was monitored at a 240-nm UV detector. Two fractions of retention time 5.5 and 8–10 min were collected and concentrated to give **6f** and a mixture of (*E*)- and (*Z*)-**5f**, respectively. The mixture of **5f** was separated on the HPLC column. The mobile phase was a mixture 50% ether in hexane for 10 min at flow rate of 5 mL/min, increased linearly to 80% in 2 min. Fractions of (*E*)-**5f** (10.0 min) and (*Z*)-**5f** (13.5 min) were collected.

(*E*)-**5f**: ^{1}H NMR ($CDCl_3$) δ 2.07–2.14 (m, 2 H), 2.40 (s, 3 H), 2.60 (d, 1 H, J = 9.5 Hz), 2.65–2.76 (m, 1 H), 2.79 (d, 1 H, J = 9.5 Hz), 2.84–2.90 (m, 1 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 5.07 (s, 1 H), 6.05 (s, 1 H), 6.45 (s, 1 H), 7.16–7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 42.25 (q), 47.94 (t), 48.14 (s), 55.25 (q), 55.38 (q), 56.93 (t), 76.45 (t), 97.22 (d), 109.98 (d), 122.62 (d), 125.95 (d), 128.26 (d, 2 C), 128.92 (d, 2 C), 138.80 (s), 143.91 (s), 147.30 (s), 150.72 (s).

(*Z*)-**5f**: ^{1}H NMR ($CDCl_3$) δ 1.56–1.62 (m, 1 H), 1.92 (ddd, 1 H, J = 12.9, 7.7, 5.2 Hz), 2.11 (s, 3 H), 2.31 (ddd, 1 H, J = 12.9, 8.5, 3.9 Hz), 2.75 (d, 1 H, J = 9.2 Hz), 2.78–2.83 (m, 1 H), 2.94 (d, 1 H, J = 9.2 Hz), 3.62 (s, 3 H), 3.73 (s, 3 H), 5.02 (s, 1 H), 5.45 (s, 1 H), 6.53 (s, 1 H), 7.13–7.39 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 41.93 (q), 44.14 (t), 47.69 (s), 55.10 (q), 55.14 (q), 55.59 (t), 72.34 (t), 104.22 (d), 110.79 (d), 126.32 (d), 126.80 (d), 127.56 (d, 2 C), 130.15 (d, 2 C), 139.27 (s), 142.58 (s), 144.47 (s), 148.97 (s).

Reaction of 3e,f with CsF in the Presence of DBU: General Procedure. To a solution of **3e,f** (2 mmol) in DMF (10 mL) prepared in a manner similar to that described in General Procedure A above was added DBU (1.52 g, 10 mmol) by syringe. Then, CsF (1.52 g, 10 mmol) was added and the mixture was stirred for 3 h at room temperature. The mixture was poured into 2% $NaHCO_3$ and extracted with ether. The extract was washed with 2% $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on an aluminum oxide column (hexane:ether = 19:1).

6-Methyl-5,6,7,8-tetrahydro-13*H*-dibenzo[*c*,*f*]azonine (**17e**): yield 281 mg (59%); bp 200 °C (8 mmHg, Kugelrohor); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.71 (t, 2 H, J = 5.9 Hz), 3.03–3.08 (m, 2 H), 3.43 (s, 2 H), 4.25 (s, 2 H), 6.99–7.52 (m, 8 H). Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07, N, 5.90. Found: C, 86.09; H, 8.03; N, 5.85.

10,11-Dimethoxy-6-methyl-5,6,7,8-tetrahydro-13*H*-dibenzo-[*c*,*f*]azonine (**17f**): yield 380 mg (64%); mp 99–100 °C (EtOH, lit.[16] mp 102–104 °C).

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Supplementary Material Available: X-ray crystallographic data for *cis*-**3f**, ^{1}H NMR data of **6f**, **11a–c**, and **17f**, and microanalyses data of **3a**, **3b**, *cis*-**3c**, *cis*-**3d**, *cis*-**3e**, *cis*-**3e**-d_3, and *cis*-**3f** (26 pages). This material is contained in many libraries on microfiche, immediately allows 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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Facile Generation and Trapping of α-Oxo-*o*-quinodimethanes: Synthesis of 3-Aryl-3,4-dihydroisocoumarins and Protoberberines

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Fluorodesilylation of *o*-((trimethylsilyl)methyl)benzoyl derivatives **5** in the presence of aromatic aldehydes and alkyl fumarates gives 3-aryl-3,4-dihydroisocoumarins **6** and α-tetralones **10**, respectively. Reaction of **5** with 3,4-dihydroisoquinolinium salts **19** leads to 8-oxoberbines **21**. Using this procedure, racemic hydrangenol, phyllodulcin, tetrahydropalmatine (**22a**), and canadine (**22b**) have been synthesized.

Ever since the firm postulation of *o*-quinodimethanes (oQDM) (**1**) by Cava in 1957,[1] these reactive intermediates have been used to construct a variety of molecular frameworks by inter- or intramolecular [4 + 2] trapping.[2] Many methods for oQDM generation have been developed over the years.[3] A particularly convenient approach, introduced by Ito,[4] entails F^--promoted desilylation to effect a 1,4-elimination in an *o*-((trimethylsilyl)alkyl)benzyltrimethylammonium compound (**2** → **1**). This procedure can be extended to functionalized oQDM which can, in turn, afford usefully functionalized target molecules.[5] For example, α-imino-oQDM (**3a**) generated in such a manner was trapped with suitable dienophiles and the obtained adduct **4a** hydrolyzed to obtain tetralone **4b**.[6] This sequence amounts to a [4 + 2] addition of α-oxo-oQDM (**3b**)

Table I. Synthesis of 3-Substituted 3,4-Dihydroisocoumarins 6 and 7, 1-Tetralones 10, and 3-Arylisocoumarin 11

entry	substrate	dienophile	product (isolated yield, %)
1	**5a**	C_6H_5CHO	**6a** (38)
2	**5a**	*o*-MeC_6H_4CHO	**6b** (38)
3	**5a**	*p*-$MeOC_6H_4CHO$	**6c** (51)
4	**5a**	3,4-$(MeO)_2C_6H_3CHO$	**6d** (62)
5	**5a**	CCl_3CHO	**7** (90)
6	**5b**	*p*-$MeOC_6H_4CHO$	**6e** (50)
7	**5b**	3-$PhCH_2O$-4-$MeOC_6H_3CHO$	**6f** (53)
8	**5a**	*trans*-MeOOCCH=CHCOOMe	**10a** (48)
9	**5a**	*trans*-EtOOCCH=CHCOOEt	**10b** (60)
10	**5a**		**11** (70)

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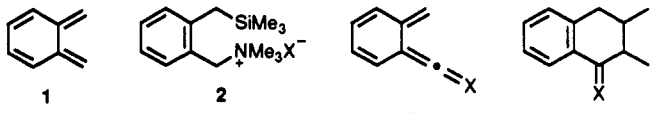
to a dienophile. We have found that desilylation of *o*-((trimethylsilyl)methyl)benzoyl derivative **5** can directly provide adducts corresponding to trapping of **3b**.[7] The present paper gives a detailed account of these observations along with a significant extension wherein iminium salts have been used as dienophiles.[8]



1 2 3 4

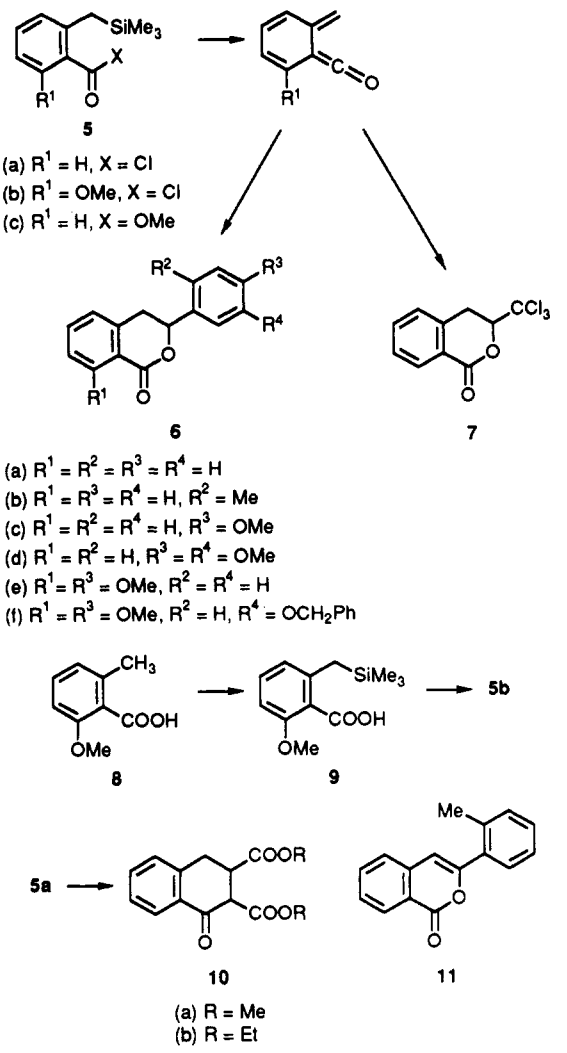
(a) X = N +
(b) X = O

Results and Discussion

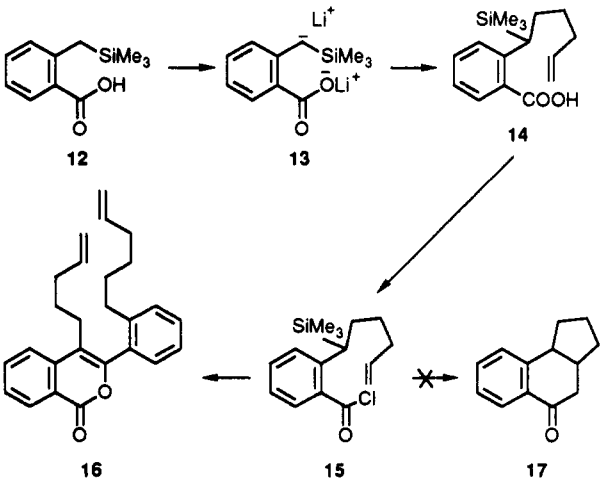
Reaction of the acid chloride **5a**[9] with anhydrous CsF in MeCN under reflux in the presence of benzaldehyde afforded 3-phenyl-3,4-dihydroisocoumarin (**6a**) in 38% yield (Scheme I). Similarly, isocoumarins **6b**, **6c**, and **6d** were obtained in yields shown in Table I. In the case of chloral which is a more reactive dienophile,[10] the cycloadduct **7** was obtained in 90% yield. This methodology was then extended to secure (±)-hydrangenol (**6**, $R^1 = R^3 = OH$, $R^2 = R^4 = H$) and (±)-phyllodulcin (**6**, $R^1 = R^4 = OH$, $R^2 = H$, $R^3 = OMe$). It should be interpolated here that there is renewed interest in the synthesis of these compounds because of their antifungal and other pharmacological activities and due to the discovery that hydrangenol is 400 times sweeter than sucrose.[11] The starting 2-methoxy-6-methylbenzoic acid (**8**) was obtained by a known sequence from crotonaldehyde and ethyl acetoacetate.[12] Its treatment with LDA in THF followed by addition of trimethylsilyl chloride afforded the silylated acid **9** which, without purification, was refluxed with thionyl chloride in benzene to obtain acid chloride **5b**. Reaction of **5b** with CsF in the presence of *p*-anisaldehyde or *O*-benzylisovanillin furnished ethers **6e** and **6f** in 50% and 53% yield, respectively. Since the conversions of **6e** and **6f** to (±)-hydrangenol and (±)-phyllodulcin are known,[11] the present work constitutes a formal synthesis of these isocoumarins.

When reaction of **5a** with CsF was carried out in the presence of dimethyl or diethyl fumarate, tetralones **10a** and **10b** were obtained in moderate yields. Efforts to improve the efficiency of this reaction by variation of the solvent, the fluorodesilylation agent, or the leaving group on the benzoyl carbon, were unrewarding (Table I). The acid chloride **5a** failed to furnish adducts with maleic anhydride, naphthoquinone, acrylonitrile, or methyl acrylate.[13] In these reactions, or in the absence of any added dienophile, product **11** corresponding to the condensation of two molecules of **5a** was obtained. Its ^1H NMR spectrum showed a three-proton methyl singlet at δ 2.4 and a one-proton singlet at δ 6.43 characteristic of 3-substituted isocoumarins. The mass spectrum revealed a molecular ion peak at m/z 236, and the IR spectrum showed carbonyl absorptions at ν 1700 and 1604 cm^{-1}. Next, an attempt was made to trap the proposed quinodimethane intermediate

Scheme I



Scheme II



(**3b**) intramolecularly, hoping that more favorable entropic factors may promote the reaction.[14] However, when the alkene **15** was subjected to CsF desilylation, only the dimer **16** was obtained and no product corresponding to **17** could be isolated (Scheme II).

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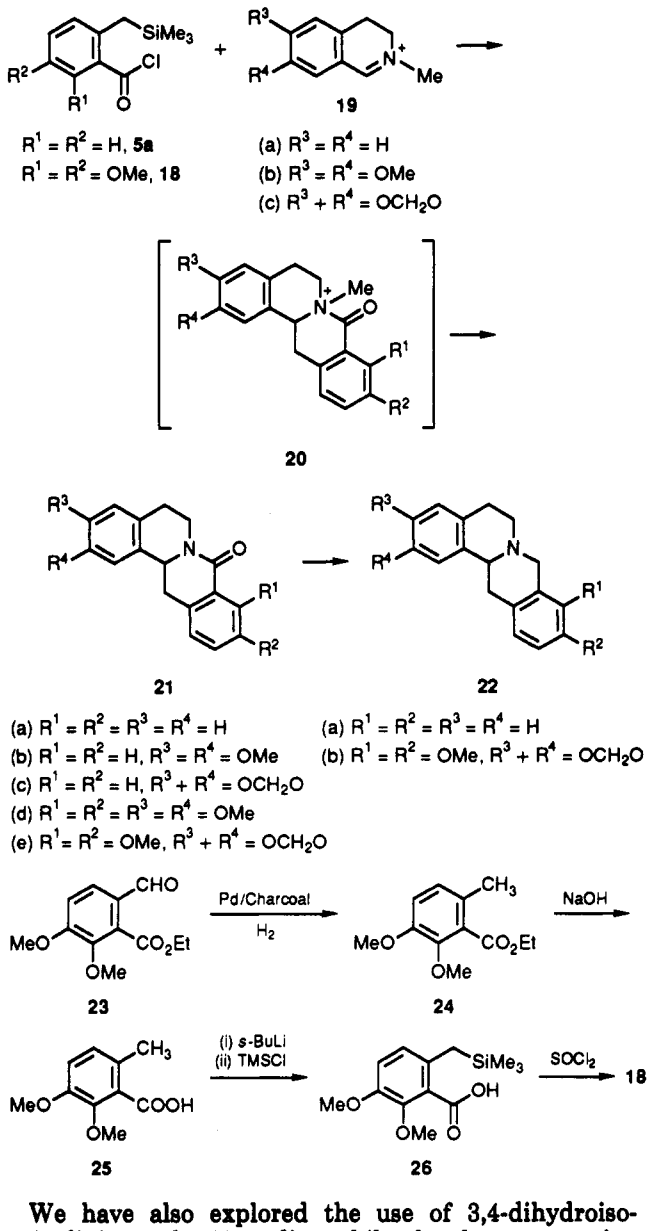
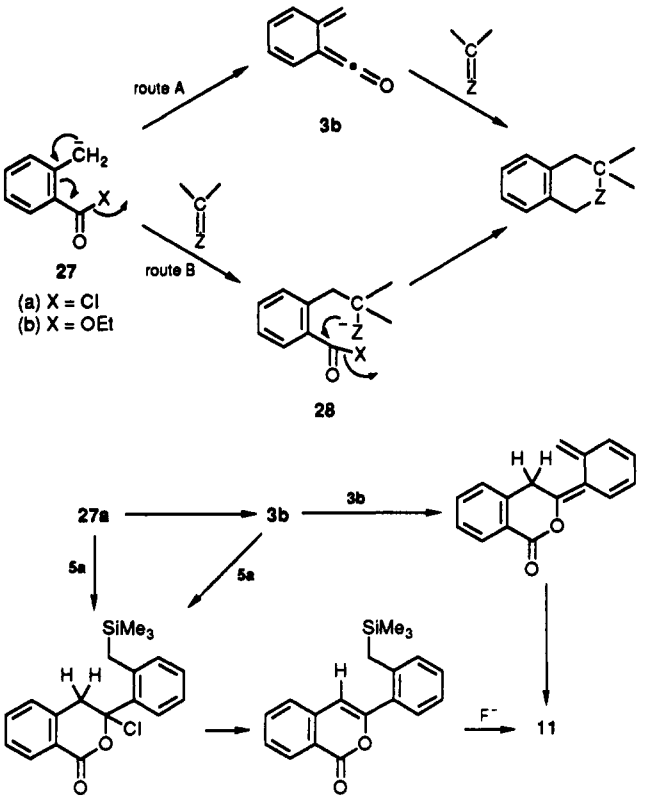
Scheme III



We have also explored the use of 3,4-dihydroisoquinolinium salts **19** as dienophiles for the construction of the protoberberine skeleton.[15] Thus, acid chloride **5a** was treated with CsF in refluxing MeCN in the presence of iminium salt **19a** to get 8-oxoberbine **21a** in 65% yield, presumably via the intermediacy of **20** (Scheme III).[16] Similarly, 2,3-disubstituted 8-oxoberbines **21b** and **21c** were generated in good yields. Reaction of 2,3-dimethoxy-6-((trimethylsilyl)methyl)benzoyl chloride (**18**), obtained from ester **23**[17] (Scheme III), with 6,7-disubstituted dihydroisoquinolinium salts **19b** and **19c** led to the formation of 8-oxotetrahydropalmatine (**21d**) and 8-oxocanadine (**21e**), respectively. Reduction with LAH afforded (±)-tetrahydropalmatine (**22a**) and (±)-canadine (**22b**).[18]

The formation of adducts from **5** has been assumed to proceed through the α-oxo-oQDM **3b** (route A), but an alternate mechanism invoking a nucleophilic addition followed by cyclization also merits consideration (route B). Formation of dimer **11** can also be rationalized in similar terms (Scheme IV). In this context, a comparison of the reaction of ester **5c** and acid chloride **5a** with CsF in CH_3CN is revealing. With the former substrate (**5c**), the only isolated product (80%) was methyl toluate which corresponds to protonation of anion **27b**. On the other hand, **5a** afforded the dimer **11** (70%). An attractive explanation for this dichotomy is that anion **27b** survives long enough to abstract a proton from the solvent whereas anion **27a** rapidly loses Cl^-, a better electrofuge, to generate **3b** and products thereof. Thus, depending upon the leaving group and the solvent,[19] reactions of *o*-((trimethylsilyl)methyl)benzoyl derivatives **5** may proceed predominantly through routes A or B.

Scheme IV



Experimental Section

The instrumentation, general chemicals, and conditions for inert reaction media have been described elsewhere.[17]

General Procedure for Fluorodesilylation. A. A solution of the benzoyl derivative **5** (1 mmol) and dienophile (3 mmol) in MeCN (14 mL) was refluxed (4.5 h) with anhydrous CsF (1.3 mmol) under nitrogen. The solvent was removed, and water (5 mL) was added. The mixture was extracted with ether (20 mL × 3), and the combined organic layer was washed with brine. The solvent was distilled off and the residue chromatographed on silica gel to get pure products.

B. A solution of the acid chloride **18** (1 mmol) and iminium salt **19** (1.0 mmol) in MeCN (10 mL) was refluxed (5 h) with anhydrous CsF (1.5 mmol) under nitrogen. The cooled reaction mixture was worked up as in A.

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3-Phenyl-3,4-dihydroisocoumarin (6a). Reaction of **5a** with benzaldehyde by procedure A afforded **6a** in 38% yield, mp 88–90 °C (lit.[11] mp 87–89 °C).

3-(2-Methylphenyl)-3,4-dihydroisocoumarin (6b). Obtained from **5a** and *o*-tolualdehyde in 38% yield by procedure A, mp 109–110 °C (lit.[11] mp 100–102 °C).

3-(4-Methoxyphenyl)-3,4-dihydroisocoumarin (6c). Secured from **5a** and *p*-anisaldehyde by procedure A in 51% yield, mp 108–109 °C (lit.[11] mp 108–109 °C).

3-(3,4-Dimethoxyphenyl)-3,4-dihydroisocoumarin (6d). Reaction of **5a** and veratraldehyde by procedure A afforded **6d** in 62% yield, mp 101–102 °C. ^{1}H NMR ($CDCl_3$): δ 3.0–3.5 (m, 2 H, CH_2Ar); 3.99 (s, 6 H, 2 × OMe); 5.55 (dd, 1 H, CHAr); 6.9–7.8 (m, 6 H, ArH); 8.25 (d, J = 8.0 Hz, 1 H, ArH). MS m/z: 284 (M^+, 63); 166 (20); 165 (40); 137 (10); 118 (100). IR (Nujol): ν 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.83, H, 5.63. Found: C, 72.73; 5.60.

3-(Trichloromethyl)-3,4-dihydroisocoumarin (7). Obtained in 90% yield from **5a** and chloral by procedure A, mp 120–121 °C (lit.[20] mp 119–121 °C).

2-Methoxy-6-((trimethylsilyl)methyl)benzoyl Chloride (5b). Into a flame-dried 100-mL two-necked round-bottom flask equipped with a stir bar and a septum cap was introduced THF (30 mL) and diisopropylamine (2.75 g, 27.2 mmol). It was cooled to −78 °C, and a 2.2 M solution of BuLi in hexane (12.3 mL, 27.2 mmol) was added via syringe. After 15 min, a solution of the acid **8**[12] (2.26 g, 13.6 mmol) in THF (10 mL) was added. The reaction mixture was further stirred for 30 min at −78 °C and quenched with trimethylsilyl chloride (1.5 g, 13.6 mmol). It was gradually allowed to come to room temperature, poured into water (20 mL), and extracted with ether (20 mL × 3). The combined organic extract was washed with water and dried. The solvent was removed under reduced pressure to afford the crude silyl acid **9** (3 g).

The crude silyl acid **9** (3 g) was refluxed (6 h) with $SOCl_2$ (1.42 g, 12 mmol) in dry benzene (30 mL) containing DMF (0.15 mL). Benzene was distilled off, and resultant dark liquid on Kugelrohr distillation afforded acid chloride **5b** (3 g, 86%). ^{1}H NMR (CCl_4): δ 0.00 (s, 9 H, $SiMe_3$); 2.25 (s, 2 H, CH_2Ar); 3.85 (s, 3 H, OMe); 6.55–7.35 (m, 3 H, ArH). IR (neat): ν 2930, 1770 cm^{-1}. MS m/z: 256 (M^+). Anal. Calcd for $C_{12}H_{17}ClO_2Si$: C, 56.25, H, 6.64. Found: C, 56.20; H, 6.55.

(±)-Hydrangenol Dimethyl Ether (6e). Secured from the acid chloride **5b** and *p*-anisaldehyde by procedure A in 50% yield, mp 151–152 °C (lit.[11] mp 153 °C).

(±)-Phyllodulcin Benzyl Methyl Ether (6f). Reaction of **5b** and *O*-benzyl isovanillin by procedure A afforded **6f** in 53% yield, mp 150–151 °C (lit.[11] mp 149–151 °C).

2,3-Dicarbomethoxytetral-1-one (10a). Reaction of **5a** and dimethyl fumarate by procedure A furnished an oil in 48% yield. Crystallization from hexane afforded pure **10a**, mp 87–88 °C (lit.[20] mp 86–88 °C).

2,3-Dicarbethoxytetral-1-one (10b). Obtained from **5a** and diethyl fumarate by procedure A in 60% yield, mp 54–55 °C. ^{1}H NMR ($CDCl_3$): δ 1.15, 1.35 (2t, 6 H, 2 × CH_3); 3.24 (m, 2 H, CH_2Ar); 3.68–4.53 (m, 6 H, 2 × $CHCO_2CH_2$); 7.32 (m, 3 H, ArH); 7.96 (d, J = 8.0 Hz, 1 H, ArH). MS m/z: 290 (M^+). IR (KBr pellet): ν 1740 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20, H, 6.20. Found: C, 66.24; H, 6.15.

3-(2-Methylphenyl)isocoumarin (11). Treatment of the acid chloride **5a** with anhydrous CsF in the absence of any addendum according to general procedure A gave the isocoumarin **11** (70%), mp 83–85 °C (lit.[21] mp 85 °C).

***o*-(1-(Trimethylsilyl)hex-5-enyl)benzoyl Chloride (15).** To a solution of the acid **12** (2 g, 9.6 mmol) in THF (25 mL) kept at −10 °C was added a 2 M solution of BuLi in hexane (9.6 mL, 19.2 mmol) under nitrogen. After 30 min of stirring 5-bromopent-1-ene (1.86 g, 12.5 mmol) was added and the reaction mixture further stirred at room temperature for 3 h. It was poured into water (50 mL) and washed with ether (50 mL × 3). The aqueous layer was acidified with HCl (15%) and extracted with ether (30 mL × 3). The ether extract was washed with brine and dried. The solvent was removed under reduced pressure to afford the crude alkylated acid **14** (2.5 g).

A solution of this crude acid **14** (2.5 g, 9 mmol) in dry THF (40 mL) was stirred with NaH (0.26 g, 10.9 mmol) for 1 h and evaporated in vacuo to dryness. The dry salt was then suspended in dry benzene (40 mL), and oxalyl chloride (1.7 g, 13.6 mmol) was added dropwise over a period of 30 min. After 1 h of further stirring, the reaction mixture was filtered and evaporated in vacuo to obtain a yellow oil which on Kugelrohr distillation afforded the pure acid chloride **15** (1.9 g, 71%). ^{1}H NMR (CCl_4): δ 0.00 (s, 9 H, $SiMe_3$); 1.07–2.29 (m, 6 H, 3 × CH_2); 3.23 (t, 1 H, CHAr); 5.04 (t, 2 H, =CH_2); 5.5–6.07 (m, 1 H, =CH); 7.13–7.72 (m, 3 H, ArH); 8.25 (d, J = 8.0 Hz, 1 H, ArH). MS m/z: 296 (M^+ + 2); 294; 259 (100); 218 (9); 145 (15); 115 (15). Anal. Calcd for $C_{16}H_{23}ClOSi$: C, 65.30; H, 7.82. Found: C, 64.97; H, 7.69.

3-(2-Hex-5-enylphenyl)-4-pent-4-enylisocoumarin (16). Reaction of the acid chloride **15** with anhydrous CsF according to procedure A furnished the isocoumarin **16** in 48% yield as an oil. ^{1}H NMR (CCl_4): δ 1.2–2.2 (m, 10 H, 5 × CH_2); 2.4–2.82 (m, 4 H, $ArCH_2$ and $ArCCH_2$); 4.85–5.2 (m, 4 H, 2 × =CH_2); 5.5–6.1 (m, 2 H, 2 × =CH); 7.2–8.1 (m, 7 H, ArH); 8.6 (d, 1 H, ArH). MS m/z: 372 (M^+, 5); 303 (40); 248 (100); 204 (40); 128 (38). Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.87; H, 7.52. Found: C, 83.92; H, 7.41.

Ethyl 2-Methyl-5,6-dimethoxybenzoate (24). A mixture of the aldehyde ester **23**[17] (3.0 g, 12.6 mmol), 10% Pd on charcoal (1.0 g), and ethanol (100 mL) was hydrogenated at 70 psi of H_2 for 10 h. The mixture was filtered through a layer of Celite, and the solvent was evaporated to yield **24** as an oil (2.7 g, 95%). ^{1}H NMR ($CDCl_3$): δ 1.3 (t, 3 H, OCH_2CH_3); 2.15 (s, 3 H, $ArCH_3$); 3.8 (s, 6 H, 2 × OMe); 4.35 (q, 2 H, OCH_2CH_3); 6.9 (s, 2 H, ArH).

2-Methyl-5,6-dimethoxybenzoic Acid (25). To a solution of **24** (2.0 g, 8.4 mmol) in ethanol (40 mL) was added a solution of sodium hydroxide (1.2 g) in water (10 mL), and the reaction mixture was refluxed for 5 h. Ethanol was evaporated, and the residual aqueous layer was washed with ether, acidified with 20% HCl, and extracted with ether (20 mL × 4). The organic extract was washed with water, dried, and evaporated under vacuo, and the residue on chromatography afforded **25** as a white solid (1.5 g, 86%), mp 89–90 °C. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3 H, $ArCH_3$); 3.87, 3.93 (2s, 6 H, 2 × OMe); 6.9 (s, 2 H, ArH). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.1. Found: C, 61.07; H, 6.23.

5,6-Dimethoxy-2-((trimethylsilyl)methyl)benzoic Acid (26). Prepared in 90% yield in a manner similar to the one described for **9** except that *sec*-BuLi was used as the base, mp 55–56 °C. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 9 H, $SiMe_3$); 2.05 (s, 2 H, CH_2SiMe_3); 3.77, 3.83 (2s, 6 H, 2 × OMe); 6.63–6.92 (m, 2 H, ArH). IR (Nujol): ν 1677 cm^{-1}. MS m/z: 268 (M^+, 71), 253 (14); 238 (13); 179 (15); 178 (31); 58 (100).

5,6-Dimethoxy-2-((trimethylsilyl)methyl)benzoyl Chloride (18). Treatment of the acid **26** (0.27 g, 1 mmol) with thionyl chloride (0.12 mL) in dry benzene (10 mL) at reflux temperature gave the acid chloride **18** (0.28 g, 95%). ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 9 H, $SiMe_3$); 2.1 (s, 2 H, CH_2SiMe_3); 3.9, 3.97 (2s, 6 H, 2 × OMe); 6.67, 6.69 (ABq, 2 H, J = 8.5 Hz, ArH). IR (Nujol): ν 1776 cm^{-1}. It was used in the next reaction without further purification.

8-Oxoberbine (21a). Reaction of the acid chloride **5a** with iminium salt **19a**[17] according to procedure B furnished oxoberbine **21a** in 65% yield, mp 169–171 °C (lit.[16] mp 169–170 °C).

2,3-Dimethoxy-8-oxoberbine (21b). The acid chloride **5a** on treatment with iminium salt **19b**[17] by procedure B afforded the title compound **21b** in 64% yield, mp 139–140 °C (lit.[16] mp 141–142 °C).

2,3-(Methylenedioxy)-8-oxoberbine (21c). Reaction of the acid chloride **5a** with iminium salt **19c**[17] by procedure B gave **21c** in 65% yield, mp 175–177 °C. ^{1}H NMR ($CDCl_3$): δ 2.83–3.35 (m, 5 H, $ArCH_2CHH$ and $C_{13}H$); 4.7–5.1 (m, 2 H, C_6 and C_{13a} H's); 5.93 (s, 2 H, OCH_2O); 6.76 (d, 2 H, J = 4.5 Hz, ArH); 7.25–7.65 (m, 3 H, ArH); 8.1–8.37 (m, 1 H, ArH). IR (Nujol): ν 1650 cm^{-1}. MS m/z: 294 (M^+ + 1, 21); 293 (100); 292 (79); 278 (24); 276 (7); 265 (7); 264 (27); 174 (9). HRMS calcd for $C_{18}H_{15}NO_3$ m/z 293.1052, obsd m/z 293.1048.

8-Oxotetrahydropalmatine (21d). Secured in 58% yield by treatment of **18** with **19b** according to procedure B, mp 167–168 °C (lit.[18a] mp 170–171 °C).

8-Oxocanadine (21e). Obtained in 52% yield by reaction of **18** with **19c** by procedure B, mp 217–218 °C. ^{1}H NMR ($CDCl_3$):

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δ 2.7–3.07 (m, 5 H, $ArCH_2CHH$ and $C_{13}H$); 3.94, 4.07 (2s, 6 H, 2 × OMe); 4.52–5.23 (m, 2 H, C_6 and $C_{13a}H$'s); 6.05 (s, 2 H, OCH_2O); 6.8 (s, 2 H, ArH); 7.13 (s, 2 H, ArH). IR (Nujol): ν 1662 cm^{-1}. MS m/z: 354 (M^+ + 1, 11); 353 (51); 352 (9); 351 (10); 179 (12); 178 (100); 176 (36); 135 (22). HRMS calcd for $C_{20}H_{19}NO_5$: m/z 353.1263, obsd m/z 353.1278.

(±)-Tetrahydropalmatine (22a). To a solution of **21d** (0.05 g, 0.13 mmol) in dry ether (10 mL) was added lithium aluminium hydride (0.05 g, 0.15 mmol), and the reaction mixture was refluxed for 2 h. After the solution was cooled, the excess LAH was destroyed by addition of water (0.5 mL) and 10% sodium hydroxide (1 mL). It was filtered, and the filtrate was washed with water, dried, and evaporated to give berbine **22a** (0.045 g, 94%), mp 150–151 °C (lit.[16] mp 149.5–150.5 °C).

(±)-Canadine (22b). Reduction of **21e** with LAH as described above afforded **22b** in 98% yield, mp 172–173 °C (lit.[18b] mp 171 °C).

Registry No. **5a**, 78752-29-1; **5b**, 144192-07-4; (±)-**6a**, 34696-49-6; (±)-**6b**, 144192-08-5; (±)-**6c**, 144192-09-6; (±)-**6d**, 144192-10-9; (±)-**6e**, 82780-51-6; (±)-**6f**, 82780-52-7; (±)-**6**(R^1 = R^3 = OH, R^2 = R^4 = H), 80394-92-9; (±)-**6**(R^1=R^4=OH,R^2+-H,R^3=OMe), 55555-33-4; (±)-**7**, 144192-11-0; **8**, 6161-65-5; **9**, 144192-12-1; **10a**, 91416-33-0; **10b**, 93007-01-3; **11**, 73318-30-6; **12**, 71435-93-3; (±)-**14**, 144192-13-2; (±)-**15**, 144192-14-3; **16**, 144192-15-4; **18**, 144192-16-5; **19a**, 3947-78-2; **19b**, 30045-07-9; **19c**, 35287-11-7; (±)-**21a**, 41173-73-3; (±)-**21b**, 58093-70-2; (±)-**21c**, 76177-40-7; (±)-**21d**, 76177-39-4; (±)-**21e**, 76177-41-8; (±)-**22a**, 2934-97-6; (±)-**22b**, 29074-38-2; **23**, 104270-87-3; **24**, 144192-17-6; **25**, 5653-57-6; **26**, 144192-18-7; C_6H_5CHO, 100-52-7; $Br(CH_2)_3C$-H=CH_2, 1119-51-3; *o*-tolualdehyde, 529-20-4; *p*-anisaldehyde, 123-11-5; veratraldehyde, 120-14-9; chloral, 75-87-6; isovanillin, 621-59-0; dimethyl fumarate, 624-49-7; diethyl fumarate, 623-91-6.

Supplementary Material Available: Spectroscopic and analytical data of known compounds (**6a**, **6b**, **6c**, **6e**, **6f**, **7**, **10a**, **11**, **21a–d**, and **22a,b**) (4 pages). This material is contained in many 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.

Novel Cryptand Chromoionophores for Determination of Lithium Ions

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The syntheses and chromogenic properties of three novel chromogenic (*p*-nitrophenyl)azo-labeled cryptands **1–3**, having inward-facing phenolic groups, are described. Cryptand chromoionophore **1** has the smallest cavity of the three cryptands and exhibits total selectivity for Li^+ over Na^+ ions in 10% aqueous diethylene glycol monoethyl ether (DEGMEE). The association constant of 3200 M^{-1} was obtained in 10% aqueous DEGMEE/TMA(OH) for the 1^-Li^+ complex. Compound **1** is potentially applicable for the colorimetric analysis of lithium ions in largely aqueous solutions. The slightly larger chromoionophore **2**, in which diaza-12-crown-4 moiety is connected with the aromatic subunit via three-carbon bridges, is highly selective for Li^+ ions in the extraction mode and shows no cation response in homogeneous aqueous media. A larger analog of **1**, chromogenic cryptand **3**, which incorporates diaza-18-crown-6 moiety, exhibits K^+ ion selectivity in aqueous solutions.

Introduction

Over the past 15 years indicator systems derived from macrocyclic compounds capable of selective ion binding have seen much interest due to their potential application in the determination of physiologically important cations.[1] Reagents for colorimetric determination of sodium and potassium ions in aqueous solutions, based on cryptahemispherands and hemispherands, have recently been reported.[2] Several attempts have been made to design an indicator system for the determination of lithium ions.[3] Lithium carbonate is a therapeutic drug used in treatment of psychiatric disorders.[4] Flame photometry and ion-selective electrodes are currently used for determination of lithium in human serum.[5] Some of the lithium chromoionophores reported thus far are capable of highly selective Li^+ complexation in organic solvents but cannot be applied in homogeneous, aqueous media.

In this paper we report the design and synthesis of an indicator system based on a chromogenic cryptand. This novel chromoionophore exhibits extraordinary selectivity for Li^+ over Na^+ in largely aqueous solutions, allowing for the first time the practical colorimetric determination of lithium in blood and other physiological fluids.[6]

Results and Discussion

Design and Syntheses of Chromoionophores 1–3. The design of lithium-selective ionophores is an intricate task, especially when the complexation of lithium ions is expected to occur in aqueous media. High selectivity of Li^+ over Na^+ could be anticipated only with ionophores which incorporate small, rigid cavities which restrict complexation with Na^+ and other ions. To ensure strong binding, which is a prerequisite for high sensitivity of the

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