Stereoselective Synthesis of Dimethylrobustadials

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A stereoselective synthesis of the methyl ethers of robustadials A and B (**24**) is described. The crucial step is the amine-catalyzed cyclization of the enone **8b** which leads to the products **9b** and **10b** with high diastereoselectivity. The choice of the amine catalyst has a strong influence on the selectivity (i.e. on the ratio of trans and cis products **9b**:**10b**); the amine must have an optimum pK_b value. The aromatic synthon and the terpene synthon of robustadials are joined *via* a Prins reaction of a substituted benzaldehyde (**3b**) with β-pinene (**4**). The reaction is strongly dependent on electronic effects, and the choice of substituents on the aromatic ring is critical. The use of (1*S*)-(−)-β-pinene ensures the synthesis of enantiomerically pure compounds.

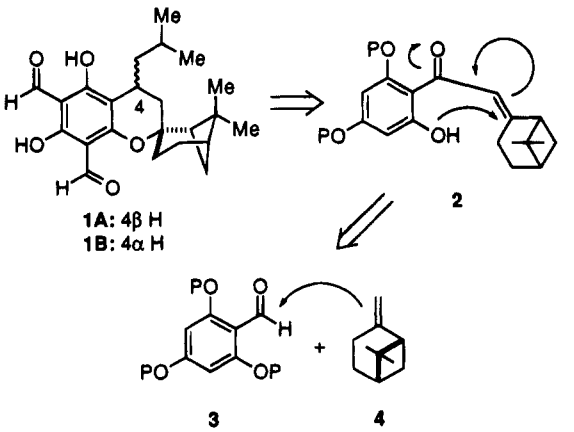
Robustadials, interesting natural products of potential significance in treating malaria, were isolated from leaves of *Eucalyptus robusta* by Nakanishi's group ten years ago.[1] After some controversy concerning structure elucidation of these compounds, structure **1** was proven to be correct.[2] The first total synthesis of robustadial dimethyl ethers, which also served as the proof of the structure, was reported by Salomon's group,[2b] and a few other studies describing partial syntheses[3] have been published since.

Our retrosynthetic analysis of robustadials is shown, in an abbreviated form, in Scheme 1.[4] We envisaged the introduction of the two formyl groups onto the aromatic ring late in the synthesis; however, the three hydroxy groups (protected) should be present in the aromatic starting material since there are relatively few methods for connecting OH or OR groups to a benzene ring. The tetrahydropyran ring was disconnected by applying a Michael-type transform.[5] The precursor **2** was further simplified by use of the Prins transform which yielded readily available starting materials (1*S*)-(−)-β-pinene (**4**) and a trisubstituted benzaldehyde derivative (**3**).

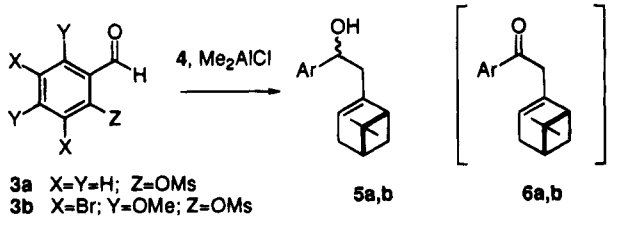
Lewis acid-catalyzed ene addition of alkenes to aldehydes (the Prins reaction), involving substituted benzaldehydes, has not been extensively studied.[6] An investigation of the reaction between substituted benzaldehydes and β-pinene (Scheme 2) led to the following conclusions:[4b]

(i) Aromatic aldehydes which are electron rich do not react with β-pinene or else give poor yields. An interesting exception here was 2-methoxybenzaldehyde: relatively high reactivity paralleled its behavior in the aldol reaction as observed by Thornton.[7]

Scheme 1



Scheme 2



(ii) Benzaldehyde, and substituted benzaldehydes having electron-withdrawing groups, react readily with β-pinene and give mixtures of two diastereoisomeric alcohols **5**.[8] This observation led to development of the fully substituted benzaldehyde **3b** as the building block for robustadials. The two bromine atoms and the mesyl group in this compound attenuate the high electron density of the carbonyl C=O resulting from the electron-donating effect of the three oxygens connected to the aromatic ring.

(iii) The organoaluminum catalyst must not be overly acidic to avoid rearrangement of the pinene ring. Alkyl groups connected to Al attenuate the Lewis acidity of the reagent. On the other hand, reagents with more alkyl groups favor transfer of the alkyl to the aldehyde C=O. Dimethyl- and diethylaluminum chlorides were the best catalysts.

(iv) Products of the Oppenauer oxidation (**6**) were observed when the aldehyde **3** was used in excess.[4b,9]

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(1) Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734.

(2) (a) Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 4562. (b) Salomon, R. G.; Lal, K.; Mazza, S. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 5213. (c) Salomon, R. G.; Mazza, S. M.; Lal, K. *J. Org. Chem.* **1989**, *54*, 1562.

(3) (a) Koser, S.; Hoffman, H. M. R.; Williams, D. J. *J. Org. Chem.* **1993**, *58*, 6163. (b) Krause, M.; Hoffman, H. M. R. *Tetrahedron Lett.* **1990**, *31*, 6629. (b) Subramanian, R. S.; Balasubramanian, K. K. *Ibid.* **1989**, *30*, 2297.

(4) Preliminary results were published: (a) Majewski, M.; Bantle, G. W. *Tetrahedron Lett.* **1989**, *30*, 6653. (b) Majewski, M.; Bantle, G. W. *Synth. Commun.* **1990**, *20*, 2549.

(5) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis;* Wiley: Toronto, 1989; Chapter 1.

(6) Snider, B. B. In *Comprehensive Organic Synthesis,* Vol. 2; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; pp 527–561.

(7) Das, G.; Thornton, E. R. *Tetrahedron Lett.* **1991**, *32*, 5239.

(8) The structure of the major isomer in each case was assigned as 1′*S* (cf. ref 4b).

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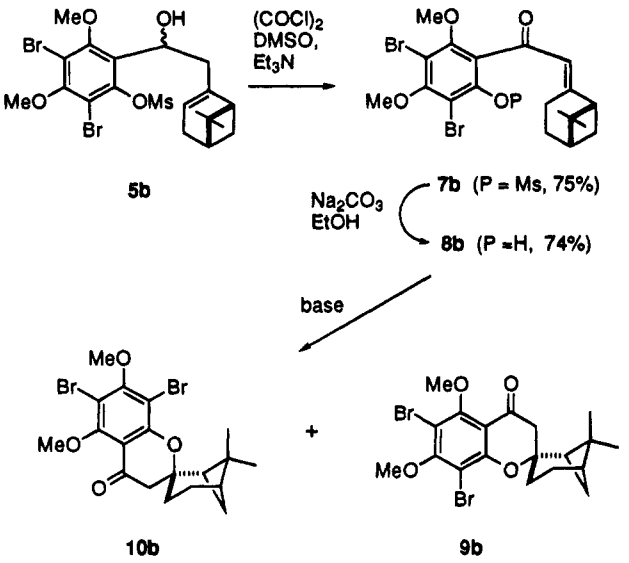
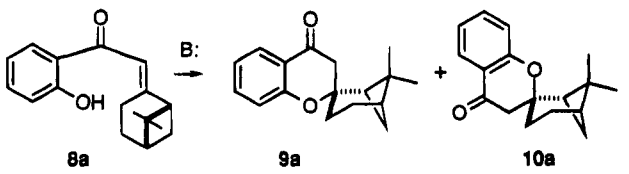
Scheme 3



Scheme 4



Thus, aldehyde **3a** reacted with β-pinene (0.5 molar equiv) in the presence of Me_2AlCl (0.45 equiv) and yielded the ketone **6a** in 87% yield.

Oxidation of compound **5b** with concomitant shift of the double bond to the α,β position using the Swern method (Scheme 3), followed by deprotection of the mesyl-protected OH group in the resulting ketone **7b**, afforded compound **8b**. With this compound in hand, the stage was set for trying the cyclization. The often-used conditions for conjugate addition of alkoxide ions to enones employ sodium or potassium carbonate in refluxing ethanol.[10] When we subjected compound **8b** to these conditions, only small amounts of the cyclic isomeric products **9b** and **10b** were detected and, furthermore, the reaction was nonstereoselective, yielding the two products in a 1:1 ratio. The trans compound **9b** was the one needed to proceed with the synthesis of robustadials, and we were faced with the necessity of minimizing the formation of **10b** and maximizing the reaction yield. A more thorough investigation of the cyclization reaction was performed at this stage.

First, as a model study, we tried the cyclization of compound **8a** (Scheme 4). Initial results were not promising: when sodium carbonate was used as the base, the cyclization yielded mostly the cis isomer **10a**. We noticed, however, that at low conversion, the ratio of the trans product **9a** to the cis product **10a** was greater. It seemed that the desired trans isomer **9a** was the kinetic product, whereas the cis isomer **10a** was the thermodynamic product. This cyclization proceeds "thermodynamically uphill", that is, the initially formed phenoxide

Scheme 5

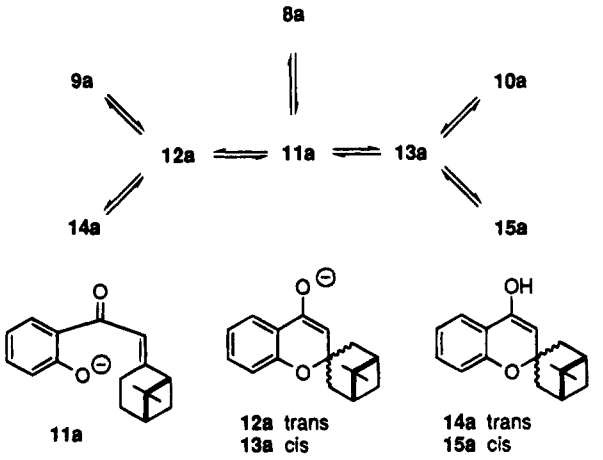


Table 1. Cyclization of Compounds 8a and 8b[4a]

entry	compound	base[a]	products[b]	yield (%)[c]
1	**8a**	Na_2CO_3	29:71	80
2		NaOH	50:50	10
3		PhONa	37:63	75
4		Et_3N	>96:4[d]	60
5	**8b**	Na_2CO_3	50:50	10
6		Et_3N	54:46	75
7		Piperidine	33:67	70
8		Morpholine	83:17	78
9		DMAP	66:34	90
10		Imidazole	*e*	*e*

[a] Reactions were done in EtOH. [b] The ratio of products was established by NMR after purification. [c] Combined yield of isolated products **9** and **10**. [d] One product only (by NMR; 4% level of detection of **10** was assumed). [e] Starting material was recovered.

ion **11a** (Scheme 5) should be more stable than the enolate ions **12a** and **13a** produced during cyclization due to a large difference in pK_a values between the ketone and the phenol. The reaction is also reversible. One might expect that a Michael-type reaction can only give a reasonable amount of the product under conditions which shift the equilibrium toward the ring-closed product, e.g., in protic solvents. Trying to maximize the amount of the kinetic product under such constrains did not seem very promising; however, we discovered that cyclization gave the kinetic trans product **9a** in reasonable yield when triethylamine was used as the catalyst (Table 1, entry 4). The tentative mechanism can be described in terms of Scheme 5.

With this information in hand, cyclization of the fully substituted analog **8b** was investigated. Using amines as bases allowed us to achieve trans-selective cyclization in good yield (Table 1, entries 6–9). Interestingly, the diastereoselectivity of cyclization correlates well with basicity[11] of the amines used (Figure 1). The linear correlation, resembling general base catalysis,[12] can not be extrapolated too far over the basicities outside the range of 2.8–5.7 pK_b units. Attempted cyclization with imidazole (pK_b = 7.00; entry 10) did not work (the starting material was regenerated).

Having successfully completed the cyclization step, we set out to convert the carbonyl group in the ketone **9b**

(9) Snider, B. B.; Goldman, B. E. *Tetrahedron* **1986**, *42*, 2951.

(10) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992, p 126. Scattered examples of use of amines as catalysts in addition of alkoxides to alkenes can be found in the literature, e.g.: (b) Varma, R. S.; Kadkhodayan, M.; Kabalka, G. W. *Synthesis* **1986**, 486. (c) Katagiri, N.; Takashima, K.; Kato, T.; Sato, S.; Tamura, C. *J. Chem. Soc., Perkin Trans. I*, **1983**, 201.

(11) (a) Gordon, A. J.; Ford, R. A. *The Chemist's Companion;* Wiley: New York, 1972; p 59. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (c) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *Chem. Commun.* **1968**, 723.

(12) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 567–569.

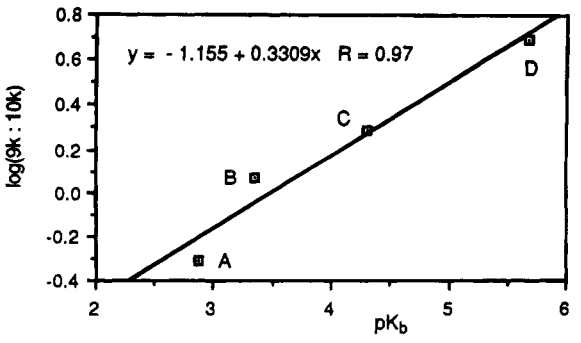
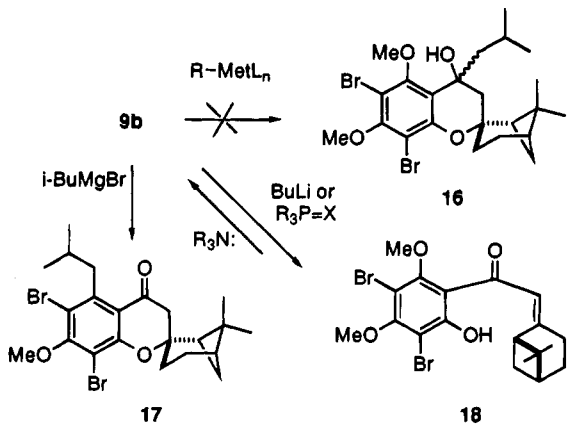


Figure 1. Dependence of the diastereoselectivity of cyclization of **8b** on the catalyst's basicity (pK_b values from ref 11): (A) piperidine (pK_b = 2.88); (B) Et_3N (3.35); (C) DMAP (4.30); (D) morpholine (5.67).

Scheme 6

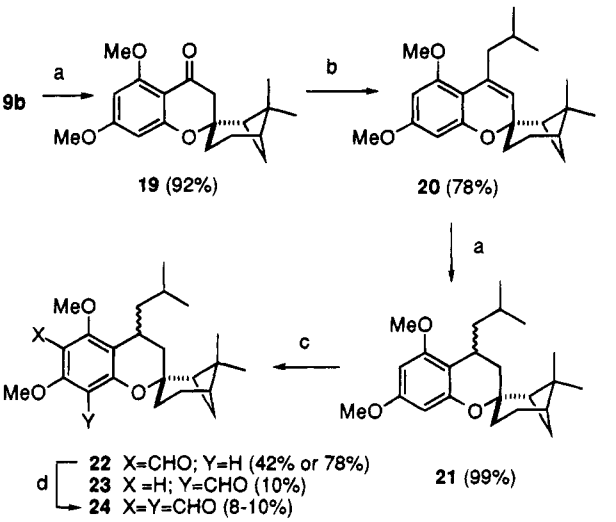


into the required isobutyl side chain. Attempted Grignard addition of isobutylmagnesium bromide to **9b**, by analogy to Salomon's synthesis,[2b] yielded only the product of the ipso substitution of OMe on the aromatic ring (**17**) in 86% yield. Treating **9b** with other organometallic reagents also did not lead to the desired compound **16** (Scheme 6). Addition of organocerium compounds to **9b**, according to the method developed by Imamoto,[13] did not work, and the starting material was recovered. Attempts to construct the side chain *via* the Wittig reaction or by alkyllithium addition were also unsuccessful; stabilized and nonstabilized ylides, Wittig–Horner reagents, and also alkyllithium reagents all reacted not as nucleophiles but as bases and caused opening of the pyran ring in **9b**, yielding compound **18**. This ring opening was remarkably stereoselective and afforded only the *Z* alkene **18** and none of the *E* isomer **8b**. The latter compound (probably the more stable of the two isomers) was synthesized previously as the only product of the Swern oxidation of **5b** (vide supra).

We were intrigued by the stereoselectivity of these reactions and, after a brief study, we established that the cis spiro isomer **10b** also yielded only the *Z* enone **18** when treated with butyllithium and that the enone **18** cyclized readily to give the spiro ring system with somewhat higher diastereoselectivity than the *E* isomer **8b**: when compound **18** was treated with morpholine in EtOH and Et_2O, the two tricyclic products **9b** and **10b** were isolated in a ratio of 96:4 (trans to cis). This interesting set of transformations allows one to obtain

(13) Imamoto, T. In *Comprehensive Organic Synthesis*, Vol. 1; Schreiber, S. L., Ed.; Pergamon: Oxford, 1991; Chapter 1.8.

Scheme 7[a]



[a] (a) H_2/Pd–C; (b) (i) i-BuMgBr, (ii) H_3O^+; (c) (i) n-BuLi/Et_2O–hexane or THF, (ii) DMF; (d) (i) lithium *N*-methylpiperazide, (ii) n-BuLi, (iii) DMF.

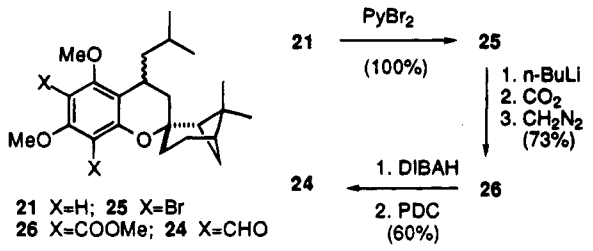
both the *E* and *Z* enones **8b** and **18** selectively and convert each of them selectively into the trans compound **9b**. In principle, this sequence of reactions could serve as a way to recycle the undesired cis diastereoisomer **10b**. Reasons for the stereoselectivity observed in the ring opening reactions (**9b** → **18** and **10b** → **18**) are not clear.

We also tried other organometallic reagents carrying the isobutyl synthon, i.e. organotitanium compounds and vinylmagnesium reagents. In all cases either the starting material was regenerated (titanium) or the ring opening occurred (vinylmagnesium). In summary, all attempts to convert the C=O group in **9b** into the isobutyl side chain *via* addition of carbanions were unsuccessful and led either to ring opening, which yielded compound **18**, or to nucleophilic aromatic substitution of the OMe group which afforded compound **17**. This behavior of compound **9b** contrasted sharply with the efficient addition of i-BuMgCl to the carbonyl group of the ketone **19** reported by Salomon (Scheme 7).[2b]

At this stage, as a model study, we investigated addition reactions of several organometallic reagents to the C=O group in compound **9a**, which has no additional substituents on the aromatic ring. The results were similar to the fully substituted ketone **9b** described above: addition of carbanions to the carbonyl group did not occur and the ring opening reactions proceeded readily. Clearly, the substituents on the aromatic ring have a strong influence on the reactions of the benzopyranone system. Presumably, the electron-donating substituents make the ArO^- a poorer leaving group, thus decreasing the likelihood of ring opening which, in their absence, is a major competing reaction. In compound **9b** the two bromine atoms decrease the electron density of the ring enough to make the ring opening favored. We realized that these two bromine substituents had to be removed before the nucleophilic addition of the isobutyl carbanion to C=O was attempted.

Ketone **9b** was efficiently debrominated to **19** by catalytic hydrogenation (Scheme 7). Grignard addition of isobutylmagnesium bromide to this compound proceeded well, in agreement with Salomon's report,[2b,c] and after dehydration of the resulting alcohol, yielded alkene

Scheme 8



20[14] which was reduced with H_2–Pd to the robustadial precursor **21** (mixture of diastereoisomers). It was expected that directed ortho-metalation of this compound with BuLi,[15] followed by treatment with a formylating reagent (e.g. DMF), would result in introduction of the two necessary formyl groups and would yield robustadial dimethyl ether (**24**). Compound **24** was indeed produced but only in 8% yield. The main product of the lithiation of **21** with n-BuLi/TMEDA in ether, followed by treatment of the resulting organolithium species with DMF, was the monoaldehyde **22**[16] (42%). In THF the reaction yielded only the two monoaldehydes **22** and **23** in 78% and 11% yields, respectively. All our efforts to increase the amount of the dialdehyde **24** by manipulating reaction conditions (time, different bases, solvents) were unsuccessful.[17]

We briefly investigated the possibility of producing the dialdehyde **24** from the monoaldehyde **22** *via* a strategy elaborated by Commins[18] involving *in situ* protection of the aldehyde functional group using lithium *N*-methylpiperazide followed by directed ortho-metalation and formylation with DMF (Scheme 7). Compound **24** was indeed produced but the yield was low (10%).

It should be noted that synthesis of the alkene **20** constitutes a formal synthesis of dimethylrobustadials A and B, since both of these compounds were prepared from **20** by Salomon.[2b] Since the last step in our synthesis (second formylation) was inefficient, we decided to follow the trail blazed by these workers to obtain a higher yield (Scheme 8): diester **26** was obtained by bromination of **21**, lithium–halogen exchange, reaction with CO_2, and methylation with diazomethane. Reduction of **26** with DIBAH gave the corresponding diol, which was oxidized to the dialdehyde **24** with a CrO_3–pyridine complex. A very good agreement of the yields with Salomon's synthesis[2b] is noteworthy.

In conclusion, the methyl ethers of robustadials A and B were synthesized stereoselectively from β-pinene. Formation of the carbon skeleton was achieved *via* a Prins reaction of substituted benzaldehyde **3b** with β-pinene. The use of natural (1*S*)-(−)-β-pinene ensured the synthesis of enantiomerically pure compounds. The crucial step was the morpholine-catalyzed cyclization of the phenolenone **8b** which proceeded with high diastereoselectivity. Direct introduction of the second aldehyde functional groups onto the aromatic ring in compound **21** proceeded in low yield. The lack of an efficient method to introduce the two required formyl groups can be bypassed by use of the multistep Salomon procedure (**21** → **25** → **26** → **24**).

Experimental Section

All air-sensitive reactions were done under inert atmosphere (Ar). THF and Et_2O were distilled from Na/benzophenone under N_2; CH_2Cl_2 was distilled from CaH_2. DMSO and Et_3N were dried with CaH_2, distilled under vacuum, and stored over 4A molecular sieves. BuLi (Aldrich) was titrated periodically using 2,5-dimethoxybenzyl alcohol as indicator.[19] Flash chromatography was carried out as described.[20] Melting points are uncorrected. All proton NMR spectra were recorded at 300 MHz using $CDCl_3$ as a solvent (referenced to δ 7.25), unless stated otherwise. All the ^{13}C NMR spectra were recorded at 75 MHz using $CDCl_3$ as a solvent. Abbreviations s′, d′, t′, and q′ refer to zero, one, two, and three protons attached to the carbon. Gas chromatography was performed using a Hewlett-Packard 5890 with a HP-1 (methyl silca gum) instrumental test column (5 m × 0.53 mm × 2.65 mm film thickness). Compounds **5a** and **5b** were prepared as described before,[4b] in somewhat higher yields (93% and 60%, respectively).

(1*R*)-2-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylidene)-1-(2-(methanesulfonyloxy)phenyl)ethanone (7a). DMSO (2.93 mL, 41.2 mmol) was added to a solution of oxalyl chloride (1.8 mL, 20.6 mmol) in CH_2Cl_2 (60 mL) under Ar at −78 °C. After 2 min, a solution of **5a** (6.30 g, 18.7 mmol) in CH_2Cl_2 (10 mL) was added over 5 min, and the resulting mixture was stirred for an additional 15 min, warmed to 0 °C, and quenched with Et_3N (15 mL, 108 mmol). After 90 min at room temperature, the mixture was diluted with CH_2Cl_2 and was extracted with saturated aqueous NH_4Cl. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (1% AcOEt in benzene) to produce **7a** (oil, 5.80 g, 93%): IR (neat) 1660 cm^{-1}; $[\alpha]^{20}_D$ −3.21° (*c* 0.0271, CH_2Cl_2); ^1H NMR δ 0.80 (s, 3H), 1.29 (s, 3H), 1.42 (d, *J* = 10.0 Hz, 1H), 1.88–2.17 (m, 3H), 2.40–2.47 (m, 1H), 2.53 (t, *J* = 5.3 Hz, 1H), 2.76–2.90 (m, 1H), 3.12 (s, 3H), 3.27–3.38 (m, 1H), 6.35 (br s, 1H), 7.33–7.61 (m, 4H); ^{13}C NMR δ 22.09 (q′), 23.51 (t′), 23.89 (t′), 25.82 (q′), 27.09 (t′), 37.53 (q′), 40.14 (d′), 40.91 (s′), 54.07 (d′), 120.32 (d′), 123.33 (d′), 127.12 (d′), 129.69 (d′), 137.77 (d′), 135.19 (s′), 145.82 (s′), 172.60 (s′), 189.93 (s′); MS, *m*/*z* (rel intensity) 334 (M^+, 10), 255 (15), 199 (84), 194 (36), 187 (16), 135 (19), 121 (100), 120 (15), 91 (22), 69 (34). Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63. Found: C, 64.54; H, 6.75.

(1*R*)-2-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylidene)-1-(2-hydroxyphenyl)ethanone (8a). A solution of **7a** (745 mg, 2.23 mmol) in absolute EtOH (150 mL) was warmed to 50 °C, NaOH (2 N, 0.5 mL) was added, and the reaction mixture was stirred for 2 h. The mixture was cooled, diluted with a saturated NH_4Cl solution to a pH of 7, and extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (10% AcOEt in hexane) gave **8a** (202 mg, 35%) as a yellow oil: IR (neat) 2700–3400, 1675 cm^{-1}; $[\alpha]^{20}_D$ +27.69° (*c* 0.0101, CH_2Cl_2); ^1H NMR δ 0.77 (s, 3H), 1.30 (s, 3H), 1.45 (d, *J* = 9.0 Hz, 1H), 1.90–2.12 (m, 3H), 2.45 (m, 1H), 2.64 (t, *J* = 5.3 Hz, 1H), 2.82–2.94 (m,1H), 3.28–3.38 (m, 1H), 6.67 (br s, 1H), 6.84 (m, 1H), 6.95 (m, 1H), 7.43 (m, 1H), 7.78 (m, 1H), 13.01 (s, 1H); ^{13}C NMR δ 22.21 (q′), 23.78 (t′), 24.16 (t′), 26.06 (q′), 27.29 (t′), 40.38 (d′), 41.20 (s′), 54.82 (d′), 116.01 (d′), 118.43 (d′), 118.73 (s′), 129.41 (d′), 135.40 (d′), 163.27 (s′), 173.04 (s′), 195.12 (s′); MS (CI, isobutane), *m*/*z* (rel intensity) 257 (M + 1, 83), 256 (25), 186 (16), 135 (12), 121 (100), 107 (11), 91 (18). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.88. Found: C, 79.43; H, 7.97.

[1′*R*-(1′α,2′α,5′α)]-6′,6′-Dimethylspiro[2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptan]-4(3*H*)-one (9a). Et_3N (0.37 mL,

(14) A small amount of the exocyclic alkene analogous to **22** was also produced, cf. the Experimental Section.
(15) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(16) The structure of compound **22** was supported by NOE experiments: aromatic H showed NOE with only one methoxy group (δ 3.79) whereas the aldehyde proton had NOEs with both methoxy groups.
(17) Difficulties associated with synthesizing a fully substituted aromatic system *via* directed ortho-metalation of 1,3,5-trimethoxybenzene are due to the steric hindrance: Cabbidu, S.; Contini, L.; Fattuoni, C.; Floris, C.; Gelli, G. *Tetrahedron* **1991**, *47*, 9279.
(18) Commins, D. L. *Synlett* **1992**, 615.
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2.6 mmol) was added to a refluxing solution of enone **8a** (61 mg, 0.24 mmol) in 95% EtOH (10 mL). After 5 h, the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (2×). The combined organic layers were washed (H_2O), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (5% AcOEt in hexane) yielded unreacted enone **8a** (15 mg, 25%) and the product **9a** (36 mg, 78% based on enone consumed, 60% conversion): IR (neat) 1690 cm^{-1}; $[\alpha]^{20}_D$ −43.71° (*c* 0.0143, CH_2Cl_2); ^1H NMR δ 0.99 (s, 3H), 1.23 (s, 3H), 1.63 (d, *J* = 10.2 Hz, 1H), 1.90−1.98 (m, 4H), 2.15−2.29 (m, 3H), 2.81 (d, *J* = 16.4, 1H), 2.94 (d, *J* = 16.4, 1H), 6.78−6.93 (m, 2H), 7.43 (m, 1H), 7.80 (m, 1H); ^{13}C NMR δ 23.23 (q′), 24.56 (t′), 26.66 (t′), 27.43 (q′), 28.69 (t′), 38.07 (s′), 40.34 (d′), 48.93 (d′), 49.88 (t′), 86.11 (s′), 118.59 (d′), 120.55 (d′), 120.95 (s′), 126.24 (d′), 136.00 (d′), 160.03 (s′), 193.16 (s′); MS, *m*/*z* (rel intensity) 256 (M^+, 100), 228 (16) 213 (23), 186 (58), 173 (14), 121 (54). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.88. Found: C, 79.40; H, 7.80.

(1*R*)-2-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylidene)-1-(3,5-dibromo-4,6-dimethoxy-2-(methanesulfonyloxy)phenyl)-ethanone (7b). Oxidation of **5b** as described above for **5a** yielded compound **7b** as an oil (75%): IR (neat) 1700 cm^{-1}; $[\alpha]^{20}_D$ +37.86° (*c* 0.035, CH_2Cl_2); ^1H NMR δ 0.80 (s, 3H), 1.27 (s, 3H), 1.42 (d, *J* = 9.9 Hz, 1H), 1.87−1.99 (m, 3H), 2.45 (m, 1H), 2.55 (m, 1H), 2.82 (m, 1H), 3.27 (s, 3H), 3.29−3.39 (m, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 6.14 (m, 1H); ^{13}C NMR δ 22.02 (q′), 23.52 (t′), 23.90 (t′), 25.83 (q′), 27.06 (t′), 39.91 (d′), 39.97 (q′), 41.05 (s′), 53.93 (d′), 60.54 (q′), 62.56 (q′), 110.70 (s′), 113.32 (s′), 121.69 (d′), 130.21 (s′), 143.37 (s′), 154.53 (s′), 156.24 (s′), 173.18 (s′), 187.48 (s′); MS, *m*/*z* (rel intensity) 554 (M + 2, 7), 552 (M^+, 14), 550 (7), 484 (11), 482 (20), 480 (11), 459 (15), 457 (26), 455 (15), 419 (89), 417 (100), 415 (46), 341 (36), 339 (59), 337(34), 122 (60), 69 (86), 43 (34). Anal. Calcd for $C_{20}H_{24}Br_2O_6S$: C, 43.49; H, 4.39. Found: C, 43.27; H, 4.53.

(1*R*)-2-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylidene)-1-(3,5-dibromo-2-hydroxy-4,6-dimethoxyphenyl)ethanone (8b). A solution of **7b** (269 mg, 0.57 mmol) in EtOH (85%, 180 mL) was heated to 70 °C and anhydrous Na_2CO_3 (2.75 g) was added. After being stirred for 20 min, the reaction mixture was diluted with saturated aqueous NH_4Cl (150 mL) and extracted with CH_2Cl_2. The combined organic layers were washed (H_2O), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (5% AcOEt in hexane) gave the *E* enone[21] **8b** (170 mg, 74%) as a yellow oil: IR (neat) 2900 cm^{-1} (very broad), 1625, 1560 cm^{-1}; $[\alpha]^{20}_D$ +7.29° (*c* 0.031, CH_2Cl_2); ^1H NMR δ 0.79 (s, 3H), 1.29 (s, 3H), 1.43 (d, *J* = 10.1 Hz, 1H), 1.85−2.16 (m, 3H), 2.41 (m, 1H), 2.62 (t, *J* = 5.2 Hz, 1H), 2.90 (m, 1H), 3.30 (m, 1H), 3.72 (s, 3H), 3.91 (s, 3H), 6.91 (br s, 1H), 11.92 (s, 1H); ^{13}C NMR δ 22.45 (q′), 23.87 (t′), 24.96 (t′), 26.29 (q′), 27.39 (t′), 40.34 (d′), 41.42 (s′), 54.89 (d′), 60.74 (q′), 62.82 (q′), 103.54 (s′), 103.98 (s′), 114.40 (d′), 122.05 (d′), 158.14 (s′), 159.46 (s′), 160.56 (s′), 175.60 (s′), 193.31 (s′); MS, *m*/*z* (rel intensity) 476 (M + 2, 17), 474 (M^+, 32), 472 (17), 444 (16), 404 (15), 393 (15), 391 (25), 389 (17), 341 (50), 339 (100), 337 (57), 135 (15), 91 (14). Anal. Calcd for $C_{19}H_{22}Br_2O_4$: C, 48.12; H, 4.69. Found: C, 47.93; H, 4.79.

[1′*R*-(1′α,2′α,5′α)]- and [1′*R*-(1′α,2′β,5′α)]-6,8-Dibromo-5,7-dimethoxy-6′,6′-dimethylspiro[2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptan]-4(3*H*)-one (9b and 10b). Cyclization analogous to the synthesis of **9a** (*vide supra*) but with morpholine as the base, **8b** as the substrate, and reaction time of 6 h yielded, after flash chromatography (5% AcOEt in hexane), unreacted enone **8b** (10 mg, 20%) and the two isomers **9b** (30.8 mg, 62%) and **10b** (4.2 mg, 8.4%). **9b**: IR (neat) 1695 cm^{-1}; $[\alpha]^{20}_D$ −21.48° (*c* 0.0454, CH_2Cl_2); ^1H NMR δ 0.97 (s, 3H), 1.24 (s, 3H), 1.75 (d, *J* = 10.0 Hz, 1H), 1.89−2.01 (m, 4H), 2.20−2.27 (m, 3H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.91 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.90 (s, 3H); ^{13}C NMR δ 23.08 (q′), 24.34 (t′), 27.18 (t′), 27.30 (q′), 28.40 (t′), 38.05 (s′), 40.26 (d′), 49.31 (d′), 50.52 (t′), 60.68 (q′), 61.69 (q′), 87.80 (s′), 104.23 (s′), 106.91 (s′), 113.48 (s′), 157.31 (s′), 157.66 (s′), 160.21 (s′), 189.52 (s′); MS, *m*/*z* (rel intensity) 476 (M + 2, 5), 474 (M^+, 9), 472 (5), 393 (4), 391 (7), 389 (4), 340 (51), 338 (100), 336 (53), 295 (18), 93 (19), 91 (24), 77 (18), 53 (15). Anal. Calcd for $C_{19}H_{22}Br_2O_4$: C, 48.12; H, 4.69. Found: C, 48.07; H, 4.73. **10b**: IR (KBr) 1695 cm^{-1}; $[\alpha]^{20}_D$ −12.12° (*c* 0.023, CH_2Cl_2); ^1H NMR δ 1.03 (d, *J* = 10.5 Hz, 1H), 1.22 (s, 6H), 1.90−2.35 (m, 7H), 2.70 (d, *J* = 15.5 Hz, 1H), 2.91 (d, *J* = 15.5 Hz, 1H), 3.86 (s, 3H), 3.90 (s, 3H); ^{13}C NMR δ 23.83 (q′), 24.34 (t′), 27.20 (t′), 27.30 (q′), 28.05 (t′), 38.11 (s′), 40.36 (d′), 48.66 (d′), 49.32 (t′), 60.68 (q′), 61.86 (q′), 87.76 (s′), 103.74 (s′), 106.64 (s′), 113.52 (s′), 157.31 (s′), 157.81 (s′), 160.27 (s′), 189.52 (s′); MS, *m*/*z* (rel intensity) 476 (M + 2, 4) 474 (8), 472 (4), 341 (50), 339 (100), 337 (50), 295 (14), 93 (17), 91 (19), 41 (38). Anal. Calcd for $C_{19}H_{22}Br_2O_4$: C, 48.12; H, 4.69. Found: C, 47.93; H, 4.61.

An identical experiment with *Z* enone **18** (115 mg, 0.24 mmol), over 3 h, yielded unreacted enone **18** (25 mg, 22%) and the two isomers **9b** (78 mg) and **10b** (6 mg). The total yield of cyclized product was 84 mg (93% based on enone consumed, 73% conversion).

Reaction of 9b and 10b with n-BuLi. A solution of **9b** (128 mg, 0.27 mmol) in Et_2O (2 mL) was cooled to −78 °C. n-BuLi (0.108 mL, 2.5 M solution in hexane) was added *via* a syringe and the yellow mixture was stirred for 2 h, quenched with aqueous NH_4Cl, and extracted with Et_2O. The organic layers were combined, washed with brine, and dried ($MgSO_4$). After being concentrated *in vacuo*, the residue was purified by column chromatography (benzene) to give 87 mg (68%) of the Z enone[21] **18** as a yellow oil: IR (KBr) 1619, 1554 cm^{-1}; ^1H NMR δ 0.79 (s, 3H), 1.37 (s, 3H), 1.48 (d, *J* = 10.1 Hz, 1H), 1.95−2.12 (m, 3H), 2.37 (m, 2H), 2.79 (m, 1H), 3.73 (s, 3H), 3.90 (m, 1H), 3.92 (s, 3H), 6.94 (br s, 1H), 10.32 (s, 1H); MS, *m*/*z* (rel intensity) 474 (M^+, 10), 391 (17), 339 (29), 91 (100). Anal. Calcd for $C_{19}H_{22}Br_2O_4$: C, 48.12; H, 4.69. Found: C, 48.21; H, 4.75.

An identical experiment with **10b** (18 mg, 0.038 mmol) in Et_2O at 0 °C (reaction time 30 min) gave, after purification by preparative TLC (benzene), the cis enone **18** (11 mg, 61%).

Reaction of 9b with Isobutylmagnesium Bromide. To a solution of **9b** (32 mg, 0.068 mmol) in THF (0.5 mL) at −78 °C was added i-BuMgBr (0.041 mL of a 2.0 M solution). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2×). The combined organic layers were washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product, purified by flash chromatography (5% AcOEt in hexane), gave **17** (29 mg, 86%): IR (KBr) 1688 cm^{-1}; ^1H NMR δ 0.90 (d, *J* = 4.0 Hz, 3H), 0.93 (d, *J* = 4.0 Hz, 3H), 0.97 (s, 3H), 1.25 (s, 3H), 1.76−2.25 (m, 11H), 2.80 (d, *J* = 15.6 Hz, 1H), 2.93 (d, *J* = 15.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR δ 22.23 (q′), 22.30 (q′), 23.07 (q′), 24.35 (t′), 26.72 (t′), 27.30 (q′), 28.17 (t′), 30.12 (d′), 38.02 (s′), 40.09 (t′), 40.25 (d′), 49.11 (d′), 51.29 (t′), 60.38 (q′), 87.01 (s′), 106.71 (s′), 115.34 (s′), 117.74 (s′) 144.70 (s′), 159.07 (s′), 161.00 (s′), 197.48 (s′); MS, *m*/*z* (rel intensity) 502 (M + 2, 3), 500 (M^+, 6), 448 (3), 366 (28), 364 (59), 362 (32), 268 (18), 266 (15), 93 (28), 91 (29), 77 (30), 69 (32), 55 (28), 43 (84), 41 (100). Anal. Calcd for $C_{22}H_{28}Br_2O_3$: C, 48.12; H, 4.69. Found: C, 47.93; H, 4.61.

[1′*R*-(1′α,2′α,5′α)]-5,7-Dimethoxy-6′,6′-dimethylspiro-[2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptan]-4(3*H*)-one (19).[2b,c] Sodium acetate (2.57 g) and 30% Pd/C (0.84 g) were added to a solution of ketone **9b** (0.64 g, 1.34 mmol) in glacial acetic acid (140 mL). The flask was fitted with a balloon of H_2, and the reaction mixture was stirred for 2 h at room temperature, diluted with Et_2O, filtered to remove the charcoal, and concentrated *in vacuo*. The crude product was purified by column chromatography (25% AcOEt in hexane)

(21) The stereochemistry (*Z*−*E* isomerism) in compounds **8b** and **18** was assigned by the solvent shift method (cf.: Timmons, C. J. *Chem. Commun.* **1965**, 576. Jackman, L. M.; Sternhell, S. *Application of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: London, 1969; p 246). In the ^1H NMR spectrum of compound **8b**, recorded in $CDCl_3$, the allylic bridgehead proton appeared at δ 2.61 and the two allylic protons from the CH_2 group at δ 3.25 and 2.81. When the spectrum was recorded in C_6D_6, the bridgehead proton shifted upfield to δ 2.36 (Δδ 0.25) and the signals due to the CH_2 group have shown no change. This indicated that **8b** is the *E* isomer. Similar experiments with compound **18** led to the downward shift of the bridgehead H (from δ 3.90 to 4.00; Δδ −0.10) and upward shift of the two CH_2 protons (from δ 2.78 to 2.43; Δδ 0.35 and from δ 2.35 to 1.96; Δδ 0.39), upon change of solvent from $CDCl_3$ to C_6D_6, indicating that compound **18** was the *Z* isomer.

to give compound **19** as a clear oil (0.39 g, 92%). Spectral details were in agreement with those reported by Salomon.[2b,c]

[1′*R*-(1′α,2′α,5′α)]-5,7-Dimethoxy-6′,6′-dimethyl-4-(2-methylpropyl)-spiro[2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]-heptane] (20).[2b,c] i-BuMgBr (1.35 mL, 2 M solution in Et_2O, 2.71 mmol) was added to a solution of **19** (214 mg, 0.677 mmol) in Et_2O at 0 °C under Ar. The reaction mixture was warmed to room temperature, stirred for 1.5 h, treated with saturated aqueous NH_4Cl, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and was stirred with 10% aqueous HCl (2 mL) at room temperature for 17 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated $NaHCO_3$ and H_2O and dried ($MgSO_4$). The crude product was purified by column chromatography (10% AcOEt in hexane) to give 188 mg (78%) of compound **20**. The NMR spectrum of this compound recorded at this stage showed the presence of ca. 15% of an isomer of **20** having the double bond in the exocyclic position. On standing overnight, any evidence of this isomer disappeared; apparently it rearranged to the alkene **20**, spectral data of which were identical with those reported by Salomon.[2b,c]

[1′*R*-[1′α,2′α(S*),5′α]]- and [1′R-[1′α,2′α(R*),5′α]]-3,4-Dihydro-5,7-dimethoxy-6′,6′-dimethyl-4-(2-methylpropyl)-spiro[2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptane] (21).[2b,c] Pd/C (30%, 18 mg) was added to a solution of **20** (188 mg, 0.528 mmol) in AcOEt (6 mL), and the mixture was stirred under H_2 at atmospheric pressure for 6 h. Filtration through Celite, followed by removal of the solvent *in vacuo* and purification *via* flash chromatography (20% AcOEt in hexane), afforded 186 mg (99%) of compound **21**. ^1H NMR showed a mixture of diastereoisomers (87:13): ^1H NMR δ 0.89 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.01 (s, 3H), 1.18 (m, 1H), 1.19 (s, 3H, minor diastereomer), 1.26 (s, 3H), 1.52–2.25 (m, 12H), 2.82–2.90 (m, 1H), 3.72 (s, 3H, minor diastereomer), 3.73 (s, 3H), 3.75 (s, 3H), 5.96 (d, J = 2.3 Hz, 1H, minor diastereomer), 5.98 (d, J = 2.4 Hz, 1H), 6.02 (d, J = 2.4 Hz, 1H).

Formylation of 21. TMEDA (0.122 mL, 0.81 mmol) was added slowly to a solution of n-BuLi (0.323 mL, 2.5 M solution in hexane) in anhydrous hexane (1 mL) at 0 °C. After 10 min, a solution of **21** (36 mg, 0.10 mmol) in Et_2O (0.5 mL) was added, the resulting mixture was stirred at 0 °C for 2 h and cooled to −20 °C, and DMF (0.63 mL, 0.81 mmol) was added. The mixture was warmed to 0 °C and was stirred for 0.5 h at 0 °C and 0.5 h at room temperature. Saturated aqueous NH_4Cl was then added at 0 °C, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The product was purified by preparative TLC (3:1 hexane:AcOEt) to give 4 mg (14%) of unreacted starting material, 16 mg (42%) of monosubstituted aldehyde **22**, 3.2 mg (8% conversion) of dialdehyde **24**, and 4 mg (10%) of monoaldehyde **23**.

Compound **22**: IR (neat) 1682, 1595 cm^{-1}; ^1H NMR δ 0.90 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 1.01 (s, 3H), 1.19 (m, 1H), 1.22 (s, 3H), 1.52–2.25 (m, 12H), 2.89 (m, 1H), 3.78 (s, 3H, minor diastereomer), 3.79 (s, 3H), 3.81 (s, 3H, minor diastereomer), 3.82 (s, 3H), 6.12 (s, 1H, minor diastereomer), 6.14 (s, 1H), 10.27 (s, 1H, minor diastereomer), 10.28 (s, 1H); MS, m/z (rel intensity) 386 (M^+, 78), 328 (89), 251 (54), 195 (100).

Compound **23**: IR (neat) 1677, 1595 cm^{-1}; ^1H NMR δ 0.89 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.3 Hz, 3H), 1.00 (s, 3H), 1.23 (m, 1H), 1.27 (s, 3H), 1.49–2.23 (m, 12H), 2.86 (m, 1H), 3.79 (s, 3H, minor diastereomer), 3.82 (s, 3H, minor diastereomer), 3.86 (s, 3H), 3.88 (s, 3H), 5.99 (s, 1H), 10.36 (s, 1H); MS, m/z (rel intensity) 386 (M^+, 68), 328 (49), 251 (94), 195 (100).

Compound **24**: Spectral data were in agreement with those of Salomon[2b,c] (cf. also supplementary material).

Formylation of 22. n-BuLi (0.09 mmol, 0.035 mL of a 2.48 M solution in hexanes) was added to a solution of *N*-methylpiperazine (0.09 mmol, 0.01 mL) in THF (0.5 mL) at −78 °C. The solution was warmed to 0 °C for 15 min and then was cooled to −78 °C. Monoaldehyde **22** (27 mg, 0.07 mmol) in THF (0.5 mL) was added, and the resulting mixture was stirred at −78 °C for 30 min. n-BuLi (0.29 mmol; 0.117 mL of a 2.48 M solution in hexanes) was then added and the solution was warmed to 0 °C for 1 h. After cooling to −78 °C, DMF (0.022 mL, 0.29 mmol) was added, and the resulting mixture was stirred at −78 °C for 30 min and for 2 h at 0 °C. Quenching with saturated NH_4Cl, followed by extraction with CH_2Cl_2 and purification of the crude product by preparative TLC (4:1 hexane:AcOEt), yielded the starting material **22** (10 mg, 36%) and the dialdehyde **24** (3 mg, 10%).

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Supplementary Material Available: Details of synthesis of compounds **3a**, **3b**, **24**, **25**, and **26** by the Salomon method and spectral data for these compounds (6 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.