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Practical Asymmetric Synthesis of a Selective Endothelin A Receptor (ETA) Antagonist

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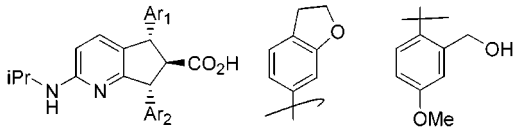
ABSTRACT



2 **Ar$_1$** **Ar$_2$**

A practical, chromotography-free asymmetric synthesis was developed for the large scale preparation of an endothelin receptor antagonist 2. This synthesis includes a new efficient process for the preparation of 6-bromo-2,3-dihydrobenzofuran, a stereoselective conjugate addition of an aryllithium followed by stereospecific addition of the Grignard reagent of the top aryl bromide, and an aminophosphate-mediated sterospecific intramolecular enolate alkylation, which led to the formation of the five-membered ring bearing three contiguous asymmetric centers.

Endothelin receptor antagonists are currently being evaluated as useful therapeutic agents for the treatment of hypertension, congestive heart failure, and renal diseases.[1,2] We recently reported an efficient large scale synthesis of an early drug candidate **1**.[3] In this paper, we report the development of a large scale, economical synthesis of a similar compound **2**, which is under development as an endothelin A receptor selective antagonist. Although structurally similar to **1**, compound **2** offers some unique and significant synthetic challenges, which are described herein. Our approach to the synthesis of the core ring system of compound **2** is similar to the previously reported synthesis for **1**. As outlined in Scheme 1, the key steps include a Michael addition of the bottom arylmetal to the Michael acceptor and addition of top arylmetal to the Michael addition product, followed by cyclization to form the five-membered ring with correct stereochemistry. To accomplish this goal, we needed to develop an efficient synthesis for the top aryl fragment as 6-bromo-2,3-dihydrobenzofuran and an efficient method to introduce the isopropyl amino group to the pyridine ring. In the process of realizing this strategy, we found that substantial modifications to the known chemistry were required for the strategy to be successful.[3]

(1) (a) Astles, P. C.; Brown, T. J.; Halley, F.; Handscombe, C. M.; Harris, N. V.; Majid, T. N.; McCarthy, C.; McLay, I. M.; Morley, A.; Porter, B.; Roach, A. G.; Sargent, C.; Smith, C.; Walsh, R. J. A. *J. Med. Chem.* **2000**, *43*, 90 and references therein. (b) Ishikawa, K.; Nagase, T.; Mase, T., Hayama, T.; Ihara, M.; Nishikibe, M.; Yano, M. PCT Int. Appl. WO 9505374, 1995.

(2) Clark, W. M. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 565.

(3) (a) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J.; Dolling, U.-H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658−9667. (b). Devine, Paul N.; Desmond, R.; Frey, L.; F.; Heid, R. M.; Song, Z.; Tillyer, R. D.; Tschaen, D. M.; Zhao, M.; Kato, Y.; Mano, E.; Okada, S.; Kato, S.; Mase, T. *Yuki Gosei Kagaku Kyokaishi* **1999**, *57*, 1016−1025

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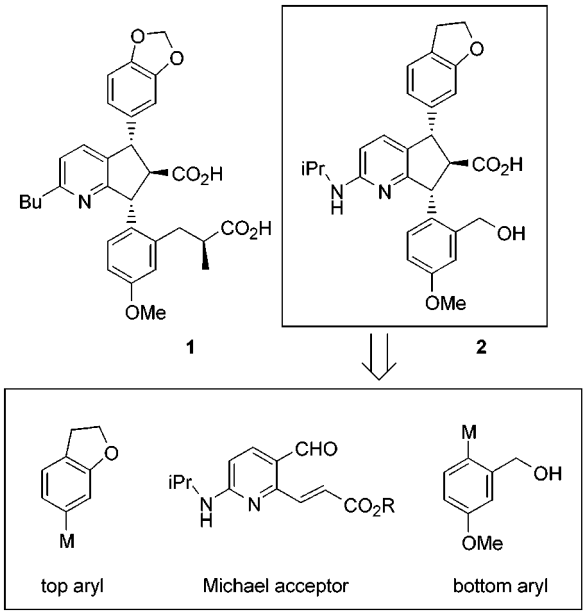
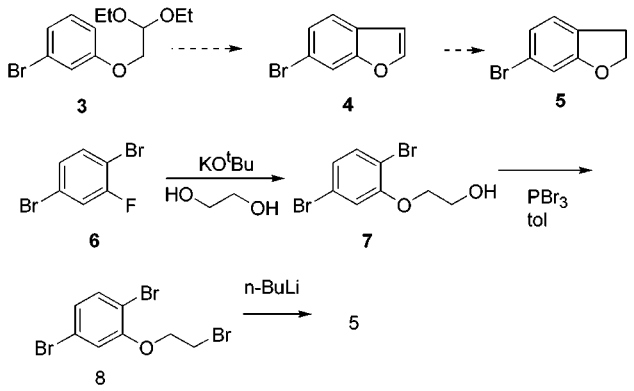
Scheme 1



Synthesis of 6-Bromo-2,3-dihydrobenzofuran (5). As shown in Scheme 2, the commonly used synthetic route to

Scheme 2



this compound is from 3-bromophenol, relying on a nonregioselective Friedel−Crafts cyclization of **3** to **4** followed by low yielding reduction (due to debromination).[5a] We desired a practical synthesis of this compound that obviated both of these problems. Thus, when readily available 1,4-dibromo-2-fluorobenzene (**6**) was treated with potassium *tert*-butoxide and ethylene glycol, compound **7** was isolated directly from the reaction mixture as a solid in 87% yield upon addition of water. Conversion of the alcohol **7** to the corresponding bromide **8** was carried out in toluene with PBr_3, and the bromide was used without purification.[5b] Treatment of the bromide with *n*-butyllithium led to lithium-bromide exchange followed by intramolecular alkylation of the resulting aryllithium to give the desired 6-bromo-2,3-dihydrobenzofuran **5** in 80% yield from the alcohol **7**.[5c] This compound was isolated from methanol−water as a crystalline solid.[5d]

Preparation of the Michael Reaction Acceptor 12. The key Michael acceptor **12** was synthesized according to Scheme 3. Starting with the readily available 2,6-dibromopyridine, direct displacement of one of the bromides with lithium benzylisopropyl amide in toluene went smoothly to give the aminopyridine **10**.[6a,7] Interestingly, the desired product was not formed in THF as reaction solvent. Formylation with Vilsmeier's reagent generated from DMF/$POCl_3$ gave the aldehyde **11** with the desired regiochemistry. The side reaction in this step was the displacement of the bromide by the chloride, which was minimized by using excess (4 equiv) Vilsmer's reagent and lower temperature (35−40 °C). Bromoaldehyde **11** was converted into the *tert*-butyl ester **12** in 85% yield via a Heck reaction with 1.05 equiv of *tert*-butyl acrylate in *N*,*N*-dimethyl acetamide with NaOAc·$3H_2O$ and $PdCl_2$(dppf) (CH_2Cl_2 complex) as the catalyst at 80 °C.[6b] Compounds **10**−**12** were oils and therefore were not purified.

Conjugate Addition. To introduce the bottom chiral center in **2**, we envisioned the strategy of using chiral amino alcohol or diamine auxiliary to form the intermediate like **13,** which could undergo diastereoselective conjugate addition to the unsaturated ester by the bottom arylmetal species. On the basis of our earlier experience with conjugate additions of this type, we expected the addition of the aryllithium to intermediate such as **13** would be straightforward.[3,4] However, we found that extensive screening was necessary to find the right protecting groups on the substrates, the right chiral auxiliary, and conditions for the reaction to proceed with high yield and diastereoselectivity. As shown in Scheme 3, the best combination we found was *N*-benzyl protection for the amino substituent of **12** along with the trityl protecting group on the alcohol of the bottom aryl compound (Ar_2)[8] and (S,S)-pseudoephedrine as the auxiliary. The bottom aryllithium (Ar_2Li) was prepared at low temperature (typically ≤50 °C), and the enoate **13** (prepared by reacting **12** with (*S*,*S*)-pseudoephedrine) was added to the aryllithium solution at temperatures typically lower than −50 °C. After the auxiliary was removed with citric acid, the

(4) (a) Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. D.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120. (b) Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 411.

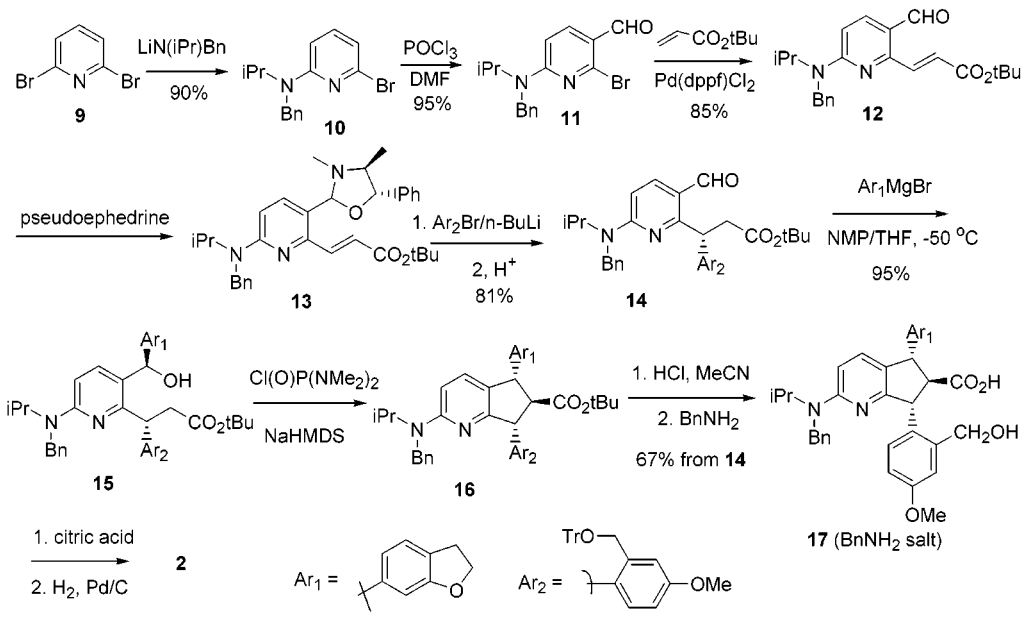
(5) (a) Paper from Banyu Medicinal Chemistry, manuscript in preparation. (b) The reaction was carried out at 90 °C with 0.45 equiv of PBr_3. After 2 h, an additional 0.1 equiv of PBr_3 and 0.3 equiv of water were added to get complete conversion. (c) Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981,** *46*,1384. (d) Data for **5**: white crystals, mp 42−45 °C; ^{1}H NMR (250 MHz, $CDCl_3$, ppm) 3.15 (t, 2H, J = 8.8 Hz), 4.58 (t, 2H, J = 8.8 Hz), 6.9−7.1 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 161.1, 126.2, 125.8, 123.3, 120.8, 112.9, 71.9, 29.3; HPLC 95% pure by area.

(6) (a) Data for **10**: colorless oil; ^{1}H NMR (250 MHz, CDCl3, ppm) 1.21 (d, J = 6.7 Hz, 6 H), 4.52 (s, 2H), 5.11 (hep, J = 6.7 Hz, 1H), 6.18 (d, J = 8.4 Hz, 1H), 6.0.68 (d, H=7.4 Hz, 1H), 7.14 (dd, J = 8.4, 7.4 Hz, 1H), 7.2−7.4 (m, 5H). (b) Data for **12**: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) 1.25 (d, 6H, J = 6.7 Hz), 1.54 (s, 9H), 4.68 (s, 2H), 5.35 (br, m, 1H), 6.41 (d, J = 10 Hz, 1H), 6.89 (d, J = 15 Hz, 1H), 7.15−7.36 (m, 5H), 7.83 (d, J = 10 Hz, 1H), 8.29 (d, J = 15 Hz, 1H), 10.20 (s 1H).

(7) Satisfactory ^{13}C NMR and elemental analysis results were obtained.

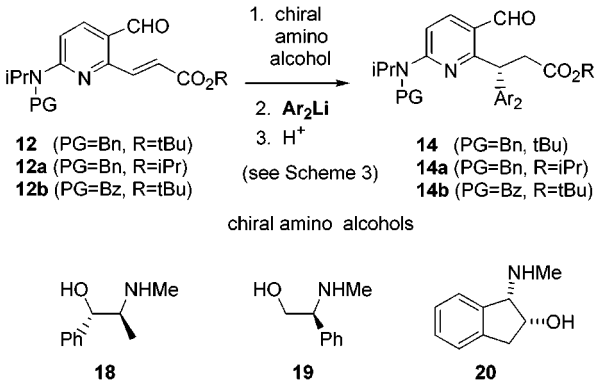
(8) The trityl ether (Ar_2Br) was made from 2-bromo-5-methoxybenzyl chloride and Ph_3COH in the presence of *t*-BuOK.

Scheme 3



desired product **14** was produced in 81% yield and 92% ee.[7−9] Several other auxiliaries and protecting group combinations gave less satisfactory results. As shown in Scheme 4 and Table 1, as chiral auxiliary, (*S*,*S*)-pseudoephedrine (**18**)

Scheme 4



gave better diastereoselectivity than *N*-mehyl-(*S*)-phenylglycinol (**19**) or *N*-methyl (1*S*,2*R*)-1-amino-2-indanol (**20**) (entries 1−3). The sterically more hindered *tert*-butyl esters gave better yields than the isopropyl ester of the enoate (entries 1 and 4). The protecting group on the isopropylamino group (PG) also affects the diastereoselectivity of the conjugate addition, e.g., when the benzyl protecting group was replaced with benzoyl, the ee of the product was much lower (entries 1 and 5). In addition, it was found that as protecting group in the bottom aryl fragment (Ar_2 in Scheme 3), the trityl group (Tr = trityl) gave much better yield for the Michael addition than *p*-methoxybenzyl.

Grignard Addition. Adding the Grignard reagent of the top aryl bromide (Ar_1MgBr) solution to aldehyde **14** in THF at −70 to −78 °C gave the product **15** in high yield (>90%) but with only modest diastereoisomeric ratio (dr) of 5/1.[10] A high stereoselectivity is important for controlling this chiral center in the final product. To improve the selectivity, a variety of solvents and additives were investigated; the key results are summarized in Table 2. Different arylmetals gave very different reactivity and selectivity. The aryl Grignard gave the best selectivity (entries 1−3). The aryllithium reacted readily but with much lower diastereoselectivity, while the arylzinc (prepared from aryllithium and zinc chloride) was unreactive. It was also found that more polar solvents improved the diastereoselectivity, e.g., the reaction in NMP gave product with higher dr (15/1), while toluene gave lower dr (5.6/1). The ratio was further improved to 25/1 by running the reaction at low temperature with NMP/THF mixed solvent.

Cyclization. In our reported synthesis of **1**, we described a novel phosphate-mediated stereospecific intramolecular ester enolate alkylation of an intermediate similar to **15.**[3]

Table 1. Stereoselectivity of the Conjugate Addition

entry	substrate	auxiliary	% ee	% yield
1	**12**	**18**	92	81
2	**12**	**19**	89	58
3	**12**	**20**	80	70
4	**12a**	**18**	91	65
5	**12b**	**18**	57	78

(9) Data for **14**: solid; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 9.64 (s, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.5−7.6 (m, 6H), 7.2−7.4 (m, 15H), 6.94 (d, J = 2.4 Hz, 1H), 6.3−6.8 (br, m, 3H), 5.09 (dd, J = 4.0, 11 Hz, 1H), 4.85 (br, s, 1H), 4.55 (d, J = 7.1 Hz, 1H), 4.42 (Abq, J = 11.2, 23.9 Hz, 2H), 3.78 (s, 3H), 3.15 (br, m, 1H), 2.7−2.8 (m, 1H), 1.26−1.31 (m, 6H), 1.19 (s, 9H).

Table 2. Diastereoselectivity of the Addition to Aldehyde **14** by Ar_1MX

entry	solvent	MX	temp	dr
1	THF	MgBr	−78 °C	5.0/1
2	THF	Li	−78 °C	
3	THF	ZnCl	rt	nr
4	PhMe	MgBr	−78 °C	5.6/1
5	NMP	MgBr	−20 °C	15/1
6	NMP/THF(1/1)	MgBr	−50 °C	25/1

Following the same protocol, we treated compound **15** with 1.5 equiv of diethyl chlorophosphate [$(EtO)_2POCl$] and 5 equiv of lithium hexamethyldisilazide (LiHMDS), expecting an stereospecific SN_2 displacement of the alcohol phosphate by the *tert*-butyl ester enolate to give **16**. Instead, a complex product mixture was produced. We reasoned that the amino substituent on the pyridine ring of **15** is much more electron-donating (than the butyl group in compound **1**) so that the phosphate intermediate from the alcohol decomposes readily. Therefore, other less active leaving groups such as phosphite, carbonate, carbamate, and phosphoroamide were investigated. Only the phosphoroamide offered promising results. Thus, treatment of **15** with $(Me_2N)_2POCl$ and LiHMDS or NaHMDS in THF or a THF/toluene mixture afforded the cyclization product **16**. The reaction was significantly faster and cleaner with NaHMDS. It was also faster in THF than in a toluene/THF mixture. Under optimized conditions, the crude Grignard addition product **15** was treated with 1.6 equiv of $(Me_2N)_2POCl$ and 5.2 equiv of NaHMDS at −20 to 0 °C. After aqueous acid workup the reaction mixture was treated with concentrated HCl in acetonitrile to remove both the trityl and the *tert*-butyl groups. The resulting acid was crystallized as the benzylamine salt **17** in 67% overall yield from the Grignard addition product **15**.[11,7] This is the first crystallized intermediate from the beginning of the synthesis, and all of the reactions were performed using crude intermediates, which is a demonstration of the robustness of the process. The ee of the acid in **17** was upgraded by this crystallization from 90% to >99%.

To finish the synthesis, the free acid from the benzylamine salt **17** was hydrogenated in MeOH at 40 °C under 40 psi hydrogen. The product was dissolved in THF to remove catalyst, and final product **2** was crystallized from methanol in 90−95% yield and ∼99% pure by HPLC.[12,7]

In summary, this work has expanded the scope and defined some of the limitations of this strategy for synthesizing this class of endothelin antagonists. Careful evaluation of the chemistry allowed for modification of the reactivity of the substrates and reagents, which led to significant improvements of the key transformations

Supporting Information Available: Procedure for the preparation of compounds **2**, **5**, **7**, **8**, **10**, **11**, **12**, **14**, **15**, and **17**. ^{13}C NMR data for compounds **2**, **14**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Data for **15**: (solid); ^1H NMR (C_6D_6) of the major isomer has a peak at 5.11 ppm (ABq, J = 10.5, 4.3 Hz)) and the minor isomer at 5.30 ppm (Ab q, J = 11.5, 3.5 Hz). The diastereoisomeric ratio was determined by HPLC on an YMC PVA column. The stereochemistry of the alcohol is assigned on the basis of the subsequent chemical transformations.

(11) Data for **17**: mp 135−137 °C; ^1H NMR (400 MHz, CD_3OD, ppm) 7.4 (m, 5H), 6.6−7.25 (m, 11H), 6.21(d, J = 87. Hz, 1H), 4.4−4.9 (m, 5H), 4.35−4.55 (m, 5H), 3.97 (s, 2H), 3.76 (s, 3H), 3.18 (t, J = 8.9 Hz, 1H), 3.11 (t, J = 8.6 Hz, 2H), 1.10 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H).

(12) Data for **2**: mp >200 °C; ^1H NMR (400 MHz, DMSO-d_6, ppm) 6.6−7.2 (m, 7H), 6.2−6.3 (m, 2H), 4.4−4.7 (m, 5H), 4.34 (d, J = 8.4 Hz, 1H), 3.6−3.8 (m, 1H), 3.1 (m, 1H), 3.14 (t, J = 8.6 Hz, 2H), 3.01 (t, J = 8.7 Hz, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H).