benzamide **15** (115 mg, 0.39 mmol) in 6 N aqueous HCl (15 mL) was stirred under nitrogen at 80 °C for 24 h. Standard workup followed by preparative TLC (EtOAc–hexane, 3:1) afforded 25 mg (27%) of product. Recrystallization (CH_2Cl_2–hexane) gave a sample of kigelin (**13e**), mp 141–142 °C (lit.[30] mp 142–143 °C), whose IR and NMR spectral data were identical with those reported in the literature.[30]

Reactions of Ortho-Metalated 2-Phenyl-4,4-dimethyloxazoline (1b) and (Methoxymethoxy)benzene (1c) with *n*-Butyraldehyde. 2-[2-(1-Hydroxybutyl)phenyl]-4,4-dimethyloxazoline (16). To a stirred THF solution (50 mL) of 2-phenyl-4,4-dimethyloxazoline (**1b**) (500 mg, 2.85 mmol) at −78 °C under nitrogen was added *sec*-BuLi (3.5 mL, 0.98 M in hexane, 3.38 mmol). After 2.75 h, the reaction mixture was allowed to warm to 0 °C and quenched with freshly distilled *n*-butyraldehyde (411 mg, 5.7 mmol). The resulting solution was allowed to warm to room temperature overnight. Standard workup gave 648 mg of crude product, which upon column chromatography afforded 467 mg (65%) of compound **16**: bp 78–82 °C (0.01 mm); IR ($CHCl_3$) ν_{max} 3300, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6.6), 1.39 (s, 6 H), 1.50–2.20 (m, 4 H), 4.11 (s, 2 H), 4.69 (m, 1 H), 7.20–7.39 (m, 3 H), 7.70–7.90 (m, 1 H); MS, m/e 247 (M^+). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

Compound **16** was also prepared in 68% yield by the general transmetalation procedure except that the lithiation was effected in 3 h.

3-(1-Hydroxybutyl)-4-(methoxymethoxy)anisole (17). To a stirred ether solution (50 mL) of 4-(methoxymethoxy)benzene (500 mg, 2.97 mmol) at 0 °C under nitrogen was added *t*-BuLi (1.78 mL, 2 M in hexane, 3.26 mmol) by syringe injection. After 2.5 h, *n*-butyraldehyde (429 mg, 5.95 mmol) was added and the resulting solution was allowed to warm to room temperature overnight. Standard workup followed by column chromatography gave 272 mg (38%) of compound **17**, bp 82–86 °C (0.01 mm); IR ($CHCl_3$) 3400 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6.6), 1.20–1.90 (m, 4 H), 2.58 (br, 1 H, OH), 3.47 (s, 3 H), 3.75 (s, 3 H), 4.93 (m, 1 H), 5.12 (s, 2 H), 6.63–7.10 (m, 3 H); MS m/e 240 (M^+). Anal. ($C_{12}H_{18}O_3$) C, H.

Compound **17** was also prepared in 66% yield by the general transmetalation method.

Acknowledgment. A sample of triply sublimed magnesium was graciously provided, via the kind offices of Prof. A. I. Meyers (Colorado State University) and Dr. J. Little (Dow Chemical Co.), by Dr. J. Robinson (Dow Chemical Co., Midland, MI) 3 days before his retirement. We are grateful to the Natural Sciences and Engineering Research Council of Canada for sustained financial support of our research. A grant from the J. P. Bickell Foundation, crucial to the operation of our GC and HPLC equipment is gratefully acknowledged.

Registry No. **1a**, 1696-17-9; **1b**, 19312-06-2; **5**, 88440-77-1; **6**, 76041-86-6; **7a**, 72424-08-9; **7b**, 3453-64-3; **7c**, 88440-78-2; **7d**, 88440-79-3; **7e**, 88440-80-6; **7f**, 88440-81-7; **8b**, 51674-10-3; **8c**, 62924-93-0; **8d**, 72003-93-1; **8e**, 88440-82-8; **10a**, 88440-83-9; **10b**, 88440-84-0; **10c**, 88440-85-1; **10d**, 88440-86-2; **10e**, 88440-87-3; **11**, 3034-28-4; **12**, 88440-88-4; **13a**, 66122-70-1; **13b**, 17397-85-2; **13c**, 88440-89-5; **13d**, 87513-52-8; **13e**, 33883-14-6; **14**, 88440-90-8; **15**, 88440-91-9; **16**, 88440-92-0; **17**, 88440-93-1; 4-(methoxymethoxy)anisole, 25458-46-2; allyl bromide, 106-95-6; butyraldehyde, 123-72-8; acetaldehyde, 75-07-0; picolinaldehyde, 1121-60-4.

Supplementary Material Available: Table of combustion analyses for compounds **5**, **7c–f**, **8e**, **10a–e**, **12**, **16**, and **17** (1 page). Ordering information is given on any current masthead page.

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Ortho-Lithiated Tertiary Benzamides. Chain Extension via *o*-Toluamide Anion and General Synthesis of Isocoumarins Including Hydrangenol and Phyllodulcin

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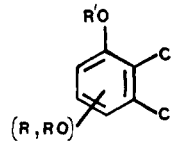
Lithiation of *N,N*-diethyl-2-methylbenzamide (**2a**) followed by condensation with aromatic aldehydes and basic hydrolysis leads to 3-aryl-3,4-dihydroisocoumarins **4** in modest overall yields. Adoption of this methodology to *N,N*-dimethyl-2-methyl-6-methoxybenzamide (**7b**) provides isocoumarins **9a** and **9b**, which by selective demethylation procedures yields hydrangenol (**10a**) and phyllodulcin (**10c**), naturally occurring isocoumarins of pharmacological interest. A one-pot, abbreviated procedure for the preparation of both **9a** and **9b** starting with *N,N*-dimethyl-2-methoxybenzamide (**6c**) is also described.

The regiospecific introduction of C_1 units at various oxidation states by the aromatic directed metalation protocol[2] allows subsequent chain extension and ring annelation to give systems that are not easily accessible by classical methodology. The strongly acidifying effect of certain Z groups promotes facile deprotonation of an *o*-methyl group to form benzylic anions that can undergo reaction with electrophiles in an overall chain extension process (Scheme I). Such processes have been demonstrated for a number of directed metalation groups,[2-4] but

(1) (a) Nagasaki University. (b) University of Waterloo.
(2) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(3) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853. Reviews: Kaiser, E. M.; Slocum, D. W. In "Organic Reactive Intermediates"; McManus, S. P., Ed.; Academic Press: New York, 1973; Chapter 5. Slocum, D. W.; Sugarman, D. I. *Adv. Chem. Ser.* **1974**, *130*, 222.

0022-3263/84/1949-0742$01.50/0

their exploitation in synthesis has been neglected.[4] Consideration of this tactic in the context of a 1,2-dicarbon–3-oxygen system (1) is useful in view of the large number

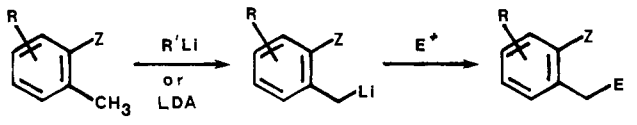


1

of derived natural products that incorporate this substitution pattern.[5]

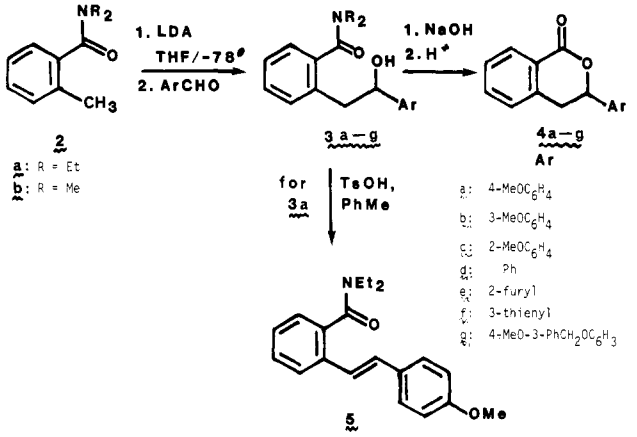
We illustrate the advantage of the combined directed and benzylic metalation strategy on tertiary benzamides[6] (Scheme I, Z = $CONR_2$) for the general synthesis of 3-aryl-3,4-dihydroisocoumarins 4[7–9] including the natural products hydrangenol (**10a**) (*Hydrangea opuloides* Stend

Scheme I



Z = $CONR_2$,[4a] CONHR,[4b] CSNHR,[4c] CO_2H,[4d] CO_2R,[4e] 2-oxazolino,[4f] CN,[4g] CH_2NR_2,[4h] SO_2NHR,[4i] NR_2,[4j] NHCOR,[4k] NC,[4l] OMe,[4m] $OCONR_2$,[4n] SMe,[4o]

Scheme II



Scheme III

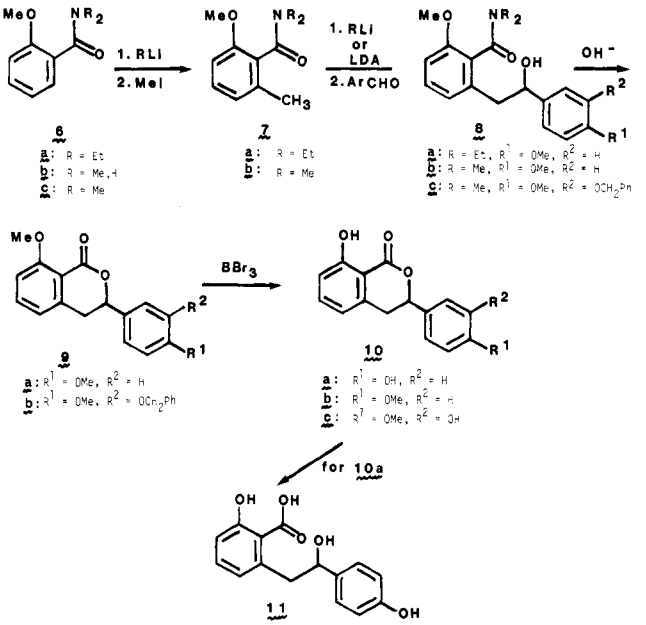


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Table I. Physical Properties of 3-Aryl-3,4-dihydroisocoumarins 4a-g and 9a-b

benzamide	ArCHO	isocoumarin[a]	yield,[b] %	mp, °C (solvent)
2a	p-$MeOC_6H_4CHO$	4a	65	109 (MeOH)[c]
2a	m-$MeOC_6H_4CHO$	4b	40	100 (MeOH)[d]
2a	o-$MeOC_6H_4CHO$	4c	45	139 (Et_2O)
2a	C_6H_5CHO	4d	30	90-91 (Et_2O)
2a	furan-2-CHO	4e	30	73 (Et_2O)
2a	thiophene-3-CHO	4f	30	77-78 (Et_2O)
2a	3-$PhCH_2O$-4-$MeOC_6H_3CHO$	4g	32	113 (Et_2O)
6c	p-$MeOC_6H_4CHO$	9a	35	153 (MeOH)[e]
6c	3-$PhCH_2O$-4-$MeOC_6H_3CHO$	9b	32	149-151 (MeOH)

[a] All new compounds show analytical data (C, H, N) in agreement (±0.3%) with expected molecular formula. [b] Yields correspond to recrystallized products. [c] mp not given by Creger, ref 4d. [d] lit.[4b] mp 95 °C. [e] lit.[27a] mp 151 °C.

var. *otakusa* Maxim) and phyllodulcin (**10c**) (*H. serrata* Seringe var. *thunbergii* Sugimoto).[10,11] The discovery that phyllodulcin is 400 times as sweet as sucrose[12,13] as well as the demonstration of antifungal and other pharmacological activity of hydrangenol, phyllodulcin, and related isocoumarins[13,14] has significantly stimulated structure–activity relationship[12,13] and synthetic[14] studies on these two natural products.

The general synthesis of 3-aryl-3,4-dihydroisocoumarin derivatives **4** is shown in Scheme II. Lithiation of *N,N*-diethyl-2-methylbenzamide (**2a**) with LDA in THF (or Et_2O) resulted in the formation of the corresponding benzylic anion as a burgundy red solution, which upon treatment with *p*-anisaldehyde led to rapid dissipation of color. Standard workup afforded the amide alcohol **3a** (65% yield),[15] which was not isolated but directly cyclized into the isocoumarin **4a** by base hydrolysis followed by acidification (quantitative yield). Attempts to use acid catalysis (TsOH in toluene) conditions, which are highly effective for the conversion of similar amide alcohols into phthalides,[16] for this cyclization led to the formation of the stilbene derivative **5** in 50% yield together with a small amount of the isocoumarin **4a** (TLC evidence). When the base hydrolysis procedure was used, however, a number of 3-aryl-3,4-dihydroisocoumarins were prepared in modest yields including two with heteroaromatic substituents at the 3-position (**4e** and **4f**) (Table I). Spectral and physical properties of these compounds are listed in Table II.

The synthesis of hydrangenol (**10a**, Scheme III) was initially modelled on the methodology established above. Thus lithiation of the *o*-toluamide **7a**, obtained in 88% yield by directed metalation and methylation of *N,N*-diethyl-2-methoxybenzamide followed by quenching with *p*-anisaldehyde yielded a mixture of the amide alcohol **8a** and starting amide **7a**, which could not be separated. Pure amide alcohol **8a** was obtained by condensation of lithiated *o*-toluamide **7a** with methyl *p*-methoxybenzoate followed by sodium borohydride reduction. Attempts to hydrolyze this compound under a number of basic conditions (e.g., aqueous 50% NaOH/EtOH, KOH/Me_2SO) led to recovery of starting material while acidic conditions (TsOH) resulted in the formation of a stilbene derivative analogous to **5** obtained from **3a** (see Experimental Section). The assumption that the additional methoxyl substituent in **8a** compared to **3** offered considerable hindrance to the formation of the tetrahedral intermediate required for hydrolysis was tested by decreasing the steric effect at the amide carbonyl function. That there exists a significant steric difference between diethyl and dimethyl amides to nucleophilic attack by RLi reagents had been previously recognized.[17] The requisite *N,N*-dimethyl-2-methyl-6-methoxybenzamide (**7b**) was prepared by dilithiation of the secondary amide **6b** or monolithiation of the tertiary amide **6c**[18] followed by treatment with methyl iodide. Since *N,N*-dimethylbenzamides suffer nucleophilic attack by *sec*-BuLi,[17] the latter result indicates that an *o*-methoxy group exerts sufficient hindrance to the trajectory of approach of the RLi reagent to the amide carbonyl, which may tend toward a perpendicular conformation with respect to the aromatic ring.[19] Further metalation of **7b** with LDA followed by treatment with *p*-anisaldehyde provided the amide alcohol **8b**, which, without isolation, was directly converted by basic hydrolysis into the isocoumarin **9a** in 35% overall yield. A one-pot, higher yield synthesis of **9a** was also devised as follows. Lithiation (*sec*-BuLi/−90 °C) of **6c** followed by sequential methylation, removal of excess methyl iodide (60 °C), lithiation (LDA/−60 °C), treatment with *p*-anisaldehyde, and basic hydrolysis afforded compound **9a** in 45% overall yield. This short synthesis of hydrangenol **10a** was concluded by BBr_3-mediated demethylation of **9a** in 94% yield. When $AlCl_3$ was used as the demethylating reagent, the phenol **10b** was isolated in 30% yield. Synthetic hydrangenol was shown to be identical by comparison of the spectral data with those of an authentic sample.[20] Since hydrangenol has been previously hydrogenolyzed to give lunularic acid (**11**), a growth inhibitor isolated from liverwort *Lunularia cruciata*,[21] this route also encompasses the synthesis of **11**.

The synthesis of phyllodulcin (**10c**) was achieved following the sequence of reactions described for the preparation of **10a**. Thus metalation of **7b** followed by condensation with *O*-benzylisovannilin furnished the amide

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(18) This result was first achieved in our laboratories by M. Iwao.

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(20) Kindly provided by Professor M. Yamato, Okayama University.

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alcohol **8c**, which, without purification, was hydrolyzed to give the isocoumarin **9b** in 32% overall yield. Adoption of the one-pot procedure used for the preparation of **9a** gave the same isocoumarin **9b** in 21% overall yield. When **9b** was treated with 2 equiv of BBr_3, selective demethylation and debenzylation occurred to provide phyllodulcin **10c** (45% yield) whose identity was established by comparison of spectral data with those of an authentic sample.[20]

Conclusions

A general synthesis of 3-aryl-3,4-dihydroisocoumarin derivatives **4a–g**, including the natural products hydrangenol (**10a**) and phyllodulcin (**10c**), has been developed by using benzamide directed ortho metalation strategy. In view of the powerful directing effect of the amide function,[6] this short and efficient route should be adaptable to the preparation of alkoxy-substituted isocoumarins that are difficult to prepare by classical routes.[8,22] Hydrangenol (**10a**) has been previously prepared in 6% yield,[14a] while phyllodulcin (**10c**) has been obtained in 14%,[14b] 0.5%,[14c] and 11%[14d] overall yields. The benzamide directed metalation approach yields hydrangenol and phyllodulcin in 42% and 14% overall yields, respectively, thus inviting the further use of this tactic for isocoumarin synthesis specifically and for regiospecific *o*-toluamide chain extension in general.

Experimental Section

General Methods (see ref 9). At Nagasaki, microanalyses were performed by using in-house facilities. IR spectra were determined on a JASCO IR-A2 spectrometer and UV spectra were run on a Hitachi 323 spectrophotometer. NMR spectra were obtained on JEOL FX 90Q and JNM-PMX 60 spectrometers using tetramethylsilane as internal standard. Mass spectra were run on a JEOL JMS-01SG spectrometer.

Benzamides. These compounds were prepared by using standard procedures, distilled, and stored in a dessicator. Amides showed IR, ^1H NMR, and analytical data consistent with the assigned structures.

***N,N*-Diethyl-2-methylbenzamide (2a)**: bp 91–94 °C (0.4 mm) [lit.[23] bp 118–120 °C (1.5 mm)].

***N,N*-Dimethyl-2-methylbenzamide (2b)**: bp 93 °C (0.9 mm) [lit.[24] bp 147 °C (18 mm)].

***N,N*-Diethyl-2-methoxybenzamide (6a)**: bp 109 °C (0.5 mm) [lit.[25] bp 169 °C (14 mm)].

***N*-Methyl-2-methoxybenzamide (6b)**: bp 104 °C (0.3 mm) [lit.[26] bp 148 °C (2 mm)].

***N,N*-Dimethyl-2-methoxybenzamide (6c)**: bp 100 °C (0.4 mm) [lit.[25] mp 74–75 °C].

***N,N*-Diethyl-2-methoxy-6-methylbenzamide (7a).** With use of the apparatus and operation described previously,[16] a stirred solution of **6a** (1.04 g, 5 mmol) and TMEDA (1.36 mL, 9 mmol) in anhydrous THF (60 mL) at −78 °C under nitrogen was treated with a solution of *sec*-BuLi (1.3 M in cyclohexane, 6.92 mL, 9 mmol) by the syringe injection technique. The resulting yellow solution was allowed to stir for 1 h at −78 °C, and dry methyl iodide (1 g, 7 mmol) was similarly injected. The cooling bath was removed and the solution was stirred for 8 h. Standard workup yielded an oil, which was distilled to give 0.97 g (88%) of **7a**: bp 99–100 °C (0.13 mm); IR (neat) ν_{max} 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7.1), 1.25 (t, 3 H, J = 7.1), 2.24 (s, 3 H), 3.11 (q, 2 H, J = 7.1), 3.49 (q, 2 H, J = 7.1), 3.78 (s, 3 H), 6.67–7.29 (m, 3 H); MS, m/e 221 (M^+). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

***N,N*-Dimethyl-2-methoxy-6-methylbenzamide (7b).** The procedure for the preparation of **7a** was adopted with the use of *N*-methyl-2-methoxybenzamide (**6b**), 2.4 equiv of *sec*-BuLi, 2.4 equiv of TMEDA, and 2 equiv of methyl iodide to give compound **7b**: 80% yield; bp 95–97 °C (0.1 mm); IR (neat) ν_{max} 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.80, 3.13 (2 × s, 6 H), 3.79 (s, 3 H); 6.68–7.43 (m, 3 H); MS, m/e 193 (M^+). Anal. ($C_{11}H_{15}NO_2$) C, H, N.

Compound **7b** was also prepared directly from **6c** as follows. As described above for the preparation of **7a**, a stirred solution of *sec*-BuLi (1.1 M in cyclohexane, 9.1 mL, 10.1 mmol) and TMEDA (1.5 mL, 10.1 mmol) in anhydrous THF (120 mL) at −78 °C under nitrogen was stirred for 10 min. The mixture was cooled to −90 °C and amide **6c** (1.52 g, 8.51 mmol) in THF (5 mL) was added. The solution was stirred for 15 min at −90 °C and dry methyl iodide (3.17 mL 50 mmol) was injected. The solution was then allowed to slowly warm to room temperature over several hours. Standard workup gave an oil, which was distilled to give 1.36 g (78%) of **7b**.

3-Aryl-3,4-dihydroisocoumarins 4a–g and 10a–c. The following procedures are representative for the preparation of compounds **4a–g** and **10a–c**. Physical and spectral data are collected in Table II.

Preparation of 3-(4-Methoxyphenyl)-3,4-dihydroisocoumarin (4a). To a solution of LDA (7.5 mmol) (prepared from a 1.4 M solution of *n*-BuLi in hexane, 5.4 mL, 7.5 mmol, and diisopropylamine, 1.05 mL, 7.5 mmol) in THF (60 mL) at −78 °C under nitrogen was added by syringe injection a solution of *N,N*-diethyl-2-methylbenzamide (**2a**) (0.96 g, 5 mmol) in THF (5 mL). After being stirred for 1 h, the burgundy red solution was treated with *p*-anisaldehyde (1.02 g, 7.5 mmol), the cooling bath was removed, and stirring was continued for 8 h. Standard workup gave 1.06 g (65%) of amide alcohol **3a**. Recrystallization gave an analytical sample of **3a**: mp 111 °C (EtOH); IR (KBr) ν_{max} 1610 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 228 (4.29), 2.78 (3.35), 2.85 (3.25); NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7), 1.21 (t, 3 H, J = 7), 2.90 (q, 2 H, J = 7), 3.08 (q, 2 H, J = 7), 3.48 (br s, 2 H), 3.70 (s, 3 H), 4.79 (br s, 1 H), 5.52 (br s, 1 H), 6.76–7.32 (m, 8 H); MS, m/e 327 (M^+). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

The above crude sample of **3a** was treated with a mixture of 50% aqueous NaOH (20 mL) and EtOH (20 mL) and the whole was refluxed for 8 h. The reaction mixture was evaporated to dryness, acidified with concentrated HCl at 0 °C, and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated to give 0.82 g (65% based on **2a**) of **4a**.

3-(4-Methoxyphenyl)-8-methoxy-3,4-dihydroisocoumarin (Hydrangenol Dimethyl Ether) (9a). To a stirred solution of LDA (8 mmol), prepared as above, in THF (60 mL) at −78 °C under nitrogen was slowly injected a solution of *N,N*-dimethyl-2-methyl-6-methoxybenzamide (**7b**) (0.77 g, 4 mmol) in THF (5 mL). The solution was stirred for 1 h and *p*-anisaldehyde (0.82 g, 6 mmol) in THF (5 mL) was injected. After being stirred for 4 h at −78 °C and a further 4 h at room temperature, the reaction mixture was processed in the standard manner to give 0.66 g (50%) of the amide alcohol **8b** as a viscous oil, which was subjected to hydrolysis in a mixture of 50% aqueous NaOH (20 mL) and EtOH (20 mL) at reflux for 8 h. Workup as for the preparation of **4a** yielded material that was chromatographed (acetone–benzene eluent, 1:5) to give 0.4 g (35% overall yield) of **9a**.

Phyllodulcin Benzyl Methyl Ether (9b). The procedure exactly as described above for the preparation of compound **9a** was used. From the condensation of compound **7b** (0.77 g, 4 mmol) with *O*-benzylisovanillin (1.45 g, 6 mmol) followed by basic hydrolysis there was obtained 0.5 g (32% overall yield) of product **9b**.

Preparation of Amide Alcohol 8a via the Corresponding Keto Amide. To a stirred solution of amide **7a** (1.54 g, 6.99 mmol) in THF (160 mL) at −78 °C was added a solution of *sec*-BuLi (1.13 M in cyclohexane, 6.5 mL, 7.3 mmol). The burgundy red solution was stirred at −78 °C for 20 min. A solution of methyl *p*-methoxybenzoate (872 mg, 5.25 mmol) in THF was slowly injected until the purple color disappeared. The clear yellow solution was stirred for 5 min, quenched with CH_3OH (0.5 mL), and allowed to warm to room temperature over 10 h. Standard workup followed by chromatography (hexane–EtOAc, 3:1) gave 1.22 g (49%) of **2-**

(22) The condensation of ortho-lithiated *secondary* benzamides with styrene oxides offers a complementary anionic route to isocoumarins.[8j] The analogous reaction of *tertiary* benzamides failed (Reed, J. N.; Snieckus, V., unpublished results).

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Table II. Spectral Data of 3-Aryl-3,4-dihydroisocoumarins 4a-g, 9a-b, and 10a-c

iso-coumarin	IR (KBr) ν_{max}, cm^{-1}	UV (EtOH) λ_{max}, nm (log ϵ)	NMR ($CDCl_3$),[a] δ	MS, *m/e* M^+ (formula)
4a	1700	230 (4.37), 276 (3.45), 282 (3.45)	3.08 (q, 1 H, J = 5, 17), 3.36 (q, 1 H, J = 11, 17), 3.84 (s, 3 H), 5.50 (q, 1 H, J = 5, 11), 6.92-8.24 (m, 8 H)	254 ($C_{16}H_{14}O_3$)
4b	1720	226 (s, 4.19), 283 (3.62)	2.85 (q, 1 H, J = 5, 17), 3.30 (q, 1 H, J = 10, 17), 3.70 (s, 3 H), 5.28 (q, 1 H, J = 5, 10), 6.67-8.07 (m, 8 H)	254 ($C_{16}H_{14}O_3$)
4c	1720	236 (4.00), 280 (3.61)	3.26 (d, 2 H, J = 7), 3.83 (s, 3 H), 5.20 (t, 1 H, J = 7), 6.73-7.90 (m, 8 H)	254 ($C_{16}H_{14}O_3$)
4d	1715	237 (4.38), 284 (3.15)	3.04 (q, 1 H, J = 5, 17), 3.36 (q, 1 H, J = 10, 17), 5.50 (q, 1 H, J = 5, 10), 7.06-8.20 (m, 9 H)	224 ($C_{15}H_{12}O_2$)
4e	1720	237 (4.87), 290 (4.26)	3.13 (q, 1 H, J = 5, 17), 3.56 (q, 1 H, J = 10, 17), 5.50 (q, 1 H, J = 5, 17), 6.33 (s, 2 H), 7.10-8.16 (m, 5 H)	214 ($C_{13}H_{10}O_3$)
4f	1720	238 (4.05), 284 (3.15)	3.08 (q, 1 H, J = 6, 19), 3.37 (q, 1 H, J = 8, 19), 5.53 (q, 1 H, J = 6, 8), 6.97-8.06 (m, 7 H)	230 ($C_{13}H_{10}O_2S$)
4g	1710	234 (4.30), 282 (3.66)	2.93 (q, 1 H, J = 4, 16), 3.27 (q, 1 H, J = 10, 16), 3.83 (s, 3 H), 5.08 (s, 2 H), 5.37 (q, 1 H, J = 4, 10), 6.70-8.13 (m, 12 H)	360 ($C_{23}H_{20}O_4$)
9a	1725	228 (s, 4.72), 284 (3.46), 310 (3.75)	2.93 (q, 1 H, J = 6, 15), 3.30 (q, 1 H, J = 10, 15), 3.80 (s, 3 H), 3.93 (s, 3 H), 5.33 (q, 1 H, J = 6, 10), 6.67-7.50 (m, 7 H)	284 ($C_{17}H_{16}O_4$)
9b	1723	232 (s, 4.20), 288 (3.70), 310 (3.78)	2.95 (q, 1 H, J = 5, 16), 3.18 (q, 1 H, J = 12, 16), 3.83 (s, 3 H), 3.90 (s, 3 H), 5.10 (s, 2 H), 5.27 (q, 1 H, J = 5, 12), 6.67-7.53 (m, 11 H)	390 ($C_{24}H_{22}O_5$)
10a	1660	248 (s, 3.89), 286 (3.40), 316 (3.70)	3.00 (q, 1 H, J = 5, 15), 3.37 (q, 1 H, J = 11, 15), 5.47 (q, 1 H, J = 5, 11), 6.43-7.53 (m, 7 H), 8.83 (br s, 1 H), 10.93 (s, 1 H)	256 ($C_{15}H_{12}O_4$)
10b	1710	230 (s), 252 (s), 284, 318	3.00 (q, 1 H, J = 6, 14), 3.32 (q, 1 H, J = 10, 14), 3.77 (s, 3 H), 5.50 (q, 1 H, J = 6, 10), 6.60-7.53 (m, 7 H), 10.87 (s, 1 H)	270 ($C_{16}H_{14}O_4$)
10c	1665	288 (3.63), 318 (3.71)	2.97 (q, 1 H, J = 6, 16), 3.28 (q, 1 H, J = 10, 16), 3.83 (s, 3 H), 5.42 (q, 1 H, J = 6, 10), 5.80 (br s, 1 H), 6.60-7.50 (m, 6 H), 10.90 (s, 1 H)	286 ($C_{16}H_{14}O_5$)

[a] Listed as chemical shifts (multiplicity, number of protons, coupling constant in hertz). Except as evident, compounds display the C-3,C-4 protons as clear ABX patterns consistent with the 3-aryl group adopting an equatorial orientation.

(diethylcarbamoyl)-3-methoxybenzyl 4-methoxyphenyl ketone as a colorless oil. Distillation gave an analytical sample, bp 207 °C (0.12 mm); IR (neat) ν_{max} 1673, 1605; NMR ($CDCl_3$) δ 0.92–1.14 (m, 6 H), 2.93–3.66 (m, 4 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 4.23 (d, 2 H), 6.77–8.07 (m, 7 H); MS, *m/e* 355 (M^+). Anal. ($C_{21}H_{25}NO_4$) C, H, N.

The purified keto amide (123 mg, 0.35 mmol) was dissolved in absolute ethanol (10 mL), sodium borohydride (60 mg) was added, and the mixture was stirred for 2 h. Water (4 mL) and aqueous 10% sodium hydroxide (1 mL) were added, and the mixture was heated on a steam bath for 5 min. Ethanol was removed by evaporation and the remainder was extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated to give an oily material, which was subjected to preparative TLC (EtOAc) to afford 123 mg (99%) of the amide alcohol **8a**: bp 155–160 °C (0.06 mm); IR (neat) ν_{max} 3325, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.89–1.36 (m, 6 H), 2.47–3.30 (m, 4 H), 3.39–3.78 (m, 2 H), 3.78 (s, 6 H), 4.57–5.4 (m, 1 H), 6.72–7.45 (m, 7 H); MS, *m/e* 356 ($M^+ - 1$). Anal. ($C_{21}H_{24}NO_4$) C, H, N.

One-Pot Procedures. Hydrangenol Dimethyl Ether (9a). A stirred solution of *sec*-BuLi (1.45 M in cyclohexane, 1.36 mL, 1.97 mmol) and TMEDA (0.3 mL, 1.97 mmol) in dry THF (50 mL) was prepared at −78 °C, cooled to −90 °C, and treated with amide **6c** (335 mg, 1.87 mmol) in THF (4 mL) by slow injection. The solution was stirred for 1 h at −90 °C, and dry methyl iodide (0.18 mL, 2.86 mmol) was injected. The solution was allowed to warm to room temperature over 2 h and then heated at 60 °C for 45 min in the presence of a continuous stream of dry nitrogen. The mixture was cooled to −60 °C and sequentially treated with freshly distilled diisopropylamine (0.43 mL, 3.1 mmol) and a solution of *sec*-BuLi (2.1 mL, 3.1 mmol). The resulting purple solution was stirred for 0.5 h and treated with *p*-anisaldehyde (420 mg, 3.1 mmol) in THF (2 mL), and the mixture was allowed to slowly warm to room temperature. Standard workup gave the amide alcohol **8b** as a viscous oil, which was hydrolyzed in a mixture of 50% aqueous NaOH (10 mL) and EtOH (10 mL) at reflux for 10 h and worked up as described for the preparation of **4a** except the reaction mixture was extracted with Et_2O prior to HCl acidification. Final extraction with CH_2Cl_2 gave a semisolid material, which was recrystallized from EtOAc–hexane to afford 246 mg (46%) of **9a**.

Phyllodulcin Benzyl Methyl Ether (9b). Following exactly the procedure described above for the one-pot preparation of **9a**, amide **6c** (390 mg, 2.18 mmol) was metalated (*sec*-BuLi) and methylated (MeI) at −90 °C. After removal of excess MeI, the reaction mixture was treated sequentially at −60 °C with diisopropylamine (0.50 mL, 3.49 mmol), *sec*-BuLi (2.4 mL, 3.49 mmol), and *O*-benzylisovanillin (844 mg, 3.49 mmol) in THF (2 mL). Standard workup, chromatography (hexane–EtOAc, 1:1), and recrystallization (hexane–EtOAc) gave 179 mg (21%) of **9b**, mp 120–121 °C (Waterloo), mp 148–149 °C (Nagasaki). These samples showed mp 147–148 °C and identical IR, NMR, and MS data and presumably differ in crystal form.

Hydrangenol (10a). To a stirred solution of hydrangenol dimethyl ether (**9a**) (180 mg, 0.63 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C was added dropwise boron tribromide (0.48 mL, 4.8

mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 1 h. The cooling bath was removed and stirring was continued for 12 h. The reaction mixture was washed successively with water and 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated to give 150 mg (94%) of hydrangenol (**10a**), mp 181–182 °C (PhH) [lit.[27] mp 181 °C], which was shown to be identical with an authentic sample by comparison of the spectral data (IR, NMR, MS) (Table II).[20]

3-(4-Methoxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin (10b). A mixture of hydrangenol dimethyl ether (**9a**) (0.1 g, 0.35 mmol) and aluminum chloride (0.1 g, 0.75 mmol) in nitrobenzene (5 mL) was heated at 80 °C for 1 h. The mixture was subjected to steam distillation to remove nitrobenzene and the residue was chromatographed ($CHCl_3$ eluent) to give material, which upon crystallization (MeOH) furnished 10 mg (30%) of **10b**, mp 120–123 °C (MeOH) [lit.[27] mp 122–123 °C].

Phyllodulcin (10c). A stirred solution of phyllodulcin benzyl methyl ether (**9b**) (200 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) at −78 °C was treated with a solution of BBr_3 (0.1 mL, 1 mmol) in CH_2Cl_2 (5 mL) by dropwise addition. The mixture was stirred for 1 h, and after removal of the cooling bath, stirring was continued for an additional 12 h. The mixture was processed as described for the preparation of **10a** to give 60 mg (45%) of phyllodulcin (**10c**), mp 128–130 °C (Et_2O–hexane) [lit.[14d] mp 130–132 °C] whose identity was established by spectral comparison (IR, NMR, MS) (Table II) with an authentic sample.[20]

2-(Diethylcarbamoyl)-4′-methoxystilbene (5). A solution of amide alcohol **3a** (1.06 g, 3.24 mmol) and *p*-toluenesulfonic acid (300 mg) in toluene (50 mL) was refluxed for 8 h. After washing with two portions of 5% aqueous $NaHCO_3$ solution, the organic layer was dried (Na_2SO_4) and evaporated to dryness to give 0.5 g (50%) of **5**: bp 206 °C (0.6 mm); IR (KBr) ν_{max} 1610 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 228 (3.97), 324 (3.84); NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz), 3.00 (q, 2 H, J = 7 Hz), 3.43 (q, 2 H, J = 7 Hz), 3.67 (s, 3 H), 6.47–7.60 (m, 10 H); MS, m/e 309 (M^+).

2-(Diethylcarbamoyl)-3,4′-dimethoxystilbene. Following the procedure described for the preparation of **5**, **8a** was converted into the title compound in 82% yield: bp 145–150 °C (0.02 mm); IR (neat) ν_{max} 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.1), 1.30 (t, 3 H, J = 7.1), 3.10 (q, 2 H, J = 7.1), 3.50 (q, 2 H, J = 7.1), 3.81 (s, 6 H, 2 × CH_3), 6.72–7.48 (m, 9 H); MS, m/e 339 (M^+). Anal. ($C_{21}H_{25}NO_3$) C, H, N.

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Registry No. **2a**, 2728-04-3; **3a**, 88430-92-6; **4a**, 37568-81-3; **4b**, 81428-86-6; **4c**, 85164-36-9; **4d**, 2674-44-4; **4e**, 88430-93-7; **4f**, 88430-94-8; **4g**, 88430-95-9; **5**, 88430-96-0; **6a**, 51674-10-3; **6b**, 3400-35-9; **6c**, 7291-34-1; **7a**, 88430-97-1; **7b**, 82780-48-1; **8a**, 88430-98-2; **9a**, 88430-99-3; **9b**, 88431-00-9; **10a**, 480-47-7; **10b**, 52213-49-7; **10c**, 480-46-6; 3-[phenyl(methyloxy)]-4-methoxybenzaldehyde, 6346-05-0; 2-(diethylcarbamoyl)-3-methoxybenzyl 4-methoxyphenyl ketone, 88431-01-0; 2-(diethylcarbamoyl)-3,4-dimethoxystilbene, 88431-02-1; furfural, 98-01-1; 3-formylthiophene, 498-62-4; methyl *p*-methoxybenzoate, 121-98-2; *p*-$MeOC_6H_4CHO$, 123-11-5; *m*-$MeOC_6H_4CHO$, 591-31-1; *o*-$MeOC_6H_4CHO$, 135-02-4; C_6H_5CHO, 100-52-7.

Supplementary Material Available: Table of combustion analyses for compounds **7a**, **7b**, **3a**, **4a–g**, **9a**, **9b**, and **3b** (1 page). Ordering information is given on any current masthead page.

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Synthetic Studies on Cembranolides. Stereoselective Synthesis of Epoxy Ester Intermediates

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A stereorational synthesis of the epimeric epoxy esters **17** and **21** from methacrolein is described. The route employs two key stereodirected steps. The first, copper-catalyzed addition of vinylmagnesium bromide to conjugated lactone **7**, gives the trans product **8**. The second, iodolactonization of the derived diesters **11** or **12**, leads to the trans lactones **16b** or **16c**. Basic methanolysis then gives the epoxides **17b** or **17c**. The latter is converted to the epimeric epoxy ester **21** via selective saponification, treatment with acid, mesylation, and basic methanolysis. Additions of isopropenylcopper reagents to epoxy esters **17a–d** and a model epoxy ester **22** were examined with a view toward a proposed cembranolide synthetic plan.

We recently formulated a synthetic plan for cembranolide natural products that entails coupling of two complex synthons, a "diene piece" II and a "lactone piece" III (Scheme I).[1] The lactone piece was prepared with 4-cycloheptenone as the starting material.[1] However, all attempts to couple the monotosylate derivative IV with various organocopper reagents were unsuccessful.[2] Under forcing conditions with HMPA as cosolvent, an interesting rearrangement took place leading to epoxy lactone V, but still no coupling product could be detected.[2]

While we were unable to isolate any other products that might provide a clue for the apparent failure of such coupling experiments, we felt that at least part of the problem might be ascribed to the multiple oxygen sites present in tosylate IV and epoxide V that could coordinate with and deactivate the organocopper reagents. We also found it difficult to produce large quantities of lactone diol III, owing to the inefficient and capricious preparation of 4-cycloheptenone.[3] We therefore decided to modify our

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