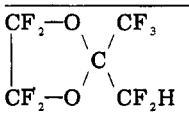
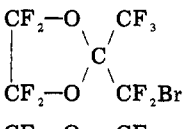
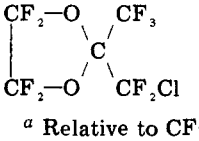
Table III. ^{19}F NMR Data[a] for 1-Substituted-*F*-2,5-dioxahexanes

CF_3-O-CF_2-CF_2-O-CF_2X
a b c d e

deriv	CF_3 (a)	CF_2 (b)	CF_2 (c)	CF_2 (d)	X (e)
1-hydryl[b]	−59.23 ppm (t)	−93.63 ppm (q)	−92.47 ppm (t)	−88.36 ppm (dt)	3.74 ppm (t)
	J_{ab} = 9.4 Hz	$J_{bc} \simeq 0$ Hz	J_{cd} = 4.5 Hz	J_{de} = 68.9 Hz	
1-bromo[c]	−55.75 ppm (t)	−91.06 ppm (q)	−90.13 ppm (t)	−19.19 ppm (t)	
	J_{ab} = 8.79 Hz	$J_{bc} \simeq 0$ Hz	J_{cd} = 10.74 Hz		
1-chloro	−55.74 ppm (t)	−91.06 ppm (q)	−90.52 ppm (t)	−27.46 ppm (t)	
	J_{ab} = 8.79 Hz	$J_{bc} \simeq 0$ Hz	J_{cd} = 10.74 Hz		

[a] Relative to $CFCl_3$ (1.0% internal) ≡ 0.0 ppm, $CDCl_3$. [b] See ref 15. [c] Anal. Calcd for $C_4F_9O_2Br$: C, 14.52; F, 51.67. Found: C, 14.38; F, 51.31.

Table IV. ^{19}F NMR[a] Data for Some *F*-1,3-Dioxolane Derivatives

F-1,3-dioxolane	CF_2	CF_3	CF_2(X)	X
	−83.35 ppm (hexet) [4][c]	−82.35 ppm (tpd) [3]	−138.01 ppm (dqp) [2]	δ_{CF_2H} = 5.996 ppm (t)[b]
	$J_{CF_2X-CF_2} = J_{CF_3-CF_2}$ = 2.0 Hz		J_{HF} = 53.1 Hz (^{19}F)	J_{HF} = 52.2 Hz (^1H)
			$J_{CF_3-CF_2H}$ = 7.8 Hz	
	−81.40 ppm (s)[d] [4]	−78.76 ppm (t) [3]	−63.71 ppm (q) [2]	
	−81.78 ppm (s)[d] [4]	−79.43 ppm (t) [3]	−68.54 ppm (q) [2]	

[a] Relative to $CFCl_3$ (1.0% internal) ≡ 0.0 ppm, $CDCl_3$. [b] See ref 15. [c] [Integral]. [d] $J_{CF_2CF_2}$ and $J_{CF_3-CF_2} < 2$ Hz. [e] Anal. Calcd for $C_5F_9O_2Br$: C, 17.51; F, 49.86. Found: C, 17.52; F, 49.35.

1-Hydryl-*F*-2,5-dioxahexane: BrCl. 1-Hydryl-*F*-2,5-dioxahexane (0.3077 mmol, 0.075 g), chlorine (0.318 mmol, 0.0225 g), and bromine (0.3206 mmol, 0.0521 g) were condensed into the quartz bulb. On warming, the mixture was irradiated for 302 before coming to equilibrium. Workup produced 1-bromo-*F*-2,5-dioxahexane (34.5%), 1-chloro-*F*-2,5-dioxahexane (37.1%), and recovered starting material (28.4%). Characterizations are given in Table III.

2-(Difluoromethyl)-2-(trifluoromethyl)-4,4,5,5-tetrafluoro-1,3-dioxolane:[17] **BrCl.** The starting material (0.563 mmol, 0.150 g), chlorine (0.588 mmol, 0.0417 g), and bromine (0.588 mmol, 0.0939 g) were condensed into the quartz bulb. On warming, the mixture was irradiated for 192 h. Workup produced 2-(bromodifluoromethyl)-2-(trifluoromethyl)-4,4,5,5-tetrafluoro-1,3-dioxolane (59.5%), the analogous chloro-*F*-dioxolane (37.5%),[17] and recovered starting material (2.3%). Characterizations are given in Table IV.

Hydryl-*F*-neopentane: BrF. The quartz bulb used in the BrCl reactions was fitted with a 9 mm × 50 mm Teflon FEP test tube, supported vertically in the bottom and charged with approximately 25 g of sodium fluoride, $^1/_8$ in. pellets (Harshaw). Approximately 1.80 mmol (0.10 mL, 0.25 g) of bromine trifluoride was syringed into the test tube under a nitrogen atmosphere. The quartz bulb was cooled with liquid nitrogen and evacuated, and 0.167 g (0.620 mmol) of hydryl-*F*-neopentane and 0.290 g (1.80 mmol) of bromine were condensed into the bulb. On warming, the mixture was irradiated for a total of 108 h, although infrared assay showed little change after 24 h. Workup produced bromo-*F*-neopentane (78.6%), *F*-neopentane (6.6%), and recovered starting material (14%). See Table I for characterization.

1,3-Dihydryl-*F*-neopentane: BrF. 1,3-Dihydryl-*F*-neopentane (0.345 mmol, 0.0868 g) and bromine 0.313 mmol, 0.050 g) were condensed into the quartz bulb containing the bromine trifluoride (0.90 mmol, 0.05 mL, 0.12 g). On warming, the mixture was irradiated for 64 h with most of the reaction occurring within the first 24 h. Workup of the product produced 1,3-dibromo-*F*-neopentane (20%), 1-bromo-3-hydryl-*F*-neopentane (15%), hydryl-*F*-neopentane (trace), and unreacted starting material (60%). See Table I for characterization.

Registry No. BrCl, 13863-41-7; BrF, 13863-59-7; hydryl-*F*-neopentane, 2993-15-9; bromo-*F*-neopentane, 71076-46-5; chloro-*F*-neopentane, 87136-72-9; 1,3-dihydryl-*F*-neopentane, 71076-43-2; 1,3-dibromo-*F*-neopentane, 87136-73-0; 1-bromo-3-chloro-*F*-neopentane, 87136-74-1; 1,3-dichloro-*F*-neopentane, 87136-75-2; 1-bromo-3-hydryl-*F*-neopentane, 87136-76-3; 1-chloro-3-hydryl-*F*-neopentane, 87136-77-4; *F*-pivaloyl chloride, 13027-23-1; *F*-2,2,5,5-tetramethylhexane, 71076-47-6; 1-hydryl-*F*-2,5-dioxahexane, 40891-98-3; 1-bromo-*F*-2,5-dioxahexane, 87136-78-5; 1-chloro-*F*-2,5-dioxahexane, 87136-79-6; 2-(difluoromethyl)-2-(trifluoromethyl)-4,4,5,5-tetrafluoro-1,3-dioxolane, 87136-80-9; 2-(bromodifluoromethyl)-2-(trifluoromethyl)-4,4,5,5-tetrafluoro-1,3-dioxolane, 87136-81-0; 2-(chlorodifluoromethyl)-2-(trifluoromethyl)-4,4,5,5-tetrafluoro-1,3-dioxolane, 64499-70-3.

(17) Bagnall, R. D.; Bell, W.; Pearson, K. *J. Fluorine Chem.* **1977**, *9*, 359–375.

Intramolecular Wittig Cyclization: A Novel Route to Previously Unknown 3-Thia and 3-Sulfinyl Analogues of Testosterone

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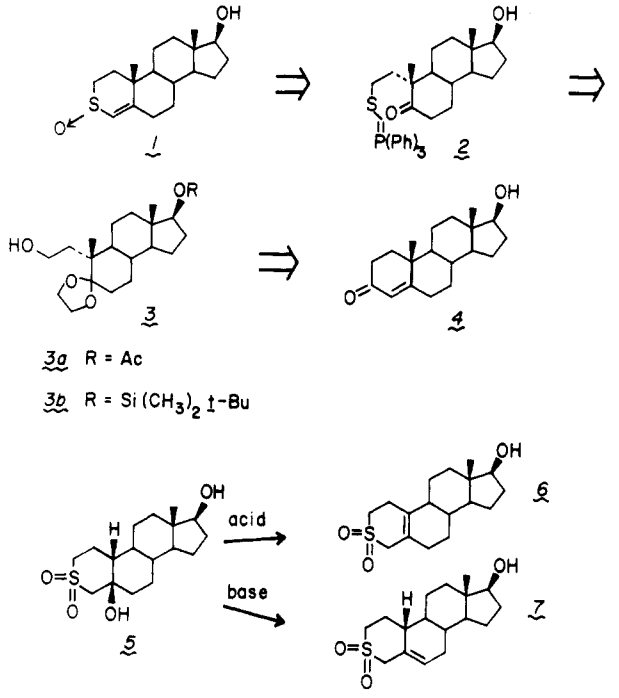
As a result of our ongoing interest in thiasteroid analogues as potential therapeutic agents,[1] we became interested in the synthesis of 3-sulfinyltestosterone analogue 1. As depicted in Scheme I, consideration of an intramolecular Wittig cyclization in our retrosynthetic analysis was prompted by the results of Bertin and Perronnet[2] in

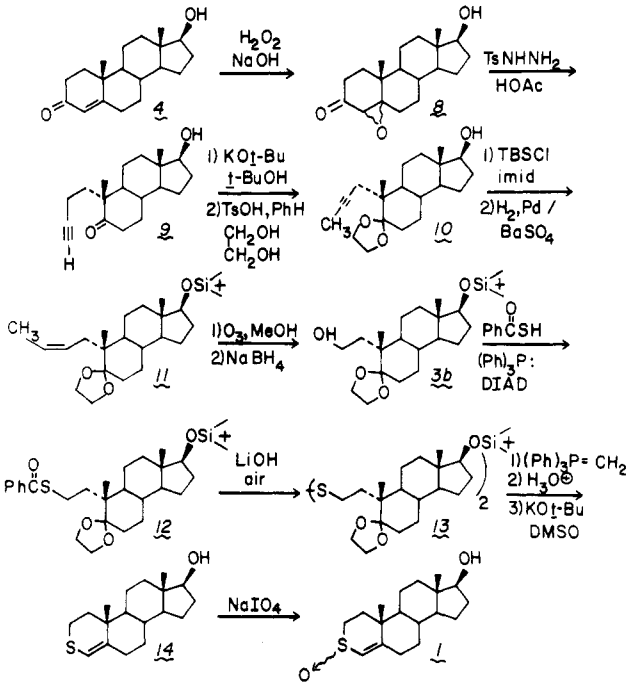
(1) Flynn, G. A.; Johnston, J. O.; Wright, C. L.; Metcalf, B. W. *Biochem. Biophys. Res. Commun.* **1981**, *103*, 913–918.
(2) Bertin, D.; Perronnet, J. *Bull. Soc. Chim. Fr.* **1968**, *4*, 1422–1426.

0022-3263/83/1948-4125$01.50/0

Scheme I



Scheme II

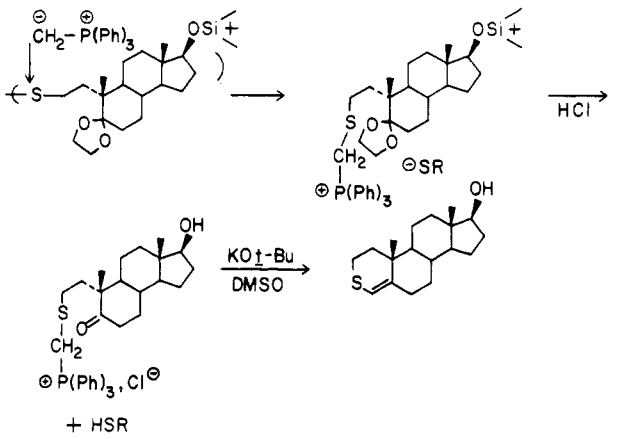


which dehydration of β-hydroxy sulfone **5** under either acid or base catalysis led to the β,γ-unsaturated sulfones **6** and **7**, respectively. With an efficient route to ring-A-degraded steroid **3a** having recently been reported[3] and the success of intramolecular Wittig reactions being well documented,[4] the methodology for conversion of our key intermediate **3b** into the requisite phosphonium ylide **2** remained to be developed.

Results and Discussion

Key intermediate **3b** was prepared in 47% overall yield from testosterone by modifying the procedure of Boar et al.[3] (Scheme II). Testosterone **4** was converted in 80% yield to epoxy ketones **8** (H_2O_2, NaOH, CH_3OH, O °C), which underwent smooth Eschenmoser fragmentation ($TsNHNH_2$, HOAc, 93% yield) to alkynyl ketone **9**. Isomerization of the terminal alkyne **9** with potassium *tert*-butoxide in *tert*-butyl alcohol followed by ketalization ($HOCH_2CH_2OH$, TsOH, PhH) gave the crystalline ethylenedioxy alkyne **10**, mp 92–95 °C (hexane), in 85% overall yield. Silylation of **10** (*t*-$BuMe_2SiCl$, imidazole, DMF, 94% yield) and selective catalytic hydrogenation of the resulting silyl ether over Pd–$BaSO_4$ provided the crystalline *cis*-alkene **11**, mp 98–99 °C (EtOH), in 83% yield. Ozonolysis of **11** (CH_3OH, CH_2Cl_2, –78 °C) including reductive workup with $NaBH_4$ cleanly gave the desired alcohol **3b**, mp 145–147 °C (hexane), in 94% yield.

Scheme III



Our overall approach to converting alcohol **3b** into the desired phosphonium ylide **2** required the synthesis of disulfide **13**, see Scheme III. Treatment of hydroxy ketal **3b** with thiobenzoic acid in the presence of excess diisopropyl azodicarboxylate–triphenylphosphine complex[5] afforded thiobenzoate **12** in 56% purified yield.[6] Alkaline hydrolysis of thio ester **12** in the presence of air gave a 94% yield of the required disulfide **13**, which was ultimately converted in 39% yield to 17β-hydroxy-3-thiaandrost-4-ene (**14**)[7] by nucleophilic attack of triphenylphosphonium methylide, acidic ketal and silyl ether hydrolysis, and intramolecular Wittig condensation. Periodate oxidation of vinyl sulfide **14** quantitatively gave a 2:1 mixture of sulfoxides **1**.

Our unorthodox entrance into thiasteroids[8] has demonstrated the feasibility of generating an [(alkylthio)methyl]phosphonium salt via addition of triphenylphosphonium methylide to a disulfide by subsequently performing an intramolecular Wittig reaction and characterizing its product. Although this process has not been optimized, the concept is broad in scope and may lend itself to further exploitation.

Experimental Section

General Methods. Proton NMR spectra were recorded on a Varian Model EM390 spectrometer; chemical shifts are reported in δ units with Me_4Si as the internal standard and deuteriochloroform as the solvent unless stated otherwise. IR spectra were

(3) Boar, R. B.; Jones, S. L.; Patel, A. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 513–516.
(4) Becker K. B. *Tetrahedron* **1980**, *36*, 1717–1745.
(5) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
(6) The poor yield observed reflects benzoic acid contamination of our thiobenzoic acid and not the optimum yield for this conversion.
(7) All intermediates and products gave satisfactory spectral and analytical data except sulfoxide mixture **15**, which gave a consistent high-resolution mass spectrum.
(8) Ramadas, S. R.; Chenchaiah, P. C.; Kumar, N. S. C.; Krishna, M. V.; Srinivasan, P.; Sastry, V. V. S. K.; Rao, J. A. *Heterocycles* **1982**, *19*, 861–933.

taken on a Perkin-Elmer Model 337 infrared spectrophotometer and are reported in reciprocal centimeters with polystyrene as the reference standard. High-resolution mass spectra were recorded on a Kratos MS-50 mass spectrometer using a Kratos DS-55 data system. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

17β-[(*tert*-Butyldimethylsilyl)oxy]-5,5-(ethylenedioxy)-2,5-seco-3,4-dinorandrostan-2-yl Thiobenzoate (12). To a stirred solution of 8.26 g (40 mmol) of triphenylphosphine in 40 mL of dry THF under argon at 0 °C was added 0.08 g (40 mmol) of diisopropyl azodicarboxylate in 8 mL of THF. A solid formed after 30 min of stirring, and a solution of 8.44 g (20 mmol) of 17β-[(*tert*-butyldimethylsilyl)oxy]-5,5-ethylenedioxy-2-hydroxy-2,5-seco-3,4-dinorandrostane (**3b**) and 4.8 mL of thiobenzoic acid in 40 mL of dry THF was added over a 5-min period. The resulting solution was stirred at 0 °C for 90 min and 1 h at 25 °C. The reaction mixture was then poured into 300 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to give 20 g of an oil that was filtered through a column of 500 mL of silica gel with 5% EtOAc/hexane and purified by preparative HPLC using 2% EtOAc/hexane. The pure fractions were combined, concentrated, and recrystallized from EtOH to give 6.2 g (11.1 mmol, 56%)[6] of pure thio ester **12**: mp 110–111 °C (EtOH); IR (KBr) 1660 cm^{-1}; NMR δ 0.08 (s, 6 H), 0.70 (s, 3 H), 0.85 (s, 9 H), 1.00 (s, 3 H), 3.25 (m, 2 H, SCH_2), 3.51 (t, 1 H, J = 7 Hz), 3.95 (m, 4 H), 7.40 (m, 3 H), 7.85 (m, 2 H).

Anal. Calcd for $C_{32}H_{50}O_4SSi$: C, 68.77; H, 9.02; S, 5.74. Found: C, 68.68; H, 9.10; S, 6.05.

17β-[(*tert*-Butyldimethylsilyl)oxy]-5,5-(ethylenedioxy)-2,5-seco-3,4-dinorandrostan-2-yl Disulfide (13). To a stirred mixture of 4.2 g (7.5 mmol) of thio ester **12** in 150 mL of 95% EtOH at 25 °C open to the air was added 10 mL of 1 N LiOH. The mixture turned pale yellow, and a precipitate formed as stirring was continued for 72 h. The mixture was gradually diluted with 50 mL of water, chilled to 0 °C, and filtered. The filtrate was washed with water and vacuum-dried to yield 3.2 g (3.5 mmol, 94% yield) of analytically pure crystals: mp 150–151 °C; NMR δ 0.09 (s, 6 H), 0.70 (s, 3 H), 0.85 (s, 9 H), 0.95 (s, 3 H), 2.75 (m, 2 H), 3.50 (t, 1 H, J = 7 Hz), 3.85 (m, 4 H).

Anal. Calcd for $C_{50}H_{90}O_6S_2Si_2$: C, 66.17; H, 10.06; S, 7.07. Found: C, 65.83; H, 9.77; S, 7.16.

17β-Hydroxy-3-thiaandrost-4-ene (14). To a stirred mixture of 1.43 g (4.0 mmol) of methyltriphenylphosphonium bromide in 50 mL of dry ether under argon at −78 °C was added 2.6 mL (4.0 mmol) of 1.55 M *n*-butyl lithium. The mixture was allowed to warm to 0 °C and stirred for 30 min. A solution of 906 mg (1.0 mmol) to disulfide **13** in 15 mL of dry ether was added over a 2-min period. After stirring at 0 °C for 30 min, 4 mL 1 N HCl was added and the ether was evaporated in vacuo. The residue was diluted with 20 mL of H_2O and triturated with three 20-mL portions of hexane to remove any thiol byproducts. These byproducts were isolated, dissolved in ethyl alcohol, and treated with excess LiOH in air to yield 288 mg (0.31 mmol) of recovered disulfide **13**.

The aqueous mixture was made homogeneous with ethyl alcohol and acidified to pH 1 with 6 N HCl and then stirred at 25 °C for 96 h. The solution was lyophilized. The residue was transferred to a 60-mL pear-shaped flask with absolute EtOH, evaporated to dryness, and heated at 80 °C under high vacuum. The resulting solid was dissolved in 6 mL of dry Me_2SO and treated with 800 mg of potassium *tert*-butoxide at 80 °C under argon for 3 h. The cooled solution was poured into 50 mL of water and extracted with three 50-mL portions of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography of the residue on 20 mL of silica gel with 20% EtOAc/hexane gave 114 mg (0.39 mmol, 39% yield) of a white solid: mp 135–136 °C; NMR δ 0.07 (s, 6 H), 0.75 (s, 3 H), 1.00 (s, 3 H), 2.5–3.0 (m, 2 H), 3.60 (t, 3 H, J = 7 Hz) 5.60 (br, 1 H).

Anal. Calcd for $C_{18}H_{28}OS$: C, 73.92; H, 9.65; S, 10.96. Found: C, 74.11; H, 9.67; S, 10.62.

17β-Hydroxy-3-sulfinylandrost-4-ene (15). To a solution of 65 mg (0.22 mmol) of 17β-hydroxy-3-thiaandrost-4-ene (**14**) in 2 mL of dioxane was added a solution of 53.5 mg (0.25 mmol) of sodium metaperiodate in 0.5 mL of H_2O. The resulting solution was stirred at 25 °C for 18 h. The resulting mixture was diluted with 10 mL of 5% EtOH/EtOAc and filtered. The filtrate was concentrated to dryness, and the residue was taken up in 10 mL of hot 5% EtOH/EtOAc, filtered, and concentrated to yield 70 mg of nonuniform crystals. High-vacuum heating caused discoloration. TLC showed two polar products in ~2:1 ratio with R_f's of 0.17 and 0.22 (20% EtOH/EtOAc), respectively: IR (KBr) 3400, 1000 cm^{-1}; NMR δ 0.80 (s, 3 H), 1.10 (s, 3 H), 3.65 (t, 1 H, J = 7 Hz), 5.95 (m, $^1/_3$H), 6.20 (br s, $^2/_3$H); mass spectrum (70 ev), M^+ calcd for $C_{18}H_{28}O_2S$ 308.1810, found 308.1795 ± 0.0024, base peak at m/e 291 (M − 17).

Acknowledgment. Appreciation is extended to Louis Shadoff of Midland Analytical Laboratories for performiong high-resolution mass spectrometry.

Registry No. **1** (isomer 1), 87116-07-2; **1** (isomer 2), 87116-08-3; **3b**, 87116-09-4; **4**, 58-22-0; **8**, 51154-10-0; **9**, 17541-44-5; **10**, 87116-10-7; **10** ($SiMe_2Bu$-*t* ester), 87116-11-8; **11**, 87116-12-9; **12**, 87136-10-5; **13**, 87136-11-6; **14**, 87116-13-0; $(Ph)_3P{=}CH_2$, 3487-44-3.

Simplified Method for O-Alkylation of N-Protected Tyrosines

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Modification of the phenolic hydroxyl group of tyrosine has proven to be a useful approach in the design of biologically active peptides.[1] This strategy has been extensively applied, for example, by Manning and Sawyer[1c,d] in the synthesis of a number of antidiuretic antagonists of vasopressin. Despite the conceptual simplicity of the phenolic alkylation of tyrosine by the Williamson synthesis, to date no direct method exists that produces aliphatic ethers of tyrosine or N-protected tyrosine in a single step by using commercially available inexpensive reagents and solvents.

Previously, Solar and Schumaker[2] prepared the C-4 to C-10 primary alkyl ethers of tyrosine, but their method was not useful for preparing secondary ethers. Additionally, these authors did not comment on the optical purity of their tyrosine ethers, despite the stringent reaction conditions (10% NaOH in Me_2SO, 80–115 °C) that could lead to partial racemization.

A recently published method by Kolodziejczyk and Manning has provided at least a partial solution to the problem of finding a direct alkylation method.[3] Their described method as applied to tyrosine carbamates, however, still lacks the elements of simplicity. Thus, the required preparation of carcinogenic alkylating agents, coupled with the use of benzene and crown ether, is undesirable in an industrial scale of operation.

We now report a safe, inexpensive, and direct method for the preparation of a wide range of N-protected tyrosine alkyl ethers (Scheme I). Our procedure is based on a chemoselective monoalkylation of tyrosine disodium salt

(1) (a) Law, H. D.; duVigneaud, V. *J. Am. Chem. Soc.* **1960**, *82*, 4579. (b) Zhuze, A. L.; Jost, K.; Kasafirek, E.; Rudinger, J. *Collect. Czech. Chem. Commun.* 1964, *29*, 2648. (c) Sawyer, W. H.; Pang, P. K. T.; Seto, J.; McEnroe, M.; Lammek, B.; Manning, M. *Science (Washington, D.C.)* **1981**, *212*, 49. (d) Manning, M.; Olma, A.; Klis, W. A.; Kolodziejczyk, A. M. *J. Med. Chem.* **1982**, *25*, 45.

(2) Solar, S. L.; Schumaker, R. *J. Org. Chem.* **1966**, *31*, 1996.

(3) Kolodziejczyk, A. M.; Manning, M. *J. Org. Chem.* **1981**, *46*, 1944.

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