. Evaporation of the washed (water, saturatred $NaHCO_3$, water) and dried ether extracts afforded pure **9** (0.41 g).

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Registry No. **3**, 7583-74-6; **6**, 87830-76-0; **7**, 87830-77-1; **8**, 87830-78-2; **9**, 36727-64-7; **10**, 591-49-1.

(12) Vogel, A. "Textbook of Practical Organic Chemistry", 4th ed.; Longman: London, 1978; p 1194.
(13) For the preparation of **10** see: Barili, P. L.; Bellucci, G.; Macchia, B.; Macchia, F.; Parmigiani, G. *Gazz. Chim. Ital.* **1971**, *101*, 300.

Synthesis and Structure of Side Chain Haloallenes in the Steroid Series

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Recently we developed a stereoselective route to 1-haloallenes by reacting optically active 2-propynylic methanesulfonates with lithium dihalocuprates.[1] In one case, viz., reaction of mestranol methanesulfonate (**1**) with lithium dibromocuprate, the allene formation even proceeded stereospecifically. Unfortunately, the well-known and valuable Lowe–Brewster rules[2] may be violated in the case of trisubstituted allenes,[3,4] so that the absolute configuration of the bromoallenes derived from **1** was still a matter of doubt. The present paper concerns an unequivocal determination of its structure together with a more elaborate study of the haloallene formation in the steroid series.

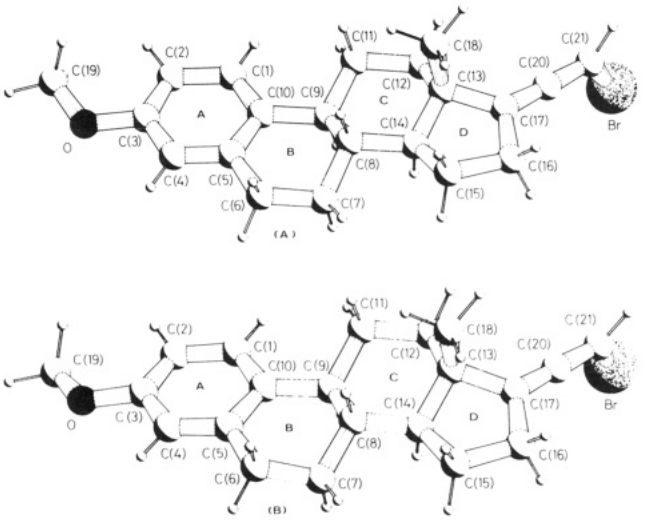
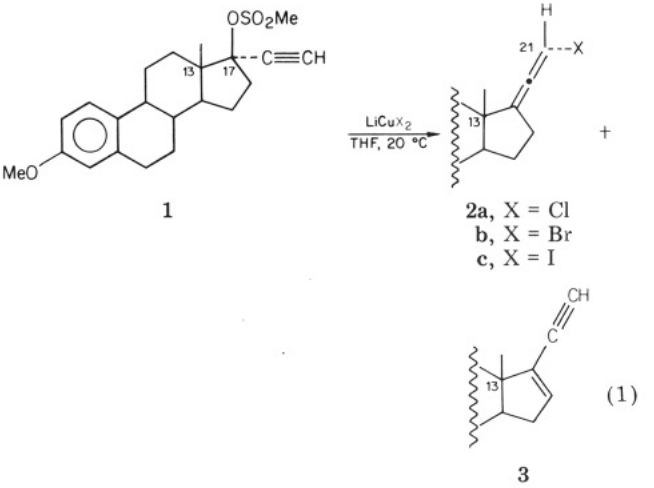


Figure 1. Molecular structure of the two independent molecules labeled A and B in the unit cell.

Equation 1 shows the stereospecific conversion of the



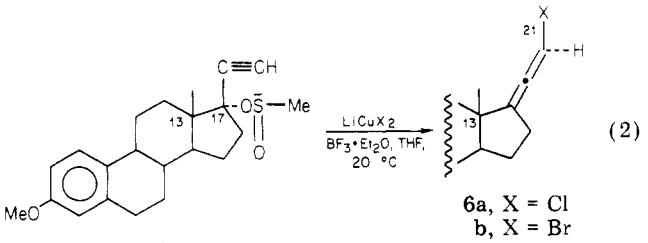
1 **2a**, X = Cl; **b**, X = Br; **c**, X = I **3** (1)

sulfonate **1** by lithium dichloro–, dibromo– (cf. ref 1), and diiodocuprate in tetrahydrofuran. In all cases only one of the two possible epimeric haloallenes **2** was obtained, together with ca. 10–15% of enyne **3** when X was Cl or Br. Allene **2** could easily be purified from **3** by crystallization. The produced halides **2** all showed high negative specific rotations $[\alpha]^{20}_D$ ($CHCl_3$), viz., −110° for **2a** (X = Cl), −173° for **2b** (X = Br), and −252° for **2c** (X = I). As the parent compound **2** in which X is hydrogen is dextrorotatory ($[\alpha]_D$ +41.2°),[5] Lowe–Brewster rules predict the 21β-haloallene structure instead of the 21α structure indicated in eq 1. Nevertheless, the rules appear to predict the wrong configuration for **2**. This follows from an X-ray study of allene **2b**. The result of this study is given in Figure 1; the α-position of X in this case is evident. In view of our previous study[1] which was mainly focussed on the preparation of 1-halo-3-phenylpropadienes, compounds for which Lowe–Brewster rules can be used, allenes **2a** and **2c** will also contain the halogen atom in the α-position as Cl and I influence the optical rotation in the same direction as Br does. As the 21α-haloallenes **2** were now readily accessible, we wondered whether also their 21-epimers could be prepared. For that study we first attempted to prepare and

(1) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P; Runge, W. *J. Org. Chem.* **1982**, *47*, 2194.
(2) (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 33.
(3) Bertrand, M.; Gil, G.; Kumar, A. *Nouv. J. Chim.* **1980**, *4*, 69.
(4) Elsevier, C. J.; Meijer, J.; Westmijze, H.; Vermeer, P.; Van Dijck, L. A. *J. Chem. Soc., Chem. Commun.* **1982**, 84.
(5) Van Dijck, L. A.; Lankwerden, B. J.; Vermeer, J. G. C. M.; Weber, A. J. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 801.

0022-3263/84/1949-0379$01.50/0

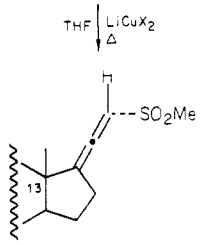
isolate the 17-epimer of 1 by sequential treatment of a THF solution of epimestranol[6] (at −60 °C) with lithium bromide, *n*-butyllithium (1.5 M solution in hexane), and methanesulfonyl chloride. This procedure works very nicely for mestranol (cf. ref 6), but, unfortunately, it appeared to be unsuccessful for the synthesis of pure epimer of 1. It was therefore decided to investigate the reactivity of the methanesulfinate ester of epimestranol (compound 4 in eq 2). This compound is easily accessible by treating



(2)

6a, X = Cl
b, X = Br

4



5

epimestranol with methanesulfinyl chloride with triethylamine as the base.[7] However, sulfinate 4 as such did not undergo the desired 1,3-substitution by lithium dihalocuprates (reacion temperature 20 °C, solvent THF); at reflux temperature it completely rearranged into sulfone 5.[8] For improvement of the leaving character of the methanesulfinate group, it was complexed with BF_3 before the addition of the lithium dihalocuprate. This procedure worked very well for X = Cl and Br (see eq 2), but for X = I a mixture of products was obtained. The produced chloro- and bromoallenes, compounds **6a,b**, both were dextrorotatory, showing $[\alpha]^{20}_D$ values ($CHCl_3$) of +167° and +197°, respectively. ^1H NMR analysis indicated that allenes **6a** and **6b** were free from their epimers **2a** and **2b**, respectively.

From this work it can be concluded that the lithium dihalocuprate induced allene formation from 2-propynylic esters in the steroid series proceeds with anti stereospecificity. This stereochemistry is quite similar to that observed for *organo*copper-induced 1,3-substitutions in steroids 1 and 4,[4,6] but it differs from that reported for the conversion of a propargylic alcohol by $HCuBr_2$.[9]

Experimental Section

General Procedures. Infrared spectra were recorded on a Perkin-Elmer 457 IR spectrometer. NMR spectra were recorded on Varian EM-390 and CFT-20 spectrometers by using $CDCl_3$ as the solvent and Me_4Si as the internal standard. Mass spectra were determined on a Kratos MS80 spectrometer. All reactions were carried out in an atmosphere of dry nitrogen.

Materials. THF was distilled from $LiAlH_4$. Mestranol was obtained as a generous gift from Organon, Oss, The Netherlands; it was converted into the methanesulfonate according to our procedure.[6] Epimestranol was prepared from mestranol as described in ref 6; for its conversion into the methanesulfinate our procedure given in ref 7 was followed.

General Procedure for the Preparation of Halides 2a–c. To a well-stirred solution of 0.78 g of 1 (2.0 mmol) in 5 mL of dry THF was added, at 20 °C, a solution of $LiCuX_2$ (4.0 mmol)[1] in 6 mL of dry THF. The mixture was stirred at 20 °C during 2 (X = Cl or Br) or 3 h (X = I). Allenes **2a–c** were isolated by pouring the reaction mixture into 50 mL of a saturated aqueous NH_4Cl solution containing 1 g of NaCN, extracting the aqueous layer with Et_2O/hexane (20/80 v/v; 2 × 25 mL), washing the combined extracts with water (5 × 50 mL), and drying the extract with K_2CO_3. The solvent was evaporated in vacuo. Allene **2a** was obtained in 85% yield together with 15% of enyne **3**, allene **2b** in 90% yield together with 10% of enyne **3**, and allene **2c** in 98% yield. The crude allenes were washed twice with 2 mL of boiling pentane. Allenes **2a** and **2b** were crystallized from methanol to give the pure compounds in 68% and 75% yields, respectively. Compound **2c** partially underwent epimerization during the crystallization procedure (yield after crystallization 77%); its physical and spectroscopic data were therefore determined for the crude compound.

21α-Chloro-3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (2a): $[\alpha]^{20}_D$ −110° (*c* 1.18, $CHCl_3$); mp 114 °C; IR 1952 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 13-Me), 6.00 (t, 21β-H), ^5J(HC=C=C—CH_2) = 3.0 Hz; ^{13}C NMR ($CDCl_3$) δ 193.2 (=C=); mass spectrum, *m/e* 328, 330 ($M^{+\cdot}$).

21α-Bromo-3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (2b): $[\alpha]^{20}_D$ −173° (*c* 1.10, $CHCl_3$); mp 117 °C; IR 1956 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 13-Me), 5.95 (t, 21β-H), ^5J(HC=C=C—CH_2) = 3.0 Hz; ^{13}C NMR ($CDCl_3$) δ 193.7 (=C=); mass spectrum, *m/e* 372, 374 ($M^{+\cdot}$).

21α-Iodo-3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (2c): $[\alpha]^{20}_D$ −252° (*c* 1.05, $CHCl_3$); mp 99–100 °C; IR 1932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 13-Me), 5.73 (t, 21β-H), ^5J(HC=C=C—CH_2) = 3.0 Hz; ^{13}C NMR ($CDCl_3$) δ 198.0 (=C=); mass spectrum, *m/e* 420 ($M^{+\cdot}$).

General Procedure for the Preparation of Halides 6a,b. To a well-stirred solution of 0.74 g of 4 (2.0 mmol) in 5 mL of dry THF was successively added, at 20 °C, BF_3·OEt_2 (2.0 mmol) and $LiCuX_2$ (4.0 mmol, added as a solution in 6 mL of dry THF). The mixture was stirred at 20 °C during 3 h and worked up as described for **2a–c**. Crude **6a** contained 5% of sulfone **5**, a compound which was obtained in quantitative yield by stirring 4 at 67 °C during 2 h with $LiCuX_2$ in the absence of BF_3·Et_2O. Crude **6b** was contaminated with 5% of enyne **3** and 5% epimestranol. Allenes **6a** and **6b** were purified by column chromatography over alumina (W200 neutral) with CH_2Cl_2/pentane 20/80 as the eluent to give pure **6a** and **6b** in yields of 80, and 75%, respectively.

21β-Chloro-3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (6a): $[\alpha]^{20}_D$ +167° (*c* 0.78, $CHCl_3$); mp 142 °C; IR 1948 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 13-Me), 6.12 (t, 21α-H), ^5J(HC=C=C—CH_2) = 2.8 Hz; ^{13}C NMR ($CDCl_3$) δ 193.0 (=C=); mass spectrum, *m/e* 328, 330 ($M^{+\cdot}$).

21β-Bromo-3-methoxy-19-nor-1,3,5(10),17(20),20-pregnapentaene (6b): $[\alpha]^{20}_D$ +197° (*c* 0.72, $CHCl_3$); mp 139 °C; IR 1941 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 13-Me), 6.04 (t, 21α-H), ^5J(HC=C=C—CH_2) = 2.8 Hz; ^{13}C NMR ($CDCl_3$) δ 193.5 (=C=); mass spectrum, *m/e* 372, 374 ($M^{+\cdot}$).

3-Methoxy-21α-(methylsulfonyl)-19-nor-1,3,5(10),17(20),20-pregnapentaene (5): $[\alpha]^{20}_D$ −108° (*c* 0.46, $CHCl_3$); mp 149 °C; IR 1948 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 13-Me), 2.99 (s, $MeSO_2$), 6.15 (t, 21β-H), ^5J(HC=C=C—CH_2) = 3.7 Hz; mass spectrum, *m/e* 372 ($M^{+\cdot}$).

Crystallographic Data and X-ray Structure Analysis of 2b. Allene **2b** was recrystallized from ethanol at −25 °C. Crystals of **2b**, $C_{21}H_{25}BrO$, are orthorombic: space group $P2_12_12_1$; a = 10.030 ((4), b = 13.286 (6), c = 27.41 (1) Å; V = 3652 (2) Å^3; Z = 8, D_c = 1.358 Mg m^{-3}; μ (Mo Kα) = 2.39 mm^{-1}; λ = 0.7107 Å. Intensity measurements were performed on an Enraf-Nonius Cad-4F ($2\theta_{max}$ = 46°; $-h, \pm k, l$ set, Zr-filtered Mo Kα radiation, $\omega/2\theta$ scan mode. A total of 3013 reflections with $I \geq 2.0\sigma(I)$ were considered to be observed. Corrections were applied for Lorentz,

(6) Westmijze, H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1980**, *21*, 2665.

(7) (a)Vermeer, P.; Westmijze, H.; Kleijn, H.; van Dijck, L. A. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 56. (b) Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* **1979**, 4101.

(8) See for a related example in the mestranol series: Van Dijck, L. A.; Lankwerden, B. J.; Vermeer, J. G. C. M. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 200.

(9) Landor, S. R.; Demetriou, B.; Evans, R. J.; Grzeskowiak, R.; Davey, P. *J. Chem. Soc., Perkin Trans 2* **1972**, 1995.

polarization, and absorption effects; minimum and maximum corrections for I are 0.87 and 0.31, respectively.

The structure was determined by the usual heavy-atom techniques after the coordinates of the two Br atoms were obtained from a Patterson map. The structure was refined by blocked full-matrix least-squares[10] methods (nonhydrogen atoms anisotropic, H atoms isotropic, applying riding model to calculate start positions, methyl H atoms as rigid groups): $R = 0.076$, $R_w = 0.067$, $w = 1.424/(\sigma^2(F) + 0.0022|F^2|)$. The enantiomeric structure was refined separately. It converged to $R = 0.085$ and $R_w = 0.087$ and could be rejected at a significance level much lower than 0.005. Figure 1 shows the two independent molecules (A and B) in the unit cell ($Z = 8$, so there must be two independent molecules in the asymmetric unit with space group $P2_12_12_1$) which are structurally equivalent in every respect except for the conformations of the methoxy groups at C(3).[11]

Acknowledgment. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

Registry No. 1, 76685-96-6; **2a**, 87901-28-8; **2b**, 81158-20-5; **2c**, 87901-29-9; **3**, 23640-47-3; **4**, 74111-55-0; **5**, 87901-30-2; **6a**, 87901-31-3; **6b**, 87901-32-4.

(10) Sheldrick, G. J. "SHELX-76. Program for Crystal Structure Determination" University of Cambridge: Cambridge, England, 1976.
(11) Full details on the structure determination will be published separately in: *Acta Crystallogr., Sect. C.*

Improved Photochemical Synthesis of 5-Methylchrysene Derivatives and Its Application to the Preparation of 7,8-Dihydro-7,8-dihydroxy-5-methylchrysene[1]

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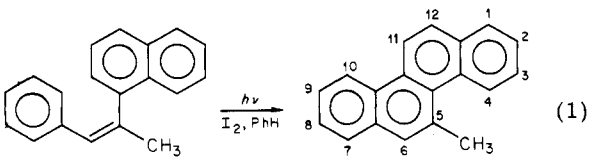
Received July 19, 1983

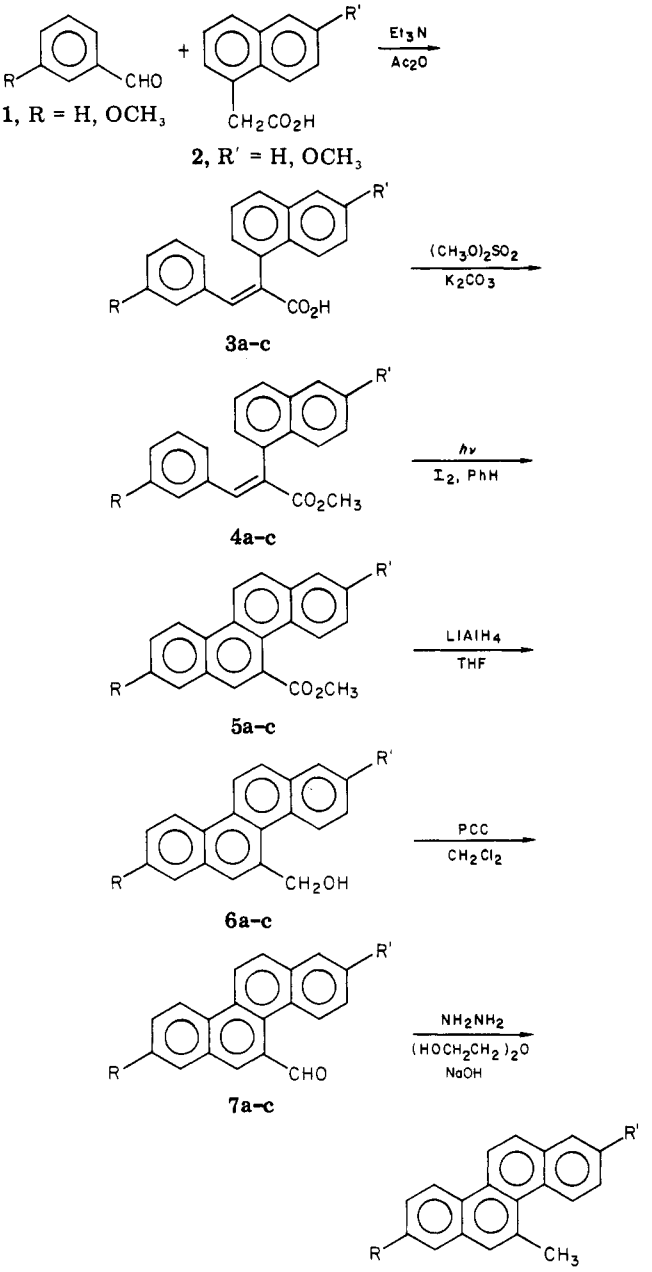
5-Methylchrysene, a potent polynuclear aromatic hydrocarbon carcinogen, is a useful compound for studies in carcinogenesis because it has two dissimilar bay regions, one of which contains a methyl group. The latter feature seems to be a key factor in its high carcinogenic activity.[2-6] The most versatile synthesis of 5-methylchrysene and its derivatives is photocyclization of the appropriate 2-(1-naphthyl)-1-phenylpropene (eq 1). However, the yields



(1)

in the photocyclization step are usually in the range of 3-30%, depending on the substitution pattern.[7-11] Only occassionally have higher yields been obtained.[8,12] In addition, the 2-(1-naphthyl)-1-phenylpropenes, which are generally obtained by dehydration of the corresponding alcohols, are contaminated with the *exo*-methylene isomer which does not undergo photocyclization and is not easily removed from the 5-methylchrysene product.[7,9] In an earlier study in which we prepared 5-(hydroxymethyl)-

Scheme I[a]



[a] For **3-8**: a, R = H, R' = H; b, R = H, R' = OCH_3; c, R = OCH_3, R' = H.

(1) A Study of Chemical Carcinogenesis. 59.
(2) Hecht, S. S.; Bondinell, W. E.; Hoffmann, D. *J. Natl. Cancer Inst.* **1974**, *53*, 1121-33.
(3) Hecht, S. S.; Amin, S.; Rivenson, A.; Hoffmann, D. *Cancer Lett.* **1979**, *8*, 65-70.
(4) Hecht, S. S.; Rivenson, A.; Hoffmann, D. *Cancer Res.* **1980**, *40*, 1396-9.
(5) Melikian, A. A.; LaVoie, E. J.; Hecht, S. S.; Hoffmann, D. *Cancer Res.* **1982**, *42*, 1239-42.
(6) Melikian, A. A.; LaVoie, E. J.; Hecht, S. S.; Hoffmann, D. *Carcinogenesis* **1983**, *4*, 843-9.
(7) Weiss, L.; Loy, M.; Hecht, S. S.; Hoffmann, D. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 119-31.
(8) Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D. *J. Med. Chem.* **1978**, *21*, 38-44.
(9) Browne, C. E.; Dobbs, T. K.; Hecht, S. S.; Eisenbraun, E. J. *J. Org. Chem.* **1978**, *43*, 1656-1660.
(10) Amin, S.; Hecht, S. S.; LaVoie, E. J.; Hoffmann, D. *J. Med. Chem.* **1979**, *22*, 1336-40.
(11) Amin, S.; Hecht, S. S.; Hoffmann, D. *J. Org. Chem.* **1981**, *46*, 2394-2398.
(12) Nagel, D. L.; Kupper, R.; Antonson, K.; Wallcave, L. *J. Org. Chem.* **1977**, *42*, 3626-8.

0022-3263/84/1949-0381$01.50/0