3-H), 4.85 (br s, 21-H), 5.84 (br s, 22-H), 9.93 (s, CHO); MS *m/e* (rel abundance) 404 (M^+, 1), 386 (3), 358 (23), 340 (100), 322 (63).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.21; H, 7.71.

Registry No.—**4,** 66-28-4; **5,** 41767-48-0; **6,** 67270-86-4; **7,** 67270-87-5; **8,** 67270-88-6; **9,** 67270-89-7; **9** 21-oxalyl derivative, 67270-90-0; **10,** 67270-91-1; **10** diacetate, 67270-92-2; **11** isomer 1, 67270-93-3; **11** isomer 2, 67335-50-6; **12** isomer 1, 67270-94-4; **12** isomer 2, 67335-51-7; **13,** 67270-95-5; **14,** 6785-67-7; **15,** 67270-96-6; **16,** 67270-97-7; **17,** 19667-18-6; **18,** 3566-40-3; **19,** 67270-98-8; **19** 19-acetate derivative, 67270-99-9; **20,** 67335-52-8; **21,** 17162-14-0; **22,** 560-54-3; methyl thiotosylate, 4973-66-4; methyl bromoacetate, 96-32-2; diethyl oxalate, 95-92-1.

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Dibenzocyclooctadiene Antileukemic Lignan Synthesis. (±)-Steganone[1]

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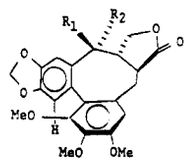
A new route to the unsaturated oxo ester **16**, an intermediate in the Raphael synthesis of steganone (**4**) and its companion antileukemic lignans steganacin (**1**) and steganangin (**2**), is described. Key reactions utilized in the synthetic sequence were photochemical ring closure of a stilbenecarboxylic acid to a phenanthrene, the trimethylsilyl azide modification of the Curtius rearrangement of carboxylic acids, and a two-carbon ring expansion of a 9-phenanthrylamine with dimethyl acetylenedicarboxylate.

Kupchan[2] has reported the isolation and structural determination of the dibenzocyclooctadiene lignan lactones[3] **1–4** from an alcoholic extract of *Steganotaenia araliacea* Hochst. Because of the significant[2] antileukemic activity reported for steganacin **1** and steganangin **2** (the *O*-acetyl and *O*-angelyl



1 R_1 = OAc, R_2 = H
2 R_1 = OOC(angelyl), R_2 = H
3 R_1 = OH, R_2 = H
4 R_1, R_2 = O

derivatives of the β-alcohol steganol **3**), there has been considerable interest in the synthesis of this class of dibenzo[*a*,*c*]cyclooctadiene.[3,4] In light of recent publications on the total syntheses of steganone **4** and its companion lignans **1–3**,[4] we wish to report our independent synthetic efforts similar to those of Raphael[4a] in this area.

The general approach which was conceived for the synthesis of the lignans **1–4** is outlined in Scheme I. The critical feature of our plan was to find a method for the formation of the dibenzocyclooctadiene skeletal system of these lignans. The precedent for our synthetic approach was the synthesis of dibenzocyclooctatetraene **5** by a 2 + 2 cycloaddition utilizing the 9,10 bond of phenanthrene, followed by electrocyclic ring opening of an intermediate cyclobutene **6**.[5] We envisioned the 2 + 2 cycloaddition of an acetylenedicarboxylic acid ester or masked acetylene equivalent to an appropriately substituted phenanthrene **7**, followed by concomitant thermal ring opening of an initially formed cyclobutene, would lead to a dienamine or dienol ether **8**. Hydrolysis might afford **9**, a template for elaboration of the lactone ring of steganone **4**. The ketone steganone **4** has been converted by Kupchan[2] to steganol **3**, the parent alcohol from which steganacin **1** and steganangin **2** are derivable.[2,4a,b]

Oxidative photochemical ring closure of stilbene α-carboxylic acids is a straightforward entry to phenanthrene-9-carboxylic acids,[6] and 3,4-methylenedioxy-3′,4′,5′-trime-

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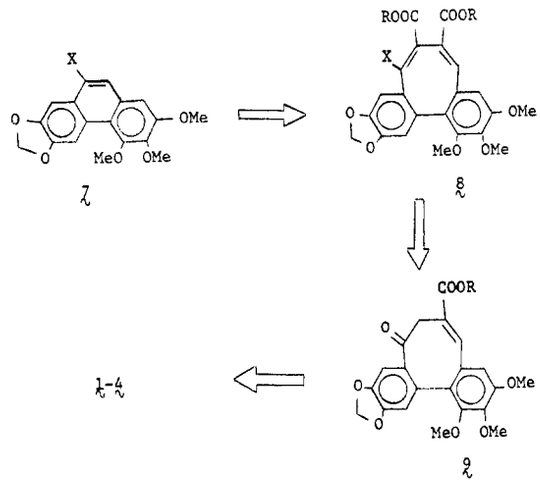
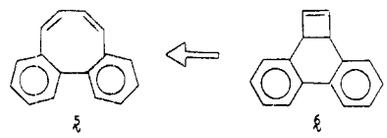
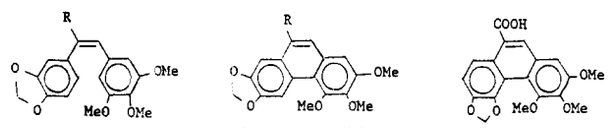
Scheme I



thoxy-α-carboxystilbene[7] (**10a**) upon irradiation for 20 h in benzene with iodine oxidant afforded in 81% yield the 9-car-



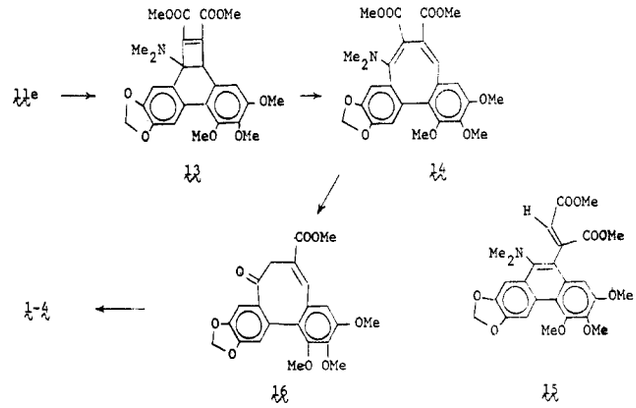
boxyphenanthrene **11a**. The structure of **11a** was distinguished from its isomer **12** by the observation of four 1-proton singlets in the aromatic region of the NMR spectrum; **12** would show ortho-proton coupling (J = 6–10 Hz).[8]



Although acids can generally be converted to amines with one less carbon atom by a variety of methods,[9] a major difficulty when we began this research was the reported[9b,c] low yield in the conversion of phenanthrene-9-carboxylic acids into the corresponding 9-phenanthrylamines by a variety of Curtius and related rearrangements. This problem was overcome[10] by refluxing the acid chloride of 9-carboxyphenanthrene **11b** with trimethylsilyl azide in refluxing benzene[11] to afford 9-phenanthryl isocyanate **11c**. Reduction of **11c** with lithium aluminum hydride in freshly distilled tetrahydrofuran afforded the N-methylamine **11d**, which was methylated with trimethyl phosphate[12] to afford dimethylamine **11e** in 80% overall yield from acid **11a**.[13]

In an attempt to prepare the methoxyphenanthrene **11f**, the α-methoxystilbene **10b**, prepared by methylation of the corresponding deoxybenzoin with methyl fluorosulfonate in hexamethylphosphoramide,[14] was irradiated under oxidative conditions. However, only the deoxybenzoin could be recovered.[15]

Although maleic anhydride, diethyl maleate, and diethyl fumarate can be photochemically added to phenanthrene,[5,16] attempted photochemical cycloadditions of diethyl fumarate, bromomaleic anhydride, or dimethyl acetylenedicarboxylate to 9-dimethylaminophenanthrene **11e** were unsuccessful.[17] However, reports of two-carbon ring expansion of enamines[18] suggested a thermal cycloaddition of dimethyl acetylenedicarboxylate with **11e** might be successful if the 9,10 bond of the phenanthrene **11e** were to have sufficient enamine character. The desired cycloaddition to afford **14** was effected in



50% yield in refluxing dioxane solvent. The NMR spectrum of **14** showed four 1-proton singlets in the downfield olefinic–aromatic region, ruling out the cyclobutene structure **13**. Structure **15** was ruled out by hydrolysis of **14** with refluxing methanolic hydrochloric acid to afford in 80% yield the unsaturated keto ester **16**, which has previously been utilized by Raphael[19] to synthesize steganone **4** and its companion lignans **1**–**3**.[20]

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were done by Atlantic Microlab, Inc., Atlanta, Ga., or Micro-Analysis, Inc., Wilmington, Del. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A60-A or XL-100 Model. Chemical shifts are reported in δ units using tetramethylsilane as an internal standard.

Tetrahydrofuran was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. In all workup procedures the drying process involved treatment with anhydrous magnesium or sodium sulfates and filtering prior to concentration in vacuo. Thin-layer chromatography was performed using precoated Woelm silica gel GF plates. Dry column chromatography was done using Woelm silica gel for the dry column from Analtec, Inc.

2,3,4-Trimethoxy-6,7-methylenedioxy-9-carboxyphenanthrene (11a). 3′,4′,5′-Trimethoxy-3,4-methylenedioxy-α-carboxystilbene (**10a**) (3.4 g, 9.6 mmol), synthesized according to a known procedure,[7] in benzene (500 mL) and iodine (120 mg) was irradiated for 20 h as described by Mallory.[6a] Workup afforded **11a** (2.75 g, 81%) as yellow needles: mp 146–147 °C; NMR (Me_2SO-d_6) δ 4.17 (9 H, s), 6.48 (2 H, s), 7.70 (1 H, s), 8.61 (2 H, s), 9.19 (1 H, s); UV (EtOH) λ_{max} 258 (ε 85 000) and 284 nm (ε 32 000).

Anal. Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53. Found C, 63.97; H, 4.56.

***N*-Methyl-2,3,4-trimethoxy-6,7-methylenedioxy-9-aminophenanthrene (11d).** Phenanthrene-9-carboxylic acid **11a** (2.0 g, 5.6 mmol) was converted to its sodium salt with sodium methoxide in methanol. After the removal of solvent, the salt was refluxed with oxalyl chloride (10 mL) in benzene (50 mL) for 2 h. Distillation of the benzene and oxalyl chloride and removal of the residual solvent in vacuo left a light-yellow solid **11b**. The acid chloride **11b** in benzene (30 mL) and trimethylsilyl azide (4 mL, TMSA, Aldrich) were stirred for 1 h at room temperature and then heated at reflux for 24 h. Removal of the benzene and excess TMSA in vacuo afforded a solid isocyanate **11c**, which was dissolved in dry tetrahydrofuran (20 mL) and added dropwise to lithium aluminum hydride (500 mg, 13.5 mmol) in tetrahydrofuran (100 mL) under nitrogen. After stirring at room temperature for 1 h, the mixture was refluxed for 1 h. After destruction of the excess $LiAlH_4$, filtration, and washing of the precipitated salts with tetrahydrofuran, the combined organic layers were dried over sodium sulfate. Removal of solvent in vacuo afforded a light-tan solid **11d**, 1.64 g (84%), mp 195–197 °C, which could be further purified by dry column chromatography (Woelm silica gel, activity III): mp 198 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (3 H, s), 4.12 (9 H, m), 6.42 (2 H, s), 6.88 (1 H, s), 7.32 (1 H, s), 8.00 (1 H, s), 9.12 (1 H, s); UV λ_{max} (ethanol) 260 (ε 60 000) and 290 nm (ε 37 000).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.87; H, 5.61; N, 4.10. Found: C, 66.95; H, 5.64; N, 4.12.

Addition of methanol to isocyanate **11c** and heating for 24 h afforded upon removal of solvent and chromatography on silica gel the

urethane, mp 215–216 °C (methanol). The urethane could be synthesized directly from the acid **11a** in 28% yield using diphenylphosphoryl azide in methanol with triethylamine catalysis.[10,21] However, there was almost no hydrolysis of the urethane of **11c** after a 48-h reflux in 1:1 ethylene glycol/50% aqueous potassium hydroxide. Lithium aluminum hydride reduction of the urethane in refluxing tetrahydrofuran afforded only a 5% yield of methylamine **11d** after 48 h.[10]

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.53; H, 4.85; N, 3.75.

***N,N*-Dimethyl-2,3,4-trimethoxy-6,7-methylenedioxy-9-aminophenanthrene (11e).** A mixture of *N*-methyl-9-aminophenanthrene **11d** (1.0 g, 2.9 mmol) and trimethyl phosphate[12] (5 mL) was refluxed under nitrogen for 2 h. Excess trimethyl phosphate was distilled in vacuo, ethanol (5 mL) was added, and aqueous sodium hydroxide (10%) was added until the solution was alkaline. The solution was refluxed for 1.5 h, and the resulting solid was filtered, washed with cold aqueous ethanol, and recrystallized from methanol to give **11e**: 0.9 g (87%); mp 157–158 °C; NMR (Me_2SO-d_6) δ 2.89 (6 H, s), 3.82–4.00 (9 H, m), 6.32 (2 H, s), 7.5 (2 H, d), 7.89 (1 H, s), 9.16 (1 H, s); UV λ_{max} (ethanol) 258 (ε 74 000) and 287 nm (ε 44 000).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.67; H, 5.95; N, 3.91.

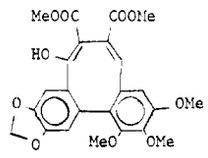
Heating of the dimethylenamine **11e** with pyrrolidine neat, in methanol, or in dioxane with *p*-toluenesulfonic acid catalysis afforded unchanged **11e** and did not result in enamine exchange.

Dimethyl 1,2,3-Trimethoxy-10,11-methylenedioxy-8-*N,N*-dimethylaminodibenzo[*a,c*]cyclooctatetraene-6,7-dicarboxylate (14). Dimethylaminophenanthrene **11e** (178 mg, 0.5 mmol) and dimethyl acetylenedicarboxylate (DMADC) (720 mg, 5 mmol) were refluxed in dioxane for 5 days. Solvent and excess DMADC were removed in vacuo to afford a dark-brown gum (0.71 g) which was chromatographed (Analtech preparative layer silica gel, 50:50 ethyl acetate/hexane and 9:1 benzene/ethyl acetate as eluents) to afford dienamine diester **14**: 124 mg (50%); mp 203–205 °C; NMR ($CDCl_3$) δ 7.26 (1 H), 6.70 (1 H), 6.60 (1 H), 6.58 (1 H), 5.98 (2 H), 3.6–3.9 (5 s, OCH_3), 2.78 (s, 6 H); IR ($CHCl_3$) 5.85 and 6.0 μm; UV (ethanol) λ_{max} 344 (log ε 4.88), 302 (log ε 5.16), 248 (shoulder) nm (log ε 5.32).

Alternately, **11e** (600 mg, 1.5 mmol) and DMADC (0.4 mL) were heated at 125 °C in dimethyl sulfoxide (25 mL) for 24 h under nitrogen. Additional DMADC (0.2 mL) was added every 12 h for 5 days until **11e** had disappeared by TLC. Workup as above afforded **14**, 252 mg (35%).

Anal. Calcd for $C_{26}H_{27}NO_9$: C, 62.77; H, 5.43; N, 2.81. Found: C, 62.65; H, 5.47; N, 2.81.

Methyl 7,8-Dihydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[*a,c*]cyclooctatetraene-6-carboxylate (16). Dibenzocyclooctatetraeneenamine diester **15** (90 mg, 0.18 mmol) was hydrolyzed by refluxing with 5:1 methanol/6 N hydrochloric acid (v/v) (6 mL) for 8 h. Water (5 mL) was added to the cooled solution, which was extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was removed to afford an oil (76 mg) which upon chromatography on silica gel (9:1 benzene/ethyl acetate) afforded keto monoester **16**: 59 mg (80%); mp 145–147 °C.[19] Also obtained was 8-hydroxydibenzocyclooctatetraene 6,7-diester **19**: 17 mg (20%); mp 177–179 °C; NMR

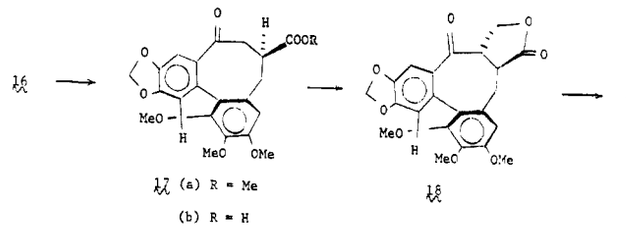


19

($CDCl_3$) δ 8.74 (1 H), 7.70 (1 H), 6.96 (1 H), 6.60 (1 H), 6.54 (1 H), 6.20 (2 H), 3.98 (3 H), 3.92 (3 H), 3.80 (6 H), 3.54 (3 H). The diester **19** and the monoester **16** need not be separated, since hydrogenation followed by basic hydrolysis of the mixture affords keto acid **17b** (80%).[20]

Methyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[*a,c*]cyclooctatetraene-6-carboxylate (17a). Dibenzocyclooctatrienone monoester **16** (95 mg, 0.45 mmol) was catalytically hydrogenated at 35 psi in methyl acetate (50 mL) with W-2 Raney nickel for 24 h at 25 °C. Filtration and removal of solvent afforded quantitatively keto ester **17a**, mp 132–132.5 °C (ether/hexane). With some batches of Raney nickel carbonyl reduction occurred to a small extent; the crude reaction mixture was then oxidized with Jones reagent to the keto ester **17a**.

It has been shown[4a,b] that upon melting or after standing in solution **17a** epimerizes partially to a less polar isomeric ester (*RR/SS*), which



upon hydrolysis and hydroxymethylation leads directly to steganone **4**. Keto ester **17a** upon similar treatment affords isosteganone **18**, which can be isomerized quantitatively to steganone **4**.[4a,b]

Acknowledgment. We gratefully acknowledge Dr. R. M. Carlson for helpful suggestions, Drs. A. S. Kende and L. S. Liebeskind for spectra and samples of **4**, **17a**, and **17b**, Dr. R. A. Raphael for spectra and a sample of **16**, P. Conroy and D. Shaw for technical assistance, and financial support from the National Institutes of Health (Grant CA-15759) and the National Science Foundation (Grant CHE-05757).

Registry No.—**4**, 58800-45-6; **10a**, 60848-05-7; **11a**, 60848-06-8; **11a** Na salt, 67316-77-2; **11b**, 67316-78-3; **11c**, 60848-09-1; **11c** urethane derivative, 60848-07-9; **11d**, 60848-08-0; **11e**, 67316-79-4; **14**, 67316-80-7; **15**, 67316-81-8; **16**, 60546-67-0; **17a**, 65310-10-3; **17b**, 65310-09-0; **18**, 65310-12-5; **19**, 67316-82-9; dimethyl acetylenedicarboxylate, 762-42-5.

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(19) Compound **16** was identical by TLC and NMR spectral comparison with a sample provided by Dr. R. A. Raphael. The position of the double bond has been assigned by Raphael.[4a]
(20) Catalytic hydrogenation of **16** in methyl acetate with W-2 Raney nickel (35 psi, 24 h) produced the keto ester **17a**, identical by TLC and NMR spectral comparison with an authentic sample provided by Drs. A. S. Kende and L. S. Liebeskind.[4b] Raphael[4a] reports hydrogenation of **16** occasionally results in the formation of a hydroxy compound, which upon oxidation with Jones reagent affords the saturated keto ester **17a**. We have also noted carbonyl reduction with some batches of Raney nickel. Keto ester **17a** has previously been converted by hydrolysis to **17b**, which reacts with formaldehyde in base to form isosteganone **18**. Thermally, **18** is converted quantitatively to steganone **4**.[4a,b]
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Synthesis of *N,N*-Dialkylaminosulfenylcarbamate Insecticides via Carbamoyl Fluorides

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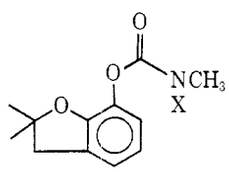
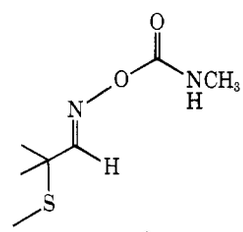
A facile and general process for the preparation of *N*-sulfenylated carbamates from carbamoyl fluorides and alcohols under phase-transfer conditions is described. Use of this method to prepare a series of 12 analogues of the carbamate insecticides carbofuran, methomyl, and carbaryl is discussed. The preparation and properties of the intermediate carbamoyl fluorides are also reported.

One of the major deficiencies of the widely used carbamate class of insecticides is their generally high mammalian toxicity. For example, carbofuran (**1a**) has an oral LD_{50} in rats of 11 mg/kg while for aldicarb (**2**) the value is only 1 mg/kg.[1]



1a, X = H
b, X = SR



2

With the goal of maintaining the insecticidal activity but decreasing the mammalian toxicity, a large number of analogues of carbamates have been synthesized. One group of analogues, which are considerably less toxic to mammals but which are cleaved by insects to the parent carbamate, is composed of *N*-sulfur compounds such as **1b**. Of particular interest to us were **1b** type compounds where R = N(alkyl)$_2$, which were originally prepared by Fukuto and Black.[2] Their preparation of these materials involved condensation of carbofuran with the appropriate sulfenyl chloride. Because of certain patent restrictions, we desired a general synthesis of dialkylaminosulfenylcarbamate analogues which did not utilize the parent carbamate either as a starting material or as an intermediate. Toward this goal we examine the approach outlined in Schemes I and II, which involves as a key intermediate an *N*-dialkylaminosulfenyl-*N*-alkylcarbamoyl fluoride. A related route, which had been previously reported for the preparation of SAr and SCX_3 (S = halogen or hydrogen) carbamate derivatives,[3] was found to work very poorly in our hands. Utilizing the process described herein, a series of dialkylaminosulfenyl derivatives of commercial carbamates was prepared in high yield and purity.[4,5]

Although *N*-methylcarbamoyl fluoride (**3**, see Scheme I) has been utilized in a number of patents,[3] a detailed report of its synthesis could not be found. There are several possible synthetic approaches to the material; however, only the reaction of methyl isocyanate (MIC) and anhydrous hydrogen fluoride (HF) was examined. All work with HF was carried out in polyethylene bottles equipped with polyethylene tubing and stopcocks.

Scheme I

$$CH_3NCO + HF \rightarrow \underset{\mathbf{3}}{CH_3NHCOF}$$

$$R^1R^2NH + S_2Cl_2 \rightarrow \underset{\mathbf{5}}{(R^1R^2NS)_2}$$
(**4**)

$$(R^1R^2NS)_2 + SO_2Cl_2 \rightarrow \underset{\mathbf{6}}{R^1R^2NSCl}$$
(**5**)

$$CH_3NHCOF + R^1R^2NSCl \rightarrow \underset{\mathbf{7}}{R^1R^2NSN(CH_3)COF}$$
(**3**, **6**)

	R^1	R^2
4a–7a	*n*-Bu	*n*-Bu
4b–7b	morpholino	
4c–7c	*n*-Pr	*n*-Pr
4d–7d	Me	$CH_2C_6H_5$
4e–7e	Et	$CH_2C_6H_5$
4f–7f	piperidino	
4g–7g	Et	Et

Treatment of a solution of MIC in methylene chloride with 2–5 equiv of gaseous HF (bp 19 °C) at 0 °C over 1 h followed by removal of the solvent and excess HF under vacuum at 30

Scheme II

$$\underset{\mathbf{7}}{R^1R^2NSN(CH_3)COF} + \underset{\mathbf{8}}{R^3OH} \rightarrow \underset{\mathbf{9}}{R^1R^2NSN(CH_3)CO_2R^3}$$

	R^1	R^2	R^3
8h			2,2-dimethylbenzofuran-7-yl
i			$CH_3S(CH_3)C{=}N$
j			napth-1-yl
k			CH_3
9l	*n*-Bu	*n*-Bu	2,2-dimethylbenzofuran-7-yl
m	morphilino		2,2-dimethylbenzofuran-7-yl
n	Et	$CH_2C_6H_5$	2,2-dimethylbenzofuran-7-yl
o	*n*-Bu	*n*-Bu	$CH_3S(CH_3)C{=}N$
p	*n*-Pr	*n*-Pr	$CH_3S(CH_3)C{=}N$
q	CH_3	$CH_2C_6H_5$	$CH_3S(CH_3)C{=}N$
r	Et	Et	$CH_3S(CH_3)C{=}N$
s	*n*-Bu	*n*-Bu	napth-1-yl
t	*n*-Pr	*n*-Pr	napth-1-yl
u	Et	$CH_2C_6H_5$	napth-1-yl
v	piperidino		napth-1-yl
w	Et	Et	napth-1-yl
x	*n*-Bu	*n*-Bu	CH_3

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