Synthesis of 4,7-Disubstituted Spirobenzofuran-2(3*H*)-cyclohexanes

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A general synthetic strategy was designed for the preparation of 7-substituted-4-methoxy- and 4-hydroxyspiro[benzofuran-2(3*H*)-cyclohexanes] **5** and **6** (Figure 1) using successive, regioselective heteroatom-facilitated aromatic lithiation reactions and subsequent reaction with various electrophiles.

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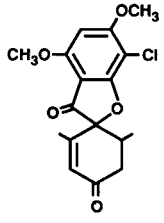
Introduction.

As part of an ongoing effort in our laboratory to develop efficient methodologies for the synthesis of partial derivatives of natural products with unique biological activities, we have investigated novel approaches to the synthesis of spirobenzofuran-2(3*H*)-cycloalkanes. A number of compounds containing this substructure are known, including griseofulvin (**1**) [2], metabolites of *Stypopodium zonale* (**2**) [3], *Siphonodictyon coralliphagum* (**3**) [4], and the complement inhibitor, K-76 (**4**) [5].



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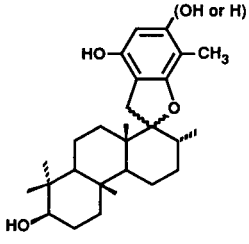

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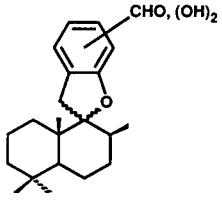

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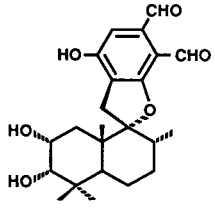

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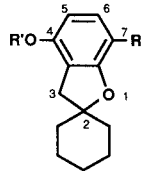
To make a series of functionally-varied partial analogs of compound **4**, a general strategy was designed for the synthesis of 7-substituted-4-methoxy- and 4-hydroxyspiro-[benzofuran-2(3*H*)-cyclohexanes] **5** and **6** (Figure 1) using successive, regioselective heteroatom-facilitated aromatic lithiation reactions. Aromatic metalation and subsequent reaction with various electrophiles has become the method of choice for *ortho* aromatic substitutions owing to higher yields and greater regioselectivity [6]. Numerous oxygen containing heterocycles have been made using metalation methodologies, but few preparations of dihydrobenzo-[*b*]furans can be found [6]. Two reported syntheses of K-76 itself [7,8] utilize metalation techniques in the coupling of the terpenoid portion to the aromatic moiety, but neither provide sufficient flexibility to allow for multiple analog preparation *via* subsequent elaboration of the aromatic ring. This approach would require the preparation of each functionalized aromatic unit prior to the ring formation. Another approach to the synthesis of the spirobenzofuran unit also functionalizes the aromatic portion prior to cyclization [9]. Our strategy optimizes the use of identical starting materials and maximizes the number of common preparative sequences. Each compound in the series would be derived from the same aromatic and aliphatic portion, whereby the 7-substituent is introduced after their coupling. This approach allows for the facile introduction of a variety of substituents at position-7 from a single intermediate, and also allows for potential further regioselective functionalization to give 6,7-disubstituted derivatives.

Figure 1

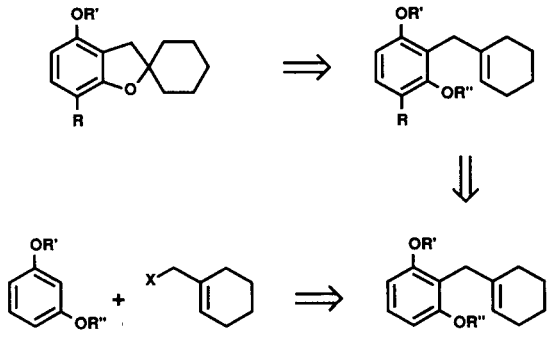
	R	R'
5a	COOH	Me
5b	CHO	Me
5c	CH_2OH	Me
5d	CONHMe	Me
6a	COOH	H
6b	CHO	H



The general route presented in the retrosynthetic sense is shown in Scheme 1. Final cyclization to the desired spirocoumaran was envisioned as an acid catalyzed addition across a double bond oriented *ortho* to the appropriate phenol and allylic to the aromatic ring. The olefin's substitution pattern should allow cyclization in a Markownikoff orientation to form a spirodihydrobenzofuran in favor of a dihydrobenzopyran. The protecting group, R', needs to be resistant to cleavage under conditions for cyclization to insure ring closure occurs on the desired oxygen *ortho* to substituent R. Protecting group R'' needs to be selectively removed in the presence of R', and should control regioselectivity of the *ortho*-lithiation needed to introduce substituent R prior to cyclization. The final retrosynthetic dissection yields an appropriately protected resorcinol and an allylic halide. These two components would be coupled *via* an aromatic lithiation reaction using the combined directing power of both phenolic protecting groups to

regioselectively introduce the olefin at the desired position.

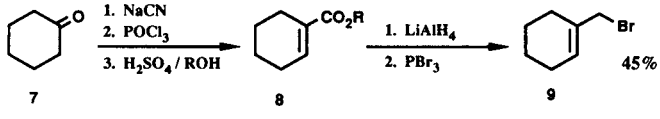
Scheme 1



Results and Discussion.

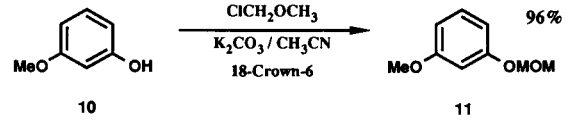
Using a combination of published procedures, the allylic bromide **9** was made from cyclohexanone (**7**) in 45% overall yield or directly from methyl 1-cyclohexene-1-carboxylate (**8**) in greater than 90% yield (Scheme 2). Cyclohexanone was converted to its cyanohydrin then dehydrated to 1-cyanocyclohexene [10]. Subsequent ethanolysis [11] to ethyl 1-cyclohexene-1-carboxylate was chosen in favor of hydrolysis to the acid because of the poor yields obtained when reducing the acid to the allylic alcohol. Lithium aluminum hydride reduction of either the methyl or ethyl ester gave 1-cyclohexenemethanol which was then brominated with phosphorous tribromide [12] to give **9**.

Scheme 2



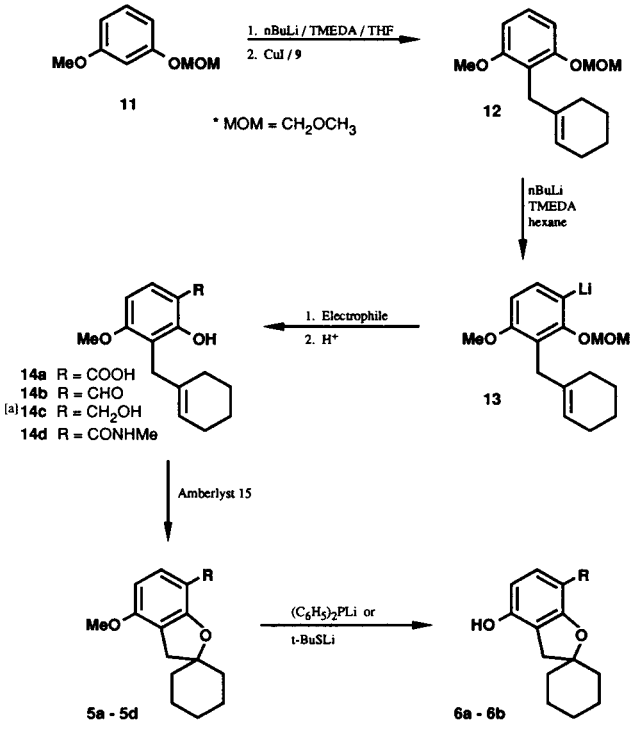
The aromatic segment **11** needed for coupling to bromide **9** (Scheme 3) was made from 3-methoxyphenol (**10**) in 96% yield by adding chloromethyl methyl ether [13] to a stirred suspension of finely ground potassium carbonate in acetonitrile. Anhydrous conditions and the proper ratio of substrate to solvent (1 gram per 100 mls acetonitrile) were critical to the success of this reaction. The methoxymethyl (MOM) and methyl ether were chosen as protecting groups for resorcinol to allow for regioselective functionalization *ortho* to the more labile MOM ether in accordance with the retrosynthetic analysis described above. MOM ethers can be easily removed in the presence of methyl ethers [14] and the *ortho* directing power of the MOM group has been shown to be greater than that of a methyl ether [15]. Work in this laboratory has successfully demonstrated that metalation occurs exclusively *ortho* to the MOM directing group in the presence of a methoxyl group using *n*-butyllithium with one equivalent of tetramethylethylenediamine (TMEDA) in hexane [16].

Scheme 3



The remainder of the synthetic sequence is shown in Scheme 4. Optimal conditions for coupling **9** to **11** were developed from extensive experimentation with *ortho*-lithiation conditions. Lithiation of **9** occurs nearly exclusively at the 2-position because of the combined directing effects of the two ethers [16]. Lithiation was effected using *n*-butyllithium and TMEDA in tetrahydrofuran (THF) at room temperature and was 90% complete after two hours as detected by deuterium oxide quenching of a reaction aliquot. Yields of the coupled intermediate **12** could be enhanced by as much as 15% using cuprous iodide to form the cuprate prior to addition of the halide. This enhancement of reactivity has been noted in similar systems when coupling lithiated aromatics to various halides [17,18]. After chromatographic purification and distillation, **12** was obtained in 69% yield (91% yield corrected for recovered starting material).

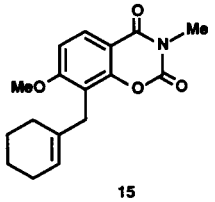
Scheme 4



[a]. 14c was isolated and characterized as the MOM ether. Attempts to remove this blocking group or effect cyclization caused product decomposition. 5c could be made by lithium aluminum hydride reduction of 5b.

Careful control of temperature was also critical for the success of the aromatic alkylation. While lithiation could be effected at room temperature, the reaction must be cooled to −78° prior to the addition of the cuprous iodide. The reaction was slowly warmed to −40° to allow for cuprate formation and was then recooled to −78° before addition of the bromide. Adding the halide at higher temperatures greatly diminished the yield of **12**.

Functionalization of **12** by a second aromatic lithiation *ortho* to the MOM ether to give **13** presents a problem of regioselectivity. MOM ethers are generally considered stronger directing groups than methoxyl groups because of their greater ability to chelate lithium anions [19]. Methoxyl groups direct lithiation by a thermodynamic, acid-base-type mechanism owing to their inductive electron-withdrawing effects [20]. In contrast, strong coordinating groups such as methoxymethyl, favor a kinetic, chelation-directed mechanism. This difference is a possible handle for achieving regioselectivity when both types of groups are present. Kinetic metalation can be favored by the proper choice of solvent system as suggested by metalation experiments on various protected resorcinols [16]. Lithiation at the 2-position of 1,3-dimethoxymethoxybenzene was effected in THF with or without TMEDA or in hexane/TMEDA but not in hexane alone. In contrast lithiation of 1,3-dimethoxybenzene occurs in less than 10% in hexane/TMEDA. Thus, metalation of **12** in hexane/TMEDA should allow exclusive metalation *ortho* to the MOM ether and was confirmed in greater than 90% yield after 3 hours at room temperature by ^{1}H nmr after quenching with deuterium oxide. No detectable metalation of **12** occurred in THF with or without TMEDA, while in hexane, without TMEDA, less than 10% lithiation was detected.



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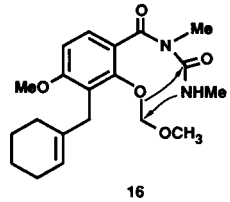

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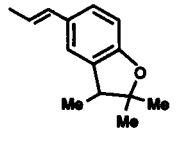

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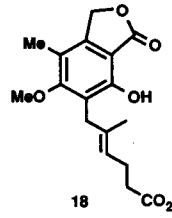

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Carboxylation of **13** to yield **14a** was achieved in 65% yield (Table 1), by bubbling dry carbon dioxide gas into the reaction mixture at −78° for one hour. Yields were optimal when the reaction was cooled to −78° to allow for greater dissolution of the carbon dioxide gas. The MOM-protected compound could not be isolated due to anchimerically-assisted acid hydrolysis. Yields for the formylation of **13** with dimethylformamide (DMF) to **14b**, hydroxymethylation with paraformaldehyde to **14c**, and carboxyamidation with methyl isocyanate to **14d** were all effected by the temperature of the reaction at the time of addition of the electrophile. Temperature control was not only critical for yield optimization but also affected the reaction events. The carboxy-amidation reaction was contaminated with an interesting side product when methyl isocyanate was added at 0°. The 1,3-benzoxazine-2,4-dione, **15**, was observed in 40% yield by gc and isolated pure in 10% yield. The structure of this product was determined by ^{1}H nmr, ^{13}H nmr, ir, and mass spectral analysis, and confirmed by elemental analysis. Formation of this product could be rationalized to proceed through intermediate **16**, a product of methyl isocyanate dimerization. The benzoxazine ring is formed by nucleophilic attack of the phenolic oxygen of the acyl urea with subsequent elimination of an aminal which hydrolyzes to methyl amine, formaldehyde and methanol. Further studies are underway to examine this reaction.

Acid catalyzed cyclization of **14a** to **5a** was most easily accomplished using a 10% suspension of amberlyst 15 ion-exchange resin in benzene [8]. In all cases, the benzofuran was obtained exclusively in favor of the benzopyran as predicted by Markownikoff's rule and confirmed by nmr analysis of the reaction product. The formation of a symmetrical spiro carbon eliminated any complication of stereoisomerism. Cyclization of intermediates **14b** and **14d**, proceeded with fewer side reactions and in higher yields if the MOM ether was first hydrolyzed by stirring overnight in equal portions of 4*N* hydrochloric acid and isopropanol. These conditions nor boron trifluoride etherate in THF at room temperature were sufficient to effect cyclization. The same regents at reflux temperature however did effect cyclization of salicylic acid **14a**, but proved too harsh for the other intermediates in series **14**. It should also be noted that removal of the MOM protecting group from unsubstituted intermediate **12** required refluxing conditions with 4*N* hydrochloric acid/2-propanol. However these conditions also effected cyclization. The benzyl alcohol **14c** decomposed when exposed to any acidic conditions for prolonged periods, therefore **5c** could not be directly synthesized by this route.

Cleavage of the methyl ether for compounds **5a** and **5b** required basic conditions to prevent reopening of the dihydrobenzofuran ring. Boron tribromide effected hydrolysis of the furan prior to demethylation even at −78° for

Table 1

Reaction Yields For Aromatic Substitution of Intermediate **12** and Subsequent Cyclization and Demethylation.

	Substitution		Cyclization	
Electrophile	Product	% Yield	Product	% Yield
CO_2	**14a**	66	**5a**	85
DMF	**14b**	92	**5b**	83
$(CH_2O)_n$	**14c**	64	**5c**	0 [a]
CH_3NCO	**14d**	61	**5d**	94

[a] no product or starting material detected by ^1H nmr

compound **5a**. Cleavage of the methyl group could be effected using lithium diphenylphosphide [20] in THF or lithium *t*-butylthiolate in dimethyl formamide [8]. Demethylation of carboxylic acid **5a** was complicated by the necessary formation of the lithium carboxylate salt prior to the reaction. Yields of **6a** were disappointingly low (31%, 55% based on recovered starting material) and was contaminated with many side products including some ring opened products. This was possibly due to an additional ionic chelation of the cleaving reagent to the carboxylate. Cleavage of the methyl ether for aldehyde **5b** however was effected cleanly in 93% yield using 1.2 equivalents of lithium *t*-butylthiolate in HMPA at 0°. Conversion of product **6b** to **6a** was attempted using silver oxide in 4*N* sodium hydroxide [21] at room temperature but only starting material was recovered. This is consistant with our observation that 2,4-dimethoxybenzaldehyde does not react under the same conditions, however 3,5-dimethoxybenzaldehyde is readily oxidized quantitatively in less than four hours. This would also explain the formation of only one acid when K-76 was oxidized under the same conditions [21]. After carefully repeating this reaction at 80° for three days, the "unfinished" reaction was worked up and was chromatographed to give a 26% isolated yield of **6a** (50% based on recovery of **6b**).

Conclusions.

The overall synthetic strategy used in the synthesis of series **5** and **6** could be applied to the synthesis of a number 7-substituted benzofurans. Of key importance to achieving the regioselective synthesis of 7-substituted dihydrobenzofurans is the nature of the directing group and the solvent system used during the heteroatom-facilitated *ortho*-lithiation methodology. Hexane with TMEDA is the solvent of choice for regioselective kinetic metalation *ortho* to the chelation-directing methoxymethoxyl group *versus* the thermodynamic-directing methoxyl group. Other allylic halides could be coupled to **11**, or other selectively protected phenols, to obtain various substituted coumarans or chromans. A series of substituted flavones has been made using similar aromatic ethers for selective formylation and cyclization [22]. Other related biologically active natural products that could be synthesized using this strategy include compounds **2** and **3** as well as anisoxide (**17**) [23], and mycophenolic acid (**18**) [24]. Additionally, further functionalization to more highly substituted benzofurans would be possible.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Nmr spectra were taken using a Varian EM-390 and a Varian VXR-300 spectrometer. The ir spectra were recorded on a Perkin-Elmer model 281b spectrophotometer. The tlc analyses were done using DC-Fertigplatten SIL G-25 UV254, 0.25 mm Silica gel 60 and silica gel columns used MN-Kieselgel 60, 0.05-0.2 mm, 70-270 mesh. The gc analyses were obtained on a Hewlett-Packard 5890A gc using a DB-5 30m x 0.25 mm capillary column. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. All samples submitted for elemental analysis were dried in an Alderhalden drying chamber under high vacuum (0.5-0.1 mm Hg) using refluxing ether, hexane or toluene. High-resolution mass spectral data were recorded in cooperation with T Cell Sciences, Inc., Cambridge, MA at the Massachusetts Institute of Technology, Cambridge, MA. Percent

yields are rounded to the nearest whole number.

1-Methoxy-3-(methoxymethoxy)benzene (**11**).

Finely powdered anhydrous potassium carbonate (32 mmoles, 4.4 g) was added to a stirring solution of 3-methoxyphenol (16 mmoles, 2.0 g) in dry acetonitrile under a nitrogen atmosphere at 0°. After 15 minutes, 18-crown-6(2 mmoles, 560 mg) was added and then stirred 15 minutes before chloromethyl methyl ether (24 mmoles, 1.4 ml) was slowly introduced. After warming to room temperature and stirring for 6 hours, the suspension was recooled to 0° and one-half the original quantities of potassium carbonate, 18-crown-6, and chloromethyl methyl ether were added. After 4 more hours of stirring at room temperature (or until complete by tlc) the suspension was filtered and the acetonitrile removed under reduced pressure. Disolution in diethyl ether, washing with 5% sodium hydroxide (3 x 50 ml portions), concentration *in vacuo*, and vacuum distillation gave **11** (2.6 g, 96%) as a clear colorless liquid, bp 45° (0.15 mm Hg) {lit [25] bp 73° (0.1 mm Hg)}; ^{1}H-nmr (deuteriochloroform): δ 3.49 (s, 3H), 3.79 (s, 3H), 5.16 (s, 2H), 6.61 (m, 3H), 7.16 (m, 1H).

2-(1′-Cyclohexenylmethyl)-1-methoxy-3-(methoxymethoxy)benzene (**12**).

n-Butyllithium (15.5 ml of a 2.1*M* solution in hexane, 34.2 mmoles) was slowly added to a stirring solution of **11** (5.0 g, 29.7 mmoles) and tetramethylethylenediamine (5.2 ml, 34.5 mmoles) in dry tetrahydrofuran (250 ml) at 0° under a nitrogen atmosphere. After stirring at room temperature for 2 hours the solution was cooled to −78° and cuprous iodide (6.8 g, 35.8 mmoles) was introduced all at once. The light gray suspension was warmed to −40° over a 90 minute period (darkens to a green-gray color) before recooling to −78°. A solution of the freshly prepared allylic bromide **9** (6.6 g, 37.8 mmoles) in tetrahydrofuran (20 ml) was then slowly added, and the mixture was allowed to slowly warm to room temperature. After 16 hours the reaction was quenched with water, followed by exhaustive washing with saturated sodium bicarbonate solution until the aqueous layer was no longer blue. Drying through a plug of potassium carbonate and evaporation of the organic layer *in vacuo* gave 8.0 g of a dark orange oil (76% **12**, 6% **11** by gc analysis). Fractional vacuum distillation of the oil gave 5.4 g (69%) of **12**, bp 105° (0.15 mm Hg) and 1.2 g of **11**. Total yield based on recovered starting material was 91%; ^{1}H-nmr (deuteriochloroform): δ 1.57 (br m, 4H), 1.95 (m, 4H), 3.32 (br s, 3H), 3.43 (s, 3H), 3.77 (s, 3H), 5.13 (s, 2H), 5.23 (br s, 1H), 6.54 (d, J = 9 Hz, 1H), 6.71 (d, J = 9 Hz, 1H), 7.03 (dd, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): δ 158.5 (C-1), 155.8 (C-3), 136.3 (C-C-1′), 126.7 (C-5), 120.0 (C-2′), 118.1 (C-2), 107.0 (C-4), 104.6 (C-6), 94.3 (MOM CH_2), 55.8 (MOM CH_3), 55.8 (OMe), 30.9, 28.8, 25.3, 23.1, 22.6 (benzyl CH_2 and C-3′-6′); ir (neat): ν 2940, 1595, 1470, 1160 cm^{-1}.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.13; H, 8.50.

General Procedure for Lithiation of **12** {2-(1′-Cyclohexenylmethyl)-4-lithio-1-methoxy-3-(methoxymethoxy)benzene (**13**)}.

n-Butyllithium (1.9 ml of a 2.2*M* solution in hexane, 4.2 mmoles) was slowly added to a stirring solution of **9** (1.0 g, 3.8 mmoles) in dry hexane (50 ml) and tetramethylethylenediamine (0.6 ml, 4.2 mmoles) at 0° under a nitrogen atmosphere. The solution is allowed to warm to room temperature and stirred for 3 hours before recooling to −78° and adding the appropriate electrophile.

3-(1′-Cyclohexenyl)methyl-2-hydroxy-4-methoxybenzoic Acid (**14a**).

A solution of **13** (260 mg of **12**, 0.99 mmole) was cooled to −78° and dried carbon dioxide gas was bubbled below the surface of the mixture for 30 minutes then warmed to room temperature with continued bubbling. The suspension was poured into water and extracted into 5% sodium hydroxide solution. Reacidification with concentrated hydrochloric acid at 0° and back-extraction into ether, followed by drying over magnesium sulfate, solvent evaporation *in vacuo*, and crystallization from ether/hexane gave 171 mg (66%) of **14a** as an off-white solid, mp 161-163°; ^{1}H-nmr (acetone-d_6m): δ 1.57 (br m, 4H), 2.01 (br m, 4H), 3.29 (br s, 2H), 3.90 (s, 3H), 4.26 (br s, exc, 2H), 5.26 (br s, 1H), 6.62 (d, J = 9 Hz, 1H), 7.81 (d, J = 9 Hz, 1H); ^{13}C-nmr (acetone-d_6): δ 173.0 (COOH), 164.3 (C-4), 162.1 (C-2), 136.5 (C-1′), 130.6 (C-6), 121.0 (C-2′), 115.9 (C-3), 106.5 (C-1), 103.3 (C-5), 56.3 (OMe), 30.9, 29.4, 25.8, 23.8, 23.2 (benzyl CH_2 and C-3′-5′); ir (potassium bromide): 1650, 1610, 1500, 1455, 1265, 1185, 1090 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.75; H, 6.95.

3-(1′-Cyclohexenyl)methyl-4-methoxy-2-hydroxybenzaldehyde (**14b**).

A solution of **13** (4.0 g of **12**, 15.25 mmoles) was cooled to −78° and *N,N*-dimethylformamide (3.0 ml, 38.13 mmoles) was added all at once. Slowly warming to room temperature, the reaction was stirred for 16 hours before it was poured into a 1% hydrochloric acid solution. Saturating with sodium chloride, the mixture was extracted into ether, passed through a plug of potassium carbonate and concentrated under vacuum to give 3-(1-cyclohexeneylmethyl)-4-methoxy-2-(methoxymethoxy)benzaldehyde as a light yellow oil (4.4 g); [^{1}H-nmr (deuteriochloroform): δ 1.57 (br m, 4H), 1.96 (br m, 4H), 3.30 (br s, 2H), 3.56 (s, 3H), 3.86 (s, 3H), 5.01 (s, 2H), 5.11 (br s, 1H), 6.76 (d, J = 9 Hz, 1H), 7.76 (d, J = 9 Hz, 1H), 10.18 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 189.4 (CHO), 163.8 (C-4), 159.8 (C-2), 135.7 (C-1′), 128.6 (C-6), 123.8 (C-3), 122.5 (C-1), 120.8 (C-2′), 107.0 (C-5), 101.2 (MOM CH_2), 57.5 (MOM CH_3), 55.8 (OMe), 31.3 (benzyl), 28.9, 25.1, 22.9, 22.4 (C-3′-6′); ir (neat): 2930, 1680, 1590, 1385, 1275, 1255, 1160, 1065 cm^{-1}]. This oil was dissolved in 2-propanol (50 ml), 4*N* hydrochloric acid (50 ml) and ether (10 ml) was added to fully solubilize the compound in the 2-propanol. After stirring for 16 hours at room temperature the solution was saturated with sodium chloride, extracted into ether and washed with two equal portions of saturated sodium bicarbonate solution. Drying over magnesium sulfate, solvent evaporation, chromatographic purification and crystallization from hexane gave **14b** (3.46 g, 92% yield), mp 48-49°; ^{1}H-nmr (deuteriochloroform): δ 1.56 (br m, 4H), 1.96 (br m, 4H), 3.26 (br s, 2H), 3.83 (s, 3H), 5.23 (br s, 1H), 6.51 (d, J = 9 Hz, 1H), 7.33 (d, J = 9 Hz, 1H), 9.64 (s, 1H), 11.42 (br s, exc, 1H); ^{13}C-nmr (deuteriochloroform): 194.7 (CHO), 164.6 (C-4), 161.3 (C-2), 135.5 (C-1′), 133.8 (C-6), 120.6 (C-2′), 115.9, 115.6 (C-1 and 3), 103.1 (C-5), 55.9 (OMe), 29.9, 28.8, 25.2, 23.0, 22.4 (Benzyl CH_2 and C-3′-5′); ir (potassium bromide): 2930, 2840, 1625, 1495, 1255, 1100, 800, 640 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.35; H, 7.39.

3-(1′-Cyclohexenyl)methyl-4-methoxy-2-(methoxymethoxy)benzyl Alcohol (**14c**).

A solution of **13** (267 mg of **12**, 1.01 mmoles) was cooled to

−78° and paraformaldehyde (200 mg in 2 ml of hexane) was added all at once. Slowly warming to room temperature, the reaction was stirred for 16 hours it was poured into a 1% hydrochloric acid solution. The mixture was extracted into ether, washed with saturated sodium bicarbonate solution, passed through a plug of potassium carbonate and concentrated under vacuum. Chromatographic purification gave **14c** as a light yellow oil (189 mg, 64% yield); ^{1}H-nmr (deuteriochloroform): δ 1.58 (br m, 4H), 1.94 (br m, 4H), 3.26 (br s, 2H), 3.57 (s, 3H), 3.79 (s, 3H), 4.93 (s, 2H), 5.13 (m, 1H), 6.68 (d, J = 9 Hz, 1H), 7.22 (d, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): 158.9 (C-4), 156.0 (C-2), 136.3 (C-1'), 128.6 (C-6), 127.3 (C-3), 122.1 (C-1), 120.8 (C-2', 107.2 (C-5), 99.9 (MOM CH_2), 61.1 (CH_2OH), 57.2 (MOM CH_3), 55.8 (OMe), 32.0 (benzyl), 29.1, 25.2, 23.0, 22.6 (C-3'-6'); ir: (neat) 3410, 2930, 1600, 1490, 1270, 1160, 1065, 990, 815 cm^{-1}.

Anal. Calcd. for $C_{17}H_{24}O$: C, 69.84; H, 8.27. Found: C, 69.70; H, 8.24.

N-Methyl-3-(1'-cyclohexenyl)methyl-2-hydroxy-4-methoxybenzamide (**14d**).

A solution of **13** (266 mg of **12**, 1.01 mmoles) was cooled to −78° and methyl isocyanate (0.18 ml in 2 ml of hexane) was slowly added. The mixture was slowly allowed to warm to room temperature and then stirred an additional 16 hours. The mixture was then poured into water, saturated with sodium chloride and extracted with ether. Drying over magnesium sulfate, solvent evaporation, and recrystallization from ether/hexane gave *N*-methyl-3-(1-cyclohexenyl)methyl-2-hydroxy-4-methoxybenzamide, mp 99-100° (245 mg); [^{1}H-nmr (deuteriochloroform): δ 1.60 (br m, 4H), 1.96 (br m, 4H), 2.99 (d, J = 5 Hz, 3H), 3.30 (br s, 2H), 3.51 (s, 3H), 3.84 (s, 3H), 4.96 (s, 2H), 5.09 (br s, 1H), 6.79 (d, J = 9 Hz, 1H), 7.56 (br s, 1H), 7.97 (d, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): δ 166.6 (CO), 161.1 (C-4), 153.9 (C-2), 136.0 (C-1'), 130.3 (C-6), 122.1 (C-3), 120.5 (C-1), 120.8 (C-2'), 107.1 (C-5), 100.8 (MOM CH_2), 58.3 (MOM CH_3), 55.9 (OMe), 26.5 (NMe), 31.7 (benzyl), 29.2, 25.2, 23.0. 22.5 (C-3'-6'); ir (potassium bromide): 3340, 2930, 1635, 1595, 1530, 1470, 1275, 1160, 1100, 1065, 980, 945, 825 cm^{-1}]. This white solid was dissolved in ether (20 ml) and 5% hydrochloric acid (20 ml) and stirred for 24 hours before the ether layer was separated, washed with two equal portions of saturated sodium bicarbonate solution, dried through a plug of potassium carbonate, evaporated *in vacuo* and recrystallized from ether to give **14d**, mp 138-139°; ^{1}H-nmr (deuteriochloroform): δ 1.58 (br m, 4H), 1.96 (br m, 4H), 2.98 (d, J = 5 Hz, 3H), 3.31 (br s, 2H), 3.84 (s, 3H), 5.26 (br s, 1H), 6.24 (br s, 1H), 6.41 (d, J = 9 Hz, 1H), 7.26 (d, J = 9 Hz, 1H), 12.57 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 170.9 (CO), 161.9 (C-4), 160.8 (C-2), 135.9 (C-1'), 124.2 (C-6), 120.1 (C-2'), 116.5 (C-3), 107.9 (C-1), 101.6 (C-5), 55.7 (OMe), 26.4 (NMe), 30.3 (benzyl), 28.9, 25.2, 23.1, 22.5 (C-3'-6'); ir (potassium bromide): 3400, 2940, 1650, 1590, 1550, 1495, 1430, 1375, 1315, 1275, 1195, 1100, 1050, cm^{-1}.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.71; H, 7.75; N, 5.04.

N-Methyl-8-(1'-cyclohexenyl)methyl-7-methoxy-1,3-benzoxazine-2,4-dione (**15**).

While repeating the procedure presented for **14d**, [1.0 g of **11** (3.8 mmoles), 0.63 ml of TMEDA (4.2 mmoles), 1.75 ml of 2.4 *M* *n*-BuLi (4.2 mmoles) in 30 ml of hexane] the methyl isocyanate (0.67 ml, 11.4 mmoles) was added at °0, instead of −78°. After work-up and chromatographic separation (chloroform/ethyl acetate, 2/1, on silica gel), 130 mg of **14b** (12 %) was recovered, and 110 mg of **15** (10%) and 500 mg of unseparated mixture was isolated. The stucture of **15** was deduced from the following data, mp 132-133°; ^{1}H-nmr (deuteriochloroform): δ 1.57 (br m, 4H), 1.92 (br m, 4H), 3.38 (br s, 2H), 3.43 (s, 3H), 3.92 (s, 3H), 5.23 (br s, 1H), 6.89 (d, J = 9 Hz, 1H), 7.96 (d, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): δ 163.5 (CO), 160.9 (CO), 151.6, 148.7 (C-7, 8a), 134.7 (C-1'), 127.1 (C-5), 121.6 (C-2'), 116.1 (C-8), 108.1 (C-6), 107.2 (C-4a), 56.2 (OMe), 30.3 (benzyl), 28.7 (C-6' and NMe), 25.2, 22.9, 22.3 (C-3'-5'); ir (potassium bromide): 2930, 1745, 1695, 1620, 1595, 1425, 1375, 1275, 1205, 1095, 755 cm^{-1}; ms: m/e (relative intensity) 301 (M+), 221 (100), 163 (82).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.67; H, 6.41; N, 4.62.

General Procedure for Cyclization.

To a stirred solution of **14** in dry benzene (10 ml) was added dried Amberlyst 15 ion-exchange resin (1.0 g). The suspension was stirred vigorously for 24 hours at room temperature before it was filtered, the resin washed with several portions of diethyl ether, and the solvent removed *in vacuo*.

4-Methoxyspiro[benzofuran-2(3*H*)-cyclohexane]-7-carboxylic Acid (**5a**).

Compound **14a** (154 mg) was reacted using the general procedure for cyclization, and the crude product was crystallized from ether-acetone to give 131 mg of **5a** (85%) as white crystals, mp 192-194°; ^{1}H-nmr (deuteriochloroform): δ 1.67-2.02 (br m, 10H), 2.91 (s, 2H), 3.30 (br s, exc, 1H), 3.91 (s, 3H), 6.61 (d, J = 9 Hz, 1H), 7.77 (d, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): δ 166.1 (COOH), 161.2 (C-4 or 7a), 158.7 (C-4 or 7a), 133.1 (C-6), 115.2 (C-3a), 107.6 (C-7), 104.2 (C-5), 92.0 [C-2(1')2], 56.1 (OMe), 38.4 (C-3), 37.2 (C-2' and 6'), 25.7 (C-4'), 23.7 (C-3' and 5'); ir (potassium bromide): 1660, 1615, 1445, 1435, 1385, 1100 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.52, H, 6.99.

4-Methoxyspiro[benzofuran-2(3*H*)-cyclohexane]-7-carboxaldehyde (**5b**).

Compound **14b** (600 mg) was reacted using the general procedure for cyclization, and the crude product crystallized from hexane to give 496 mg of **5b** (83%), mp 62-63°; ^{1}H-nmr (deuteriochloroform): δ 1.4-2.0 (br m, 10H), 2.88 (s, 2H), 3.88 (s, 3H), 6.46 (d, J = 9 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 10.16 (s, exc, 1H); ^{13}C nmr (deuteriochloroform): δ 187.5 (CHO), 163.2 (C-7a), 161.5 (C-4), 129.0 (C-6), 114.7 (C-3a or 7), 114.4 (C-3a or 7), 103.6 (C-5), 92.1 [C-2(1')], 55.6 (OMe), 37.5 (C-3), 37.2 (C-2' and 6'), 25.0 (C-4'), 23.0 (C-3' and 5'); ir (potassium bromide): 2940, 2860, 1680, 1610, 1395, 1100, 1040, 805, 615 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.40.

N-Methyl-4-methoxyspiro[benzofuran-2(3*H*)-cyclohexane]-7-carboxamide (**5d**).

Using the general procedure for cyclization, 152 mg of **14d** was reacted for 168 hours, and the resulting product cyrstallized from ether-hexane to give 143 mg of **5d** (94%) as white needles, mp 147-148°, ^{1}H-nmr (deuteriochloroform): δ 1.46-1.90 (br m, 10H), 2.90 (s, 2H), 2.99 (d, J = 5 Hz, 3H), 3.84 (s, 3H), 6.49 (d, J = 9 Hz, 1H), 7.52 (br s, 1H), 7.97 (d, J = 9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 165.5 (CO), 158.9 (C-7a), 157.5 (C-4), 131.1 (C-6), 113.4 (C-3a or 7), 109.8 (C-3a or 7), 103.4 (C-5), 92.0 [C-2(1')], 55.5 (OMe), 37.9 (C-3), 37.2 (C-2' and 6'), 26.3 (C-4'), 25.0 (NMe),

23.3 (C-3' and 5'); ir (potassium bromide): 3370, 2940, 1620, 1530, 1495, 1285, 1220, 1100, 775 cm^{-1}.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.7; H, 7.75; N, 5.05.

4-Hydroxyspiro[benzofuran-2(3*H*)-cyclohexane]-7-carboxaldehyde (**6b**).

n-Butyllithium (0.7 ml of a 2.4*M* solution in hexanes, 1.7 mmoles) was slowly added to a stirring solution of 2-methyl-2-propanethiol (0.22 ml, 1.9 mmoles) in dry hexamethylphosphoramide (2 ml) at 0° and allowed to stir for 20 minutes under a nitrogen atmosphere. This mixture was then slowly transfered to a stirring solution of **5b** (400 mg, 1.62 mmoles) in hexamethylphosphoramide (5 ml) at 0° under a nitrogen atmosphere. This mixture was allowed to stir at room temperature overnight, then quenched by pouring into a cooled solution 5% sodium hydroxide. Diethyl ether was added and the layers separated. The ether layer was washed with another portion of 5% sodium hydroxide (stirred for 30 minutes) and the two aqueous layers were combined. Acidification at 0° with concentrated hydrochloric acid, extraction into two portions of diethyl ether, drying over magnesium sulfate, and solvent removal *in vacuo* and recrystallization from ether gave 350 mg (93%) of **6b** as a white solid, mp 142-143°; ^{1}H-nmr (deuteriochloroform): δ 1.71-1.98 (br m, 10H), 2.92 (s, 2H), 6.43 (d, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 10.1 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 186.7 (CHO), 164.8 (C-7a), 161.1 (C-4), 128.6 (C-6), 114.3 (C-3a or 7), 113.6 (C-3a or 7), 109.9 (C-5), 92.4 (C-2), 38.0 (C-3), 37.7 (C-2' and 6'), 25.7 (C-4'), 23.6 (C-3' and 5'); ir (potassium bromide): 3200, 2930, 2860, 1660, 1615, 1590, 1500, 1450, 1380, 1305, 1265, 1225, 1145, 1040, 925, 795 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.42; H, 6.97.

4-Hydroxyspiro[benzofuran-2(3*H*)-cyclohexane]-7-carboxylic Acid (**6a**).

Method A.

n-Butyllithium (1.7 ml of a 2.4*M* solution in hexanes, 4.1 mmoles) was slowly added to a stirring solution of 2-methyl-2-propanethiol (0.50 ml, 4.4 mmoles) in dry hexamethylphosphoramide (2 ml) at 0° and allowed to stir for 20 minutes under a nitrogen atmosphere. This mixture was then slowly transfered to a stirring solution of **5a** (232 mg, 0.88 mmole) in hexamethylphosphoramide (10 ml) at 0° under a nitrogen atmosphere. This mixture was allowed to stir at room temperature for 96 hours, then quenched by pouring into a cooled solution 5% sodium hydroxide. Diethyl ether was added and the layers separated. The ether layer was washed with another portion of 5% sodium hydroxide (stirred for 30 minutes) and the two aqueous layers were combine. Acidification at 0° with concentrated hydrochloric acid, extraction into two portions of diethyl ether, drying over magnesium sulfate, and solvent removal *in vacuo* gave the crude product. Column chromatography purification (chloroform/ethyl acetate, 3/2 with 2.5% acetic acid, on silica gel) gave 101 mg of recovered **5a** (44%), and 68 mg of **6a** (31%, 55% based on recovered starting material) as an off-white powder.

Method B.

Aldehyde **6b** (220 mg, 0.95 mmole) was oxidized in a suspension of silver oxide (550 mg, 2.38 mmoles) in 10 ml of 5% sodium hydroxide and heated to 80°. After 72 hours the suspension was cooled to 25°, filtered with thorough rinsing, cooled to 0°, acidified with concentrated hydrochloric aicd, and extracted into ether (3 x 50 ml). The combined ether layers were evaporated *in vacuo*, and the crude product chromatographed as above to give 104 mg of recovered **6b** (47%), and 62 mg of **6a** (26%, 50% based on recovered **6b**), mp 173-174°; ^{1}H-nmr (deuteriochloroform): δ 1.66-1.88 (br m, 10H), 2.93 (s, 2H), 3.92 (br s, exc, 2H), 6.47 (d, J = 9 Hz, 1H), 7.62 (d, J = 9 Hz, 1H); ^{13}C-nmr (deuteriochloroform): δ 166.3 (COOH), 162.1 (C-7a), 159.6 (C-4), 132.6 (C-6), 113.7 (C-3a), 105.9 (C-7), 109.1 (C-5), 92.1 [C-2(1')], 38.2 (C-3), 37.7 (C-2' and 6'), 25.7 (C-4'), 23.7 (C-3' and 5'); ir (potassium bromide): 3240, 2930, 1705, 1610, 1450, 1385, 1265, 1215, 1050, 895, 830, 785 cm^{-1}.

High resolution ms, exact for $C_{14}H_{16}O_4$, Calcd. m/e 248.1049; Observed: m/e 248.1049.

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