Practical Asymmetric Synthesis of an Endothelin Receptor Antagonist

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Received August 13, 1999

An efficient, practical, asymmetric synthesis of the endothelin receptor antagonist **1** is reported. The key pyridine-fused cyclopentane ring bearing three consecutive chiral centers was constructed by first an auxiliary induced asymmetric conjugate addition of the bottom aryllithium from **19** to an unsaturated ester **21** in high diastereoselectivity. After a highly diastereoselective addition of the top aryl Grignard reagent to the aldehyde **22**, the alcohol product then underwent a stereospecific intramolecular alkylation of the ester enolate by the phosphate of the alcohol, resulting in the desired trans−trans relative stereochemistry on the cyclopentane ring. The two key chiral centers that set the chirality of the molecule were both induced from *cis*-1-amino-2-indanol-derived chiral auxiliaries, one in the conjugate addition reaction, the other in setting the chiral center of the bottom side chain via chiral alkylation of an enolate. Oxidation of the primary alcohol to the carboxylic acid in the bottom side chain was carried out with the newly developed TEMPO/bleach-catalyzed oxidation by sodium chlorite ($NaClO_2$) or chromium oxide catalyzed oxidation by periodic acid. The overall process has been run successfully to make multikilograms of the drug in high purity.

Introduction

Endothelin receptor antagonists are useful therapeutic agents which are being developed for possible indications in congestive heart failure, hypertension, and some other areas. Extensive work in medicinal chemistry has been reported in the literature.[1] Practical syntheses of some compounds in development were also described.[2] In this paper, we report a practical, concise synthesis of one of the endothelin receptor antagonists which is under development jointly by Merck and Banyu.[1a] The objective of this work was to develop an efficient, safe, cost-effective, and environmentally friendly synthesis of this compound suitable for scale-up so that kilogram quantities of this drug candidate could be made via this chemistry for safety assessment and clinical studies. The synthesis should also be suitable for eventual commercial production if necessary.

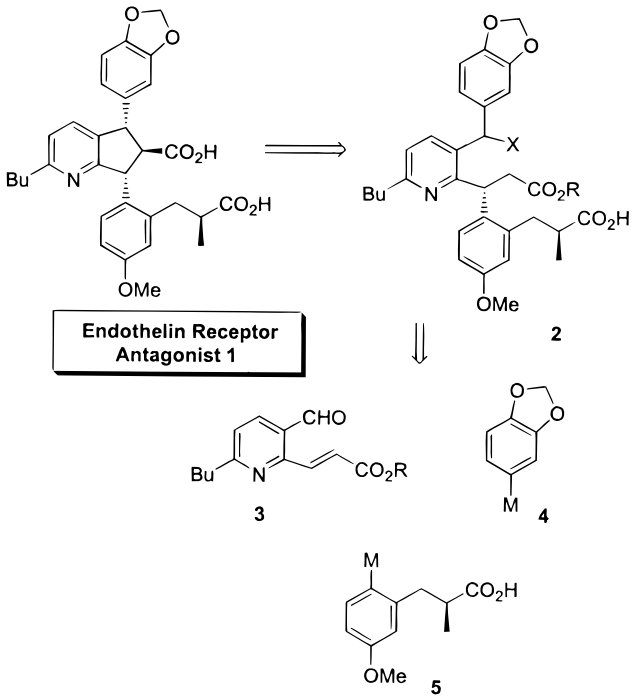
The structure of the target molecule **1** is shown in Scheme 1. The key feature of this compound is the cyclopentane ring fused with pyridine, which bears three consecutive chiral centers. Substitution on the cyclopentane ring includes the center carboxylic acid and the two adjacent aryl groups, one of which has a side chain bearing an additional chiral center. While the core cyclopentane ring with three consecutive chiral centers is common in this class of endothelin receptor antagonists, the synthesis of these compounds has been very tedious. The enantiospecific preparation is even more challenging and very few synthetic approaches have been reported.[1a,2] The two unique aryl side chains and the fused pyridine structure make the synthesis of this compound in large scale at low cost a uniquely challenging task. Scheme 1 shows the retrosynthetic analysis we envisioned to construct this compound. The key steps involve a chiral Michael addition reaction of the bottom aryl piece organometallic species **5** into the conjugate pyridine ester **3** which has been properly functionalized on the pyridine. Introduction of the chirality would be either through a chiral auxiliary or an external additive. The top aryl group can be introduced by addition of the arylmetal to the aldehyde. The cyclopentane ring can then be closed via intramolecular alkylation of the ester enolate. While the chiral conjugate addition reaction based on chiral auxiliary is well precedent in the literature,[3−6] the subsequent steps are rather exploratory in nature.

(1) (a) Ishikawa, K.; Nagase, T.; Mase, T.; Hayama, T.; Masaki, I.; Nishikibe, M.; Yano, M. PCT Int. Appl. WO 9505374, 1995. (b) Berryman, K. A.; Edmunds, J. J.; Bunker, A. M.; Haleen, S.; Bryant, J.; Welch, K. M.; Doherty, A. M. *Bioorg. Med. Chem.* **1998**, *6*, 1447. (c) Tasker, A. S.; Boyd, S. A.; Sorensen, B. K.; Winn, M.; Jae, H.-S.; von Geldern, T. M.; Henry, K. J. PCT Int. Appl. WO 9730046, 1997. (d) Astles, P. C.; Brown, T. J.; Halley, F.; Handscome, C. M.; Harris, N. V.; McCarthy, C.; McLay, I. M.; Lockey, P.; Majid, T.; Porter, B.; Roach, A. G.; Smith, C.; Walsh, R. *J. Med. Chem.* **1998**, *41*, 2745. (e) Bagley, S. W.; Broten, T. P.; Chakravarty, P. K.; Dhanoa, D. S.; Fitch, K. J.; Greenlee, W. J.; Kevin, N. J.; Pettibone, D. J.; Rivero, R. A.; Tata, J. R.; Wash, T. F.; Williams, D. L., Jr. US Patent 5767310, 1998.

(2) (a) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G.; K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550. (b) Pridgen, L. N.; Huang, G. K. *Tetrahedron Lett.* **1998**, *39*, 8421. (c) Bhagwat, S.; Gude, C.; Chan, K. *Tetrahedron Lett.* **1996**, *37*, 4627.

10.1021/jo991292t CCC: $18.00
Published on Web 12/24/1999

Scheme 1

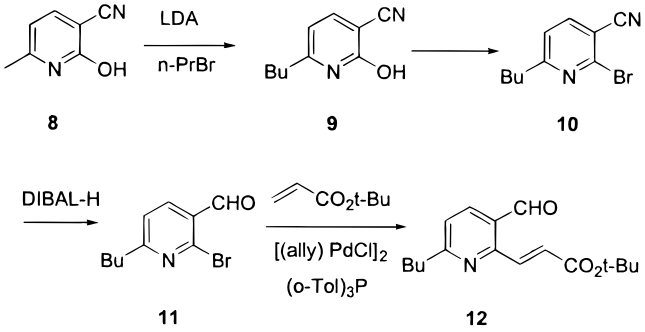


Results and Discussion

Preparation of the Michael Acceptor 12. There are several possible approaches for the chiral Michael addition reaction. One approach was based on a preliminary report by Alexakis et al.,[4] where aryl-substituted unsaturated esters **6** bearing an *o*-aldehyde group can undergo conjugate addition reactions with simple organocuprates. When the aldehyde is protected as the chiral acetal (by chiral diol) or chiral diaminoacetal (by chiral diamine), the organocuprate addition products **7** were obtained in high ee after removal of the protecting groups. Recent work at Merck by Frey et al. has extended the application of this strategy to Michael addition by aryllithium species.[5] To apply a similar strategy for our target molecule, we needed to make compound **12** as the Michael acceptor, which could also be used in an alternate approach using an external chiral additive in the conjugate addition.[7]

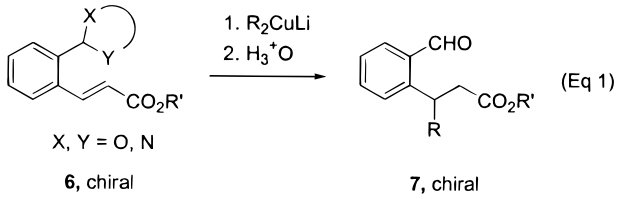
Thus, as shown in Scheme 2, 3-cyano-6-methyl-2-pyridone (**8**) was alkylated with propyl bromide under basic conditions to the *n*-butylpyridine[8] **9** and then converted to the bromide with P_2O_5/Bu_4NBr in 64% overall yield. DIBAL-H reduction of the cyano group to the aldehyde **11** gave nearly quantitative yield. The *tert*-butyl acrylate was installed by Heck reaction with *tert*-butyl acrylate, using allyl palladium chloride dimer and tri-*o*-tolylphosphine as catalyst to produce **12** in 83% yield. It should be pointed out that all of these compounds were oils and were used directly without any purification.

Scheme 2



Preparation of the Bottom Aryl Bromide. For the synthesis of the chiral aryl bromide fragment, we turned our attention to the use of *cis*-aminoindanol ketal as the possible chiral auxiliary for alkylation of propionyl enolate by the benzyl chloride **14**.[9] (1*R*,2*S*)-*cis*-Aminoidanol is readily available as part of the Merck AIDS drug CRIXIVAN process and has been used as a chiral auxiliary extensively.[10] Thus, the propionyl amide of aminoidanol ketal **15** was enolized and reacted with the benzyl chloride **14** at −30 °C to give the product **16** in excellent de (98/2). Subsequent hydrolysis gave the free acid **17** as an oil in 60% overall yield. Thus, the aminoindanol ketal is a useful alternative as the chiral auxiliary for enolate alkylation reactions because it is readily available, easy to install and to remove, and can be recycled easily if necessary.[9] To protect the acid against epimerization of the chiral center as well as reaction toward organometallic species (e.g. aryllithium compounds), the acid was reduced to the alcohol **18** with borane in 95% yield. Crystallization of the alcohol improved the ee to >99%. Subsequent protection of the alcohol as the TBS ether **19** (99% yield) made this piece ready for organometallic reactions.

Conjugate Addition. Two approaches for the chiral Michael addition reaction were systematically explored. The first involved installing a chiral auxiliary on the aldehyde, similar to the reaction reported by Alexakis et al. (eq 1) and the recent work by Frey et al.[4,5] In the



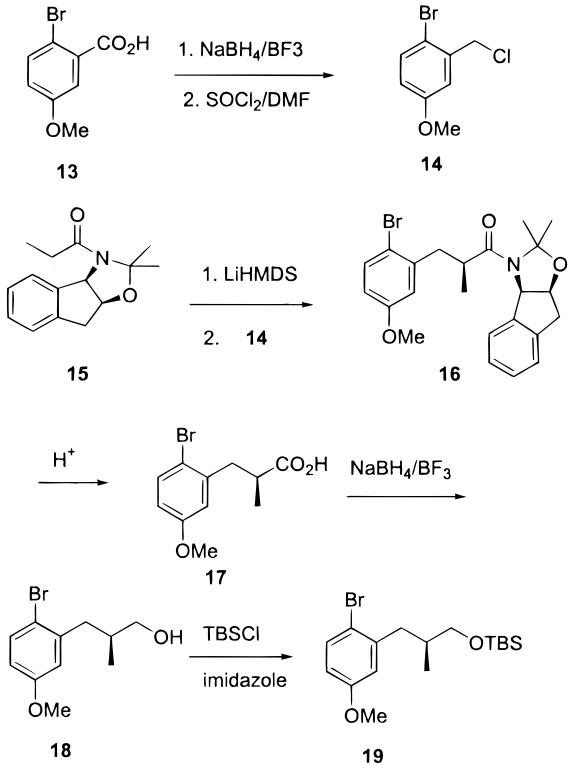
(Eq 1)

reaction of the compound **12**, we found that both (1*S*,2*S*)-(+)-pseudoephedrine (**20B**) and *N*-methyl-(1*S*,2*R*)-*cis*-1-amino-2-indanol (**20A**) were good auxiliaries. Although pseudoephedrine is readily available in the United States, it is not so in Japan due to government regulations on the substance. So we developed methods to use either auxiliary. The crude aldehyde **12** from the Heck reaction was treated with either amino alcohol in toluene to give the *N*,*O*-acetal **21A** or **21B** in quantitative yield. This compound was then treated with the aryllithium generated from aryl bromide **19** and *n*-butyllithium at-

(3) For a review on conjugate addition reactions, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
(4) Alexakis, A.; Sedrani, R.;, Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411.
(5) Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120.
(6) Takaya, T.; Ogasawara, M.; Hayashi, M., Sakai, M.; Miyura, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579.
(7) Xu, Feng; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1651.
(8) Related method: Okada, S.; Ushijima, R.; Ishikawa, K. PCT Int. Appl. WO 9825906, 1998.

(9) A similar alkylation reaction: Lee, J.; Choi, W.-B.; Lynch, J. E.; Volante, R.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3679.
(10) (a) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. *Tetrahedron Lett.* **1994**, *35*, 673. (b) Senanayake, C. H *Aldrichimica Act.* **1998**, *31*, 3.

Scheme 3



low temperature (<−65 °C). Optimal yield was observed when the aryllithium was *added to* the ester **21** at low temperature (<−50 °C). Use of mostly toluene with some THF (4/1 ratio) as the solvent was also necessary for the lithium bromide exchange reaction in large scale (long time cycle) in order to avoid the side reaction between the butyl bromide and the resulting aryllithium. After acidic workup, the amino alcohol was removed to give the free aldehyde **22** in 92% overall yield from **12** and 96/4 diastereomeric ratio. This crude product was used for the next step without purification because it was an oil. The amino alcohol auxiliary can be recovered easily. Because of the easy installation, removal, and recycle of the amino alcohol, this approach offers an economically attractive method to install this strategic chiral center in high yield and selectivity for this synthesis. Two aspects of this reaction greatly expand the scope of the reactions reported by Alexakis et al. The first is the use of the more readily available, easily recyclable amino alcohols as the auxiliaries compared to the less available and more expensive chiral diamines. The other is the use of only 1 equiv of organolithium as the nucleophile instead of the organocuperate species, which would require at least 2 equiv of the rather expensive aryl bromide **19**.

The second approach to the chiral conjugate addition reaction involved the use of external chiral additives. Thus, the dimethyl acetal **27** of the aldehyde reacted with the aryllithium derived from **19** in the presence of a stoicheometric amount of (−)-sparteine. The product **28** was isolated in 67% de, as shown in Scheme 5. The lithium bromide exchange had to be done with a minimum amount of THF (0.3 equiv) in order to optimize the de. A few other similar reactions under these conditions were also investigated and the results were published.[7]

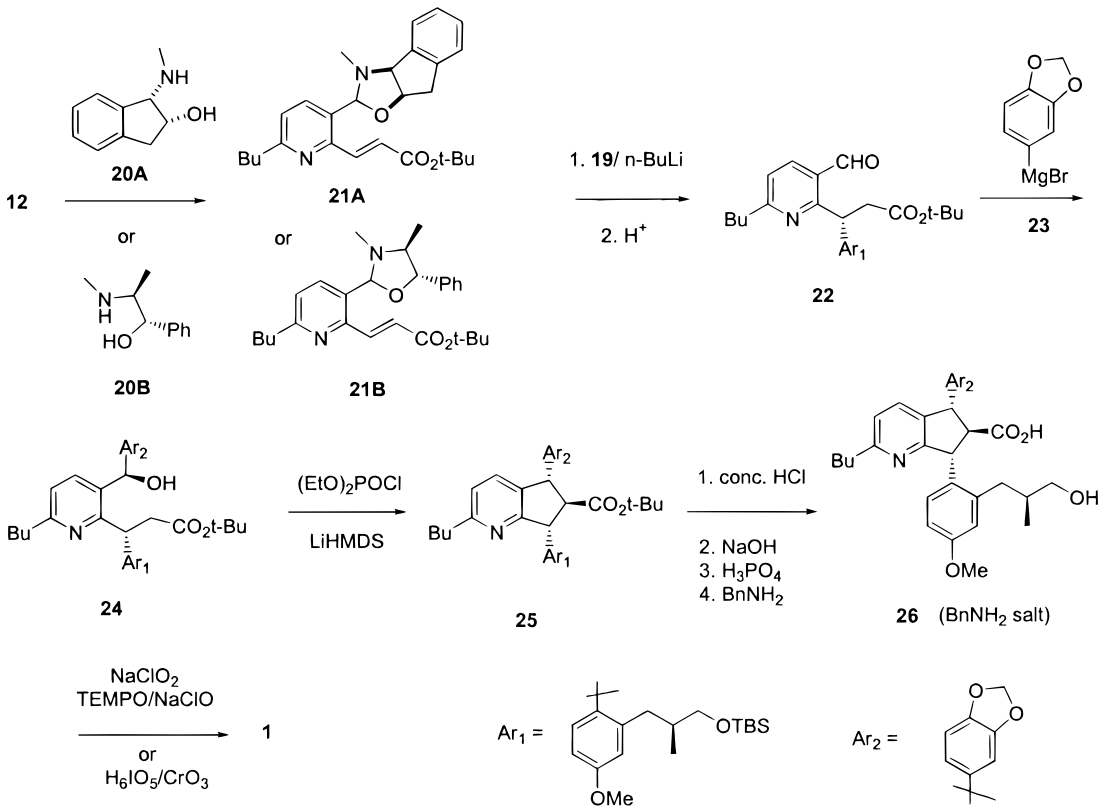
Grignard Addition. To install the top aryl group (Ar_2 in Scheme 5) the Grignard **23** of the commercially available, corresponding bromide was added in high yield to the crude aldehyde **22** in THF at low temperature (<−65 °C). This reaction was stereoselective, i.e., it produced one diatereoisomer over the other by a 94/6 ratio. On the basis of the chemistry carried out in the later steps, the stereochemistry was assigned as shown in **24**. This stereoselectivity became extremely critical for the stereospecific ring closure reaction later on. Interestingly, the selectivity became lower when more toluene was used in the reaction or when the aryllithium was used instead of Grignard reagent. This Grignard addition product was again used without purification because it was an oil.

Cyclization. With the alcohol in hand, it was obvious that the most straightforward route to the cyclopentane ring was to convert the alcohol in **24** to a leaving group and react that with the enolate of the *tert*-butyl ester. Because the configuration at the alcohol center was not known at the time, it was not clear whether retention or inversion of configuration was needed at the alcohol carbon in order to obtain the correct stereochmistry of the cyclization product. (i.e. the trans,trans configuration as in **25)**. Initial attempts to make the mesylate of the alcohol using mesyl chloride gave the chloride instead of the mesylate, as a 3/1 diastereomeric mixture at the chloride center. Treatment of the chloride with LDA at low temperature gave the cyclized product as a mixture of the stereoisomers on the ring with the desired trans,-trans-isomer as the minor product. Use of mesyl anhydride in the preparation of the mesylate led to complex undesired products, presumably through intramolecular Friedel−Crafts reaction of the extremely reactive intermediates. Similar results were observed when trying to make the tosylate or trifluoromethane sulfonate. These results indicated that the sulfonates of the benzylic alcohol **24** are too reactive due to the extra activation from the diaryl substitution as well as the *p*-alkoxyl group on the top aryl moiety, which leads to decomposition of these compounds. We reasoned that a much less active leaving group might solve the problem. A phosphate appears to be a good candidate due to its lower reactivity as leaving group and rather low reactivity toward nucleophiles at the phosphorus center. To our delight, when we treated the alcohol **24** with 1.5 equiv of diethyl chlorophosphate and 4.5 equiv of lithium bis-(trimethylsilyl)amide at 0 °C, the desired cyclization occurred, giving the desired trans,trans-isomer **25** in high yield (85% with pure starting material). Presumably, the diethyl phosphate ester of the chiral alcohol was formed first which underwent intramolecular alkylation of the enolate of the *tert*-butyl ester.

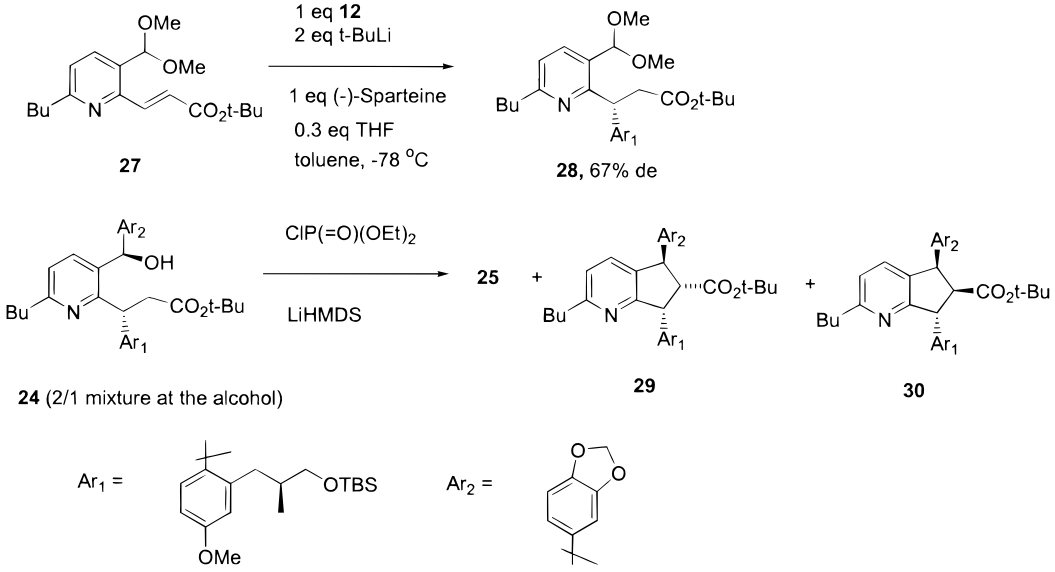
To probe whether the cyclization reaction went through stereospecific S_N2 type displacement, we made the alcohol **24** as a 2/1 diastereomeric mixture at the alcohol center (major isomer shown in Scheme 5). Under the cyclization conditions, a mixture of stereoisomers **25**, **29**, and **30** was produced with **25** as the major product. The assignment of these structures was based on NOE data of the proton NMR. The ratio was approximately **25**/(**29** + **30**) = 2/1, consistent with S_N2 type displacement of the phosphate ester by the *tert*-butyl ester enolate.

After the cyclization reaction, crude product **25** was then treated with concentrated HCl in acetonitrile to remove both the TBS group and the *tert*-butyl ester group. Salt formation with benzylamine afforded the salt of **26** as the first crystalline intermediate over several steps with an isolated yield of 70−75% from the Michael addition product **22**. This crystallization was important

Scheme 4



Scheme 5



in that it allowed purification of this penultimate intermediate after more than six steps without any purification. The purity of the isolated salt was over 95% by HPLC.

Oxidation. With the alcohol **26** in hand, the only step left is to convert the alcohol to the acid. A survey of several available methods from the literature showed that an economical method which can tolerate electron-rich aromatic rings as well as an adjacent chiral center was needed. For example, oxidation with CrO_3/H_2SO_4 gave the desired product in reasonable yield, but the use of stoichiometric quantities of chromium is not practical on large scale due to toxicity and waste disposal concerns. Use of a $RuCl_3/H_5IO_6$ protocol offered a low yield of the desired product,[11] which was probably due to the destruction of the electron rich aromatic ring. Swern oxidation to the aldehyde followed by sodium chlorite ($NaClO_2$) oxidation to the acid gave a reasonably good yield but could lead to epimerization of the neighboring chiral center.[12] TEMPO-catalyzed oxidation with bleach also

(11) (a) Carlsen, P. H. J.; Katsuki, T.; Martin V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Oxidation of alcohols to acids catalyzed by Na_2WO_4 was reported recently: Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386−12387.

(12) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567. (c) Ireland, R.; Norbeck, D. *J. Org. Chem.* **1985**, *50*, 2198.

gave a low yield due to significant chlorination of the aromatic rings.[13a] Other oxidants (H_2O_2, $MeCO_3H$, *t*-BuO_2H etc.) examined for the TEMPO-catalyzed oxidations did not give satisfactory results.

As part of this work, a new protocol of oxidizing primary alcohols to the corresponding carboxylic acids using sodium chlorite and catalytic amount of TEMPO and bleach has been shown to be a generally applicable method to a variety of different alcohols.[14b] Under optimized conditions, the starting material alcohol **26** was dissolved in acetonitrile and mixed with pH = 6.7 buffer. At 35 °C, a catalytic amount (5 mol %) of TEMPO was added followed by simultaneous addition of $NaClO_2$ and a catalytic amount of bleach (3 mol %).[14a] The yield of the acid **1** was over 90%. The reaction has been optimized to minimize chlorination of the aryl ring and to enhance the safety for scale-up. The reaction was faster at lower pH, but it was accompanied by increased the amount of chlorination products (up to 0.5% and difficult to remove). It was slower at lower temperature, as expected, but surprisingly, the chlorination level appeared to be slightly elevated. Increasing the amount of TEMPO and bleach increased the reaction rate, but the TEMPO/NaClO molar ratio should be >2 to minimize chlorination. Thus, the TEMPO-catalyzed oxidation of alcohol to has been proven to be mild, economical, and environmentally benign.[14b] Finally, the disodium salt of **1** was isolated in 85% overall yield from the alcohol and over 99% purity by treatment of the diacid of **1** with sodium ethoxide.

We also developed a chromium oxide catalyzed oxidation with periodic acid, and the general protocol was published recently.[15] With that method, the alcohol **26** can also be converted to the acid **1** with 2.5 equiv of periodic acid and 1.5 mol % of CrO_3 in wet acetonitrile in over 90% yield. The disodium salt was isolated in 85% yield in over 99% purity.

Conclusion

We have developed a highly convergent synthesis of the structurally complex endothelin receptor antagonist **1**. The key steps involved the efficient chiral conjugate addition reaction of an aryllithium to an unsaturated ester in high diastereoselectivity and yield. The stereoselective Grignard addition and the novel, phosphate-mediated stereospecific intramolecular cyclization build the fused cyclopentane ring efficiently.[16] The synthesis was finished by an economical, environmentally benign TEMPO-catalyzed oxidation of the alcohol to the acid. The overall yield from the commercially available compound **8** is 32% over 8−10 steps. The efficiency of the chemistry was demonstrated by the fact that multiple steps were carried out without the need for purification. This process has been scaled up in the pilot plant to make over 10 kg of the compound **1** to be used for safety assessment and clinical studies for this important drug candidate.

Experimental Section

General. All substrates and reagents were obtained commercially and used without purification. Nuclear magnetic resonance (NMR) chemical shifts (δ) are referenced on the deuterated solvents. Elemental analyses were done by QTI at Whitehouse Station, NJ. LC−MS were done on a HP series 1100 MSD mass spectrometer. Melting points were uncorrected. Anhydrous solvents were obtained commercially and used as is or dried with molecular sieves. Moisture contents in solvents or reaction mixtures were measured by Karl Fischer titrators and are presented as KF values. HPLC results are presented as area percent of the peak (*A*%) for a particular compound relative to the total area of all the peaks integrated.

6-Butyl-3-cyano-2-pyridone (9). To a solution of diisopropylamine (413 mL, 3.15 mol) in THF (1 L) at −30 °C was added *n*-BuLi (315 mL, 10 M). The resulting LDA was cannulated into a solution of 2-hydroxy-6-methylpyridine (200 g, 1.83 mol) in THF (1 L) over 40 min while the temperature was maintained at <−20 °C. The mixture was stirred for 2.5 h at 0−5 °C to form an orange slurry. 1-Bromopropane (140 mL, 1.54 mol) was added over 10 min and the mixture was stirred for 3 h. Water (1 L) was added and the THF was distilled off under vacuum. Toluene (1.5 L) was added in one portion followed by slow addition of sulfuric acid (3.6 M, 300 mL). The layers were separated, and the toluene layer was washed with brine (500 mL), filtered, and concentrated to a total volume of 650 mL. Hexane (750 mL) was added dropwise and the resulting slurry was cooled to 5 °C and filtered to collect the solid product. The product was washed with hexane (500 mL) and air-dried to yield 199 g the title compound as an orange solid (76% yield): mp 109 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.36 (m, 2H), 1.67 (m, 2H), 2.67 (t, 2H, J = 7.5 Hz), 6.20 (d, 1H, J = 7.5 Hz), 7.79 (d, 1H, J = 7.5 Hz); ^{13}C (63 MHz, $CDCl_3$) δ 163.3, 157.7, 148.5, 115.70, 105.80, 100.98, 33.40, 30.54, 22.07, 13.63; LC−EIMS *m*/*z* 177 (M^+ + 1). Anal. Calcd for C_8H_8BrClO: C, 40.8; H, 3.42. Found: C, 41.1; H, 3.3.

2-Bromo-6-butyl-3-cyanopyridine (10). 6-Butyl-3-cyano-2-hydroxypyridine (177 g, 1.01 mol), phosphorus pentoxide (300 g, 1.06 mol), and tetrabutylammonium bromide (391 g,1.21 mol) were mixed in toluene (2L) and heated to reflux for 4 h. The mixture was cooled to rt and water (1L) was added carefully with stirring and cooling. The mixture was stirred for 2 h and then filtered through a pad of Celite, and the layers were separated. The toluene layer was washed with brine and concentrated in vacuo. The product was passed through a pad of silica gel (50 g) and eluted with ethyl acetate:hexane (10:1) to give 202 g (84% yield) of product as a clear yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.30 (m,-2H,) 1.70 (m, 2H), 2.82 (t, 2H, J = 7.3 Hz), 7.22 (d, 1H, J = 7.9 Hz), 7.82 (d, 1H, J = 7.9 Hz); ^{13}C (63 MHz, $CDCl_3$) 13.77, 22.26, 31.21, 37.98, 110.82, 116.05, 121.71, 142.29,142.79,-168.21; LC−EIMS *m*/*z* 239 (M^+ + 1), 290 (M^+ + 1 + MeCN). Anal. Calcd for $C_{10}H_{11}N_2Br$: C, 50.23; H, 4.64; N, 11.72 Found: C, 50.61; H, 4.73; N, 11.68.

2-Bromo-6-butyl-3-formylpyridine (11). A solution of 2-bromo-6-butyl-3-cyanopyridine (202 g, 0.845 mol) in toluene (1.3 L) was cooled to −60 °C. DIBAL solution (676 mL, 1.01 mol) was added dropwise over 45 min while the temperature was maintained at −50 °C. The reaction mixture was aged for 2.5 h and then carefully quenched into a mixture of 2 M sulfuric acid (2 L), toluene (200 mL), and THF (100 mL). The resulting mixture was stirred for 16h at rt, water (1.9 L) was added, and the layers were separated. The organic layer was washed with water (1 L) and concentrated in vacuo to a yellow

(13) (a) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem*. **1985**, *50*, 1332. (b) $NaBrO_2$ has been reported in the literature as the co-oxidant with TEMPO, but it is not readily available: Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem*. **1990**, *55*, 462.

(14) (a) For safety reasons, especially on larger scale, the bleach was added slowly and simultaneously with $NaClO_2$ to the batch at 35 °C, with a slow nitrogen sweep over the reaction mixture, to prevent build up of the oxidants and the risk of a runaway reaction. It should be noted that mixing of bleach and $NaClO_2$ prior to the addition is not advised, since some toxic and potentially explosive chlorine dioxide (ClO_2) may be generated. (b) Zhao, M.; Li, J.; Mano, E, Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J.;. *J. Org. Chem*. **1999**, *64*, 2564.

(15) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett*. **1998**, *39*, 5323.

(16) We could find only one related cyclization to form cyclopropane ring from an ester enolate and a strained phosphate: Braschwitz, W.-D.; Otten, T.; Rucker, C.; Fritz, H.; Prinzbach, H. *Angew. Chem*. **1989**, *101*, 1384.

oil (197 g, 96% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.39 (m, 2H), 1.69 (m, 2H), 2.82 (t, 2H, J = 7.3 Hz), 7.23 (d, 1H, J = 7.9 Hz), 8.05 (d, 2H, J = 7.9 Hz), 10.28 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) 13.77, 22.31, 31.35, 37.96, 122.46, 128.08, 137.98, 144.85, 169.65, 190.79; LC−EIMS m/z 242 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{12}NOBr$: C, 49.61; H, 5.00; N, 5.79 Found: C, 49.54; H, 4.79; N, 5.73.

***tert*-Butyl (6-Butyl-3-formylpyridin-2-yl)acrylate (12).** 2-Bromo-6-butyl-3-formylpyridine **11** (30.2 kg, 125 mol), sodium acetate (30.7 kg, 374 mol), tris-*O*-tolylphosphine (3.8 kg, 12.5 mol), toluene (150 L), allylpalladium chloride dimer (1.83 kg, 5 mol), and *tert*-butyl acrylate (19.2 kg, 150 mol) were mixed together, and the resulting slurry was heated under N_2 atmosphere at 108−112 °C for 18.5 h. The reaction mixture was cooled to ambient temperature, and the precipitates were filtered off with a filter. Water (100 L) was mixed with the filtrate and the organic layer was separated, washed with saturated sodium bicarbonate and 1M aqueous citric acid, and then dried ($MgSO_4$). The mixture was filtered and concentrated in vacuo. The resulting oil was quantitated by HPLC (29.8 kg of **12**, 82% yield) and used in the next step without isolation. HPLC assay: column, YMC ODS AQ 302; eluent, acetonitrile: water (70:30); flow rate, 1 mL/min; t_R for bromide **11**, 4.5 min; unsaturated ester **12**, 8.9 min. A pure sample of **12** was isolated as an oil by column chromatography through silica gel: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (d, J = 7.2 Hz, 3H), 1.23−1.38 (m, 2H), 1.46 (s, 9H), 1.60−1.72 (m, 2H), 2.76 (t, J = 7.6 Hz, 2H), 7.03 (d, J = 15.2 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 15.2 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.85, 22.38, 28.06, 31.28, 38.41, 80.91, 123.49, 127.07, 128.55, 136.83, 138.15, 153.06, 165.65, 167.58, 189.92; IR (cm^{-1}) 2959, 2932, 2872, 1710, 1580, 1458, 1311; LC−EIMS m/z 290 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.55; H, 8.02; N, 4.84. Found: C, 70.21; H, 7.96; N, 4.74.

4-Bromo-2-chloromethylanisole (14). Step 1: Reduction of the Acid 13. Sodium borohydride (8.6 g, 0.23 mol) was slurried in THF (150 mL of KF = 150 μg/mL) in a round-bottom flask equipped with a thermocouple, an addition funnel, a nitrogen inlet, a mechanical stirrer, and a cooling bath. 2-Bromo-5-methoxybenzoic acid **13** (50 g, 0.22 mol) dissolved in THF (100 mL, KF = 150 μg/mL) was added to the sodium borohydride slurry over 45 min while the temperature was maintained at 20−25 °C. **Caution: Hydrogen gas is evolved! Exothermic!** The mixture was aged for 30 min at 20−25 °C. Boron trifluoride etherate (36.9 g, 0.26 mol) was added over a period of 30 min at 30−35 °C. (**Caution: delayed exotherm!**). The resulting white slurry was aged for 1 h at 30−35 °C and then was cooled to 15 °C and carefully quenched into a cold (10 °C) saturated aqueous ammonium chloride solution (150 mL) while the temperature was maintained at <25 °C. (**Caution: Hydrogen gas was generated!**) Ethyl acetate (500 mL) was added, and the layers were separated. The organic layer was washed with water (100 mL) and then transferred to a 1 L round-bottom flask equipped for distillation. The solution was concentrated and charged with fresh ethyl acetate. This was repeated until a solution with a volume of 200 mL has KF < 200 μg/mL. The solvent was then switched to DMF to give the final volume of 200 mL with a KF < 200 μg/mL.

Step 2: Chlorination. A DMF solution of the benzyl alcohol from the proceeding step(91.3 g, 0.42 mol, in 400 mL, KF = 300 μg/mL) was charged to a 2 L flask equipped with a mechanical stirrer, thermocouple, N_2 inlet, and cooling bath. The solution was cooled to 0−5 °C and the addition funnel was charged with thionyl chloride (55.0 g, 0.46 mol). The thionyl chloride was added over a period of 45 min while the temperature was maintained at 5−10 °C. The mixture was aged for 1 h at 5 °C and assayed by HPLC. The HPLC sample was prepared by evaporating a sample of the DMF solution with a N_2 stream and then dissolving the sample in column eluent. HPLC typically indicates <1% of the benzyl alcohol. Adding the DMF solution directly into the column eluent could result in some hydrolysis of the chloride to the alcohol. The addition funnel is charged with water (400 mL), which is added dropwise to the reaction mixture over a period of 30 min while the temperature is maintained at <15 °C. The temperature is controlled by cooling and monitoring the rate of addition. The initial addition of water is highly exothermic. Using a large excess of thionyl chloride results in a more exothermic quench. If the quench temperature is not controlled, hydrolysis of the benzyl chloride back to the alcohol may result. The resulting thick white slurry is aged for 1 h at 0−5 °C. The benzyl chloride is isolated by filtration. The cake is washed with (1:1) DMF:H_2O (100 mL) and then water (200 mL). The solid is dried in vacuo to give 93 g of the benzyl chloride (94% yield, 96 *A*% by HPLC) as a white solid: mp 74 °C; HPLC assay: column, Waters Symmetry C8, 4.6 × 250 mm; UV detection, 220 nm; column temp, 25 °C; flow rate, 1 mL/min; eluent, CH_3CN:0.1% H_3PO_4 (70:30); t_R for alcohol, 3.9 min; chloride, 7.3 min; DMF, 2.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 1 H), 7.01 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 8.8 Hz, 3.0 Hz, 1H), 4.63 (s, 2H), 3.78 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 137.5, 133.7, 127.3, 116.3, 115.9, 114.3, 55.6, 46.3; GC−EIMS m/z 234 (M^+). Anal. Calcd for C_8H_8OBrCl: C, 40.8; H, 3.4. Found C, 41.1; H, 3.3.

Acetonide 15. To a 5 L three-neck round-bottom flask equipped with a mechanical stirrer, N_2 inlet, thermocouple probe, heating mantle, and addition funnel were charged (1*R*,2*S*)-*cis*-aminoindanol (100 g, 0.670 mol), tetrahydrofuran (1.2 L, KF = 120 μg/mL), and triethylamine (96 mL, 0.69 mol, KF = 500 μg/mL). The resulting slurry was heated under a N_2 atmosphere to 40−45 °C, giving a yellow solution. Propionyl chloride (59 mL, 0.679 mol) was charged to an addition funnel and slowly added to the solution while the temperature was maintained at 45−50 °C. The temperature was controlled by the rate of addition and a cooling bath. After completion of the amide formation, methanesulfonic acid (3 mL) was added and then 2-methoxypropene (140 mL) was charged to an addition funnel and added over 30 min at 50 °C. The reaction slurry was stirred at 50 °C until the reaction was complete (1−2 h as judged by HPLC). The reaction mixture was cooled to 0−5 °C and quenched with Na_2CO_3 (1 L, 5% aqueous) and heptane (1 L). The organic layer was separated, washed with water (300 mL), and then concentrated to 700 mL at 50 °C under reduced pressure. Heptane (1.0 L) was added and the solution was again concentrated to 700 mL. The solution was allowed to cool and seeded with the acetonide at 35−40 °C. The thick slurry was stirred for 1 h at ambient temperature then cooled to 0−5 °C and stirred for 1 h. The slurry was filtered and the filter cake was washed with cold heptane (200 mL) and air-dried to yield the acetonide as a crystalline white solid (141.1 g, 85% yield): mp 79 °C. $[\alpha]^{20}_D = -163°$ (*c* 1.18, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (t, J = 7.4 Hz, 3H), 1.35 (s, 3H), 1.63 (s, 3H), 2.71, (m, 2H), 3.12 (d, 2H, J = 1.7 Hz), 4.87 (m, 1H), 5.30 (d, 1H, J = 4.5 Hz), 7.2−7.3 (bm, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) 9.51, 24.23, 26.64, 29.40, 36.37, 65.90, 78.80, 96.44, 124.27, 125.92, 127.22, 128.52, 140.83, 141.03, 170.43; LC−EIMS m/z 246 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.45; H, 7.86; N, 5.64.

(*S*)-2-Methyl-3-(2′-bromo-5-methoxyphenyl)propionic Acid (17). A solution of the acetonide **15** (252 g, 1.03 mol) and the benzyl chloride **14** (255 g, 1.08 mol) in THF (2 L, KF < 200 μg/mL) was cooled to −10 °C. Lithium bis(trimethylsilyl)amide (1.45 L, 1.45 mol) was added dropwise over 5 h at 0−2 °C and the mixture was stirred for 1.5 h. After completion of the reaction (HPLC), NH_4Cl (saturated aqueous, 1 L) was added. The quenched reaction mixture was then transferred into a mixture of aqueous ammonium chloride (1.5 L), water (0.5 L), and ethyl acetate (3 L) with stirring. The organic layer was separated, washed sequentially with water (1 L) and brine (0.5 L), and then concentrated to low volume. It was then solvent switched to 1,4-dioxane by flushing with the latter solvent (~4 L total). The dioxane solution was adjusted to 1.8 L and 6 N HCl (1.5 L) was added. The mixture was heated to reflux and the hydrolysis was monitored by HPLC. The reaction mixture quickly becomes a thick slurry due to precipitation of the amide intermediate. It then became a two-phase solution as the amide was gradually hydrolyzed. Upon

the completion of the reaction (~2 h), the reaction mixture was cooled to 20 °C and MTBE (methyl *tert*-butyl ether, 3 L) was added with stirring. The organic layer was separated and washed with water (1 L). The product was then extracted into aqueous phase by 0.6 N NaOH (2 L) solution. To the aqueous layer was added MTBE (2.5 L) and the mixture was cooled to 10 °C and then acidified with 5.4 M sulfuric acid (250 mL) with stirring. The organic layer was separated and washed with water (0.5 L). The MTBE solution of the acid was dried by distillation and then solvent switched to THF. The final volume of the THF solution was 2 L with a KF < 250 μg/mL. It was used directly for the next step. The purity of the acid at this stage was >95 *A*% by HPLC. HPLC conditions: column, Waters Symmetry C8; mobile phase, acetontrile/0.1% aqueous H_3PO_4 (70:30); flow rate, 1.00 mL/min; t_R for acetonide, 4.5 min; benzyl chloride, 7.5 min; alkylation product, 11.5 min; aminoindanol, 1.7 min; acid **17** t_R = 4.5 min. A pure sample of **17** was isolated through silica gel column chromatography as a colorless oil: $[\alpha]^{25}_D$ = +19.4° (*c* 1.04, MTBE); ^{1}H NMR ($CDCl_3$) δ 10.5−8.7 (br, 1 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 6.78 (d, *J* = 3.0 Hz, 1 H), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1 H), 3.75 (s, 3 H), 3.14 (dd, *J* = 13.1, 6.7 Hz, 1 H), 3.20−3.06 (m, 1 H), 2.77 (dd, *J* = 13.1, 7.4 Hz, 1 H), 1.23 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 182.32, 158.71, 139.33, 133.37, 116.86, 115.08, 113.88, 55.36, 39.42, 39.39, 16.72; IR (thin film) 3500−2500 (br), 1701 (s), 1473, 1294, 1241 cm^{-1}. Anal. Calcd for $C_{11}H_{13}O_3$-Br: C, 48.37; H, 4.80. Found C, 48.33; H, 4.56.

(2*S*)-(2′-Bromo-5′-methoxyphenyl)-2-methylpropan-1-ol (18). A solution of the acid **17** (225 g, 0.82 mol) in THF (2 L) was added to a slurry of $NaBH_4$ (33 g, 0.86 mol) in THF (0.5 L KF = 200 μg/mL) over 1 h while the temperature was maintained at 20−25 °C. **(Caution: Hydrogen gas evolution and exothermic!)** The mixture was stirred for 30 min at 20−25 °C, then BF_3·Et_2O (152 g, 1.07 mol) was carefully added over 1 h while the temperature was maintained at 25−35 °C. (**Caution: Delayed exotherm!**) The resulting milky white slurry was stirred for 1 h at 30 °C. HPLC assay indicated completion of the reaction. The reaction mixture was cooled to 15 °C and carefully quenched by transferring into cold (10 °C) saturated aqueous NH_4Cl (1.5 L) while the temperature was maintained at 25 °C. (**Caution: Hydrogen gas!**) Most of the THF was removed by distillation in vacuo (crucial for good crystallization) and the aqueous layer was extracted with MTBE (1.5 L). The organic layer was dried by flushing with additional MTBE and then solvent switched to hexanes and adjusted to a volume of 350 mL. It was seeded and stirred for 2 h at 20 °C and then cooled to 0−5 °C and stirred for 1 h. The product was collected by filtration and the filter cake was washed with cold hexanes (200 mL). The solid was dried under a nitrogen sweep. The isolated solid (164 g) was >99 *A*% and >99% ee by reverse phase and chiral HPLC assays. Reverse phase HPLC: Column, Waters Symmetry C8; mobile phase, MeCN/0.1% aqueous H_3PO_4 (50:50); flow rate, 1.00 mL/min; UV detection at 220 nm; acid t_R = 10.2 min, alcohol t_R = 10.7 min. Chiral HPLC: column, Chiracel OD-H; mobile phase, hexane:2-propanol (97:3); flow rate, 1.00 mL/ min; UV detection at 220 nm; (*R*)-isomer t_R = 23.6 min, (*S*)-isomer t_R = 29.2 min. White solid, mp 59−60 °C; $[\alpha]^{25}_D$ = −0.68° (*c* 1.03, MTBE); ^{1}H NMR ($CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 1 H), 6.75 (d, *J* = 3.1 Hz, 1 H), 6.63 (dd, *J* = 8.8, 3.1 Hz, 1 H), 3.76 (s, 3 H), 3.59−3.46 (m, 2 H), 2.85 (dd, *J* = 13.4, 6.5 Hz, 1 H), 2.48 (dd, *J* = 13.4, 8.1 Hz, 1 H), 2.12−1.95 (m, 1 H), 1.76 (s, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.63, 141.07, 133.24, 116.97, 113.16, 67.35, 55.36, 39.67, 36.32, 16.38; IR (cm^{-1}) (KBr) 3431 (br), 1571, 1473, 1039; GC−EIMS *m*/*z* 258 (M^+). Anal. Calcd for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.83. Found: C, 51.02; H, 5.74.

(2*S*)-3-(2-Bromo-5-methoxyphenyl)-1-(*tert*-butyldimethylsilyoxy)-2-methylpropane (19). *tert*-Butyldimethylsilyl chloride (30.45 g, 0.202 mol) was added to a solution of the alcohol **18** (51.8 g, 0.200 mol) in dry DMF (104 mL, KF < 100 μg/mL) at 20 °C. A solution of imidazole (16.34 g, 0.24 mol) in DMF (52 mL) was then added slowly, the temperature of the reaction mixture being maintained between 20 and 30 °C. The reaction mixture was aged at room temperature for 2 h and the completion of the reaction was confirmed by HPLC assay (<1 *A*% alcohol). Toluene (156 mL) was added to the reaction mixture along with water (235 mL) and the phases were separated. The organic was washed with water (100 mL × 3) and then concentrated (~40 °C, 40 mmHg) to 150 mL to dry the crude product solution (KF <100 μg/mL) (flush with more toluene if necessary). The crude product was used directly for the next step. It may be further purified by silica gel column to give analytically pure samples as a colorless liquid. HPLC assay: column, Zorbax SB-C8; mobile phase, 60−95% acetonitrile in 15 min, 10 mM pH = 7.0 Trizma buffer; flow rate, 1.50 mL/min; UV detection, 220 nm; t_R for DMF, 1.8 min; imidazole, 2.1 min; alcohol (SM), 3.5 min; product, 14.5 min. $[\alpha]^{25}_D$ = +14.3° (*c* 1.52, hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6H, $SiMe_2$), 0.91 (d, *J* = 7 Hz, 3H, Me), 0.93 (s, 9H, CMe_3), 1.17−2.08 (m, 1H, CH), 2.44 (dd, *J* = 13.3, 8.3 Hz, 1H, CH_2), 2.88 (dd, *J* = 13.3, 6.2 Hz, 1H, CH_2), 3.49 (d, *J* = 5.6 Hz, 2H, CH_2), 3.77 (s, 3H, OMe), 6.62 (dd, *J* = 8.7, 3.0 Hz, 1H, ArH), 6.76 (d, *J* = 3.0 Hz, 1H, ArH), 7.40 (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.37 (q), −5.32 (q), 16.48 (t), 18.35 (s), 25.97 (q), 36.26 (q), 39.70 (t), 55.36 (d), 67.36 (t), 113.11 (d), 115.42 (s), 116.98 (d), 133.20 (d), 141.59 (s), 158.62 (s); IR (cm^{-1}) 2955, 2856, 1570, 1472, 1250, 838; LC−EIMS *m*/*z* 373 (M^+ + 1). Anal. Calcd for $C_{17}H_{29}O_2BrSi$: C, 54.82; H, 7.85. Found: C, 55.19; H, 7.92.

***N*-Formyl-(1*S*,2*R*)-1-amino-2-indanol.** (1*S*,2*R*)-1-Amino-2-indanol (10 g, 0.067 mol) was dissolved in THF (100 mL) at 50 °C. Acetic acid (0.192 mL, 0.003 mol) was added followed by ethyl formate (43.2 mL, 0.53 mol) and the mixture was heated to 62 °C for 20 h. The mixture was then cooled to rt and the solid filtered, washed with THF (2 × 15 mL), and air-dried to yield (10.76 g, 91% yield) of title compound as a white crystalline solid: mp 192 °C; $[\alpha]^{20}_D$ = +83° (*c* 1.18, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$/DMSO-d_6) δ 2.30 (dd, 1H, *J* = 1.5, 16.4 Hz), 2.50 (dd, 1H, *J* = 4.9, 16.4 Hz), 2.75 (s, 3H), 3.92 (m, 1H), 4.35 (d, 1H, *J* = 4.6 Hz), 4.76 (dd, 1H, *J* = 4.9, 8.9 Hz), 6.60 (m, 3H), 7.28 (m, 1H), 7.73 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$/DMSO) δ 39.59, 55.43, 71.97, 123.83, 124.59, 126.12, 127.17, 140.25, 141.09, 161.41; LC−EIMS *m*/*z* 133 (M^+ + 1 − $HCONH_2$). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.72; H, 6.23; N, 7.77.

***N*-Methyl (1*S*,2*R*)-1-Amino-2-indanol (20A).** *N*-Formyl-(1*S*,2*R*)-1-amino-2-indanol (20 g, 0.112 mol) was added to a slurry of sodium borohydride (6.4 g, 0.169 mol) in 150 mL of THF. Boron trifluoride etherate (28.8 mL, 0.227 mol) was slowly added over 30 min while the temperature was maintained at 25−35 °C using an ice bath to control the exotherm. The mixture was aged at 29−32 °C for 6 h and then carefully quenched by transferring over 15 min into 3 N HCl (240 mL) using an ice bath to control the temperature (15−25 °C). After stirring for 15 min, 50% NaOH (50−55 mL) was added to adjust the pH to 12.5 using an ice bath to control the temperature (20−30 °C). MTBE (100 mL) was added, the layers were separated, and the aqueous layer was extracted with MTBE (100 mL). The combined organic layers were then distilled and switched into EtOH and concentrated to 40 mL. Water was added (80 mL) over 20 min and the slurry was aged for 2 h at rt and then cooled to 5 °C and aged for 1 h. The product was collected by filtration and washed with a cold EtOH:water mixture (40 mL of 1:4) and air-dried to yield 16.1 g (87% yield) of the title compound: mp 114 °C; $[\alpha]_D^{20}$ = −29° (*c* 1.18, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.57 (s, 3H), 2.97 (bm, 4H CH_2, NH,OH), 3.92 (d, 1H, *J* = 5.2), 4.45 (m, 1H), 7.23 (m, 4H); ^{13}C (63 MHz, $CDCl_3$) 35.14, 39.67, 67.67, 70.53, 123.86, 125.63, 126.67, 128.01, 141.12, 142.22; LC−EIMS *m*/*z* 164 (M^+ + 1). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.63; H, 8.09; N, 8.54.

***N,O*-Acetal 21A from *N*-Methyl-(1*R*,2*S*)-1-amino-1-indanol.** To a solution of the Heck reaction product **12** in toluene (5.18 g in a total of 12.8 g, 17.9 mmol) was added solid (*1R,2S*)-*N*-methyl 1-amino-1-indanol (2.92 g, 17.9 mmol), followed by acetic acid (20 mg). The reaction mixture was then heated to reflux to remove water by azeotrope with a Dean−Stark trap. After HPLC assay indicated that the Heck product has been consumed (<2 *A*%), the reaction was cooled to 20 °C and

poured into saturated aqueous $NaHCO_3$ (15 mL) with stirring. The organic layer was washed with water (20 mL × 2) and concentrated to minimum volume under reduce pressure (40−50 °C, 40 mmHg) and flushed with additional toluene if necessary to dry the crude product by azeotrope until KF < 100 μg/mL. HPLC: column, Zorbax SB-C8, 4.6 × 250 mm; mobile phase, acetonitrile/10 mM Trizma buffer (with 5% MeCN), 60−95% MeCN in 15 min; flow rate, 1.50 mL/min; UV detection at 220 nm; t_R for toluene, 3.8 min; Heck product, 7.7 min; *N*,*O*-acetal, 12.0, 12.5 min (two diastereomers). ^{1}H NMR (250 MHz, $CDCl_3$) (A mixture of two compounds in about 55/45 was observed; all peaks are listed and some peaks are paired up if they appear to be from the same hydrogens of the two diastereomers) δ 0.85−1.0 (m, 3H), 1.25−1.45 (m, 2H), 1.53, 1.54 (s, s, 9H), 1.6−1.8 (m, 2H), 2.18, 2.51 (s, s, 3H), 2.65−2.80 (m, 2H), 3,21−3.24 (m, 2H), 4.88, 4.25 (d, J = 5.1 Hz, d, J = 7.7 Hz, 1 H), 5.04−5.11 (m, 1 H), 5.13, 5.44 (s, s, 1H), 6.9−7.4 (m, 5H), 7.5−8.2 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.5, 166.2, 162.4, 162.1, 155.6, 155.0, 142.6, 142.1, 141.1, 139.7, 138.8, 138.7, 136.4, 135.9, 130.3, 128.7, 128.5, 128.3, 127.2, 126.9, 126.0, 125.4, 125.3, 125.03, 124.96, 123.3, 122.7, 95.7, 91.7, 81.5, 80.4, 80.2, 77.3, 76.0, 74.1, 39.4, 38.7, 37.9, 37.8, 37.0, 31.7, 31.6, 28.2, 27.0, 22.5, 22.4, 14.0.

***N*,*O*-Acetal 21B from Pseudoephedrine.** The same procedure was used. One isomer was observed; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.3), 1.25 (d, 3H, J = 6.0 Hz), 1.39 (m, 2H), 1.55 (s, 9H), 1.72 (m, 2H), 2.18 (s, 3H), 2.55 (m, 1H), 2.79 (t, 2H, J = 7.9), 4.79 (d, 1H, J = 8.7 Hz), 5.30 (s, 1H), 7.0(d, 1H, J = 15.3 Hz), 7.14 (d, 1H, J = 8.0 Hz), 7.2−7.4 (bm, 4H), 7.85 (d, 1H, J = 8.0), 8.24 (d, 1H, J = 15.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.97, 14.38, 22.44, 28.24, 31.72, 35.18, 37.96, 68.91, 80.33, 86.43, 95.89, 123.19, 125.22, 126.55, 128.02, 128.45, 130.50, 137.38, 139.02, 140.08, 151.22, 162.73, 166.44.

Conjugate Addition To Prepare 22. To a dry and degassed (put under vacuum and nitrogen two or three times) solution of aryl bromide **19** (3.80 g, 98 wt %, 10.0 mmol) in toluene (20 mL, KF < 100 μg/mL) and THF (5.0 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (4.0 mL, 10.0 mmol) in ∼15 min. The mixture was stirred at −78 °C for 1 h. The cold solution was then cannulated into the cold solution (−78 °C) of *N*,*O*-acetal from *N*-methyl-(1*R*,2*S*)-1-amino-2-indanol (9.0 mmol) in THF (20 mL) rapidly. The exotherm raises the temperature of the reaction mixture to approximately −50 °C. It was stirred at −50 to −60 °C for 1 h and then quenched carefully with 2.85 mL of acetic acid. (**Caution: Exothermic reaction!**) After warming to ∼0 °C, aqueous citric acid solution (4.8 g of citric acid in 15 mL of water) was added and the two-phase mixture was rapidly stirred for 16 h at room temperature. HPLC assay indicates that the *N*,*O*-acetal hydrolysis was complete. The organic layer was separated and successively washed with 14 wt % NaCl (20 mL), saturated aqueous $NaHCO_3$ (30 mL), 14 wt % NaCl (20 mL), and finally brine (20 mL). The $NaHCO_3$ wash should be slightly basic (pH = 7.5−8.5), otherwise more bicarbonate washes were done. The organic layer was dried by azeotropic distillation under reduced pressure (40−50 °C, ∼40 mmHg) to minimum volume. Flush with additional toluene if necessary to achieve KF < 100μg/mL. HPLC assay indicated 90−95% overall yield from the Heck reaction product. The de of the product was determined by HPLC to be 90%. These steps have been run on 10 kg scale. HPLC conditions were the same as described in the *N*,*O*-acetal formation; t_R for toluene, 3.8 min; Ar_1H, 12.9 min; Ar_1Br, 14.5 min; Ar_1Bu, 16.5 min; aldehyde product **22**, 17.7 min; *N*,*O*-acetal product, 20.9, 22.1 min (two diastereomers epimeric at the acetal moiety). Chiral HPLC assay: column, (R, R) Whelk-O; mobile phase, hexane:IPA 97:3; flow rate, 1.00 mL/min; t_R for major isomer, 6.3 min; minor isomer, 7.1 min. A pure sample was isolated as an amorphous solid through silica gel column chromatography: $[\alpha]^{25}_D$ = −116.4° (*c* 1.42, hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 0.91−1.00 (m, 6H), 1.30 (s, 9H), 1.33−1.48 (m, 2H), 1.73−1.86 (m, 2H), 1.98−2.12 (m, 1H), 2.46 (dd, J = 14.3, 9.0 Hz, 1H), 2.60 (dd, J = 16.5, 3.5 Hz, 1H), 2.86 (t, J = 7.6 Hz, 2H), 3.07 (dd, J = 14.3, 5.8 Hz, 1H), 3.49−3.61 (m, 3H), 3.73 (s, 3H), 5.45 (dd, J = 11.2, 3.7 Hz, 1H), 6.57 (dd, J = 8.6, 2.6 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.33, 13.95, 16.74, 22.42, 25.97, 27.96, 31.06, 36.18, 38.28, 39.28, 41.23, 55.05, 67.87, 79.97, 111.49, 115.58, 120.77, 126.87, 129.96, 133.52, 137.43, 139.06, 157.77, 163.38, 166.38, 171.35, 191.18; IR (cm^{-1}) 2956, 2930, 2857, 1729, 1584, 1463. Anal. Calcd for $C_{34}H_{53}NO_5Si$: C, 69.94; H, 9.15; N, 2.40. Found: C, 70.24; H, 9.27; N, 2.38.

Grignard Addition. Preparation of the Grignard Reagent (Ar_2MgBr). To a 22 L reaction flask equipped with an efficient condenser were added Mg (240 g, 9.87 mol) and dry THF (8.2 L, KF < 100 μg/mL). After degassing by two vacuum/N_2 cycles, the mixture was heated to 50 °C and then the 4-bromo-1,2-(methylenedioxy)benzene (1.89 kg, 9.40 mol) was added carefully. **(Caution: Due to the induction period and the very exothermic reaction, the aryl bromide should be added very carefully! No more than 10% should be added before the reaction is initiated as indicated by the color change from colorless to brown and exotherm.)** Once the reaction was initiated, the remaining aryl bromide was added slowly to maintain a gentle reflux. The reaction mixture was then stirred at 50 °C for 2 h to give a solution of ArMgBr (∼9.4 L, 1.0 M). The reaction was monitored by HPLC: Column, Zorbax SB−C8 (4.6 × 250 mm); column temperature, 30 °C; mobile phase, MeCN/0.1% aqueous H_3PO_4 (40/60−70/30 in 15 min); flow rate, 1.50 mL/min; UV detection, 220 nm; t_R for Ar_2Br, 6.2 min; Ar_2H, 9.2 min.

Grignard Addition to the Aldehyde 22 To Prepare 24. To a 72 L flask were added a dry solution of the crude Michael addition product **22** (4.22 kg in ∼4.7 L of toluene and 2.5 L of THF, KF < 200 μg/mL) and more dry THF (20 L, KF < 100 μg/mL). The mixture was degassed by a vacuum/N_2 cycle and cooled to −75 °C with a dry ice−methanol bath. The Ar_2MgBr prepared was added slowly to maintain the reaction mixture below −65 °C. The mixture was stirred at −70 °C for 3 h and the completion of the reaction was confirmed by HPLC (<1 *A*% aldehyde). The reaction mixture was then pumped into saturated aqueous NH_4Cl (14 L, 20 wt %) to quench the reaction. Toluene (14 L) was added and the mixture warmed to 20 °C. The organic layer was separated and washed with brine (14 L) to give a solution of the crude Grignard addition product (50.11 kg). Assay by HPLC indicates the presence of 4.67 kg (91% yield) of the product **24** in the solution as a 93/7 mixture of two diastereomers. HPLC conditions: column, Zorbax SB-C8, 4.6 × 250 mm; temperature, 30 °C; mobile phase, CH_3CN/ 0.1% aqueous H_3PO_4, 80:20 gradient to 100:0 over 15 min; flow rate, 1.5 mL/min; t_R for aldehyde, 12.15 min; major stereoisomer, 9.93 min; minor stereoisomer, 10.65 min. The crude product solution was dried by azeotropic distillation of toluene to a final volume of 15 L (∼40 °C, 40 mmHg). The KF of the residue should be below 150 μg/mL (flush with additional toluene if necessary). The crude product was used directly for the cyclization. The analytical sample was obtained as an amorphous solid by silica gel column purification. $[\alpha]^{25}_D$ = −38.3° (*c* 1.50, hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 0.90−1.00 (m, 6H), 1.32 (s, 9H), 1.34−1.50 (m, 2H), 1.72−1.83 (m, 2H), 1.84 (d, J = 3.3 Hz, 1H), 1.92−2.10 (m, 1H), 2.40 (dd, J = 14.3, 8.8 Hz, 1H), 2.53 (dd, J = 16.3, 4.0 Hz, 1H), 2.80 (t, J = 7.6 Hz, 2H), 2.96 (dd, J = 14.3, 6.0 Hz, 1H), 3.38−3.50 (m, 3H), 3.73 (s, 3H), 4.97 (dd, J = 10.9, 3.9 Hz, 1H), 5.86 (d, J = 2.4 Hz, 1H), 5.91 (d, J = 2.3 Hz, 2H), 6.59 (dd, J = 8.6, 2.8 Hz, 1H), 6.70−6.80 (m, 4H), 6.86 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.40, 13.97, 16.76, 18.30, 22.45, 25.92, 27.95, 31.36, 35.98, 36.23, 37.55, 40.28, 41.24, 54.98, 67.84, 70.47, 79.54, 100.85, 107.32, 107.86, 111.36, 115.73, 119.89, 120.49, 129.56, 133.93, 134.18, 136.28, 136.42, 139.26, 146.61, 147.50, 157.78, 158.10, 159.96, 171.50; IR (cm^{-1}) 3451, 2857, 1731, 1608, 1573; LC−EIMS *m*/*z* 706 (M^+ + 1). Anal. Calcd for $C_{41}H_{59}NO_7Si$: C, 69.75; H, 8.42; N, 1.98. Found: C, 69.99; H, 8.47; N, 1.93.

Cyclization−Deprotection. Diethyl chlorophosphate (1.65 kg, 9.6 mol, 1.45 equiv) was added to the dry Grignard addition

product **22** in toluene (~15 L) at −15 °C. Then $LiN(SiMe_3)_2$ (1.0 M in THF, 28.75 L, 4.35 equiv) was added while the reaction temperature was kept at <5 °C. The slurry was stirred at 0−10 °C for 4 h. More diethyl chlorophosphate and $LiN(SiMe_3)_2$ may be added to complete the reaction if required. HPLC: Column, Zorbax SB C-8 (4.6 × 50 mm); mobile phase, MeCN/0.1% aqueous H_3PO_4, gradient 80/20, 10 min 95/5, 20 min A/B 98/2; flow rate, 1.5 mL/min; UV detection, 220 nm; t_R for starting material, 10.9 min; intermediate, 11.7 min; intermediate, 13.2 min; cyclization product, 12.2 min. After the reaction was completed (SM < 1%), water (17 L) and acetic acid (4.5 kg, **exothermic!**) were added while the reaction temperature was kept at <30 °C. The organic layer was separated, washed with brine (14 L), concentrated under vacuum to 10−12 L, mixed with acetonitrile (20 L), and then cooled to 0 °C. Concentrated HCl (13.2 kg) was added slowly while the reaction temperature was kept at <25 °C. The mixture was stirred at 20−25 °C overnight to give a mixture of the acid alcohol and the lactone. HPLC conditions: (same column and eluents as above) gradient, time 0 A/B 50/50, 10 min A/B 90/10, 15 min 90/10; t_R for *tert*-butyl ester alcohol, 6.4 min; lactone, 4.7 min; acid alcohol, 2.9 min. After the *tert*-butyl ester alcohol was consumed (19 h), the reaction mixture was cooled to 0 °C and neutralized with 40% NaOH until pH = 3−5 (~12.4 kg) while the temperature was kept at <25 °C. Water (6 L) was also added to dissolve all the salt. The two layers were separated and the top organic layer was mixed with 3.3 kg of 40% NaOH (5 equiv) and 12 L of water. The mixture was vigorously stirred for 3 h until all the lactone was hydrolyzed (organic layer sample). The two layers were then separated and then MTBE (20 L), water (20 L), and 40% NaOH (200 g) were added to the organic layer with stirring. The two layers were separated, and the organic layer was mixed with NaOH (100 g, 40% NaOH), water (10 L), and heptane (20 L). The layers were separated, and the organic layer was discarded. Acetonitrile was mostly with the top layer in the first separation but with the bottom layer in the second separation, which was a difficult cut because both layers were dark brown. The combined aqueous layers were mixed with MTBE (12 L) and then neutralized with H_3PO_4 (85%, 4.6 kg, 6 equiv) until pH = 3−4 (exothermic, keep the temperature <25 °C). The two layers were separated and the aqueous layer was extracted with toluene (20 L). The combined organic layers were dried by azeotropic distillation of toluene to a volume of 10 L. Flush with more toluene if necessary to achieve KF < 500 μg/mL. The residue was then diluted with 50 L of MTBE. Benzylamine (0.85 kg, 1.2 equiv) was added as a solution in 3 L of MTBE in an addition funnel. Only 1.5 L of this solution was added initially and the batch was seeded and stirred for 1 h for the salt to precipitate. The rest of the benzylamine solution was added over 30 min. An additional 7 L of MTBE was used for rinse of the addition funnel. The batch was stirred at ambient temperature overnight. The solid was collected by filtration and washed (3 × 4 L MTBE) until the wash was nearly colorless. The batch was dried with nitrogen flow and suction. The title compound was obtained as an off white solid (2.96 kg, 72% yield). HPLC showed ~95 wt % pure and 98.5 *A*%: mp 131−133 °C (dec); $[\alpha]^{25}_D = +28.5°$ (*c* 0.98, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.83−0.89 (m, 6H), 1.21−1.36 (m, 2H), 1.51−1.63 (m, 2H), 1.89−2.00 (m, 1H), 2.54 (dd, J = 14.2, 7.8 Hz, 1H), 2.66 (t, J = 7.7 Hz, 2H), 2.77 (dd, J = 14.2, 6.0 Hz, 1H), 3.04 (t, J = 9.2 Hz, 1H), 3.20 (dd, J = 10.7, 6.7 Hz, 1H), 3.36 (dd, J = 10.7, 4.7 Hz, 1H), 3.47 (s, 2H), 3.67 (s, 3 H), 4.42 (d, J = 9.0 Hz, 1H), 4.90 (d, J = 9.2 Ha, 1H), 5.84 (s, 2H), 6.58−6.69 (m, 5H), 6.78 (d, J = 8.5 Hz, 1H), 6.89−6.93 (m, 5H), 7.07−7.16 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.9, 17.1, 22.3, 32.3, 36.7, 36.8, 37.5, 43.4, 50.3, 52.0, 54.9, 66.2, 66.9, 100.9, 108.2, 108.6, 111.6, 114.8, 120.6, 121.6, 128.1, 128.4, 128.6, 129.7, 132.7, 134.3, 135.4, 135.8, 137.7, 141.4, 146.3, 147.8, 157.4, 162.2, 165.1, 179.8; LC−EIMS *m/z* 518 (M^+ + 1). Anal. Calcd for $C_{38}H_{44}N_2O_6$: C, 73.05; H, 7.10; N, 4.48. Found: C, 73.18, H, 7.09; N, 4.45.

CrO_3-Catalyzed Oxidation To Prepare 1. Preparation of the Oxidant Solution. A solution of H_5IO_6/CrO_3 was prepared by adding water (1.1 mL) and MeCN to H_5IO_6 (15.95 g, 70 mmol) to a total volume of 160 mL. An aqueous solution of CrO_3 (0.16 mL, KF = 200 μg/mL) was then added and the mixture was stirred until all of the solid dissolves. The solubility of H_5IO_6 in MeCN was limited and it may take 2 h to dissolve it completely. The reaction was sensitive to the content of water, and it appears that 0.5−1.0 vol % was optimal.

Preparation of the Free Acid 1. To a mixture of the benzylamine salt of the hydroxy acid **26** (12.50 g, 20.0 mmol) in MTBE (100 mL) and water (50 mL) was added 2.0 N HCl (~10 mL) until pH = 3−4. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and then concentrated to ~30 mL. It was flushed with acetonitrile (100 mL) and then diluted with MeCN (to 100 mL). Water (0.75 mL) was then added and the mixture was cooled to −5 °C. A portion of the H_5IO_6/CrO_3 solution (50 mL, 1.1 equiv) was added in 5−10 min. The remaining portion (110 mL) was added in 30−60 min while the batch temperature was maintained at −3 to 0 °C. No significant oxidation occurs until after the addition of the first equivalent of the reagent. The mixture was stirred for 0.5 h at 0 °C and the completion of the reaction was confirmed by HPLC. The reaction was quenched with Na_2HPO_4 solution (8.52 g in 150 mL of H_2O) and then brine (50 mL). Some inorganic solid remains and was filtered off. The pH of the aqueous layer should be 3−4. Toluene (150 mL) was added and organic layer was separated and washed with 1/1 brine/water mixture (2 × 100 mL). The organic layer was concentrated to 160 mL to remove most of the acetonitrile (40 mmHg, 30 °C bath). Loss in the aqueous washes was minimal (~0.01 mg/mL). The acetonitrile should not be completely distilled in order to avoid the appearance of some red brown gummy material which may be the HCl salt of the product based on HPLC. The mixture was treated with 0.30 N NaOH (150 mL) for 0.5 h and the organic layer was separated and discarded. MTBE was added (100 mL) to the aqueous layer and the mixture was acidified with 2.0 N HCl (~22.5 mL) to pH = 3.5. The organic layer was separated and washed with water (2 × 50 mL) and brine (50 mL) and then concentrated to give the crude product as a brown foam. HPLC indicates 9.5−10.9 g of **1** (90−95% yield) and 94−97 *A*% HPLC conditions: Column, YMC-ODS AM, 4.6 × 250 mm; solvent: CH_3CN:0.1% H_3PO_4 50:50 gradient to 80:20 over 15 min; flow rate, 1.0 mL/min; temperature, 30 °C; UV detection, 220 nm; t_R for hydroxy acid, 5.8 min; diacid, 7.8 min.

TEMPO/NaClO-catalyzed Oxidation To Prepare 1. A mixture of the benzylamine salt of the hydroxy acid **26** (6.60 kg by assay, 10.56 mol) in MTBE (66 L) and water (26 L) was treated with 2.0 N HCl (5.5 L) until pH = 3−4. The organic layer was washed with water (2 × 26 L) and then extracted with NaOH (37 L, 0.63 N NaOH). To the NaOH extract were added MeCN (53 L) and NaH_2PO_4 (4.2 kg), and the mixture was heated to 35 °C. The pH of the mixture should be 6.7. TEMPO (165 g, 1.06 mol) was added followed by a simultaneous addition (over 2 h) of a solution of sodium chlorite ($NaClO_2$, 2.4 kg, 80%, 21 mol in 9.9 L of water) and a solution of dilute bleach (550 g of 5.25% bleach diluted into 5.3 L of water). The sodium chlorite solution and bleach should not be mixed prior to the addition since the mixture appears to be unstable. The addition was carried out as follows: with a slow nitrogen sweep over the batch, approximately 20% of the sodium chlorite solution was added followed by 20% of the dilute bleach. Then the rest of the $NaClO_2$ solution and dilute bleach were added simultaneously over 2 h. The reaction was slightly exothermic. The mixture was stirred at 35 °C until the reaction was complete by HPLC (2−4 h). The batch was cooled to room temperature, water (79 L) was added, and the pH was adjusted to 8.0 with 2.0 N NaOH (12.7 L). The reaction was quenched by pouring into cold (0 °C) Na_2SO_3 solution (3.22 kg in 53 L water) maintained at <20 °C. The pH of the aqueous layer should be 8.5−9.0. After aging for 0.5 h at room temperature, MTBE (53 L) was added with stirring. The organic layer was discarded and the aqueous layer was acidified with 2.0 N HCl (32.2 L) to pH = 3−4 and extracted with MTBE (80 L). The organic layer was washed with water (2 × 26 L) and brine (40 L) to give a solution of the crude dicarboxylic acid **1** (90−95% yield by HPLC assay).

Preparation of the Disodium Salt of 1. The organic layer from last step was concentrated under vacuum and flushed with dry ethyl acetate repeatedly (2 × 20 L) and the final residue dissolved in 28 L of dry ethyl acetate. To this solution was added a solution of sodium ethoxide (1.44 kg, 21.1 mol) in 5.75 kg of ethanol over 10 min at 30−35 °C. After seeding, additional ethyl acetate (140 L) was added over 2 h at 25 °C. After aging for 16 h, the slurry was filtered and the cake washed with 70 L of ethyl acetate. The crystals were dried in a vacuum oven at 60 °C overnight to give the disodium salt as a slightly hygroscopic, white solid (5.22 kg, 86% yield from the alcohol): HPLC 99.1 *A*%. $[\alpha]^{25}_{D} = +100°$ (*c* 1.135, H_2O); ^1H NMR (250 MHz, H_2O) δ 6.96 (d, $J = 7.8$ Hz, 1 H), 6.80 (d, $J = 2.3$ Hz, 1 H), 6.75−6.56 (m, 6H), 5.68 (s, 2H), 4.88 (d, $J = 9.2$ Hz, 1H), 4.47 (d, $J = 9.3$ Hz, 1H), 3.68 (s, 3H), 3.00−2.74 (m, 3 H), 2.65−2.50 (m, 3H), 1.48−1.36 (m, 2H), 1.15−1.03 (m, 5H), 0.69 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (63 MHz, H_2O) δ 186.34, 181.88, 165.21, 162.80, 157.85, 148.28, 146.84, 142.39, 138.02, 137.71, 135.05, 134.29, 130.51, 122.37, 122.13, 115.82, 112.93, 109.28, 108.96, 101.81, 69.39, 56.03, 53.12, 51.18, 46.13, 38.34, 37.26, 32.91, 22.48, 18.77, 14.26; LC−EIMS *m*/*z* 532 ($M^+ + 1$).

JO991292T