Reaction of Benzocyclobutenoxides with Aldehydes: Synthesis of Peshawarine and Other 3,4-Dihydroisocoumarins

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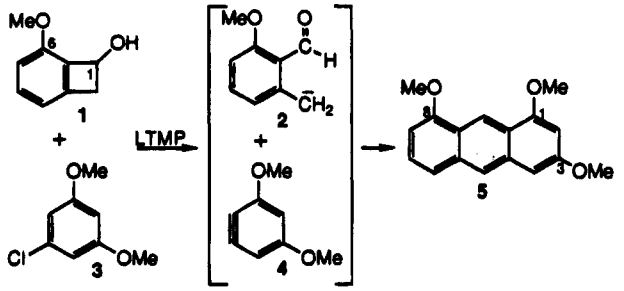
Deprotonation of benzocyclobutenols **6** in the presence of aromatic aldehydes affords benzopyranols **7** in high yield. In the key step of this process, an *o*-tolualdehyde anion generated by the known ring-opening of benzocyclobutenoxides adds to the aldehyde to give **7** which is easily oxidized to 3-substituted 3,4-dihydroisocoumarins **8** including intermediates in some natural product syntheses. For example, reaction of 6-methoxybenzocyclobutenol (**1**) with LTMP and *p*-anisaldehyde gave in 96% yield the benzopyranol **16**, which subsequently was converted to (±)-hydrangenol (**17**). Similar treatment of **1** with LDA and isovanillin benzyl ether afforded the benzopyranol **19** (87% yield) which already has been converted to (±)-phyllodulcin (**21**). Finally, reaction of 5,6-(methylenedioxy)-benzocyclobutenol (**10**) with LTMP and the aldehyde **26** (from treatment of hydrastinine with $ClCO_2$-Me) followed by methanolysis produced the acetal **28** in 96% yield. The overall yield was 65% for the five-step synthesis of the alkaloid (±)-peshawawine (**24**) from **10** and **26**. Extension of the process to aliphatic aldehydes was illustrated by the preparation of **32** from benzocyclobutenol and isobutyraldehyde in 69% overall yield after oxidation with PCC.

Recently, we reported a facile synthesis of unsymmetrical anthracenes by the simultaneous treatment of benzocyclobutenols and halobenzenes with lithium 2,2,6,6-tetramethylpiperidide (LTMP).[1] The method is illustrated by the reaction of 6-methoxybenzocyclobutenol (**1**) and 5-chloro-1,3-dimethoxybenzene (**3**) with LTMP to regiospecifically produce the trimethoxyanthracene (**5**) in 48% yield. In this process, the intermediate benzocyclobutenoxide ring opens to the *o*-tolualdehyde anion **2** which then adds to the benzyne **4** generated from **3**.



Keys to the success of this scheme include the very low addition reactivity of LTMP toward benzynes[2] and the ability to generate **2** in the absence of its conjugate acid so aldehyde–enolate condensations do not complicate the process. Also, benzocyclobutenols are now readily available by methodology developed by Stevens[3] and improved by Liebeskind.[4] For example, **1** is made regiospecifically by dehydrohalogenation of *o*- or *m*-chloroanisole with $NaNH_2$ in the presence of ketene diethyl acetal followed by *in situ* acid hydrolysis of the diethoxybenzocyclobutene and then high-yield reduction of the product ketone with $NaBH_4$.[1,4]

The classic precedent for the ring scission, **1** → **2**, was the isolation in 1960 of *o*-tolualdehyde from treatment of benzocyclobutenol with base by Cava and Muth.[5] Similar ring openings were described by Caubere[6] and Fleming[7] as part of more complex processes. More recently, Choy and Yang[8] reported that some ring cleavages occur below 0 °C and trapped the tolualdehyde anions with maleic and fumaric esters (the analogous thermal opening of benzocyclobutenol only occurs above 100 °C[9]).

In this paper, benzocyclobutenols **6** again are used as surrogates for *o*-tolualdehyde anions, and the addition of these intermediates to aldehydes is utilized as the basis for a new route to 3,4-dihydroisocoumarins **8**. Many synthetic efforts have targeted **8** because naturally occurring 3,4-dihydroisocoumarins range in biological activity from sweetening agents to bactericides.[10] Treatment of **6** with an appropriate base in the presence of a benzaldehyde should give the benzopyranol **7** which on oxidation would yield **8**. Because an equilibrating proton source is absent, these mixed aldol condensations should proceed cleanly. If the addition step is rapid, the reaction might even be extended to aldehydes with enolizable α-hydrogens.

The first tests of the transformation were successful. When a mixture of **9**[11] and piperonal (**11**) was added to LTMP in THF at −78 °C, the benzopyranol **12** was obtained in 98% yield after the mixture was warmed to

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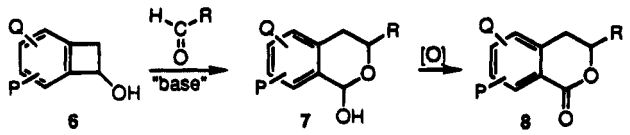
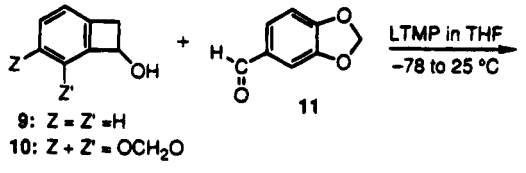
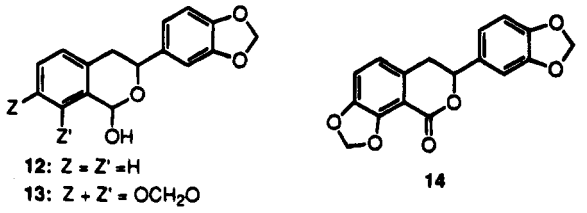


rt. The yield of **12** still was 95% with *t*BuOK as the base. In an attempt to make **12** by a thermal ring opening and cycloaddition, a mixture of **9** and **11** in toluene was refluxed for 5 h, the conditions Sammes[9] had used to obtain Diels–Alder adducts with standard dienophiles.

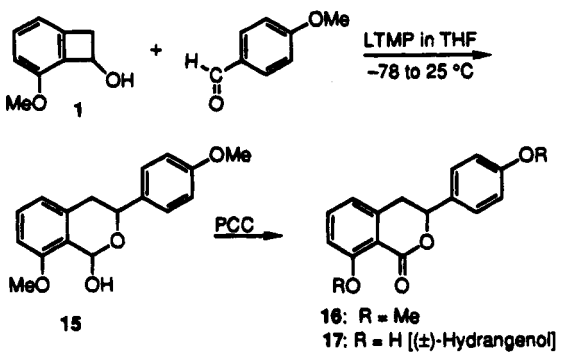




Almost all of **9** was converted to *o*-tolualdehyde and decomposition products. Only 10% of **12** was found, and almost all the piperonal remained. In the next experiment, a mixture of the benzocyclobutenol **10**[1] and **11** was added to LTMP in THF. After a standard extraction workup, the benzopyranol **13** was isolated in 95% yield. Curiously, with *t*BuOK as the base, **10** decomposed to a tar in this reaction. Oxidation of **13** with Jones reagent[12] afforded the peshawarine model **14** (*vide infra*) in 79% yield.

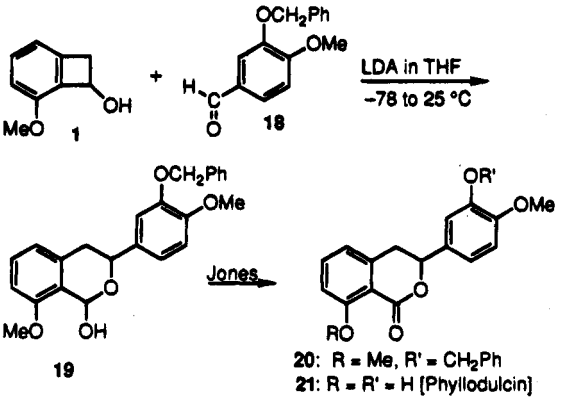
Hydrangenol (**17**),[13] a mild antimicrobial agent isolated from *Hydrangea serrata* Seringe *var. thunbergii* (Japanese name Amacha), was the first natural product target chosen to illustrate the value of the new process. When a mixture of **1** and *p*-anisaldehyde was treated with LTMP, the benzopyranol **15** was isolated in 96% yield. Oxidation of **15** with PCC gave the known hydrangenol dimethyl ether (**16**[14]) in 77% yield. *O*-Demethylation of **16** with BBr_3 by the literature process[14] afforded (±)-**17** in 83% yield (natural **17** also racemic[15]).

A natural analog of **17** is lunularic acid,[16] a potent inhibitor of rice seed germination which also exhibits antiallergic, antifungal, antihyaluroniase, and piscicidal activity.[17] It has been made from **17** by Asakawa[17] in 99% yield by reductive ring-opening at the benzylic



carbon. Thus, the present route to **17** also constitutes a formal synthesis of lunularic acid.

Phyllodulcin[13,14] (**21**), the sweet principal of the Japanese herbal tea, Amacha, is 400 times sweeter than sucrose and thus of interest as a dietary sweetener lead.[18] When **1** and isovanillin benzyl ether (**18**[19]) were treated with LDA, the benzopyranol **19** was obtained in 87% yield. Subsequent Jones oxidation of **19** gave **20**[14] (85% yield) which already has been converted to (±)-**21** in 45% yield by selective *O*-dealkylation with BBr_3.[14]



Hydrangenol dimethyl ether (**16**) and phyllodulcin benzyl methyl ether (**20**) previously have been made by several routes.[15] Among published syntheses, the two most recent are the most efficient.[14,20] In one of these schemes, Watanabe and Snieckus *et al.*[14] reported that homologation of the lithiated *o*-toluamides **22** with the appropriate aldehydes followed by base hydrolysis and lactonization gave **16** and **20** in 35% and 32% yields, respectively. In the other route, Kessar[20] desilylated the benzylsilane **23** with CsF in the presence of the required aldehydes to obtain **16** and **20** in 50% and 53% yields. Both schemes have the advantage of producing **16** and **20** in the lactone oxidation state directly. However, the reactants **22**, and, certainly, **23** are more difficult to make than the benzocyclobutenol **1**. Also, the processes used to obtain **22** and **23** are not easily adapted to the formation of the reactant required for a synthesis of peshawarine, our next synthetic target. Finally, our overall yields in the conversion of **1** to **16** (74%) and **20** (74%) compare well with the yields from **22** and **23**.

(−)-Peshawarine[21] (**24**) was isolated by Shamma in 1976 from *Hypecoum parviflorum* Kar., & Kir. (Papav-

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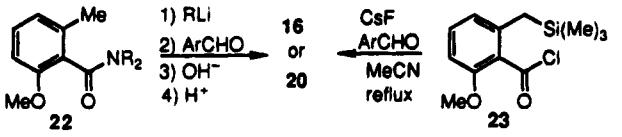

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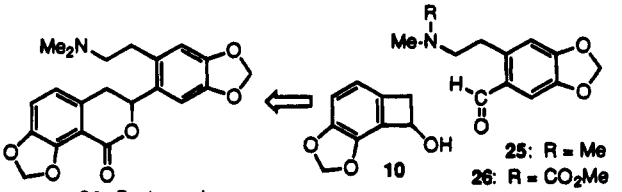
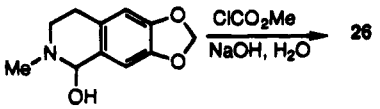
eraceae), a plant native to Northern Pakistan. He also determined the structure of **24**, the first member of the secoberbine class of isoquinoline alkaloids.[12,21] The two reactants required for a synthesis of (±)-**24** by the route introduced here would be the benzocyclobutenol **10** and a protected version of the aminoaldehyde **25**.



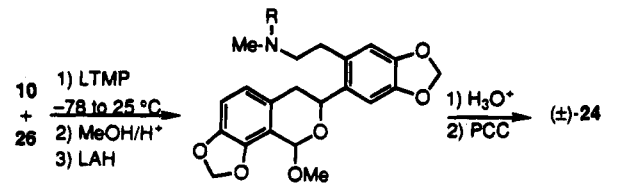
24: Peshawarine

To play the role of **25**, the carbomethoxy derivative **26** was chosen because it could be reduced to the *N*-methyl when desired.[12] Also, **26** already was known from treatment of hydrastinine (**27**) with methyl chloroformate.[22] Hydrastinine was made by oxidation of commercial hydrastine with nitric acid[23] in 85% yield and then converted to **26** in 92% yield.



27: (±)-Hydrastinine

When a mixture of **10** and **26** was reacted with LTMP followed by treatment of the intermediate benzopyranol with methanolic acid containing $HC(OMe)_3$, the acetal **28** was obtained in 96% yield. Significantly, *t*BuOK failed as the base. Next, reduction of the urethane **28** with LAH afforded the *N,N*-dimethylamino product **29** in 88% yield. Racemic **29** already had been prepared by Shamma[12] who kindly made its ^1H NMR spectrum available to us. The ^1H NMR spectra and mp's of the two products were identical.

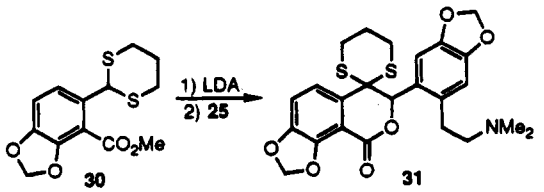


28: R = CO_2Me
29: R = Me

Shamma had made **29** from **24** and also had converted **29** to (±)-**24** by hydrolysis of the acetal followed by oxidation with PCC.[12] In our hands, this hydrolysis–oxidation was accomplished in 77% yield (82% by Shamma[12]), and again the mp's and ^1H NMR spectra of his product and ours were identical. In summary, the synthesis of (±)-**24** from **10** and **26** by the present five-step sequence has been achieved in an excellent overall yield of 65%.

(22) Rozwadowska, M. D. *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **1971**, *19*, 673.
(23) Gear, J. R.; Spenser, I. D. *Can. J. Chem.* **1963**, *41*, 783.

Three other syntheses of (±)-**24** have been published. The oldest route is Shamma's conversion of the alkaloid, coptisine iodide, to (±)-**24** (28% yield), used as part of his structure proof for the latter.[12] In 1977, Santavy and co-workers[24] used a similar sequence to prepare (±)-**24** from (+)-rhoeadine in 17% yield. The only previous synthesis from simple, commercially available compounds is that of Chrzanowska and Rozwadowska.[25] In their key step, they treated the dithiane **30** with LDA and then added the amino aldehyde **25** to obtain the cyclized product **31** in 86% yield. Production of **31** from piperonal (**11**) required four steps (50% overall yield[25,26]) while **25** was made in three steps from hydrastinine (**27**) in 64% yield.[22] Unfortunately, their final step, the reductive desulfurization of **31** to give (±)-**24**, was very poor. The major product was either partially desulfurized material or the over-reduction product carboxylic acid from hydrogenolysis at the benzylic carbon of the lactone. Under optimum conditions, the best yield of (±)-**24** in this last step was only 26%.[25]



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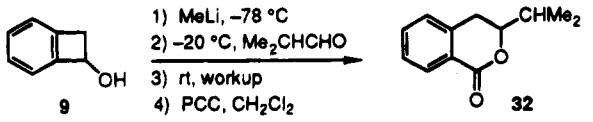

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Another model study relevant to the scope and limitations of our process was performed. In these tests, the precursor isobutyraldehyde is enolizable so enolate formation and aldol condensations would be expected reaction complications. And indeed, when **9** was treated with LTMP or with KH at −78 °C followed by addition of aldehyde at temperatures up to −15 °C, no cyclized product was found. When *t*BuOK was added to a mixture of **9** and aldehyde at 0 °C (then oxidation with PCC), some cyclized products were present in a complex mixture. However, when **9** was treated with 1.2 equiv of ethereal MeLi at −78 °C and the solution warmed, the color became deep red at *ca.* −20 °C. At this point, the color was discharged by adding a little isobutyraldehyde, and the process was repeated several times as the color reappeared (slow addition was used to reduce complications from self-condensation of the aldehyde). Finally, excess aldehyde was added to the clear solution. After workup, the crude benzopyranol was oxidized to the isopropyl product **32**[27] (69% overall yield). Thus, although the reaction with aliphatic aldehydes is very sensitive to conditions,[28] the extension of this work to the

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(28) Because of this great variation in ring-opening rates, these conditions were not used with ArCHO. Since MeLi adds to ArCHO, LTMP was used with mixtures of **6** and ArCHO.

preparation of important natural 3-alkyl-3,4-dihydroisocoumarins seems achievable.[29]

Experimental Section

General.[30] Melting points are uncorrected. Reactions were performed in dried, distilled THF under anhydrous N_2. The benzocyclobutenols **1**, **9**, and **10** were prepared as outlined in ref 1. The LTMP was made *in situ* by dripping MeLi (1.4 M in ether) into HTMP in THF at rt slowly enough to permit methane evolution at a convenient rate.

3-(3′,4′-(Methylenedioxy)phenyl)-1-hydroxyisochroman (12). A solution of **9** (0.500 g, 3.8 mmol) and piperonal (**11**) (0.571 g, 3.8 mmol) in THF (5 mL) was dripped into LTMP (4.0 mmol) in THF (5 mL) at −78 °C. After 5 min, the mixture was warmed to rt, stirred for 1 h, and then poured into 10% aqueous HCl (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The dried ($MgSO_4$) organic extracts were concentrated to obtain **12** as a white solid crystallized from EtOAc: mp 212−213 °C, 0.952 g (98% yield); ^{1}H NMR ($CDCl_3$) δ 7.3−6.9 (m, 7 H), 6.33 (s, 1 H), 6.01 (s, 2 H), 5.26 (dd, 1 H, J = 11.2, 3.61 Hz), 3.1−2.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.2, 135.7, 134.2, 133.4, 128.3, 128.2, 127.2, 126.5, 119.6, 108.3, 106.9, 101.1, 94.3, 69.6, 35.9.[31]

3-(3′,4′-(Methylenedioxy)phenyl)-1-hydroxy-7,8-(methylenedioxy)isochroman (13). A solution of **10** (0.443 g, 2.70 mmol) and **11** (0.405 g, 2.70 mmol) in THF (5 mL) was added to LTMP (2.80 mmol) in THF (5 mL) at −78 °C. The mixture was warmed to rt, stirred for another 45 min, and then subjected to the extraction workup above to obtain **13** as a white solid of mp 151−155 °C dec after crystallization from EtOAc, 0.805 g (95% yield): ^{1}H NMR ($CDCl_3$) δ 7.0−6.7 (m, 5 H), 6.28 (s, 1 H), 6.07 (d, J = 1.3 Hz, 1 H), 5.97 (d, J = 1.3 Hz, 1 H), 5.96 (s, 2 H), 5.15 (dd, 1 H, J = 10.4, 4.6 Hz), 3.1−2.7 (m, 2 H).

3-(3′,4′-(Methylenedioxy)phenyl)-7,8-(methylenedioxy)isochroman-1-one (14). Using Shamma's[12] process for a related reaction, the isochroman **13** (0.200 g, 0.64 mmol) in acetone (1 mL) was stirred with Jones reagent (0.5 mL) [from H_2SO_4 (0.25 mL), CrO_3 (0.27 g), and water (1 mL)] at rt for 30 min. The black solution was extracted with aqueous 10% NaOH (10 mL), filtered through Celite, concentrated, and chromatographed (50% EtOAc/hexane) to obtain **14**: mp 193−195 °C, 0.158 g (79% yield); ^{1}H NMR ($CDCl_3$) δ 7.0−6.7 (m, 5 H), 6.14 (dd, 2 H, J = 10.2, 1.0 Hz), 5.97 (s, 2 H), 5.39 (dd, 1 H, J = 11.6, 3.4 Hz), 3.2−3.0 (m, 2 H).

3-(4′-Methoxyphenyl)-1-hydroxy-8-methoxyisochroman (15). A solution of **1** (0.403 g, 2.70 mmol) and *p*-anisaldehyde (0.368 g, 2.70 mmol) in THF (3 mL) was dripped into LTMP (2.79 mmol) in THF (5 mL) over 5 min at −78 °C and then stirred overnight at rt. Standard extraction workup followed by chromatography (50% EtOAc/hexane) afforded **15** as a yellow oil: 0.741 g (96% yield); ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (m, 3 H), 7.0−6.7 (m, 4 H), 6.27 (s, 1 H), 5.27 (dd, 1 H, J = 11.0, 4.1 Hz), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.1−2.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 156.8, 136.1, 135.1, 129.0, 126.7, 122.4, 120.6, 113.6, 108.3, 89.4, 67.2, 55.3, 55.0, 35.1.

3-(4′-Methoxyphenyl)-8-methoxyisochroman-1-one ((±)-Hydrangenol Dimethyl Ether) (16). The isochroman **15** (0.169 g, 0.59 mmol) in CH_2Cl_2 (5 mL) was stirred with PCC (0.220 g, 1.03 mmol) at rt. After 12 h, the black solution was diluted with ether (100 mL), washed with 4 M NaOH (3 × 40 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated to a white solid which was triturated with hexane to isolate **16**: mp 152−153 °C from EtOAc (lit.[14] mp 151 °C), 0.129 g (77% yield); ^{1}H NMR ($CDCl_3$) δ 7.55−7.3 (m, 3 H), 7.0−6.8 (m, 4 H), 5.35 (dd, 1 H, J = 12.0, 2.5 Hz), 3.95 (s, 3 H), 3.78 (s, 3 H), 3.35−2.80 (m, 2 H)

(±)-Hydrangenol (17). Following Watanabe's[14] procedure, BBr_3 (1 M in CH_2Cl_2, 5.0 mL, 5.0 mmol) was dripped into **16** (0.392 g, 1.4 mmol) in CH_2Cl_2 (3 mL) at −78 °C which then was warmed to rt. After 3 h, the mixture was concentrated *in vacuo* and the residue dissolved in 10% NaOH. This was washed with ether and then acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 5 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated, and the residue was chromatographed (50% EtOAc/hexane) to obtain (±)-**17** as a yellow solid: mp 179−180 °C (lit.[14] 181−182 °C), 0.298 g (83% yield); ^{1}H NMR (acetone-d_6) δ 10.56 (s, 1 H), 8.54 (s, 1 H), 7.5−7.35 (m, 3 H), 6.9−6.8 (m, 4 H), 5.63 (dd, 1 H, J = 12.0, 3.4 Hz), 3.45−3.1 (m, 2 H); ^{1}H NMR ($CDCl_3$) δ 11.0 (s, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.33 (d, J = 8.6 Hz, 2 H), 6.90 (m, 3 H), 6.74 (d, J = 8.6 Hz, 1 H), 5.54 (dd, 1 H, J = 12.2, 3.4 Hz), 5.05 (br s, 1 H), 3.25 (dd, 1 H, J = 16.0, 12.2 Hz), 3.02 (dd, 1 H, J = 16.0, 3.4 Hz).

3-(3′-(Benzyloxy)-4′-methoxyphenyl)-1-hydroxy-8-methoxyisochroman (19). A mixture of **1** (0.250 g, 1.67 mmol) and isovanillin benzyl ether (**18**[19]) (0.401 g, 1.66 mmol) in THF (3 mL) was dripped into a solution of LDA (1.70 mmol in THF (3 mL) at −78 °C over 5 min. The solution was warmed to rt, stirred for 12 h, and then poured into aqueous HCl (10%, 15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The dried (Na_2SO_4) organic extract was concentrated to obtain **19** as an oily solid: 0.540 g (83% yield); ^{1}H NMR ($CDCl_3$) δ 7.5−6.7 (m, 11 H), 6.28 (s, 1 H), 5.23 (dd, 1 H, J = 10.8, 4.3 Hz), 5.15 (s, 2 H), 4.50 (s, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.02−2.72 (m, 2 H).

3-(3′-(Benzyloxy)-4′-methoxyphenyl)-8-methoxyisochroman-1-one. ((±)-Phyllodulcin Benzyl Methyl Ether) (20). The isochroman **19** (0.130 g, 0.33 mmol) in acetone (3 mL) was stirred with Jones reagent (0.5 mL) for 1 h. Extraction workup followed by chromatography (50% EtOAc/hexane) gave **20** as a white solid: mp 148−150 °C after crystallization from MeOH (lit.[14] mp 149−151 °C), 0.109 g (85% yield); ^{1}H NMR ($CDCl_3$) δ 7.5−7.3 (m, 6 H), 7.1−6.8 (m, 5 H), 5.31 (dd, 1 H, J = 11.8, 3 Hz), 5.16 (s, 2 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.3−2.9 (m, 2 H).

3-(2′-(β-(*N*-(Methoxycarbonyl)-*N*-methylamino)-ethyl)-4′,5′-(methylenedioxy)phenyl)-1-methoxy-7,8-(methylenedioxy)isochroman (28). A mixture of **10** (0.181 g, 1.1 mmol) and **26** (from hydrastinine (**27**)[23] and $ClCO_2Me$[22]) (0.300 g, 1.1 mmol) in THF (5 mL) was dripped into LTMP (1.1 mmol, 5 mL THF) at −78 °C over 5 min. After the mixture was warmed to rt, stirring was continued for 2 h and the mixture then was poured into cold aqueous 10% HCl (15 mL), extracted with CH_2Cl_2

(29) An early challenge would be AI-77-B, a potent gastroprotective from *Bacillus pumils*. For a recent synthesis and references to earlier routes, see: Ward, R. A.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3359.

(30) For apparatuses used in physical and spectral measurments and procedures used in solvent−reagent purification see: Dang, V. A.; Olofson, R. A.; Wolf, P. R.; Piteau, M. D.; Senet, J.-P. G. *J. Org. Chem.* **1990**, *55*, 1847.

(31) On the basis of the ^{1}H and ^{13}C NMR data for **12** as well as **13**, **15**, **19**, **28**, and **29**, only one of the two possible diastereomeric products was found, presumably a result of thermodynamic control. No evidence permitting a stereochemical assignment was obtained.

(3 × 15 mL), dried (Na_2SO_4), and concentrated to an oily solid. This was added to trimethyl orthoformate (3 mL) in MeOH (20 mL) containing 1 drop of concd H_2SO_4 and stirred for 5 h. The precipitated white solid was filtered off and crystallized from MeOH: mp 155–156 °C dec, 0.480 g (96% yield, two steps); ^{1}H NMR ($CDCl_3$) δ 7.06 (s, 1 H), 6.77 (d, J = 8.0 Hz, 1 H), 6.65 (s, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.08 (d, J = 1.4 Hz, 1 H), 5.94 (m, 3 H), 5.72 (s, 1 H), 5.31 (d, J = 10.0 Hz, 1 H), 3.7–3.3 (m, 9 H), 3.0–2.8 (m, 8 H).

3-(2′-(β-(*N*,*N*-Dimethylamino)ethyl)-4′,5′-(methylenedioxy)phenyl)-1-methoxy-7,8-(methylenedioxy)-isochroman (29). Shamma's[12] general procedure was followed. Powdered LAH (0.03 g, 0.8 mmol) was added to stirred **28** (0.100 g, 0.23 mmol) in dry THF (10 mL). After 1 h, the mixture was carefully poured into cold aqueous saturated Na_2SO_4 (10 mL). The mixture was extracted with ether (3 × 5 mL), dried (Na_2SO_4), and concentrated, and **29** was crystallized from CCl_4 as white crystals: mp 195–197 °C (lit.[12] mp 197 °C), 80 mg (88% yield); ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 1 H), 6.76 (d, J = 8.0 Hz, 1 H), 6.69 (s, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.08 (d, J = 1.5 Hz, 1 H), 5.96 (d, J = 1.5 Hz, 1 H), 5.94 (dd, 2 H, J = 2.8, 1.4 Hz), 5.71 (s, 1 H), 5.27 (dd, 1 H, J = 11.2, 3.4 Hz), 3.55 (s, 3 H), 3.0–2.4 (m, 6 H), 2.27 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 147.2, 146.5, 146.1, 144.7, 132.9, 130.8, 128.1, 120.7, 116.2, 109.6, 108.7, 106.9, 101.6, 101.0, 95.8, 65.9, 61.5, 55.7, 45.3, 35.2, 30.6.

(±)-Peshawarine (24). Using Shamma's[12] procedure, a mixture of **29** (0.200 g, 0.50 mmol), aqueous 5% HCl (10 mL), and 1,4-dioxane (10 mL) was stirred at rt for 2 h and then made basic with aqueous NaOH (20%) and extracted with CH_2Cl_2 (3 × 15 mL). The extracts were dried (K_2CO_3) and concentrated to a white solid which was dissolved in $CHCl_3$ (10 mL) and stirred with PCC (70 mg) for 30 min. The mixture was washed with aqueous NaOH (10 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed (3:1 $CHCl_3$/MeOH) and crystallized from MeOH to give (±)-**24** as white crystals: mp 179–181 °C (lit.[12] mp 181 °C), 0.151 g (77% yield); ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1 H), 6.97 (d, J = 8.5 Hz, 1 H), 6.72 (s, 1 H), 6.71 (d, J = 8.5 Hz, 1 H), 6.17 (dd, 2 H, J = 10.5, 1.0 Hz), 5.95 (s, 2 H), 5.65 (dd, 1 H, J = 12.0, 3.1 Hz), 3.30 (dd, 1 H, J = 16.0, 12.0 Hz), 3.2–2.7 (m, 5 H), 2.39 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 162.7, 149.6, 148.3, 147.8, 146.5, 131.7, 129.4, 119.5, 112.8, 109.8, 108.2, 106.9, 65.8, 61.2, 45.2, 35.1, 30.9 (^{1}H NMR and MS in accord with original spectra of Shamma).

3-Isopropylisochroman-1-one (32). MeLi (2.90 mL, 1.4 M in ether, 4.06 mmol) was dripped (7 min) into stirred benzocyclobutenol (**9**) (0.415 g, 3.45 mmol) in THF (10 mL) at −78 °C (clear solution). After *ca.* 10 min, the mixture was allowed to warm to −20 °C (ice–methanol), and the resulting red solution was titrated (*ca.* 15 min, color dissipated as each portion of aldehyde was added and then red color was allowed to reform before adding next portion) with isobutyraldehyde (Fluka, stored over $CaSO_4$ and fractionally distilled) (0.460 g, 6.38 mmol) in THF (10 mL) until colorless. The remaining isobutyraldehyde was added, and the mixture was warmed to rt, stirred for 10 min, and then poured into 1 M aqueous HCl (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The dried ($MgSO_4$) extracts were concentrated to a colorless oil, dissolved in CH_2Cl_2 (10 mL), and then stirred with PCC (Aldrich, 1.51 g, 7.01 mmol) at rt. After 16 h, the black mixture was diluted with ether (60 mL), filtered through a bed of Celite, and concentrated to a dark oil. Chromatography (25% EtOAc/hexane) gave **32** as a white solid: mp 31–32 °C (lit.[27] no mp data given), 0.455 g (69% yield); ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1 H, J = 7.7 Hz), 7.6–7.2 (m, 3 H), 4.35–4.15 (m, 1 H), 3.1–2.7 (m, 2 H), 2.25–1.9 (m, 1 H), 1.06 (app t, 6 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.4, 139.1, 133.3, 129.7, 127.3, 127.2, 124.9, 83.1, 31.8, 29.8, 17.7, 17.6.

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Supplementary Material Available: Additional spectral (*e.g.*, IR, MS, and HRMS) data, copies of ^{1}H and ^{13}C NMR spectra of new compounds, and details on other experiments noted in the Discussion (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.