45 min. After workup (extraction with dichloromethane), the crude material was analyzed on a 3% OV 17 on Chromosorb W/HP column, with *m*-nitrobenzaldehyde as internal standard.

Acknowledgment. The continued financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. **1a**, 619-25-0; **1b**, 1515-84-0; **1c**, 80171-39-7; **1d**, 101999-47-7; **1e**, 101999-48-8; **1f**, 21388-97-6; **1g**, 7409-18-9; **1g**·H^+, 101999-54-6; **1h**, 101999-49-9; **1i**, 5400-78-2; **1j**, 6925-96-8; **1k**, 17414-84-5; **1l**, 101999-50-2; **1m**, 101999-51-3; **1n**, 73585-54-3; **1o**, 101999-52-4; **1p**, 101999-53-5; **1q**, 39896-32-7; **1r**, 99-08-1; *m*-nitrobenzaldehyde, 99-61-6; *m*-nitroacetophenone, 121-89-1; *m*-nitrosobenzaldehyde, 52944-86-2; D_2, 7782-39-0; D_2O, 7789-20-0.

A Regioselective Entry to 13-Substituted 8-Oxoprotoberberines. Total Synthesis of (±)-Corydaline

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13-Alkyl and 13-aryl substituted 8-oxoprotoberberines were obtained by intermolecular benzyne cycloaddition of isoquinolinopyrrolinediones with arynes. This convergent and highly regioselective reaction has been applied to the synthesis of (±)-corydaline.

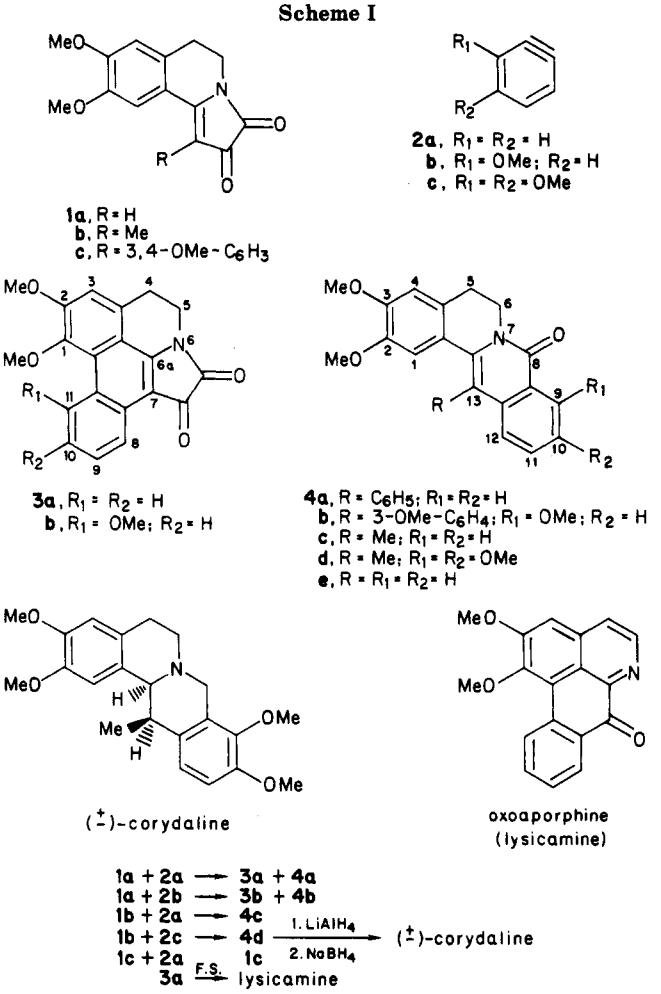
During the past few years we have been working on the development of new synthetic approaches to several types of isoquinoline alkaloids.[1] In particular, recognition of the common phenantrene or dihydrophenantrene structures led to our recently devising what appears to be a highly convergent general approach to the quite large aporphinoid subgroup of isoquinolines.[2]

In continuation of our work with benzyne cycloadditions, the reactions of **1** with arynes **2** were investigated and led to an efficient route to **4** (Scheme I). In our opinion, this unexpected route to the pharmacologically important protoberberines[3] shows promise as a synthetic tool both because of its convergence and its high regioselectivity. As a final demonstration, an efficient regioselective synthesis of (±)-corydaline is described.

The isoquinolinopyrrolidinediones **1** were prepared uneventfully by reaction of 1-alkyl-3,4-dihydroisoquinolines[4] with a molar equivalent of oxalyl chloride in pyridine.[5] With large quantities of both these precursors and anthranilic acids **6a**, **6b**,[6] and **6c**[7] we were now prepared to carry out the key intermolecular cycloaddition step.

In the event, reaction of **1a** with in situ generated benzyne[8] led to an easily separable mixture of the expected red-violet [4 + 2] adduct **3a**[9] (readily convertible into the oxoaporphine lysicamine by Fremy's salt oxidation[10]) and

Scheme I



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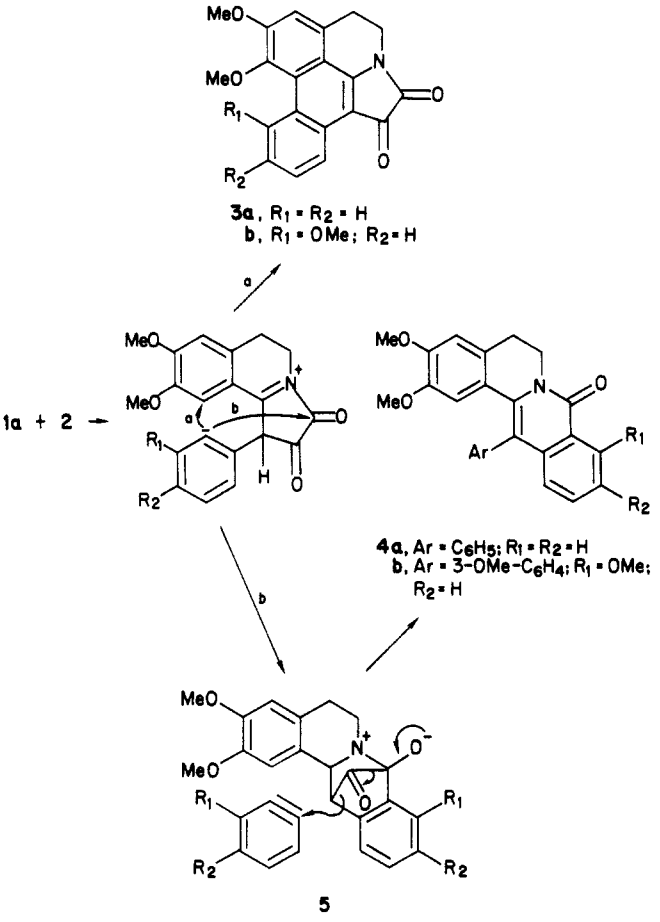
(8) Friedman, L.; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3410.

0022-3263/86/1951-2781$01.50/0

Scheme II

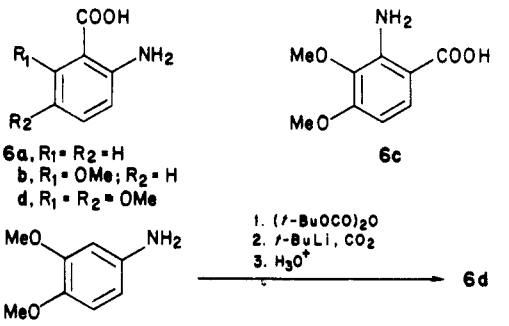


the colorless crystalline cycloadduct **4a** in 10% and 40%, respectively. The most characteristic features of the latter cycloadduct (MS, *m/e* (relative intensity) 383 (100)) were its IR spectrum ($\nu_{C=O}$, 1675 cm^{-1}) and ^1H NMR spectrum which showed a high field methoxy group at 3.17 ppm. These significant spectroscopic data immediately allowed us to assign structure **4a** to this adduct, which had been synthesized by a photochemical route.[11]

Improved overall yield (72% vs. 50%) was subsequently achieved by employing preformed[12] benzenediazonium-2-carboxylate as benzyne precursor. Cycloadducts **3a** and **4a** were then obtained in 11% and 61% yields, respectively. This unexpected but nonetheless quite interesting result is thought to be a consequence of at least two competing pathways, a and b (Scheme II).

The available experimental evidence regarding the reactivity of enamides with benzyne (vide infra) suggests that the most likely mechanistic pathway leading to cycloadducts **4** is that shown in Scheme II, i.e., with phenylation on carbon 13 (protoberberine numbering) taking place directly on the bicyclic intermediate **5** rather than on the 8-oxoprotoberberine[13] whose possession of an enamide system might make it the expected product of decarbonylation. In keeping with this scheme, enamide **1c** was recovered unchanged (90–95%) after treatment with

Scheme III



benzyne under typical reaction conditions.

Similar results were obtained when **1a** was treated with the unsymmetrically substituted benzyne **2b** generated in situ from precursor **6b**. Interestingly, only cycloadducts **3b** (3%) and **4b** (42%) were found, thus proving the highly regioselective nature of the intermolecular benzyne cycloaddition.[2] The ^1H NMR spectrum (250 MHz) of **4b** clearly shows it to be a 9-methoxyberberine (it lacks the low field H-9 multiplet present in **4a**) and although the exact substitution pattern of the aryl group on C-13 can not be firmly established, we believe structure **4b** is the most reasonable assumption in light of the regioselectivity observed by ourselves and other workers for this and related reaction.[14]

At this point, we reasoned that having a substituent already present at the pyrrolidinone moiety of **1** might prevent the final phenylation step. Furthermore, by using an unsymmetrical benzyne such as **2c** we expected the pathway toward the oxoberberine skeleton to be highly favored as a consequence of increased steric hindrance. Pleasingly, reaction of **1b** prepared from 1-ethyl-3,4-dihydroisoquinoline[4] with benzyne **2a** generated by thermal decomposition of preformed benzenediazonium-2-carboxylate yielded only 13-methyl-8-oxoprotoberberine **4c**[15] in 51% yield. No traces of other cycloadducts were found.

As a consequence of this promising result, it was decided to work toward the synthesis of a 13-alkyl-substituted protoberberine such as (±)-corydaline (see Scheme I). Reaction of **1b** with in situ generated benzyne **2c** from anthranilic acid **6c** yielded only cycloadduct **4d**, albeit in low yield (10%). It soon became evident that we were using the wrong benzyne precursor, i.e., the anthranilic acid having the amino function flanked by the carboxy and alkoxy groups. As suggested by Paquette et al.,[16] we needed anthranilic acid **6d** with the NH_2 group peripheral to the other substituents. This was obtained by the sequence shown in Scheme III. Thus the N-Boc derivative of 3,4-dimethoxyaniline was treated with *t*-BuLi and the resulting dilithiated derivative quenched with CO_2,[17] affording a good yield of a mixture of isomeric N-protected anthranilic acids. Final deprotection and subsequent chromatographic separation produced the required **6d**[18] in 60% yield.

Reaction of **1b** with in situ prepared benzyne **2c** (from **6d**) gave cycloadduct **4d** in 32% isolated yield (40% based on recovered starting material). No other regioisomer was

(9) The oxidation step in the formation of **3a** is apparently a dehydrogenation by benzyne (see ref 2a).
(10) Castedo, L; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1982**, *47*, 513.
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(13) We are at present working toward definitively clarifying this mechanistic assumption by examining the reaction of 8-oxoprotoberberine **4e** with benzyne.
(14) Stevens, R. V.; Bisachi, G. S. *J. Org. Chem.* **1982**, *47*, 513.
(15) Ninomiya, I.; Naito, T.; Takasugi, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1791. Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1151.
(16) Snow, R. A.; Cothrell, D. M.; Paquette, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 3734.
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(18) Grosso, J. A.; Nichols, D. E.; Kohli, J. D.; Glock, D. *J. Med. Chem.* **1982**, *25*, 703.

detected (NMR). Final conversion of cycloadduct **4d** into (±)-corydaline was achieved by the well-known methodology described for closely related systems.[15] Thus $LiAlH_4$ reduction followed by $NaBH_4$ reduction of the resulting enamine afforded a 70% yield of (±)-corydaline whose spectroscopic properties were identical with those reported and whose identity was confirmed by direct comparison with an authentic sample.[19]

To sum up we have described a novel regioselective, convergent entry to the protoberberine skeleton. Further work will allow other synthetic applications of this intermolecular benzyne cycloaddition to isoquinoline alkaloids.

Experimental Section

General Procedures. All melting points were determined on a Büchi apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian Model CFT-20 (80 MHz) or a Bruker (250 MHz) spectrometer (Me_4Si as an internal standard). Infrared spectra were taken in KBr pellets with a Pye-Unicam 1100 spectrometer. Ultraviolet–visible spectra were run on a Pye-Unicam 1700 instrument and mass spectra were recorded on a Kratos MS-25 instrument operating at 70 eV. Combustion analyses were performed with a Perkin-Elmer Model 240 B at the Inorganic Chemistry Department (Universidad de Santiago).

1-Alkyl-3,4-dihydroisoquinolines were prepared as described.[4] Aryne precursors **6b** and **6c** were obtained by the methods described Warrener[6] and Pschorr,[7] respectively. All other chemicals, oxalyl chloride, isoamyl nitrite, *tert*-butyl pyrocarbonate, anthranilic acid, etc., were used as obtained from the suppliers.

Dry solvents (THF, DME, dioxane, pyridine, etc.) were prepared by standard methods.[20]

Isoquinolinopyrrolinediones 1. General Method. To a cold (0 °C) stirred mixture of 1-alkyl-3,4-dihydroisoquinoline[4] (typically 10 mmol) in dry DME (25 mL) and dry pyridine (1 mL) was added a slight excess of oxalyl chloride (12 mmol) dropwise under an inert atmosphere (N_2 or argon). Stirring was continued for an additional 15 min. The resulting heterogeneous mixture was then filtered and the deep red solid washed several times with cold DME. This solid was dissolved in CH_2Cl_2 and then washed successively with 5% HCl and water. Evaporation of the dry (anhydrous Na_2SO_4) solution yielded highly pure samples of isoquinolinopyrrolinediones 1. Analytical samples were usually obtained by crystallization from methanol or ethanol–CH_2Cl_2.

Isoquinolinopyrrolinedione (**1a** was obtained in 70% yield as deep red crystals: mp 238–240 °C (from EtOH–CH_2Cl_2); IR (KBr) 1750, 1710 cm^{-1}; UV (EtOH) λ_{max} 260 (log ϵ 3.83), 310 (3.85), 376 (3.89), 434 (sh, 3.81), 470 (sh, 3.72); ^1H NMR ($CDCl_3$) δ 7.14 (s, 1 H), 6.79 (s, 1 H), 5.67 (s, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 3.81 (t, 2 H, J = 5.5 Hz), 3.11 (t, 2 H, J = 5.5 Hz); mass spectrum, m/e (relative intensity) 259 (65, M^+), 231 (100), 200 (50), 175 (85), 129.5 (2.5, M^{2+}).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.02; N, 5.40. Found: C, 64.29; H, 4.87; N, 5.42.

Isoquinolinopyrrolinedione **1b** was obtained in 75% isolated yield as deep red prisms: mp 202–204 °C (from MeOH–CH_2Cl_2); IR (KBr) 1750, 1710 cm^{-1}; UV (MeOH) λ_{max} 264 (log ϵ 3.91), 312 (3.80), 370 (3.85), 446 (sh, 3.66), 480 (sh, 3.64); ^1H NMR ($CDCl_3$) δ 7.38 (s, 1 H), 6.82 (s, 1 H), 3.99 (s, 3 H), 3.94 (s, 3 H), 3.77 (t, 2 H, J = 6 Hz), 3.01 (t, 2 H, J = 6 Hz), 2.12 (s, 3 H); mass spectrum, m/e (relative intensity) 273 (100, M^+), 245 (20), 217 (91), 202 (100), 136.5 (1, M^{2+}).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.49; N, 5.12. Found: C, 65.39; H, 5.48; N, 5.01.

Intermolecular Cycloaddition of Isoquinolinopyrrolinediones 1 with Arynes 2. Method A. In Situ Generation[8] of Arynes 2 by Aprotic Diazotization of Anthranilic Acids 6. To a refluxing dry dioxane solution of isoquinolinopyrrolinediones **1** (2 mmol) with a catalytic amount of trichloroacetic acid in a three-necked flask with two addition funnels were simultaneously added dry dioxane solutions of anthranilic acids **6**[6,7,18] and isoamyl nitrite dropwise (90 min) until TLC showed no starting material **1** to be present (usually a 5 M excess of both anthranilic acids **6** and isoamyl nitrite were needed). Refluxing was continued for an additional 30 min. Workup was carried out as follows: evaporation to dryness in a rotary evaporator under vacuum yielded a solid residue which was dissolved in CH_2Cl_2 (100 mL) and then successively washed with 5% HCl, 5% NaOH, and water. The dry solution (anhydrous Na_2SO_4) was then evaporated to dryness, and the residue was subjected to column chromatography (silica gel 60 Merck) using CH_2Cl_2 polarized with variable amounts of EtOH (0–5%). In this manner biphenylene was easily removed (CH_2Cl_2 as eluent) and "isatins" **3** and oxoprotoberberines **4** were then eluted successively.

Method B. Benzyne Generation from Preformed[12] Benzenediazonium-2-carboxylate. The methodology described by Oda[12] was used (DME instead of THF) to generate the diazonium salt **6a**. The resulting suspension of **6a** in DME was added dropwise to the refluxing dioxane solution of **1** with a catalytic amount of trichloroacetic acid by means of a plastic syringe with Teflon tubing (*Precaution*! No metallic needle should be used.). Addition was discontinued when starting material **1** had disappeared (TLC monitoring). The residue obtained by evaporation to dryness was loaded in a chromatography column (silica gel) and treated as in method A.

Isatin **3a** (mp 229–231 °C) was isolated in 10% (method A) and 11% (method B) yields. It was found to be identical (mp; ^1H NMR; TLC; etc.) with an authentic sample.[10]

8-Oxoprotoberberine **4a**,[11] colorless needles, mp 231–232 °C (MeOH), was isolated in 40% (method A) and 61% (method B) yields: IR (KBr) 1675 cm^{-1}; UV (EtOH) λ_{max}; 250 (sh, log ϵ 4.24), 330 (4.31), 364 (sh, 4.14); ^1H NMR ($CDCl_3$) δ 8.50 (m, 1 H), 7.54–7.26 (m, 8 H), 6.67 (s, 1 H), 6.46 (s, 1 H), 4.37 (t, 2 H, J = 5.8 Hz), 3.87 (s, 3 H), 3.17 (s, 3 H), 2.91 (t, 2 H, J = 5.8 Hz); mass spectrum, m/e (relative intensity) 383 (100, M^+), 368 (71).

Isatin **3b** was isolated as deep red crystals (from EtOH–CH_2Cl_2), mp 242–243 °C, in 3% yield (method A): IR (KBr) 1750, 1690 cm^{-1}; UV (EtOH) λ_{max} 260 (log ϵ 4.31), 292 (4.07), 352 (3.95), 520 (3.31); ^1H NMR ($CDCl_3$) δ 8.15 (d, 1 H, J = 7.8 Hz), 7.57 (t, 1 H, J = 7.8 Hz), 7.13 (s, 1 H), 6.97 (d, 1 H, J = 7.8 Hz), 4.07 (s, 3 H), 4.02 (s, 3 H), 3.96 (t, 2 H, J = 6.5 Hz), 3.6 (s, 3 H), 3.33 (t, 2 H, J = 6.5 Hz); mass spectrum, m/e (relative intensity) 363 (100, M^+), 335 (84), 181.5 (5, M^{2+}), 167.5 (10).

8-Oxoprotoberberine **4b** was obtained in 42% yield (method A). It crystallized (benzene–hexane) as an amorphous powder: mp 127–128 °C; IR (KBr) 1650 cm^{-1}; UV (MeOH) λ_{max} 250 (sh, log ϵ 4.24), 326 (sh, 4.15), 366 (4.22), 376 (4.16); ^1H NMR ($CDCl_3$) δ 7.32–7.24 (m, 2 H), 6.82–6.72 (m, 5 H), 6.57 (s, 1 H), 6.46 (s, 1 H), 4.24–4.18 (m, 2 H), 3.92 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.14 (s, 3 H), 2.8 (t, 2 H, J = 5.8 Hz); high-resolution mass spectrum calcd for $C_{27}H_{25}NO_5$ 443.1732742, found 443.1731087.

8-Oxoprotoberberine **4c** was obtained as colorless prisms, mp 161–162 °C (ether–hexane) (lit.[15] mp 163.5–165 °C) in 52% yield (method B): IR (KBr) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (d, 1 H), 7.76–7.70 (m, 2 H), 7.5 (t, 1 H), 7.10 (s, 1 H), 6.80 (s, 1 H), 4.27 (t, 2 H, J = 5.8 Hz), 3.96 (s, 3 H), 3.92 (s, 3 H), 2.87 (t, 2 H, J = 5.8 Hz), 2.63 (s, 3 H); mass spectrum, m/e (relative intensity) 321 (54, M^+), 306 (57), 195 (100), 161.5 (6, M^{2+}).

8-Oxoprotoberberine **4d** was isolated as colorless prisms (from MeOH), mp 228–230 °C, in 10% yield (method A) when prepared starting from anthranilic acid **6c**. Alternatively, **4d** was isolated in 32% unoptimized yield (method A) when prepared starting from anthranilic acid **6d**: IR (KBr) 1640 cm^{-1}; UV (MeOH) λ_{max} 254 (sh, log ϵ 4.25), 330 (4.41), 360 (sh, 4.12), 380 (sh, 3.97); ^1H NMR ($CDCl_3$) δ 7.51 (d, 1 H, J = 8 Hz), 7.36 (d, 1 H, J = 8 Hz), 7.08 (s, 1 H), 6.79 (s, 1 H), 4.23 (m, 2 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.86 (m, 2 H), 2.56 (s, 3 H); high-resolution mass spectrum calcd for $C_{22}H_{23}NO_5$ 381.157624, found 381.1574196.

(±)-Corydaline from 8-Oxoprotoberberine 4d. A mixture of the 8-oxoprotoberberine **4d** (40 mg, 1.3 mmol), lithium aluminium hydride (114 mg), and THF (10 mL) was refluxed for 3 h with stirring. After cooling to 0 °C, the excess of hydride was decomposed with water, and the resulting mixture was filtered

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(20) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Academic Press: New York, 1966.

through Celite, $NaBH_4$ (200 mg) was added little by little to the filtrate with stirring at room temperature, and the mixture was stirred for a further 1 h at the same temperature. The solvent was distilled off and the residue was dissolved in $CHCl_3$. The solution was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellowish solid which was subjected to PLC. The major band was then extracted with CH_2Cl_2 and the extracts were evaporated to dryness (26 mg, 70%). The resulting solid residue (mp 133-134 °C) was found to be identical with an authentic sample of (±)-corydaline (mp 133-134 °C; lit.[19] mp 135 °C).

Attempted Phenylation of Isatin 1c.[10] A refluxing dioxane solution of "istin" **1c** (100 mg, 0.25 mmol) was treated with in situ generated benzyne **2a** as described in method A. Usual workup yielded 90 mg of starting material.

Preparation of Anthranilic Acid 6d[18] from 3,4-Dimethoxyaniline. To a solution of 4.34 g (28.4 mmol) of 3,4-dimethoxyaniline in 120 mL of dry THF was added 6.8 g (31.2 mmol) of di-*tert*-butyl pyrocarbonate all at once. The resulting solution was refluxed for 2 h. After cooling, the solvent was stripped off and the solid residue crystallized from hexane (5.05 g, 74% yield) as colorless needles: mp 87-89 °C; IR (KBr) 3350, 1700 cm^{-1}; UV (EtOH) λ_{max} 240 (log ϵ 4.18), 284 (3.63); ^1H NMR ($CDCl_3$) δ 7.15 (d, 1 H, J = 1.3 Hz), 6.75 (br s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 1.51 (s, 9 H); mass spectrum, m/e 253 (relative intensity) (17, M^+), 197 (61), 57 (100).

The previous *tert*-butyl carbamate (2 g, 8.2 mmol) dissolved in dry THF (20 mL) at 0 °C was treated with 11.2 mL (20.1 mmol) of a 1.81 M solution of *tert*-butyllithium at -78 °C. Stirring at -78 °C was continued for 15 min and then for 2 h at -20 °C. The resulting yellow solution was transferred via canula, under an argon atmosphere, to a slurry of CO_2 (excess) in THF (75 mL) cooled at -78 °C. The mixture was then stirred while slowly reaching room temperature, and 2 h further at this temperature. Ether (150 mL) was added and the solution washed with 5% aqueous $NaHCO_3$ 3 times. The basic aqueous solution was then acidified with citric acid and extracted with ether. Once washed with water and dried (anhydrous Na_2SO_4), the ethereal solution was evaporated to dryness leaving a crude solid (2.2 g, 95% yield) mixture of protected anthranilics acids which was subjected to final deprotection without further purification. This was achieved by treating a THF solution of the above mixture with concentrated HCl (40 mL) at room temperature overnight. Careful basification (10% NaOH) to neutrality was followed by extraction subjected to open column chromatography (silica gel, CH_2Cl_2). Pure anthranilic acid **6d** was eluted first and obtained (61%) as crystalline material from ethanol, mp 98-99 °C (lit.[18] mp 98.8-100 °C). Spectroscopic data are identical with that described.[18]

Registry No. **1a**, 102421-38-5; **1b**, 102421-39-6; **3a**, 64938-92-7; **3b**, 102421-40-9; **4a**, 15495-36-0; **4b**, 102421-41-0; **4c**, 58471-28-6; **4d**, 102421-42-1; **6a**, 118-92-3; **6b**, 53600-33-2; **6c**, 5701-87-1; **6d**, 5653-51-0; ClC(O)C(O)Cl, 79-37-8; 1-methyl-3,4-dihydroisoquinoline, 2412-58-0; 1-ethyl-3,4-dihydroisoquinoline, 41173-70-0; (±)-corydaline, 6018-35-5; 3,4-dimethoxyaniline, 6315-89-5; *N*-(*tert*-butoxycarbonyl)-3,4-dimethyoxybenzenamine, 102421-43-2; benzenediazonium-2-carboxylate, 1608-42-0.

2,7-Diphenyloxepin

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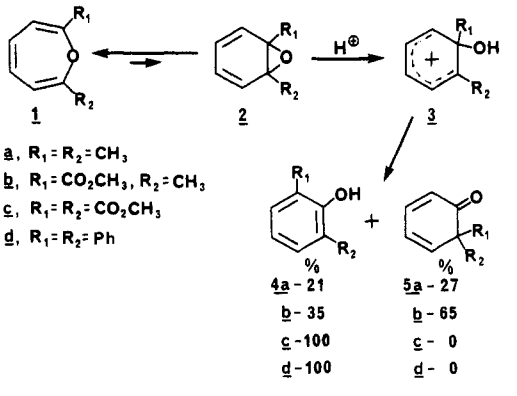
A synthesis of 2,7-diphenyloxepin (**1d**) is described. Acid-catalyzed isomerization of **1d** gives 2,6-diphenylphenol (**4d**) in quantitative yield. X-ray crystal structure analysis indicates that oxepin **1d** exists in a boat conformation in the solid state.

Oxepin valence tautomer **1** is more stable than oxide valence tautomer **2** in 1,2-disubstituted arene 1,2-oxides.[1] With few exceptions sufficient **2** is present in solution to observe acid-catalyzed isomerization via the NIH shift pathway, which involves migration of R_1 of cation **3** to either adjacent carbon atom with ultimate formation of **4** and/or **5** (Scheme I). Although the factors that determine the direction of substituent migration are not fully understood, the product ratios (**4**/**5**) from acid-catalyzed isomerization of 1,2-disubstituted arene 1,2-oxides such as **2a**,[2,3] **2b**,[4] and **2c**[4] support the expectation that substituent migration to the adjacent carbon atom with the higher

Scheme I



degree of carbonium ion character ought to be the favored pathway. Under appropriate reaction conditions, further isomerization of **5b** (migration of CO_2CH_3) to a 2,3-disubstituted phenol is observed.[4] The acid-catalyzed isomerization of **1a** affords 2,3-dimethylphenol (2%) and

(1) For a recent review of arene oxides-oxepines, see: Boyd, D. R.; Jerina, D. M. In *Small Ring Heterocycles*; Hassner, A., Ed.; Wiley-Interscience: New York, 1984; Part 3, Vol. 42, pp 197-282.
(2) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385-401.
(3) Kaubisch, N.; Daly, J. W.; Jerina, D. W. *Biochemistry* **1972**, *11*, 3080-3088.
(4) Boyd, D. R.; Berchtold, G. A. *J. Am. Chem. Soc.* **1979**, *101*, 2470-2474.

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