JOC Article

Synthesis of Optically Pure (+)-Puraquinonic Acid and Assignment of Absolute Configuration to Natural (−)-Puraquinonic Acid. Use of Radical Cyclization for Asymmetric Generation of a Quaternary Center

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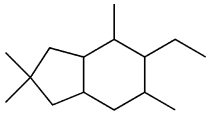
An asymmetric aldol reaction between aldehyde **31** and imide **32**, followed at a later stage by ring-closing metathesis (**38** → **40**), are key reactions used to make optically pure allylic alcohol **40**. Radical cyclization of the derived Stork bromo acetals gives lactol ethers **43**, which were degraded to generate a quaternary center carrying a methoxycarboxyl group (**44** → **47**). Compound **47** was converted into (+)-puraquinonic acid; and comparison with a natural sample established that the configuration of the natural compound is 2*R* (**1**).

Introduction

Puraquinonic acid (**1**)[1] is a norilludalane[2] fungal metabolite with the property of inducing differentiation in HL-60 cells (human promyelocytic leukemia). This is an important property because there is evidence[3] that induction of cell differentiation suppresses cell proliferation. Puraquinonic acid may, therefore, serve as a lead compound in the design of drugs to treat leukemia. The absolute configuration was established by an asymmetric synthesis reported from this laboratory;[4] the present paper gives full details of that work, as well as of model studies on the method for constructing the quaternary center. This method is probably a general one. The structurally related compounds **2** (deliquinone) and **3** (2,9-epoxydeliquinone) have been isolated[5] from injured fruit bodies of the fungus *Russula delica*, but no evaluation of the biological properties of these metabolites has been reported.

(1) Becker, U.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 229−236.

(2) Illudalanes have the skeleton (i): (a) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199−2248. (b) Arnone, A.; Cardillo, R.; Di Modugno, V.; Nasini, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1995−2000.



i

(3) (a) Degos, L. *Leukemia Res.* **1990**, *14*, 717−719. (b) Suh, N.; Luyengi, L.; Fong, H. H. S.; Kinghorn, A. D.; Pezzuto, J. M. *Anticancer Res.* **1995**, *15*, 233−240. (c) Mason, M. D. In *Molecular Biology for Oncologists*; Yarnold, J. R., Stratton, M. R., McMillan, T. J., Eds.; Chapman and Hall: London, 1996; pp 112−121.

(4) Clive, D. L. J.; Yu, M. *J. Chem. Soc., Chem. Commun.* **2002**, 2380−2381.

(5) Clericuzio, M.; Han, F.; Pan, F.; Pang, Z.; Sterner, O. *Acta Chem. Scand.* **1998**, *52*, 1333−1337.

Discussion

The main obvious challenge posed by an asymmetric synthesis[6,7] of puraquinonic acid is construction of the quaternary[8] center C(2); this is a complex problem because the asymmetry is due to structural differences far removed from C(2) (Figure 1). Our first approach was based on an attempt at asymmetric acylation. To this end, indanone **4** was converted into its SAMP hydrazone **6** (Scheme 1) and subjected first to alkylation[9] (LDA, MeI) and then to conditions[10] for acylation (*n*-BuLi, *t*-BuOK, MeOC(O)CN). Although this sequence did indeed serve to introduce both a methyl and MeO_2C group, the product **7** was a 1:1 mixture of both possible diastereoisomers. We did not examine other potential methods for asymmetric acylation[11] (or alkylation[8]); instead, we decided to generate the required quaternary center by radical cyclization, along the lines of Scheme 2. This scheme summarizes several experiments done with racemic materials.

Luche reduction of the simple indenone **8**,[12] which served us as a test model, gave the expected racemic

(6) Synthesis of racemic puraquinonic acid: (a) Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954−961. (b) Hisaindee, S.; Clive, D. L. J. *Tetrahedron Lett.* **2001**, *42*, 2253−2255.

(7) Synthesis of (±)-deliquinone and (±)-puraquinonic acid ethyl ester: Kraus, G. A.; Choudhury, P. K. *Tetrahedron Lett.* **2001**, *42*, 6649−6650.

(8) Construction of quaternary centers: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389−401. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (e) Hayashi, T.; Tang, J.; Kato, K. *Org. Lett.* **1999**, *1*, 1487−1489.

(9) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253−2329.

(10) Enders, D.; Zamponi, A.; Raabe, G. *Synlett* **1992**, 897−900.

(11) Compare: Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050−4051 and references therein.

(12) (a) Floyd, M. B.; Allen, G. R., Jr. *J. Org. Chem.* **1970**, *35*, 2647−2653. (b) Galatsis, P.; Manwell, J. J.; Blackwell, J. M. *Can. J. Chem.* **1994**, *72*, 1656−1659.

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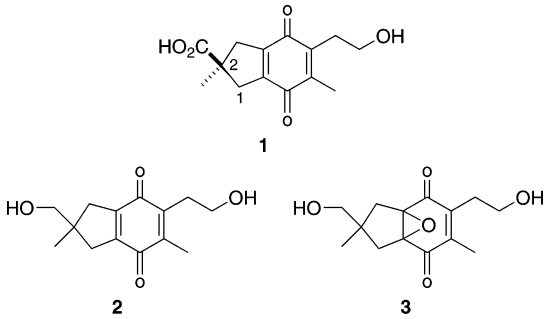
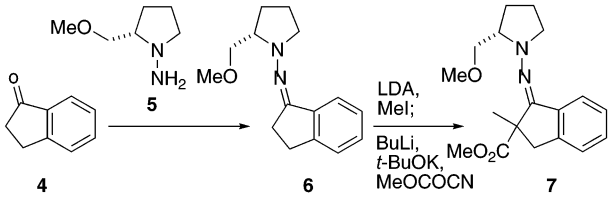


1 **2** **3**

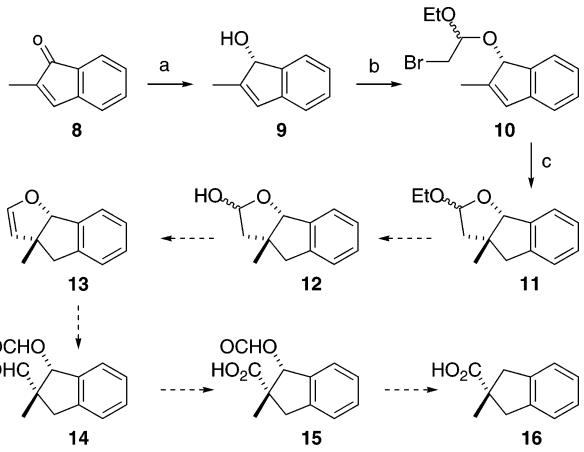
FIGURE 1.

SCHEME 1



4 **5** **6** **7**

SCHEME 2[a]

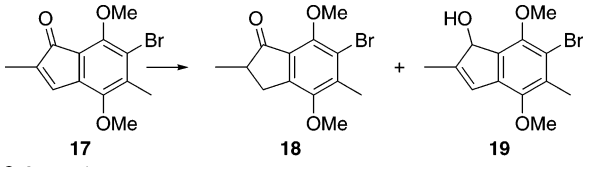


8 **9** **10** **11** **12** **13** **14** **15** **16**

[a] Reagents and conditions: (a) $LiBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 99%; (b) ethyl vinyl ether, −20 °C, NBS, 90%; (c) Bu_3SnH and AIBN (added in one lot), PhH, 80 °C, 70%, or Bu_3SnCl, AIBN, $NaBCNH_3$, *t*-BuOH, 80 °C, 68%.

alcohol **9**, and this was converted into the derived Stork bromo acetals[13] (**10**) by reaction with ethyl vinyl ether in the presence of NBS. Radical cyclization then gave the lactol ethyl ethers **11**. Unlike most radical cyclizations, this one worked best (70%) when the stannane and initiator were added in one lot, rather than by slow addition. A similar yield (68%) was obtained using Bu_3SnCl, AIBN, and $NaCNBH_3$ in refluxing *t*-BuOH.[14] Because the cyclization **10** → **11** is a 5-*exo* closure onto a double bond contained in a five-membered ring, it must proceed with the stereochemical outcome shown.[13b,15] The formation of **11** established that a quaternary center could indeed be generated efficiently, with the stereochemistry being controlled by the stereochemistry of the starting alcohol. We decided not take this model sequence any further, because we were confidant that the subsequent steps—hydrolysis to **12**, dehydration to **13**, and degradation of **13**, **14**, and **15** to give the (achiral) acid **16**—would be straightforward, as indeed they later proved to be when applied to appropriately substituted compounds.

SCHEME 3



17 **18** **19**

Application of the model sequence of Scheme 2 to the actual asymmetric synthesis of puraquinonic acid depends, of course, on the ability to generate an optically pure alcohol corresponding to **9**, but carrying appropriate substituents on the aromatic ring. However, attempts to reduce enone **17** (which we regarded as a suitable[16] starting ketone) with (*S*)-CBS-$BH_3 \cdot SMe_2$[18] or with $LiAlH(O\text{-menthyl})_3$[19] were unsuccessful,[20] and we were prompted to develop a different route to the required optically active allylic alcohol. This route, which leads to allylic alcohol **40** (see Scheme 5), is based on an asymmetric aldol reaction to set the hyrdoxyl stereochemistry (see Scheme 5, **31** → **33**), followed by ring-closing metathesis to generate the double bond of the allylic alcohol (Scheme 5, **38** → **40**).

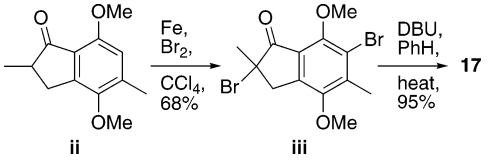
Aldehyde **31**, required for the aldol step, was made as summarized in Scheme 4. The known phenolic aldehyde **20**[21] was allylated in the standard way (NaH, DMF, allyl bromide, 79%), and then Claisen rearrangement (ca. 200 °C, 66%) produced the expected phenol **22**. This was converted (83%) into quinone acetal **23** by oxidation[25]

(13) (a) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500−501.

(14) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384−6385.

(15) Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353−355.

(16) The bromine should provide an opportunity for attachment of a vinyl group that would serve as a precursor for the required CH_2CH_2OH substituent. Compound ii, made by methylation (MeI, K_2CO_3, DMF, 70 °C, 5 h, 64%) of the corresponding bisphenol,[17] was brominated (ii → iii, Fe, Br_2, CCl_4, 68%), and treatment with DBU then gave **17**:



ii **iii**

(17) Kundiger, D. G.; Ovist, E. B. W. U.S. Patent 2,881,218.

(18) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(19) Cf. Andrisano, R.; Angeloni, A. S.; Marzocchi, S. *Tetrahedron* **1973**, *29*, 913−916.

(20) With (*S*)-CBS−$BH_3 \cdot SMe_2$ the yield of allylic alcohol (of unestablished chirality) was low (13%) and formation of the corresponding saturated ketone was a major pathway (34%). With $LiAlH(O\text{-menthyl})_3$, the allylic alcohol (69%) was racemic.

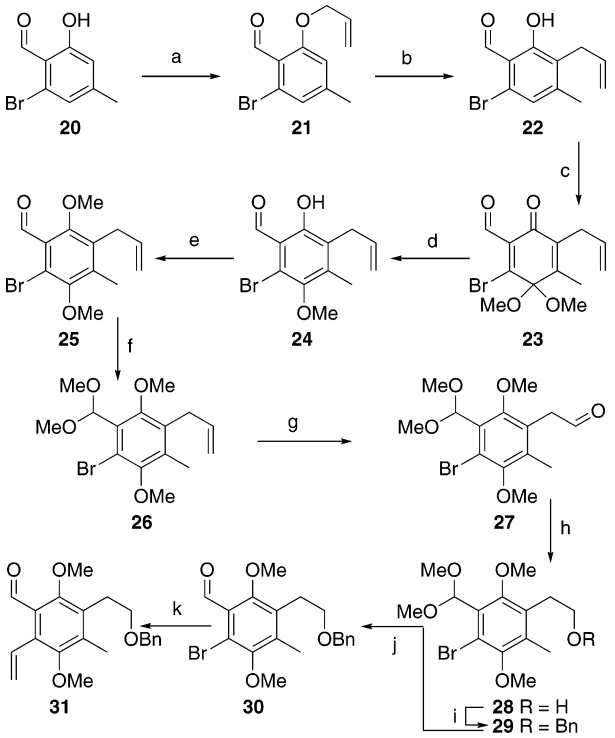
(21) Made from 2,5-dimethylphenol by the method of ref 22, except that the formyl group was best generated by benzylic bromination,[23] followed by oxidation with DMSO (see ref 24 and Supporting Information).

(22) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774−2783.

(23) Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098−1106.

(24) Compare: (a) Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227−6238. (b) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 7, 247−260.

SCHEME 4[a]



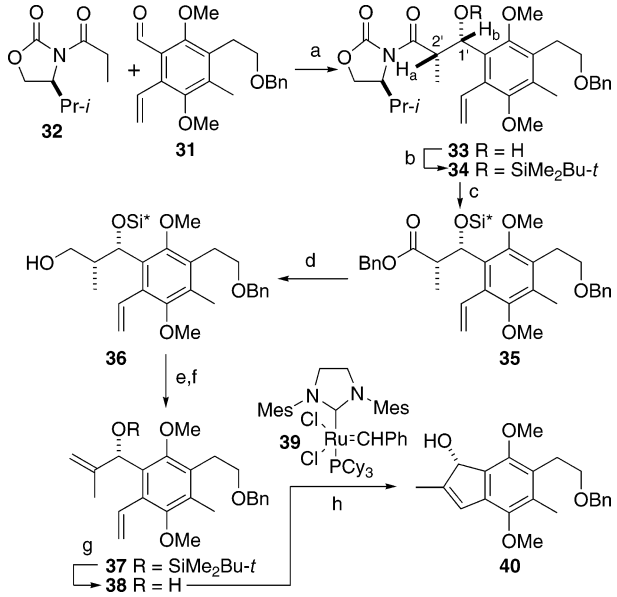
[a] Reagents and conditions: (a) NaH, allyl bromide, DMF, 2 h, 79%; (b) degassed *trans* Decalin, reflux, 7 h, 66%; (c) $PhI(OAc)_2$, MeOH, 12 h, 83%; (d) Zn powder, AcOH, 7 h, 70%; (e) MeI, K_2CO_3, DMF, 12 h, 92%; (f) $(MeO)_3CH$, $TsOH{\cdot}H_2O$, MeOH, reflux, 12 h, 97%; (g) OsO_4 (catalytic), $NaIO_4$, 5:2:2 CCl_4−water−*t*-BuOH, 1.5 h, 95%; (h) $NaBH_4$, MeOH, 0 °C, 1.5 h, 95%; (i) NaH, BnBr, THF, 12 h, 92%; (j) 1:1 acetone−water, Amberlite IR-120, 12 h, 95%; (k) $Bu_3(CH_2{=}CH)Sn$, CuI, $Pd(PPh_3)_4$, PhMe, reflux, 40 h, 66%.

with $PhI(OAc)_2$ in MeOH, and the benzene ring was then regenerated by reduction with Zn dust[26] (**23** → **24**, 70%). Finally, the remaining phenolic hydroxyl was protected by *O*-methylation (MeI, K_2CO_3, DMF, 92%), bringing the work as far as aldehyde **25**.

At this point it was necessary to replace the bromine by a vinyl group and to cleave the pendant double bond oxidatively. To this end, aldehyde **25** was protected as its dimethyl acetal [**25** → **26**, $(MeO)_3CH$, MeOH, $TsOH{\cdot}H_2O$, 97%], and the pendant double bond was cleaved with the OsO_4−$NaIO_4$ combination (**26** → **27**, 95%); reduction ($NaBH_4$) then gave an alcohol (**27** → **28**, 95%), which was protected as its benzyl ether (**28** → **29**; NaH, BnBr, 92%). Acid-catalyzed hydrolysis of the acetal function (**29** → **30**, 95%) and Stille coupling with tributylvinylstannane in the presence of $(Ph_3P)_4Pd$ served to introduce the required vinyl group (**30** → **31**, 66%), bringing us to the point at which we were ready to try the asymmetric aldol reaction.

Condensation of **31** with (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone (**32**),[27] mediated by $Bu_2BOSO_2CF_3$,[28] gave

SCHEME 5[a]



[a] Reagents and conditions: (a) $Bu_2BOSO_2CF_3$, *i*-Pr_2NEt, CH_2Cl_2, −78 to 25 °C, 87%; (b) *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 1 h, 95%; (c) BnOLi, THF, 0 °C, 6 h, 89%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 89%; (e) *o*-$(NO_2)C_6H_4SeCN$, Bu_3P, THF, 12 h; (f) 30% H_2O_2, THF, 5 h, 81% from **36**; (g) Bu_4NF, THF, 36 h, 95%; (h) tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-yliden][benzylidene]ruthenium(IV) dichloride (**37**), CH_2Cl_2, reflux, 20 h, 88%.

the condensation product **33** in high yield (87%). We used a boron-mediated aldol process because of its generally excellent stereoselectivity, and in the event, we did not detect any other stereoisomer. The hydroxyl was protected by silylation (**33** → **34**, *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, 95%), and the chiral auxiliary was removed by treatment with BnOLi[27] (95%). The resulting ester **35** was then reduced to alcohol **36** (DIBAL-H, CH_2Cl_2, 89%). At this point, conversion to olefin **37** was achieved by replacing the hydroxyl with an *o*-nitrophenylseleno group [*o*-$(NO_2)C_6H_4SeCN$, Bu_3P, THF][29] and oxidizing the resulting selenide (H_2O_2, THF, 81% overall). Treatment of **37** with Bu_4NF in THF effected desilylation (**37** → **38**, 95%), and the stage was now set for the crucial ring-closing metathesis that would form the five-membered ring of puraquinonic acid. Heating alcohol **38** with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride[30] (**39**) in CH_2Cl_2 gave the optically active allylic alcohol **40** in 88% yield. The ring-closing metathesis is sensitive to steric factors, since attempts to effect the reaction with the silicon protecting group in place were unsuccessful.[31] Examination of alcohol **40** by HPLC, using a chiral column, and comparison with a racemic sample[32] showed that **40** had ee >98%.

(25) (a) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891−1896. (b) Camps, P.; González, A.; Muñoz-Torreo, D.; Simon, M.; Zúñiga, A.; Martins, M. A.; Font-Bardia, M.; Solans, X. *Tetrahedron* **2000**, *56*, 8141−8151.

(26) Compare: Iguchi, M.; Nishiyama, A.; Etoh, H.; Okamoto, K.; Yamamura, S.; Kato, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4910−4915.

(27) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5313.

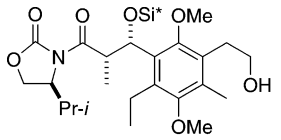
(28) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Entwistle, D. A.; Jordan, S. I.; Montgomery, J.; Pattenden, G. *Synthesis* **1998**, 603−612.

(29) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

(30) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147.

(31) We tried Schrock's catalyst (2,6-diisopropylphenylimidoneophylidene molybdenum(VI) bis(hexafluoro)-*tert*-butoxide) and Grubbs' first generation catalyst (bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride).

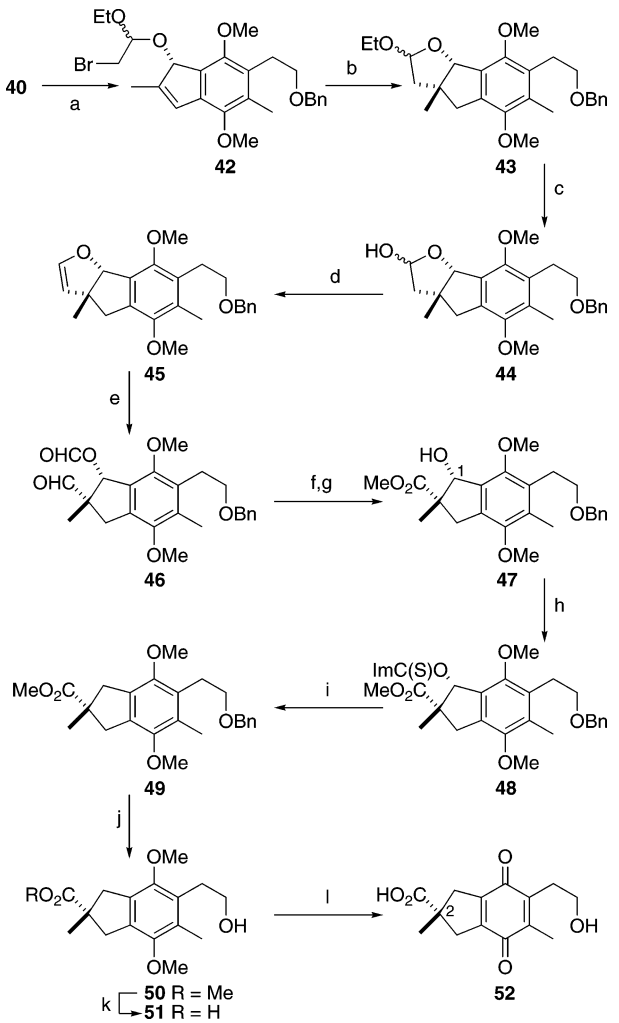
The absolute configuration of **40** is, of course, set by the configuration of the aldol product **33**. We initially[4] assigned the *anti* stereochemistry (H_a and Me at C(2′) in **33** interchanged) because the coupling constant for the C(1′)H_a signal (J_{ab} = 9.3 Hz) suggested[33,34] such a relationship for the substituents at C(1′) and C(2′). This interpretation assumes the extended conformation shown for **33**, and we later sought additional evidence for the assignment. Attempts to obtain a crystalline derivative eventually led us to hydrogenate **35** (Pd/C, H_2). The resulting alcohol **41** is crystalline, and X-ray analysis revealed that the aldol reaction actually gives the normal *syn* product shown (**33**). The C(2′) stereochemistry is destroyed in a later step (**36** → **37**), but the X-ray determination serves both to clarify the outcome of the aldol condensation and confirm the absolute configuration at the hydroxyl-bearing carbon. The alcohol was



41 Si* = $SiMe_2Bu$-*t*

converted into the Stork bromo acetals (**40** → **42**, 91%) by adding bromine to ethyl vinyl ether, followed by addition of a mixture of the alcohol and 2,6-lutidine. This procedure generally works well for making bromo acetals.[35] The acetals were then subjected to free radical cyclization (**42** → **43**, 85%), by adding Bu_3SnH and AIBN in one lot, conditions that had been established in the model study of Scheme 2. The next task was to degrade the newly formed heterocycle so as to eventually release both the desired carboxyl and the original hydroxyl; the latter, having served its purpose, would then be removed. Acid hydrolysis of the lactol ethyl ethers **43** replaced the ethoxy group by a hydroxyl (**43** → **44**, 91%), and mesylation in refluxing THF then gave the required elimination product **45** directly (75%). The stage was now set for cleavage of the heterocyclic ring. This was best done with OsO_4 and $NaIO_4$ rather than with O_3 and gave aldehyde formate **46**. The aldehyde group was oxidized directly under standard conditions[36] to a carboxyl group, which was immediately trapped as its methyl ester. Finally, methanolysis (MeOH, K_2CO_3) served to hydrolyze the formyl ester at C(1) (**45** → **46** → **47**, 54% overall). The resulting hydroxyl group was removed by Barton deoxygenation[6b,37] via the thiocarbonylimidazolide (**47** → **48**, 96%; **48** → **49**, 77%). The benzyl group was now removed by hydrogenolysis (**49** → **50**, Pd−C, H_2, 96%), and the ester was hydrolyzed (LiOH·H_2O, THF, 95%), bringing the work as far as the bismethyl ether **51**.

SCHEME 6[a]



[a] Reagents and conditions: (a) ethyl vinyl ether, Br_2, CH_2Cl_2, 2,6-lutidine, 20 h, 91%; (b) Bu_3SnH and AIBN (both added in one portion), PhMe, reflux, 1.5 h, 85%; (c) 1:4 AcOH−water, THF, reflux, 12 h, 91%; (d) MsCl, Et_3N, THF, 2 h, then reflux, 1 h, 75%; (e) OsO_4 (catalytic), $NaIO_4$, 5:2:2 CCl_4−water−*t*-BuOH, 9 h; (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, 3 h; (g) CH_2N_2, Et_2O, then MeOH, K_2CO_3, 54% from **45**; (h) Im_2CS, DMAP, CH_2Cl_2, reflux, 19 h, ca. 96%; (i) Bu_3SnH, AIBN, PhMe, reflux, 1.5 h, 73−77%; (j) H_2 (balloon), Pd−C, MeOH, 30 min, 96%; (k) LiOH·H_2O, 1:1 dioxane−water, 3 h, 95%; (l) $Ce(NH_4)_2(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide, 2:1 MeCN−water, 5 h, 81%.

Generation of the quinone was initially troublesome, but we quickly found that $(NH_4)_2Ce(NO_2)_6$ in the presence of 2,6-pyridinedicarboxylic acid *N*-oxide[38] is an effective reagent combination, which liberates (+)-puraquinonic acid (**52**) in 81% yield. The presence of the pyridine diacid is essential; without it there is hardly any oxidation. Our synthetic material has $[\alpha]^{22}_D$ +3.2 (*c* 0.3 $CHCl_3$), $[\alpha]^{22}_D$ +3.1 (*c* 0.7 CH_2Cl_2), values close to that reported ($[\alpha]^{22}_D$ +1 (*c* 1.0 $CHCl_3$)]. However, HPLC comparison (CHIRACEL OD-RH) with an authentic sample showed that the synthetic and natural compounds were enantiomeric. Consequently, we remeasured the specific rotation of the natural compound and found that the value

(32) Made by reduction ($LiBH_4$, $CeCl_3$·$7H_2O$; 90%) of the ketone corresponding to **40**. We thank S. Hisaindee of this laboratory for a sample of the ketone.

(33) Cf. Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173−181.

(34) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 111−212.

(35) For another example where this method was the best of several we tried, see: Clive, D. L. J.; Huang, X. *Tetrahedron* **2002**, *58*, 10243−10250.

(36) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(37) Compare: Miyazaki, T.; Sato, H.; Sakakibara, T.; Kajihara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5678−5694.

(38) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521−522.

is actually −2.2 [*c* 0.55, $CHCl_3$]; therefore we assign the 2*R* absolute configuration to natural (−)-puraquinonic acid, as shown in **1**.

Conclusion

The present synthesis illustrates how sequential use of an asymmetric aldol reaction, ring-closing metathesis, and radical cyclization can be used to construct a quaternary asymmetric center whose stereochemistry is determined by the outcome of the initial aldol process. In the case of puraquinonic acid, the asymmetry of C(2) is due to differences far removed from that site, and the present approach is probably a general one for handling such situations. Our work has also established the absolute configuration of puraquinonic acid.

Experimental Section

2-Allyloxy-6-bromo-4-methylbenzaldehyde (21). A solution of aldehyde **20**[21,22] (0.783 g, 3.66 mmol) in dry DMF (3 mL) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) slurry of NaH (60% in mineral oil, 182.8 mg, 4.57 mmol) in dry DMF (10 mL). The cool bath was removed, and stirring was continued for 2 h. The solution was recooled to 0 °C, and allyl bromide (0.628 mL, 7.3 mmol) was added dropwise over ca. 5 min. The cold bath was removed, and stirring was continued for 7 h. The mixture was poured into brine (10 mL) and extracted with Et_2O (4 × 20 mL). The combined organic extracts were washed with KOH (10%, 2 × 5 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:20 EtOAc−hexane, gave allyl ether **21** (0.733 g, 79%) as white needles: mp 59 °C; FTIR (acetone cast) 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3 H), 4.56 (d, J = 5.2 Hz, 2 H), 5.27 (d, J = 12.0 Hz, 1 H), 5.43 (d, J = 18.0 Hz, 1 H), 5.94−6.04 (m, 1 H), 6.68 (s, 1 H), 7.00 (s, 1 H), 10.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 69.5 (t), 113.1 (d), 118.0 (t), 121.0 (s), 124.3 (s), 127.4 (d), 132.0 (d), 146.3 (s), 161.1 (s), 189.5 (d); exact mass *m*/*z* calcd for $C_{11}H_{11}{}^{79}BrO_2$ 253.99425, found 253.99434.

3-Allyl-6-bromo-2-hydroxy-4-methylbenzaldehyde (22). *trans*-Decalin was degassed by several freeze−thaw cycles (dry ice/acetone and oil-pump vacuum). A solution of allyl ether **21** (197.9 mg, 0.778 mmol) in degassed Decalin (8 mL) was refluxed under N_2 for 7 h and then cooled to room temperature. Flash chromatography of the mixture (without evaporation of the solvent) over silica gel (1.5 × 20 cm), using 1:40 EtOAc−hexane, gave phenol **22** (130.2 mg, 66%) as a slightly yellow oil: FTIR (CH_2Cl_2 cast) 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3 H), 3.35−3.37 (m, 2 H), 4.88−4.99 (m, 2 H), 5.76−5.92 (m, 1 H), 6.94 (s, 1 H), 10.17 (s, 1 H), 12.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (q), 29.3 (t), 115.2 (t), 115.7 (s), 124.7 (s), 126.2 (d), 126.7 (s), 134.3 (d), 148.3 (s), 162.0 (s), 197.4 (d); exact mass *m*/*z* calcd for $C_{11}H_{11}{}^{79}BrO_2$ 253.99425, found 253.99411.

5-Allyl-2-bromo-3,3-dimethoxy-4-methyl-6-oxo-1,4-cyclohexadienecarbaldehyde (23). A solution of $PhI(OAc)_2$ (362 mg, 1.126 mmol) in MeOH (5 mL) was added dropwise over 30 min to a stirred solution of phenol **22** (130 mg, 0.512 mmol) in MeOH (5 mL), and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the yellow residue over silica gel (2 × 20 cm), using 7:40 EtOAc−hexane, gave ketal **23** (133 mg, 83%) as a yellow oil: FTIR (CH_2Cl_2 cast) 1737, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (s, 3 H), 3.07 (s, 6 H), 3.21 (d, J = 6.2 Hz, 2 H), 4.99−5.06 (m, 2 H), 5.68−5.82 (m, 1 H), 10.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4 (q), 29.5 (t), 51.1 (q), 97.3 (s), 116.2 (t), 133.6 (d), 137.2 (s), 138.4 (s), 150.6 (s), 150.9 (s), 180.2 (s), 189.0 (d); exact mass *m*/*z* calcd for $C_{13}H_{15}{}^{79}BrO_4$ 314.01538, found 314.01534.

3-Allyl-6-bromo-2-hydroxy-5-methoxy-4-methylbenzaldehyde (24). Zinc powder (2.30 g, 35.4 mmol) was added to a stirred solution of ketal **23** (3.75 g, 11.8 mmol) in AcOH (80 mL), and the mixture was stirred for 7 h. The excess of Zn powder was removed by gravity filtration, and the mixture was diluted with water (20 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 21 cm), using 1:20 EtOAc−hexane, gave phenol **24** (2.36 g, 70%) as yellow oil: FTIR (CH_2Cl_2 cast) 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.32 (s, 3 H), 3.40−3.42 (m, 2 H), 3.74 (s, 3 H), 4.91−5.01 (m, 2 H), 5.82−5.90 (m, 1 H), 10.26 (s, 1 H), 12.24 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (q), 29.7 (t), 60.5 (q), 115.4 (t), 115.5 (s), 119.1 (s), 127.7 (s), 134.3 (d), 142.7 (s), 148.5 (s), 158.7 (s), 197.7 (d); exact mass *m*/*z* calcd for $C_{12}H_{13}{}^{79}BrO_3$ 284.00479, found 284.00464.

3-Allyl-6-bromo-2,5-dimethoxy-4-methylbenzaldehyde (25). MeI (1.06 mL, 17.0 mmol) was added dropwise over ca. 5 min to a stirred mixture of phenol **24** (483 mg, 1.70 mmol) and K_2CO_3 (2.35 g, 17.0 mmol) in dry DMF (40 mL). Stirring was continued overnight, and the solids were then filtered off. The filtrate was poured into brine (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:20 EtOAc−hexane, gave aldehyde **25** (464.5 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1738, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 3.41−3.43 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.84−4.89 (m, 1 H), 5.02−5.05 (m, 1 H), 5.84−5.94 (m, 1 H), 10.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 13.6 (q), 30.5 (t), 60.4 (q), 64.0 (q), 115.8 (t), 118.1 (s), 126.5 (s), 133.6 (s), 135.0 (d), 139.4 (s), 152.4 (s), 156.8 (s), 190.7 (d); exact mass *m*/*z* calcd for $C_{13}H_{15}O_3{}^{79}Br$ 298.02045, found 298.02097.

1-Allyl-4-bromo-3-dimethoxymethyl-2,5-dimethoxy-6-methylbenzene (26). $HC(OMe)_3$ (5 mL, 45.75 mmol) was added dropwise over ca. 5 min to a stirred solution of aldehyde **25** (464.5 mg, 1.56 mmol) in dry MeOH (20 mL) containing $TsOH{\cdot}H_2O$ (29.6 mg, 0.156 mmol). The mixture was refluxed overnight, cooled, filtered, and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:20 EtOAc−hexane, gave acetal **26** (520.5 mg, 97%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 3 H), 3.38−3.42 (m, 2 H), 3.44 (s, 6 H), 3.719 (s, 3 H), 3.722 (s, 3 H), 4.82−4.87 (m, 1 H), 4.99−5.02 (m, 1 H), 5.64 (s, 3 H), 5.86−5.96 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0 (q), 31.0 (t), 55.9 (q), 60.2 (q), 63.4 (q), 105.2 (d), 115.4 (t), 116.2 (s), 128.8 (s), 132.6 (s), 133.5 (s), 135.6 (d), 152.2 (s), 154.2 (s); exact mass *m*/*z* calcd for $C_{15}H_{21}O_4{}^{79}Br$ 344.06232, found 344.06215.

(4-Bromo-3-dimethoxymethyl-2,5-dimethoxy-6-methylphenyl)acetaldehyde (27). OsO_4 (1.4 mg, 5% mol) was added to a stirred solution of acetal **26** (38 mg, 0.11 mmol) in 5:2:2 CCl_4−H_2O−*t*-BuOH (5 mL) (the starting material was dissolved in CCl_4−*t*-BuOH, and H_2O was added last). After 30 min, $NaIO_4$ (59 mg, 0.276 mmol) was added in one portion. Stirring was continued for 1.5 h, and the suspension was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 10% aqueous $NaHSO_3$ (8 mL) and water (8 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 7:40 EtOAc−hexane, gave aldehyde **27** (36.5 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3 H), 3.45 (s, 6 H), 3.67 (s 3 H), 3.72−3.73 (m, 5 H), 5.63 (s, 1 H), 9.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (q), 42.5 (t), 56.0 (q), 60.3 (q), 62.9 (q), 105.4 (d), 118.0 (s), 126.7 (s), 129.3 (s), 133.6 (s), 152.3 (s), 154.4 (s), 198.3 (d); exact mass *m*/*z* calcd for $C_{14}H_{19}O_5{}^{79}Br$ 346.04160, found 346.04108.

2-(4-Bromo-3-dimethoxymethyl-2,5-dimethoxy-6-methylphenyl)ethanol (28). A solution of aldehyde **27** (400 mg,

1.18 mmol) in dry MeOH (20 mL) was cooled in an ice bath, and $NaBH_4$ (52 mg, 1.36 mmol) was added. Stirring at 0 °C was continued for 1.5 h, water (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:1 EtOAc−hexane, gave alcohol **28** (380 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3439 cm^{-1} (br); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.88 (br s, 1 H), 2.29 (s, 3 H), 2.91 (t, J = 7.0 Hz, 2 H), 3.45 (s, 6 H), 3.73−3.77 (m, 5 H), 3.78 (s, 3 H), 5.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5 (q), 30.6 (t), 56.0 (q), 60.3 (q), 62.3 (t), 63.2 (q), 105.2 (d), 116.6 (s), 128.8 (s), 131.7 (s), 133.2 (s), 152.3 (s), 154.3 (s); exact mass m/z calcd for $C_{14}H_{21}{}^{79}BrO_5$ 348.05722, found 348.05776.

1-(2-Benzyloxyethyl)-4-bromo-3-dimethoxymethyl-2,5-dimethoxy-6-methylbenzene (29). A solution of alcohol **28** (301 mg, 0.865 mmol) in THF (10 mL) was added dropwise over about 10 min to a stirred and cooled (0 °C) slurry of NaH (60% in oil, 66 mg, 1.72 mmol) in THF (10 mL). The cooling bath was removed, and stirring was continued for 3.5 h. The mixture was then recooled to 0 °C, and BnBr (0.197 mL, 1.67 mmol) was added dropwise over ca. 2 min. The cold bath was left in place, and stirring was continued overnight. Brine (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 7:40 EtOAc−hexane, gave benzyl ether **29** (346 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2933, 2856 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3 H), 2.96 (t, J = 7.5 Hz, 2 H), 3.44 (s, 6 H), 3.55 (t, J = 7.5 Hz, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 4.49 (s, 2 H), 5.61 (s, 1 H), 7.22−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3 (q), 27.9 (t), 55.9 (q), 60.2 (q), 63.3 (q), 69.3 (t), 72.9 (t), 105.2 (d), 116.3 (s), 127.5 (d), 128.3 (d), 128.8 (s), 131.8 (s), 133.4 (s), 138.3 (s), 152.2 (s), 154.6 (s); exact mass (electrospray) m/z calcd for $C_{21}H_{27}{}^{79}BrNaO_5$ (M + Na) 461.093955, found 461.093774.

3-(2-Benzyloxyethyl)-6-bromo-2,5-dimethoxy-4-methylbenzaldehyde (30). Amberlite IR 120 (10 mg) was added to a stirred solution of acetal **29** (60 mg, 0.137 mmol) in acetone (5 mL) containing H_2O (5 mL), and stirring was continued overnight. The resin was removed by gravity filtration, and the filtrate was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 1:8 EtOAc−hexane, gave aldehyde **30** (51 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3 H), 2.98 (t, J = 7.0 Hz, 2 H), 3.58 (t, J = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.49 (s, 2 H), 7.22−7.32 (m, 5 H), 10.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 27.6 (t), 60.4 (q), 63.8 (q), 69.1 (t), 76.0 (t), 118.5 (s), 126.1 (s), 127.4 (d), 127.5 (d), 128.3 (d), 132.9 (s), 138.1 (s), 139.5 (s), 152.2 (s), 157.0 (s), 190.6 (d); exact mass m/z calcd for $C_{19}H_{21}{}^{79}BrO_4$ 392.06232, found 392.06222.

3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-2-vinylbenzaldehyde (31). $(Ph_3P)_4Pd$ (13.2 mg, 0.011 mmol) was added to a stirred mixture of bromide **30** (90 mg, 0.229 mmol), tributyl vinyl tin (87.1 mg, 0.275 mmol), CuI (3.0 mg, 0.016 mmol), and PhMe (15 mL) under N_2. The mixture was stirred and refluxed for 4 h, and then a second portion of $(Ph_3P)_4Pd$ (ca 6.0 mg, 0.005 mmol) was added. Refluxing was continued for 24 h, and a third portion of $(Ph_3P)_4Pd$ (ca 6.0 mg, 0.005 mmol) was added. Refluxing was continued for 12 h, and the solution was cooled, filtered, and evaporated. Flash chromatography of the residue over silica gel (2 × 17 cm), using 30:10:1 CH_2Cl_2−hexanes−EtOAc, gave aldehyde **31** (51 mg, 66%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1693, 1716, 1759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3 H), 3.00 (t, J = 7.5 Hz, 2 H), 3.58 (t, J = 7.5 Hz, 2 H), 3.60 (s, 3 H), 3.79 (s, 3 H), 4.50 (s, 2 H), 5.47 (AB q, $\Delta\nu_{AB}$ = 17.5 Hz, J = 2.0 Hz, 1 H), 5.63 (AB q, $\Delta\nu_{AB}$ = 11.5 Hz, J = 2.0 Hz, 1 H), 7.03 (AB q, $\Delta\nu_{AB}$ = 17.5 Hz, J = 11.5 Hz, 1 H), 7.23−7.28 (m, 5 H), 10.18 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2 (q), 27.5 (t), 60.0 (q), 64.1 (q), 69.3 (t), 72.9 (t), 122.8 (t), 126.6 (s), 127.51 (d), 127.53 (d), 128.3 (d), 129.9 (d), 132.1 (s), 133.1 (s), 138.3 (s), 138.4 (s), 152.7 (s), 156.5 (s), 191.5 (d); exact mass calcd for $C_{21}H_{24}O_4$ 340.16745, found 340.16690.

(4*S*)-3-[(2*S*,3*S*)-3-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-3-hydroxy-2-methylpropionyl]-4-isopropyloxazolidin-2-one (33). A solution of $Bu_2BOSO_2CF_3$ (1.0 M in CH_2Cl_2, 12.97 mL, 12.97 mmol) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of oxazolidinone **32** (2.00 g, 10.8 mmol) in CH_2Cl_2 (30 mL) under N_2. i-Pr_2NEt (2.54 mL, 14.59 mmol) was then added over 10 min. The mixture was stirred at 0 °C for 30 min, then cooled to −78 °C, and stirred for a further 1.5 h. Aldehyde **31** (3.60 g, 10.59 mmol) in CH_2Cl_2 (10 mL) was added over 10 min. Stirring at −78 °C was continued for 1.5 h, the ice bath was removed, and stirring was continued for 6 h. The solution was cooled to 0 °C and quenched by addition of a mixture of MeOH (60 mL) and aqueous buffer (pH = 7, 30 mL). H_2O_2 (30%, 35 mL) was then added, and the solution was stirred at 0 °C for 1 h and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:4 EtOAc−hexane, gave alcohol **33** (4.85 g, 87%) as a colorless oil: $[\alpha]^{25}_D$ +40.154 (c 1.3, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3490 cm^{-1} (br); ^1H NMR (C_6D_6, 300 MHz) δ 0.31 (d, J = 7.0 Hz, 3 H), 0.47 (d, J = 7.0 Hz, 3 H), 1.62 (d, J = 7.0 Hz, 3 H), 1.92−2.04 (m, 1 H), 2.15 (s, 3 H), 2.21 (d, J = 6.5 Hz, 1 H), 2.92−3.08 (m, 2 H), 3.10−3.14 (m, 1 H), 3.22−3.28 (m, 1 H), 3.36 (s, 3 H), 3.50−3.60 (m, 2 H), 3.64−3.69 (m, 1 H), 3.70 (s, 3 H), 4.34 (s, 2 H), 5.00−5.12 (m, 1 H), 5.44−5.50 (m, 2 H), 5.68 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 2.5 Hz, 1 H), 7.02−7.22 (m, 6 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 12.7 (q), 14.7 (q), 16.9 (q), 17.5 (q), 28.4 (t), 28.7 (d), 44.1 (d), 58.3 (q), 59.4 (q), 62.8 (t), 62.9 (d), 70.0 (t), 72.2 (d), 72.9 (t), 120.5 (t), 127.5 (d), 127.6 (d), 128.5 (d), 131.6 (s), 132.16 (s), 132.20 (s), 133.0 (d), 139.2 (s), 153.2 (s), 153.5 (s), 154.5 (s), 175.2 (s), (one peak is obscured by a solvent signal); exact mass m/z calcd for $C_{30}H_{39}NO_7$ 525.27264, found 525.27148.

(4*S*)-3-[(2*S*,3*S*)-3-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-3-(*tert*-butyldimethylsilanyloxy))-2-methylpropionyl]-4-isopropyloxazolidin-2-one (34). Dry 2,6-lutidine (0.40 mL, 3.45 mmol) and then t-$BuMe_2SiOSO_2CF_3$ (0.396 mL, 1.726 mmol) were added dropwise over ca. 3 min to a stirred and cooled (0 °C) solution of alcohol **33** (302 mg, 0.575 mmol) in CH_2Cl_2 (3 mL). The ice bath was removed, and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm), using 30:10:1 CH_2Cl_2−hexanes−EtOAc, gave silyl ether **34** (350 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ +8.1 (c 1.0, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1697, 1785 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) (mixture of rotamers) δ −0.14 (s, 1.34 H), −0.10 (s, 1.70 H), 0.22 (s, 1.31 H), 0.27 (s, 1.76 H), 0.29−0.32 (m, 3 H), 0.46−0.52 (m, 3.49 H), 0.89 (s, 4.08 H), 0.94 (s, 5.35 H), 1.66 (d, J = 6.2 Hz, 1.32 H), 1.70 (d, J = 6.8 Hz, 1.78 H), 1.94−2.04 (m, 1 H), 2.14 (s, 1.23 H), 2.18 (s, 1.73 H), 2.94−3.18 (m, 3 H), 3.22−3.32 (m, 1 H), 3.37 (s, 3 H), 3.50−3.72 (m, 3 H), 3.91 (s, 1.27 H), 4.00 (s, 1.75 H), 4.38−4.42 (m, 2 H), 5.08−5.18 (m, 0.59 H), 5.44−5.56 (m, 0.86 H), 5.62−5.73 (m, 1.63 H), 6.03−6.14 (m, 1 H), 7.0−7.30 (m, 5 H), 7.48 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 11.8 Hz, 0.72 H); ^{13}C NMR (CD_3OD, 100 MHz) (mixture of rotamers) δ −5.0 (q), −4.7 (q), −4.3 (q), −3.8 (q), 12.9 (q), 15.14 (q), 15.19 (q), 17.68 (q), 17.74 (q), 17.94 (q), 17.99 (q), 19.08 (s), 19.11 (s), 26.4 (q), 26.6 (q), 28.7 (t), 29.2 (t), 30.14 (d), 30.19 (d), 44.9 (d), 46.2 (d), 59.7 (q), 59.9 (q), 60.1 (q), 60.2 (q), 62.7 (d), 63.5 (d), 64.83 (t), 64.86 (t), 70.50 (t), 70.60 (t), 72.6 (d), 73.7 (t), 73.8 (t), 74.5 (d), 120.3 (t), 122.0 (t), 128.58 (d), 128.61 (d), 128.63 (d), 128.76 (d), 129.3 (d), 129.4 (d), 130.9 (s), 132.0 (s), 132.76 (s), 132.79 (s), 133.1 (d), 133.3 (s), 133.4 (s), 133.6 (d), 139.8 (s), 139.9 (s), 153.4 (s), 154.2 (s), 154.6 (s), 155.2 (s), 155.4 (s), 155.8 (s), 176.1 (s), 177.1 (s); exact mass

(electrospray) *m*/*z* calcd for $C_{36}H_{53}NNaO_7Si$ (M + Na) 662.348902, found 662.348778.

(2*S*,3*S*)-3-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropionic Acid Benzyl Ester (35). *n*-BuLi (2.5 M in hexane, 6.11 mL, 15.3 mmol was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of BnOH (2.09 g, 19.1 mmol) in THF (9 mL). Stirring at 0 °C was continued for 15 min, and an aliquot of the solution (0.3 mL, 0.262 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of imide **34** (28 mg, 0.0438 mmol) in THF (3 mL). Stirring at 0 °C was continued for 6 h. Water (2 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 EtOAc−hexane, gave ester **35** (24 mg, 89%) as a colorless oil: $[\alpha]^{22}_D$ −58.1 (*c* 1.6, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1731 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) (mixture of rotamers) δ −0.34 (s, 2.15 H), −0.24 (s, 0.81 H), 0.06 (s, 2.13 H), 0.12 (s, 0.86 H), 0.79 (s, 6.55 H), 0.82 (s, 2.66 H), 1.28 (d, J = 6.8 Hz, 3 H), 2.17 (s, 0.82 H), 2.20 (s, 2.20 H), 2.80−2.86 (m, 2 H), 3.36−3.54 (m, 8 H), 3.76 (s, 1 H), 4.34−4.45 (m, 2 H), 4.62−4.67 (m, 1.19 H), 4.79−4.86 (m, 0.56 H), 4.99−5.01 (m, 0.26 H), 5.12−5.15 (m, 0.95 H), 5.38−5.51 (m, 1.26 H), 5.67 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 2.5 Hz, 0.68 H), 6.71 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 11.8 Hz, 0.26 H), 6.81−6.85 (m, 1.87 H), 7.08−7.34 (m, 8.75 H); ^{13}C NMR (CD_3OD, 100 MHz) (mixture of rotamers) δ −5.0 (q), −4.7 (q), −4.3 (q), −3.7 (q), 12.95 (q), 13.05 (q), 16.1 (q), 16.7 (q), 19.1 (s), 19.2 (s), 26.4 (q), 26.7 (q), 28.8 (t), 29.2 (t), 46.6 (d), 47.1 (d), 59.9 (q), 60.3 (q), 62.8 (q), 63.7 (q), 66.8 (t), 66.9 (t), 70.4 (t), 70.6 (t), 72.9 (d), 73.8 (t), 74.3 (d), 120.5 (t), 122.0 (t), 128.6 (d), 128.7 (d), 128.77 (d), 128.82 (d), 129.2 (d), 129.3 (d), 129.5 (d), 129.6 (d), 131.88 (s), 131.94 (s), 132.1 (s), 132.5 (s), 132.7 (s), 132.9 (s), 133.20 (d), 133.28 (s), 133.31 (d), 137.2 (s), 137.4 (s), 139.75 (s), 139.80 (s), 153.4 (s), 154.0 (s), 155.0 (s), 156.6 (s), 175.9 (s), 176.5 (s); exact mass *m*/*z* calcd for $C_{37}H_{50}O_6Si$ 618.33765, found 618.33653.

(2*R*,3*S*)-3-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropan-1-ol (36). *i*-Bu_2AlH (1.0 M in CH_2Cl_2, 0.0223 mL, 0.0223 mmol) was added dropwise over 5 min to a stirred and cooled (−78 °C) solution of ester **35** (23 mg, 0.0372 mmol) in CH_2Cl_2 (5 mL). Stirring at −78 °C was continued for 45 min, and then the cooling bath was replaced by an ice bath. Stirring at 0 °C was continued for 1 h. MeOH (0.5 mL) was added to quench the excess of *i*-Bu_2AlH. The mixture was diluted with CH_2Cl_2 (3 mL), and aqueous sodium potassium tartrate (0.5 M, 3 mL) was added over 10 min. The mixture was stirred at room temperature for 4 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 EtOAc−hexane, gave alcohol **36** (7.1 mg, 89%) as a colorless oil: $[\alpha]^{22}_D$ −58.0 (*c* 1.5, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3458 cm^{-1} (br); ^1H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ −0.22 (s, 3 H), 0.10 (s, 3 H), 0.84 (s, 1.06 H), 0.88 (s, 8.10 H), 1.08 (d, J = 6.8 Hz, 0.35 H), 1.17 (d, J = 6.8 Hz, 2.71 H), 2.12−2.16 (m, 1 H), 2.23 (s, 3 H), 2.30−2.34 (m, 1 H), 2.98 (t, J = 7.8 Hz, 2 H), 3.13−3.16 (m, 1 H), 3.21−3.25 (m, 1 H), 3.48−3.65 (m, 5 H), 3.79 (s, 2.67 H), 3.81 (s, 0.35 H), 4.51 (AB q, $\Delta\nu_{AB}$ = 22.5 Hz, J = 12.0 Hz, 2 H), 4.76 (d, J = 9.5 Hz, 0.14 H), 4.94 (d, J = 10.0 Hz, 0.95 H), 5.35−5.46 (m, 1 H), 5.57 (AB q, $\Delta\nu_{AB}$ = 11.5 Hz, J = 2.2 Hz, 0.16 H), 5.72 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 2.5 Hz, 0.96 H), 6.77 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 11.5 Hz, 0.16 H), 7.25−7.38 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.2 (q), −4.7 (q), 12.4 (q), 14.7 (q), 15.2 (q), 18.1 (s), 18.2 (s), 25.8 (q), 26.0 (q), 27.7 (t), 28.2 (t), 40.8 (d), 42.3 (d), 59.2 (q), 59.8 (q) 62.0 (q), 62.9 (q), 65.2 (t), 65.6 (t), 69.3 (t), 69.5 (t), 72.4 (d), 72.8 (t), 72.9 (t), 74.3 (d), 118.8 (t), 121.3 (t), 127.5 (d), 127.58 (d), 127.59(d), 128.36 (d), 128.38 (d), 129.7 (s), 130.1 (s), 131.5 (s), 131.9 (s), 132.1 (d), 132.2 (d), 132.5 (s), 138.4 (s), 152.0 (s), 152.2 (s), 154.6 (s), 155.0 (s); exact mass *m*/*z* calcd for $C_{30}H_{46}O_5Si$ 514.31146, found 514.31153.

[(*S*)-1-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-2-methylallyloxy]-*tert*-butyldimethylsilane (37). (a) [(1*S*,2*S*)-1-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-2-methyl-3-(2-nitrophenylselanyl)propoxy]-*tert*-butyldimethylsilane. *n*-Bu_3P (0.027 mL, 0.109 mmol) was added dropwise over ca. 2 min to a stirred solution of alcohol **36** (28 mg, 0.0545 mmol) and *o*-nitrobenzeneselenocyanate (24.7 mg, 0.109 mmol) in THF (1 mL). Stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 20 cm), using 1:10 EtOAc−hexane, gave the expected selenide (ca. 35 mg, 93%) as a yellow oil, which was used directly in the next step.

(b) [(*S*)-1-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-2-methylallyloxy]-*tert*-butyldimethylsilane (37). H_2O_2 (30%, 0.051 mL, 0.504 mmol) was added dropwise to a stirred and cooled (0°) solution of the above selenide (ca. 35 mg, 0.0504 mmol) in THF (1 mL). After addition, the ice bath was removed, and stirring was continued for 5 h. Ice−water (3 mL) was added to quench the reaction, and the organic solvent was evaporated in vacuo. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 18 cm), using 1:25 EtOAc−hexane, gave olefin **37** (22 mg, 81% over two steps) as a colorless oil: $[\alpha]^{22}_D$ −75.5 (*c* 1.7, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2951 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ −0.31 (s, 3 H), 0.04 (s, 3 H), 0.81 (s, 9 H), 1.74 (s, 3 H), 2.23 (s, 3 H), 2.99 (t, J = 8 Hz, 2 H), 3.50−3.55 (m, 4 H), 3.59−3.65 (m, 4 H), 4.49 (AB q, $\Delta\nu_{AB}$ = 15.0 Hz, J = 11.2 Hz, 2 H), 4.80−4.85 (m, 2 H), 5.25 (AB q, $\Delta\nu_{AB}$ = 7.0 Hz, J = 3.0 Hz, 1 H), 5.68−5.69 (m, 1 H), 5.80 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 3.0 Hz, 1 H), 7.00 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 7.0 Hz, 1 H), 7.23−7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1 (q), −5.0 (q), 12.6 (q), 18.3 (s), 20.7 (q), 25.9 (q), 28.3 (t), 29.2 (q), 62.3 (q), 69.7 (t), 71.3 (d), 72.9 (t), 110.8 (t), 118.1 (t), 127.4 (d), 127.5 (d), 128.2 (d), 129.9 (s), 130.0 (s), 131.3 (s), 131.9 (s), 132.3 (d), 138.4 (s), 147.1 (s), 153.1 (s), 153.8 (s); exact mass *m*/*z* calcd for $C_{30}H_{44}O_4Si$ 496.30090, found 496.29948.

(*S*)-1-[3-(2-Benzyloxyethyl)-2,5-dimethoxy-4-methyl-6-vinylphenyl]-2-methylprop-2-en-1-ol (38). A solution of Bu_4NF (1.0 M in THF, 0.675 mL, 0.675 mmol) was added to a stirred and cooled (0 °C) solution of bisolefin **37** (67 mg, 0.135 mmol) in THF (3 mL), and stirring was continued for 36 h. Brine (2 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 EtOAc−hexane, gave bisolefin **38** (49 mg, 95%), as a colorless oil: $[\alpha]^{22}_D$ −38.9 (*c* 1.5, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3468 cm^{-1} (br); ^1H NMR (CD_3OD, 300 MHz) δ 2.25 (s, 3 H), 2.99−3.01 (m, 2 H), 3.54 (s, 3 H), 3.56−3.62 (m, 2 H), 3.71 (s, 3 H), 4.35 (d, J = 6.2 Hz, 1 H), 4.52 (s, 2 H), 4.85−4.86 (m, 1 H), 4.99−5.00 (m, 1 H), 5.35 (AB q, $\Delta\nu_{AB}$ = 11.8 Hz, J = 2.8 Hz, 1 H), 5.51−5.52 (m, 1 H), 5.73 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 2.8 Hz, 1 H), 7.00 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 11.8 Hz, 1 H), 7.24−7.32 (m, 5 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 12.7 (q), 20.5 (q), 28.8 (t), 59.6 (q), 62.9 (q), 70.3 (t), 71.7 (d), 73.2 (t), 109.7 (t), 119.2 (t), 128.0 (d), 128.1 (d), 128.9 (d), 131.0 (s), 131.7 (s), 131.9 (s), 132.6 (s), 132.8 (d), 139.8 (s), 148.4 (s), 154.1 (s), 154.5 (s); exact mass *m*/*z* calcd for $C_{24}H_{30}O_4$ 382.21442, found 382.21384.

(*S*)-6-(2-Benzyloxyethyl)-4,7-dimethoxy-2,5-dimethyl-1*H*-inden-1-ol (40). Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine] ruthenium(IV) dichloride (**39**) (12.3 mg, 0.0144 mmol) was added to a stirred solution of bisolefin **38** (55 mg, 0.144 mmol) in CH_2Cl_2 (6 mL) under N_2. The mixture was refluxed for 20 h, cooled, and evaporated. Flash chromatography of the residue

over silica gel (2 × 16 cm), using 1:6 EtOAc−hexane, gave allylic alcohol **40** (45 mg, 88%) as a colorless oil: $[\alpha]^{22}_D$ +91.8 (*c* 1.2, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3386 cm^{-1} (br); ^1H NMR (CD_3OD, 300 MHz) δ 2.01−2.02 (m, 3 H), 2.17 (s, 3 H), 2.94 (t, J = 7.5 Hz, 2 H), 3.53 (t, J = 7.5 Hz, 2 H), 3.68 (s, 3 H), 3.92 (s, 3 H), 4.50 (s, 2 H), 5.03 (s, 1 H), 6.37−6.38 (m, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 12.4 (q), 13.9 (q), 28.6 (t), 60.3 (q), 61.8 (q), 70.8 (t), 73.8 (t),78.7 (d), 123.6 (d), 128.5 (s), 128.6 (d), 128.8 (d), 129.3 (d), 132.3 (s), 133.5 (s), 136.0 (s), 139.8 (s), 148.0 (s), 148.9 (s), 152.9 (s); exact mass m/z calcd for $C_{22}H_{26}O_4$ 354.18311, found 354.18259. The compound had ee >98% (HPLC, Chiracel OD-RH column, 1:1 *i*-PrOH−water).

(*S*)-6-(2-Benzyloxyethyl)-1-(2-bromo-1-ethoxyethoxy)-4,7-dimethoxy-2,5-dimethyl-1*H*-indene (42). Br_2 (0.076 mL, 1.2 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of ethyl vinyl ether (0.183 mL, 1.92 mmol) in CH_2Cl_2 (4 mL) under N_2. After 20 min, the cooling bath was removed, and stirring was continued for ca. 1 h. A solution of allylic alcohol **40** (85 mg, 0.24 mmol) and 2,6-lutidine (0.139 mL, 1.20 mmol) in CH_2Cl_2 (6 mL) was added slowly to the resulting solution of 1,2-dibromoethyl ethyl ether at −78 °C. After 30 min at −78 °C, the cold bath was removed, and stirring was continued for 20 h. The solution was diluted with CH_2Cl_2 (30 mL), washed with aqueous $Na_2S_2O_3$ (10%, 10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:15 EtOAc−hexane, gave bromo acetals **42** (100 mg, 91%), as a yellow oil that was a mixture (ca. 1:1; ^1H NMR) of diastereoisomers. Early and late fractions from the chromatography provided samples of the individual compounds. Less polar diastereoisomer: $[\alpha]^{22}_D$ +161.6 (*c* 1.1, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, J = 7.0 Hz, 3 H), 2.08−2.09 (m, 3 H), 2.21 (s, 3 H), 2.94−3.01 (m, 2 H), 3.22−3.33 (m, 4 H), 3.44−3.58 (m, 2 H), 3.70 (s, 3 H), 3.89 (s, 3 H), 4.28 (t, J = 5.0 Hz, 1 H), 4.51 (s, 2 H), 5.22 (s, 1 H), 6.44−6.45 (m, 1 H), 7.23−7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3 (q), 14.5 (q), 15.0 (q), 27.8 (t), 33.0 (t), 58.5 (q), 61.4 (q), 63.8 (t), 69.6 (t), 72.8 (t), 82.9 (d), 98.6 (d), 123.5 (d), 126.3 (s), 127.40 (d), 127.48 (s), 127.50 (d), 128.3 (d), 132.3 (s), 135.2 (s), 138.6 (s), 146.2 (s), 146.8 (s), 151.3 (s); exact mass m/z calcd for $C_{26}H_{33}{}^{79}BrO_5$ 504.15112, found 504.15179. More polar diastereoisomer: $[\alpha]^{22}_D$ +143.3 (*c* 1.2, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (t, J = 7.0 Hz, 3 H), 2.069−2.074 (m, 3 H), 2.21 (s, 3 H), 2.92−3.04 (m, 2 H), 3.28−3.45 (m, 4 H), 3.46−3.60 (m, 2 H), 3.71 (s, 3 H), 3.91 (s, 3 H), 4.53 (AB q, $\Delta\nu_{AB}$ = 14.0 Hz, J = 12.0 Hz, 2 H), 4.66 (AB q, $\Delta\nu_{AB}$ = 6.0 Hz, J = 4.2 Hz, 1 H), 5.20 (s, 1 H), 6.52−6.53 (m, 1 H), 7.24−7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.2 (q), 14.5 (q), 15.0 (q), 27.8 (t), 32.9 (t), 59.4 (q), 61.4 (q), 63.1 (t), 69.6 (t), 72.8 (t), 82.2 (d), 99.6 (d), 125.5 (d), 127.4 (d), 127.5 (d), 127.9 (s), 128.3 (d), 129.2 (d), 132.1 (d), 134.5 (d), 138.5 (d), 143.6 (d), 147.1 (d), 151.6 (d).

(3a*R*,8b*S*)-7-(2-Benzyloxyethyl)-2-ethoxy-5,8-dimethoxy-3a,6-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (43). Bu_3SnH (0.112 mL, 0.416 mmol) and AIBN (6.8 mg, 0.0416 mmol) were added to a stirred solution of bromo acetals **42** (105 mg, 0.208 mmol) in PhMe (15 mL). The flask was then lowered into a preheated oil bath set at 115 °C, and the reaction mixture was stirred at this temperature for 1.5 h and then cooled. Flash chromatography of the solution over silica gel (2 × 15 cm, using 3:80 EtOAc−hexane, gave the isomeric lactol ethyl ethers **43** (75 mg, 85%) as a colorless oil: $[\alpha]^{22}_D$ +50.4 (*c* 1.3, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3028, 2971, 2868 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (mixture of isomers) δ 0.76 (t, J = 7.0 Hz, 1.27 H), 1.22 (t, J = 7.0 Hz, 1.72 H), 1.28 (s, 1.39 H), 1.33 (s, 1.73 H), 1.94−1.99 (m, 1.06 H), 2.13−2.21 (m, 4.09 H), 2.75−2.80 (m, 1.03 H), 2.95−3.01 (m, 2.58 H), 3.16−3.22 (m, 0.45 H), 3.30−3.38 (m, 0.47 H), 3.42−3.48 (m, 1.02 H), 3.52−3.56 (m, 2.09 H), 3.64 (two s, 2.94 H), 3.77−3.79 (m, 0.60 H), 3.91 (two s, 2.97 H), 4.52 (s, 2 H), 5.14−5.23 (m, 1.94 H), 7.24−7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of two isomers) δ 12.3 (q), 12.4 (q), 15.0 (q), 15.4 (q), 25.8 (q), 26.9 (q), 27.9 (t), 43.80 (t), 43.84 (t), 47.1 (t), 47.2 (t), 48.9 (s), 49.8 (s), 59.7 (q), 59.8 (q), 61.4 (q), 61.7 (q), 62.0 (t), 63.1 (t), 69.7 (t), 69.8 (t), 72.84 (t), 72.87 (t), 90.7 (d), 92.5 (d), 105.2 (d), 127.4 (d), 127.5 (d), 128.2 (d), 128.7 (s), 129.2 (s), 130.9 (s), 131.1 (s), 131.7 (s), 132.9 (s), 135.0 (s), 135.4 (s), 138.50 (s), 138.51 (s), 150.28 (s), 150.34 (s), 152.3 (s), 152.4 (s); exact mass m/z calcd for $C_{26}H_{34}O_5$ 426.24063, found 426.24038.

(3a*R*,8b*S*)-7-(2-Benzyloxyethyl)-5,8-dimethoxy-3a,6-dimethyl-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-ol (44). AcOH−H_2O (1:4, 5 mL) was added dropwise to a stirred solution of lactol ethyl ethers **43** (17 mg, 0.040 mmol) in THF (3 mL). The mixture was then stirred at 50 °C for 12 h, cooled, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 7:30 EtOAc−hexane, gave the two isomeric lactols **44** (14.5 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ +54.3 (*c* 0.8, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3430 cm^{-1} (br); ^1H NMR ($CDCl_3$, 500 MHz) (mixture of two isomers) 1.28 (s, 1.25 H), 1.41 (s, 1.96 H), 1.97 (AB q, $\Delta\nu_{AB}$ = 8.5 Hz, J = 2.2 Hz, 0.67 H), 2.02−2.08 (m, 0.5 H), 2.13−2.67 (m, 4.5 H), 2.68 (d, J = 3.0 Hz, 0.61 H), 2.76−2.81 (m, 1.01 H), 2.94−3.04 (m, 2.63 H), 3.45 (d, J = 16.5 Hz, 0.4 H), 3.50−3.58 (m, 2.05 H), 3.65 (s, 1.66 H), 3.66 (s, 1.31 H), 3.87 (s, 1.68 H), 3.89 (s, 1.17 H), 4.52 (s, 1.90 H), 5.14 (s, 0.29 H), 5.35 (s, 0.55 H), 5.59−5.62 (m, 0.90 H), 7.24−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of two isomers) δ 12.4 (q), 26.2 (q), 26.5 (q), 27.9 (t), 43.3 (t), 43.6 (t), 47.7 (t), 47.8 (t), 49.5 (s), 49.7 (s), 59.82 (q), 59.84 (q), 61.3 (q), 61.6 (q), 69.7 (q), 72.9 (q), 91.4 (d), 92.8 (d), 100.0 (d), 100.8 (d), 127.4 (d), 127.5 (d), 128.2 (d), 129.2 (s), 129.4 (s), 131.3 (s), 131.6 (s), 131.8 (s), 132.7 (s), 134.6 (s), 134.9 (s), 138.5 (s), 150.4 (s), 150.5 (s), 152.33 (s), 152.34 (s); exact mass m/z calcd for $C_{24}H_{30}O_5$ 398.20932, found 398.20915.

(3a*R*,8b*S*)-7-(2-Benzyloxyethyl)-5,8-dimethoxy-3a,6-dimethyl-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan (45). Et_3N (0.039 mL, 0.28 mmol) and then $MeSO_2Cl$ (0.008 mL, 0.106 mmol) were added dropwise to a stirred and cooled (0 °C) solution of lactols **44** (14 mg, 0.035 mmol) in THF (2 mL). Stirring at 0 °C was continued for 15 min, the cooling bath was removed, and stirring was continued for 2 h. The mixture was then refluxed for 1 h, cooled, and filtered through a pad of Celite (2 × 3 cm). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 × 15 cm), using 2:25 EtOAc−hexane, gave **45** (9.9 mg, 75%) as a colorless oil: $[\alpha]^{25}_D$ +183.8 (*c* 1.1, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 3 H), 2.21 (s, 3 H), 2.85 (d, J = 16.5 Hz, 1 H), 2.94−3.04 (m, 2 H), 3.14 (d, J = 16.5 Hz, 1 H), 3.55 (t, J = 8.0 Hz, 2 H), 3.66 (s, 3 H), 3.89 (s, 3 H), 4.52 (s, 2 H), 4.91 (d, J = 2.8 Hz, 1 H), 5.60 (s, 2 H), 6.21 (d, J = 2.8 Hz, 1 H), 7.30−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5 (q), 26.9 (q), 27.8 (t), 43.9 (t), 53.1 (s), 59.7 (q), 61.2 (q), 69.7 (t), 72.9 (t), 93.7 (d), 110.0 (d), 127.4 (d), 127.5 (d), 128.2 (d), 129.7 (s), 131.7 (s), 132.2 (s), 134.5 (s) 138.5 (s), 143.4 (d), 150.4 (s), 152.4 (s); exact mass m/z calcd for $C_{24}H_{28}O_4$ 380.19876, found 380.19782.

Formic Acid (1*R*,2*S*)-6-(2-Benzyloxyethyl)-2-formyl-4,7-dimethoxy-2,5-dimethylindan-1-yl Ester (46). OsO_4 (0.35 mL, 2.5w/w% in *t*-BuOH) was added to a stirred solution of **45** (53 mg, 0.139 mmol) in CCl_4−H_2O−*t*-BuOH (5:2:2, 9 mL). The mixture was stirred for 30 min, and then $NaIO_4$ (0.155 g, 0.724 mmol) was added in one portion. Stirring was continued for 9 h, and the mixture was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 5 cm), using 1:3 EtOAc−hexane, gave crude aldehyde formate **46** (75 mg) as a colorless oil, which was used directly in the next step.

(1*R*,2*S*)-6-(2-Benzyloxyethyl)-1-hydroxy-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid Methyl Ester (47).

(a) (1*R*,2*S*)-6-(2-Benzyloxyethyl)-1-formyloxy-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid. A solution of $NaClO_2 \cdot 2H_2O$ (126 mg, 1.395 mmol) and $NaH_2PO_4 \cdot H_2O$ (126 mg, 0.91 mmol) in H_2O (1 mL) was added to a stirred and cooled (0 °C) solution of the above crude aldehyde formate **46** (ca 75 mg) in *t*-BuOH (2.5 mL) containing 2-methyl-2-butene (1 mL). The ice bath was removed, and stirring was continued for 3 h. The organic solvents were evaporated under reduced pressure. The residue was diluted with H_2O (2 mL), acidified with 1 N HCl (to pH ca. 3), saturated with NaCl and extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a sticky residue, which was used directly in the next step.

(b) (1*R*,2*S*)-6-(2-Benzyloxyethyl)-1-formyloxy-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid Methyl Ester. Freshly prepared CH_2N_2 in Et_2O was added dropwise to a stirred and cooled (0 °C) solution of the above crude acid (80 mg) in Et_2O (5 mL). The resulting solution was stirred at 0 °C for 10 min and evaporated to give a thick oil (85 mg), which was used directly in the next step.

(c) (1*R*,2*S*)-6-(2-Benzyloxyethyl)-1-hydroxy-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid Methyl Ester (47). K_2CO_3 (0.2 g) was added to a stirred solution of the above crude ester in dry MeOH (6 mL). The mixture was stirred for 1 h. The solvent was evaporated, and EtOAc (30 mL) was added. The mixture was washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 21 cm), using 1:2 EtOAc−hexane, gave hydroxy ester **47** (31 mg, 54% over 4 steps) as a colorless oil: $[\alpha]^{22}_D$ −1.739 (*c* 1.2, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3436, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 3 H), 2.20 (s, 3 H), 2.77 (d, J = 16.0 Hz, 1 H), 2.78 (d, J = 4.5 Hz, 1 H), 2.95−3.00 (m, 2 H), 3.51−3.56 (m, 2 H), 3.60 (d, J = 16.0 Hz, 1 H), 3.69 (s, 3 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 4.52 (s, 2 H), 5.04 (d, J = 3.5 Hz, 1 H), 7.22−7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3 (q), 23.3 (q), 27.7 (t), 36.9 (t), 52.1 (q), 55.1 (s), 60.0 (q), 62.2 (q), 69.6 (t), 72.8 (t), 79.8 (d), 127.46 (d), 127.54 (d), 128.3 (d), 129.8 (s), 131.6 (s), 132.1 (s), 133.3 (s), 138.5 (s), 151.1 (s), 152.5 (s), 176.1 (s); exact mass *m*/*z* calcd for $C_{24}H_{30}O_6$ 414.20425, found 414.20339.

(1*R*,2*S*)-6-(2-Benzyloxyethyl)-1-(imidazole-1-carbothioyloxy)-4,7-dimethoxy-2,5-dimethylindan-2-carboxylic Acid Methyl Ester (48). DMAP (0.88 mg, 0.0072 mmol) and 1,1′-thiocarbonydiimidazole (64.5 mg, 0.362 mmol) were added to a stirred solution of hydroxy ester **47** (30 mg, 0.0725 mmol) in CH_2Cl_2 (2 mL). The mixture was refluxed for 19 h. The solution was then cooled, and MeOH (0.2 mL) was added, followed by EtOAc (30 mL). The mixture was washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 17:20 EtOAc−hexane, gave imidazolide **48** (37 mg, 96%) as a colorless oil, which was used without further purification in the next step.

(*S*)-5-(2-Benzyloxyethyl)-4,7-dimethoxy-2,6-dimethylindan-2-carboxylic Acid Methyl Ester (49). A mixture of imidazolide **48** (37 mg, 0.070 mmol), Bu_3SnH (0.056 mL, 0.211 mmol), and AIBN (3.4 mg, 0.021 mmol) in dry PhMe (4 mL) was refluxed for 1.5 h (oil bath). The solution was cooled and evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using 1:12 EtOAc−hexane, gave ester **49** (20.3 mg, 73%) as a colorless oil: $[\alpha]^{22}_D$ +2.58 (*c* 3.1, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3 H), 2.18 (s, 3 H), 2.84 (AB q, $\Delta\nu_{AB}$ = 16.0 Hz, J = 2.0 Hz, 2 H), 2.93−2.98 (m, 2 H), 3.46−3.83 (m, 2 H), 3.49−3.55 (m, 2 H), 3.66 (s, 3 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 4.52 (s, 2 H), 7.23−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0 (q), 25.1 (q), 27.7 (t), 41.1 (t), 41.5 (t), 50.0 (s), 52.1 (q), 59.9 (q), 60.2 (q), 69.7 (t), 72.8 (t), 127.4 (d), 127.5 (d), 128.3 (d), 128.9 (s), 129.1 (s), 131.1 (s), 132.7 (s), 138.5 (s), 150.8 (s), 151.3 (s), 177.8 (s); exact mass *m*/*z* calcd for $C_{24}H_{30}O_5$ 398.20932, found 398.20915.

(*S*)-5-(2-Hydroxyethyl)-4,7-dimethoxy-2,6-dimethylindan-2-carboxylic Acid Methyl Ester (50). Benzyl ether **49** (8.5 mg, 0.0214 mmol) was dissolved in MeOH (5 mL) covering 10% Pd−C (5 mg), and the flask was flushed with H_2 (hydrogen-filled balloon). The mixture was stirred for 30 min and then filtered through a pad of Celite (1 × 2.5 cm), which was washed with MeOH. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:1 EtOAc−hexane, gave alcohol **50** (6.3 mg, 96%) as a colorless oil: $[\alpha]^{22}_D$ −4.0 (*c* 0.4, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3435, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3 H), 1.90 (br s, 1 H), 2.20 (s, 3 H), 2.84−2.93 (m containing a doublet of doublets at δ 2.86, J = 16.0, 3.5 Hz and a triplet of triplets at δ 2.91, J = 6.80 Hz, 4 H in all), 3.43 (d, J = 15.8 Hz, 1 H), 3.47 (d, J = 15.8 Hz, 1 H), 3.69 (s, 3 H), 3.72−3.75 (m containing two singlets at δ 3.72 and 3.75, 8 H in all); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (q), 25.2 (q), 30.5 (t), 41.1 (t), 41.5 (t), 50.0 (s), 52.1 (q), 59.9 (q), 60.0 (q), 62.7 (t), 129.0 (two overlapping s), 131.1 (s), 133.0 (s), 151.06 (s), 151.17 (s), 177.7 (s); exact mass *m*/*z* calcd for $C_{17}H_{24}O_5$ 308.16238, found 308.16249.

(*S*)-5-(2-Hydroxyethyl)-4,7-dimethoxy-2,6-dimethylindan-2-carboxylic Acid (51). $LiOH \cdot H_2O$ (57.2 mg, 1.364 mmol) was added to a stirred solution of ester **50** (21 mg, 0.068 mmol) in 1:1 dioxane−H_2O (4 mL). After 3 h, the mixture was acidified with hydrochloric acid (1.0 M, 4 mL), saturated with NaCl, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:15 MeOH−CH_2Cl_2, gave acid **51** (9.1 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ −0.7 (*c* 0.7, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3 H), 2.19 (s, 3 H), 2.85−2.93 (m, 4 H), 3.47 (d, J = 12.0 Hz, 1 H), 3.51 (d, J = 11.5 Hz, 1 H), 3.68 (s, 3 H), 3.71−3.78 (m containing one singlet at δ 3.74, 5 H in all); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (q), 24.9 (q), 30.4 (t), 41.0 (t), 41.4 (t), 49.9 (s), 59.9 (q), 60.1 (q), 62.7 (t), 129.08 (s), 129.11 (s), 131.0 (s), 132.9 (s), 151.0 (s), 151.1 (s), 182.9 (s); exact mass *m*/*z* calcd for $C_{16}H_{22}O_5$ 294.14673, found 294.14641.

(*S*)-5-(2-Hydroxyethyl)-2,6-dimethyl-4,7-dioxo-2,3,4,7-tetrahydro-1*H*-indene-2-carboxyylic Acid (52) [(+)-Puraquinonic Acid]. An ice-cold solution of $(NH_4)_2Ce(NO_3)_6$ (46.6 mg, 0.085 mmol) in 1:1 MeCN−water (0.6 mL) was added over ca. 3 min to a stirred and cooled (0 °C) solution of bis-ether **51** (10 mg, 0.034 mmol) in 2:1 MeCN−water (0.6 mL) containing pyridine-2,6-dicarboxylic acid *N*-oxide (15.6 mg, 0.085 mmol). The solution was stirred at 0 °C for 1 h, the cold bath was removed, and stirring was continued for 5 h. The resulting solution was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 17 cm), using 1:3 CH_2Cl_2−EtOAc, gave (+)-puraquinonic acid **52** (8.0 mg, 81%) as a yellowish oil: $[\alpha]^{22}_D$ +3.2 (*c* 0.3, $CHCl_3$); $[\alpha]^{22}_D$ +3.1 (*c* 0.7, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1705, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 3 H), 2.06 (s, 3 H), 2.69−2.79 (m, 4 H), 3.33−3.41 (m, 2 H), 3.74 (t, J = 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3 (q), 25.8 (q), 30.0 (t), 42.35 (t), 42.39 (t), 46.92 (s), 61.5 (t), 141.3 (s), 142.7 (s), 145.2 (s), 145.6 (s), 181.2 (s), 185.5 (s), 186.0 (s); exact mass *m*/*z* calcd for $C_{14}H_{16}O_5$ 264.09976, found 264.09970. HPLC comparison with a racemic sample and also with the natural product was done using a Chiracel OD-RH column (1:1 *i*-PrOH−water, 0.3 mL/min, sample dissolved in MeOH).

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Supporting Information Available: X-ray data for **41**; ^{13}C NMR spectra of compounds **9**−**11**, **21**−**31**, **33**−**38**, **40**, **41**, **42** (more polar), **42** (less polar), **43**−**45**, **47**, and **49**−**52**; experimental general techniques; and procedures for **9**−**11**, **41** and for 2-bromo-5-methoxy-4-methylbenzaldehyde. This material is available free of charge via the Internet at http://pubs.acs.org.

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