Facile Synthesis of 2-Substituted Indoles and Indolo[3,2-*b*]carbazoles from 2-(Benzotriazol-1-ylmethyl)indole

Alan R. Katritzky,* Jianqing Li, and Christian V. Stevens

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida 32611-7200

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Replacement of the benzotriazole moiety of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6** and **9**, prepared from 1-propargylbenzotriazole and *o*-iodoaniline followed by alkylation, with Grignard reagents gave the corresponding 2-substituted indoles **10** in good yield. Treatment of compounds **6** or **9** with zinc chloride afforded 6,12-disubstituted-6,12-dihydroindolo[3,2-*b*]carbazoles **11** in moderate to good yields. 6,12-Disubstituted-5,11-dihydroindolo[3,2-*b*]carbazoles **13** were prepared readily and in good yield from 2-(benzotriazol-1-ylalkyl)indoles **8** *via* dimerization in the presence of zinc chloride followed by dehydrogenation on exposure to air.

Introduction

2-Substituted indoles are pharmacologically important substances and are precursors for a wide variety of alkaloids[1] such as vindoline, vindorosine,[2] ellipticine,[3] etc. Perhaps, the most general approach to 2-substituted indoles involves 2-lithiation of indoles, promoted by directing groups such as 1-(benzenesulfonyl),[4] 1-(lithio carboxylate),[5] 1-[(dimethylamino)methyl],[6] 1-(*tert*-butylcarbamoyl)[7] and 1-(2-oxazolinyl),[8] followed by reaction with a wide range of electrophiles. Recently, several methods for the preparation of 2-substituted indoles were developed which involve elaboration of 2-methylindole, eg. α-bromination[9–11] followed by substitution of the bromine atom or α-deprotonation followed by alkylation of protected indoles.[12,13] However, protection of the indole 3-position is a problem associated with many of these methods. In our previous work, we described a useful methodology in which a variety of 2-substituted indoles were afforded by 2-alkyl lithiation of 2-alkylindoles activated by carbon dioxide and subsequent electrophilic substitution.[14]

Indolo[3,2-*b*]carbazoles have gained significant importance pharmacologically since they inhibit the specific binding of toxic dioxins which give rise to thymic atrophy, hyperkeratosis, and chloracne in liver cytosol.[15] A number of synthetic methods for the preparation of 5,11-dihydroindolo[3,2-*b*]carbazoles have been described: (i) vapor phase catalytic cyclodehydrogenation of *N,N'*-diphenyl-*p*-phenylenediamine;[16] (ii) Fischer indolization of cyclohexane-1,4-dione bis(phenylhydrazone);[17] (iii) condensation of indole and formaldehyde in the presence of air and sensitizers;[18] (iv) polymerization of indole with *p*-toluenesulfonic acid in Dowtherm A;[19] and (v) transformation of 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones in the presence of mineral acids.[20] However, all of these methods suffer from low yields and require vigorous reaction conditions. No general method for the conversion of 2-substituted indoles to indolo[3,2-*b*]carbazoles has been reported previously.

We now present a convenient method for the synthesis of 2-substituted indoles from 1-propargylbenzotriazole and *o*-iodoaniline involving alkylation and subsequent displacement of the benzotriazole moiety and a general method for the preparation of 6,12-dihydroindolo[3,2-*b*]-carbazoles and 5,11-dihydroindolo[3,2-*b*]carbazoles.

Results and Discussion

Preparation of 2-(Benzotriazol-1-ylmethyl)indole. Castro and co-workers[21] developed an efficient method for the formation of 2-alkyl- and 2-arylindoles from a variety of cupric acetylides of *o*-iodoaniline derivatives. However, the possibility of employing this method for the preparation of functionalized 2-alkylindoles had not been exploited until the present work. We have now prepared 2-(benzotriazol-1-ylmethyl)indole (**3**) (Scheme 1) which contains a side chain methylene group that can be further elaborated because the benzotriazolyl group acts as both an activator for deprotonation and as a good leaving group, as has been demonstrated extensively in our laboratory.[22]

Deprotonation of 2-(Benzotriazol-1-ylmethyl)indole and Reaction of the Lithiated Derivatives with Electrophiles. Compound **3** was treated with 2.1 equiv of *n*-butyllithium in THF at −30 °C for 30 min or at −78 °C for 5 h to generate the dianion **5** which was then

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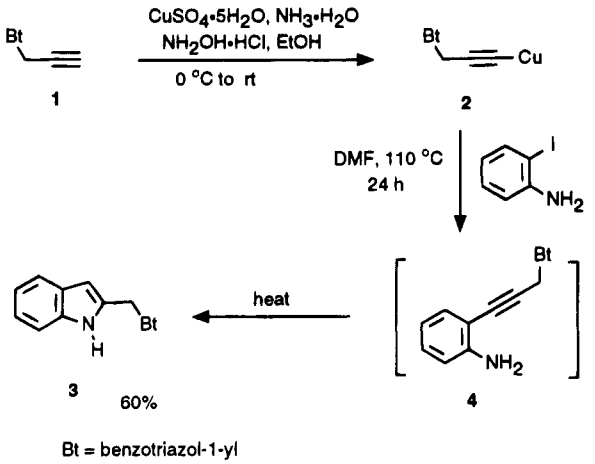
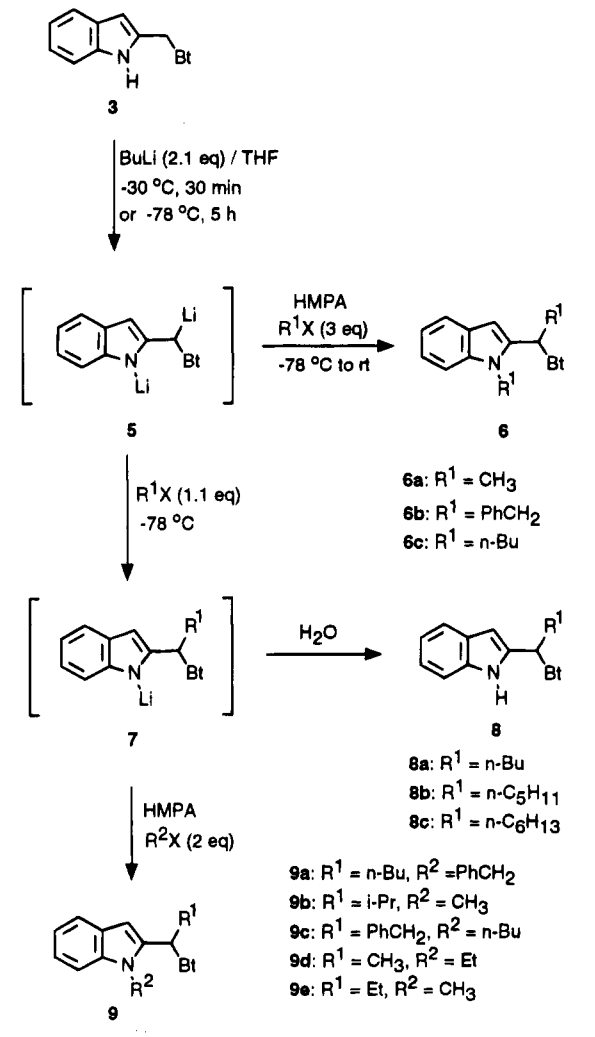
Scheme 1



Bt = benzotriazol-1-yl

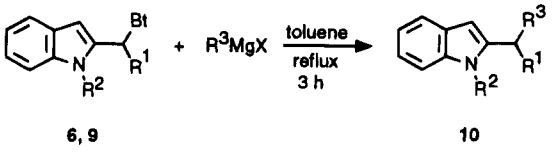
Scheme 2



reacted with 1.1 equiv of alkyl halide to form anions **7**. These anions **7** were quenched with water to afford the alkylated indoles **8** in high yield.

The *N*-alkylation of indole has been well studied.[23-25] The general method involves *N*-metalation followed by substitution with alkyl halides. The reaction solvents are

Scheme 3



especially important and the site-specific *N*-alkylation is favored by dipolar aprotic solvents such as HMPA and DMSO.[24,25] When anions **7** were quenched with excess halide ($PhCH_2Br$ or *n*-BuI) in THF at room temperature for 24 h, only trace amounts of *N*-alkylated products were detected by ^1H NMR. Presumably, the nucleophilicities of indole lithium salts are weaker than those of indole sodium salts.[23] However, when HMPA was added to comprise 50% of the total solvent, high yields of *N*-alkylated products were obtained. Thus, after the generation of dianion **5** in THF, an equal amount of HMPA as solvent and 3 equiv of alkyl halide were added to the reaction mixture at −30 °C. The solution was allowed to warm to room temperature overnight to give the dialkylated products **6** in good yield.

Alternatively, the dianion **5** was first reacted with 1.1 equiv of alkyl halide at −78 °C in THF for several hours. Two equivalents of a second alkyl halide and an amount of HMPA equal to that of THF were added at −30 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight to form the regiospecifically 1,2-dialkylated products **9**. A variety of mono- and dialkylated compounds were prepared similarly (Scheme 2). The structures of products **6**, **8**, and **9** were confirmed by ^1H, ^{13}C, and APT NMR spectra (see Tables 4 and 5 in the supplementary material) and elemental analyses (Table 1).

Substitution of 2-(1-Benzotriazol-1-ylakyl)indoles with Grignard Reagents. It is well-known that the benzotriazole moiety acts as a good leaving group in reactions with Grignard reagents.[22] Therefore, reaction of compounds **6** and **9** with aryl or alkyl magnesium halides in refluxing toluene for 3 h gave the corresponding products **10** in good yield (Scheme 3). Following this procedure, a wide range of 2-alkylindoles **10** was obtained (Table 2).

The structures of compounds **10** were elucidated by ^1H, ^{13}C, and APT NMR spectra (see Tables 6 and 7 in the supplementary material) and combustion analyses (Table 2). Interestingly, the ^1H NMR spectra of compounds **10b** and **10f** showed typical diastereotopic CH_2 patterns. The presence of two doublet of doublet signals at δ 3.06−3.48 ppm in each compound indicated that the CH_2 protons were attached to the chiral centers. The two doublets (δ 4.90, 5.12) with larger coupling constants (J = 17.1 Hz) in the ^1H NMR spectrum of compound **10b** showed strong through space interaction between the NCH_2Ph and the chiral center. Moreover, the second CH_2 protons in the *N*-butyl chain of compound **10f** resonated at greatly different fields (δ 1.26−1.41 and 0.81−1.06, respectively), indicating a short distance between the $NCH_2CH_2CH_2$-CH_3 and the chiral center. The detailed assignments of the ^1H and ^{13}C NMR signals are given in Tables 6 and 7.

Dimerization and Dehydrogenation. It has been previously reported that Lewis acids readily assist the formation of the benzotriazolyl anion and the corresponding carbocations from benzotriazole adducts. Such carbocations are then available for reaction with nucleo-

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Table 1. Preparation of 2-(1-Benzotriazol-1-ylalkyl)indoles 3, 6, 8, and 9

compd	R^1X	R^2X	yield (%)	mp (°C)	crystal form	molecular formula	found (calcd) C	H	N
3	–	–	60	123–124	needles[a]	$C_{15}H_{12}N_4$	72.51 (72.56)	4.85 (4.87)	22.71 (22.57)
6a	CH_3I	–	80	143–144	powder[b]	$C_{17}H_{16}N_4$	73.76 (73.89)	5.83 (5.86)	20.26 (20.27)
6b	$PhCH_2Br$	–	92	170–172	needles[c]	$C_{29}H_{24}N_4$	81.24 (81.27)	5.62 (5.65)	13.04 (13.08)
6c	*n*-BuI	–	89	68–70	needles[c]	$C_{23}H_{28}N_4$	76.92 (76.62)	8.08 (7.83)	15.15 (15.55)
8a	*n*-BuI	–	98	103–104	prisms[c]	$C_{19}H_{20}N_4$	74.84 (74.97)	6.59 (6.62)	18.36 (18.41)
8b	n-$C_5H_{11}I$	–	74	99–100	powder[c]	$C_{20}H_{22}N_4$	75.22 (75.43)	6.93 (6.97)	17.68 (17.60)
8c	n-$C_6H_{13}I$	–	75	86–87	powder[c]	$C_{21}H_{24}N_4$	76.22 (75.86)	7.53 (7.28)	16.58 (16.86)
9a	*n*-BuI	$PhCH_2Br$	83	103–105	powder[c]	$C_{26}H_{26}N_4$	79.44 (79.14)	6.73 (6.65)	13.84 (14.21)
9b	*i*-PrI	CH_3I	84	132–133	needles[c]	$C_{19}H_{20}N_4$	75.30 (74.96)	6.70 (6.63)	18.30 (18.41)
9c	$PhCH_2Br$	*n*-BuI	76	–	oil[b]	$C_{26}H_{26}N_4$	79.48 (79.14)	6.74 (6.65)	13.99 (14.21)
9d	CH_3I	EtI	76	–	oil[b]	$C_{18}H_{18}N_4$	74.72 (74.44)	6.25 (6.25)	19.24 (19.30)
9e	EtI	CH_3I	84	–	oil[b]	$C_{18}H_{18}N_4$	74.76 (74.44)	6.46 (6.25)	19.31 (19.30)

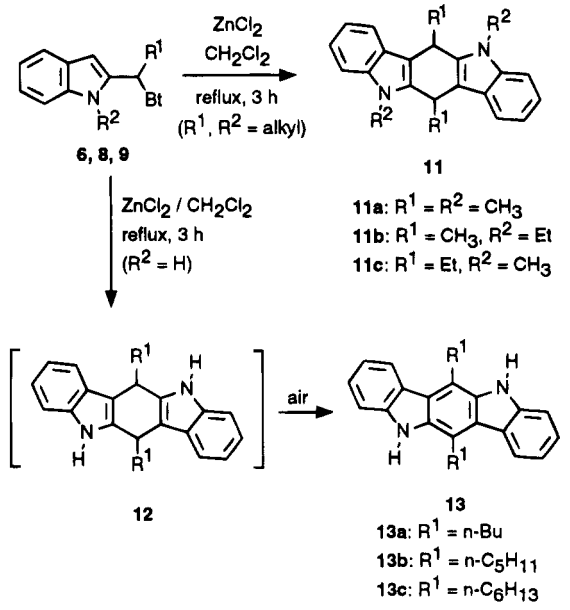
[a] From chloroform. [b] Column chromatography ($CHCl_3$/hexane). [c] From ethyl acetate and hexane.

Table 2. Preparation of 2-Substituted Indoles 10

compd[a]	R^1	R^2	R^3MgX	yield (%)	mp (°C)	molecular formula	found (calcd) C	H	N
10a	CH_3	CH_3	CH_3MgI	90	oil	$C_{12}H_{15}N$	82.95 (83.19)	8.80 (8.73)	7.93 (8.08)
10b	$PhCH_2$	$PhCH_2$	PhMgBr	78	115–116	$C_{29}H_{25}N$	89.71 (89.88)	6.53 (6.51)	3.60 (3.62)
10c	*n*-Bu	*n*-Bu	EtMgI	68	oil	$C_{19}H_{29}N$	84.15 (84.07)	11.03 (10.77)	5.10 (5.16)
10d	*n*-Bu	$PhCH_2$	EtMgI	62	oil	$C_{22}H_{27}N$	86.81 (86.50)	9.07 (8.92)	4.47 (4.59)
10e	*i*-Pr	CH_3	CH_3MgI	88	oil	$C_{14}H_{19}N$	83.80 (83.52)	9.73 (9.52)	6.83 (6.96)
10f	$PhCH_2$	*n*-Bu	PhMgBr	70	oil	$C_{26}H_{27}N$	88.63 (88.33)	7.89 (7.70)	3.84 (3.96)

[a] Isolated by column chromatography (CH_2Cl_2/hexane).

Scheme 4



philes.[26] Therefore, compounds **6**, **8**, and **9** can act not only as nucleophiles due to the unoccupied 3-position of the indole ring, but also as carbocations with the assistance of Lewis acids. Hence, treatment of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6** and **9** with zinc chloride in refluxing methylene chloride yielded 6,12-dihydroindolo[3,2-*b*]carbazoles **11** which were relatively stable in air. No dehydrogenated product was detected by ^1H NMR spectroscopy. When compounds **8** were refluxed with zinc chloride in methylene chloride for 3 h, dimeric intermediates **12** were formed which rapidly dehydrogenated in air to give 6,12-di(*n*-alkyl)-5,11-dihydroindolo[3,2-*b*]carbazoles **13** (Scheme 4). Surprisingly, under similar reaction conditions, 2-(benzotriazol-1-ylmethyl)indole (**3**) did not undergo dimerization in either CH_2Cl_2 or $CHCl_3$. This indicates that the alkyl group of **8** efficiently stabilizes the cation and lowers the activation energy of the carbocation formation.

Conclusion

In summary, 2-(benzotriazol-1-ylmethyl)indole (**3**), derived from 1-propargylbenzotriazole cupric salt (**2**) and *o*-iodoaniline (Scheme 1),[21] was treated with *n*-butyllithium to generate anion **5** which was subsequently trapped by electrophiles to give 2-(1-benzotriazol-1-ylalkyl)indoles **8** in high yield (Scheme 2). Compounds **8** underwent dimerization under the action of a Lewis acid, followed by dehydrogenation in air to afford 6,12-dialkyl-5,11-dihydroindolo[3,2-*b*]carbazoles **13** in good yield (Scheme 4). The treatment of **3** with 2 equiv of *n*-butyllithium followed by quenching with 3 equiv of alkyl halide using HMPA as the solvent gave *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6**. Reaction of dianion **5** sequentially with two different halides afforded compounds of type **9**. Under similar reaction conditions, **6** and **9** were converted to 6,12-dihydroindolo[3,2-*b*]carbazoles **11**. The benzotriazolyl group of compounds **6** and **9** was conveniently displaced by Grignard reagents to give 2-alkylindoles **10** in good yield. The reaction of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6** and **9** with Grignard reagents provides a convenient route to a variety of 2-alkylindoles.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak as the reference. Elemental analyses (C, H, N) were carried out within the department.

o-Iodoaniline was purchased neat and used without further purification (Aldrich, $67.15/25 g). 1-Propargylbenzotriazole (**1**) was prepared from benzotriazole and propargyl bromide (80% in toluene) in ethanolic sodium hydroxide.[27] The cupric

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Table 3. Preparation of Indolo[3,2-*b*]carbazoles 11 and 13

compd[a]	yield (%)	mp (°C)	molecular formula	analysis/HRMS found C	found H	found N	calcd C	calcd H	calcd N
11a	80	262–263	$C_{22}H_{22}N_2$	84.02	7.03	8.82	84.03	7.06	8.91
11b	61	208–210	$C_{24}H_{26}N_2$	84.51	7.72	8.07	84.16	7.66	8.18
11c	48	90–91	$C_{24}H_{26}N_2$		342.2096			342.2096	
13a	63	287–290	$C_{26}H_{28}N_2$	84.59	7.75	7.56	84.74	7.66	7.60
13b	57	271–273	$C_{28}H_{32}N_2$		396.2590			396.2565	
13c	64	257–258	$C_{30}H_{36}N_2$	84.77	8.64	6.56	84.85	8.55	6.60

[a] All compounds were isolated as powders.

salt **2** of 1-propargylbenzotriazole was prepared quantitatively according to the literature procedure.[21]

Preparation of 2-(Benzotriazol-1-ylmethyl)indole (3). A mixture of the cupric salt **2** of 1-propargylbenzotriazole (3.64 g, 20 mmol) and *o*-iodoaniline (4.38, 20 mmol) in absolute DMF (100 mL) was heated at 110 °C under nitrogen for 22 h. The dark reaction mixture was filtered and the DMF distilled off under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with water (3 × 100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the crude product, which was purified by recrystallization from chloroform (2.98 g, 60%) (Table 1): ^1H NMR ($CDCl_3$) δ 10.84 (s, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.41–7.29 (m, 3 H), 7.12–7.06 (m, 1 H), 7.03–6.98 (m, 1 H), 6.53 (s, 1 H), 6.01 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 136.1, 131.9, 130.7, 126.9, 126.5, 123.1, 121.1, 119.5, 118.8, 118.6, 110.7, 109.4, 101.4, 45.1.

General Procedure for the Lithiation of 3 and Subsequent Reaction with Electrophiles. To a stirred solution of 2-(benzotriazol-1-ylmethyl)indole (**3**) (1 equiv) in THF was added dropwise a solution of *n*-butyllithium (2.1 equiv, 2.0 *M* in hexane) at −78 °C under nitrogen. The mixture was warmed to −30 °C for 30 min (or stirred at −78 °C for 5 h) and then cooled to −78 °C. The appropriate alkyl halide (1.1 equiv, see Table 1) was added to the mixture, and the solution was stirred for an additional 3 h at −78 °C. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was separated, washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the corresponding crude products **8**, which were purified either by recrystallization or column chromatography (Tables 1, 4, and 5).

Compounds **6** were obtained by quenching the dilithium salt **5** with 3 equiv of alkyl halide together with HMPA (equal amount to THF) at −30 °C. The solution was allowed to warm to room temperature and stirred overnight. The isolation and purification procedure was as described above (Tables 1, 4, and 5).

Compounds **9** were obtained by the treatment of dilithium salt **5** with 1.1 equiv of alkyl halide at −78 °C for 3 h, followed by the addition of 2 equiv of a second alkyl halide together with HMPA (equal amount to THF) at −30 °C. The reaction mixture was stirred at room temperature overnight. The isolation and purification procedure was the same as described above (Tables 1, 4, and 5).

Substitution of *N*-Alkyl-2-(1-benzotriazol-1-ylalkyl)-indoles 6 and 9 with Grignard Reagents. To a solution of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indole **6** or **9** (2 mmol) in toluene was added a Grignard reagent (5 mmol in diethyl ether) under nitrogen. The mixture was refluxed for 3 h. After cooling, the solvent was distilled off under reduced pressure and the residue was dissolved in diethyl ether (50 mL), washed with water (3 × 30 mL), and dried ($MgSO_4$). The solvent was removed, and the crude products were purified by column chromatography to afford the pure products **10** (Tables 2, 6, and 7).

Preparation of 6,12-Dihydroindolo[3,2-*b*]carbazoles 11 and 5,11-Dihydroindolo[3,2-*b*]carbazoles 13. A solution of compounds **6** or **8** or **9** (2 mmol) and $ZnCl_2$ (4 mmol) in CH_2Cl_2 (100 mL) was refluxed for 3 h. After cooling, hydrochloric acid (2 N, 100 mL) was added and the organic phase was separated, washed with aqueous sodium hydroxide (5%, 3 × 100 mL), and dried ($MgSO_4$). The solvent was removed, and the residue was subjected to column chromatography on silica gel uising CH_2Cl_2/hexane (1:4) as the eluent to afford the pure products **11**. Alternatively, the residue was washed with a small amount of CH_2Cl_2 to give the pure compounds **13** (Tables 3, 8, and 9).

Supplementary Material Available: Tables 4–9 for the ^1H NMR and ^{13}C NMR spectral data of compounds **6**, **8**–**11**, and **13** with peak assignments (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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