A Catalytic Enantioselective Synthesis of the Endothelin Receptor Antagonists SB-209670 and SB-217242. A Base-Catalyzed Stereospecific Formal 1,3-Hydrogen Transfer of a Chiral 3-Arylindenol

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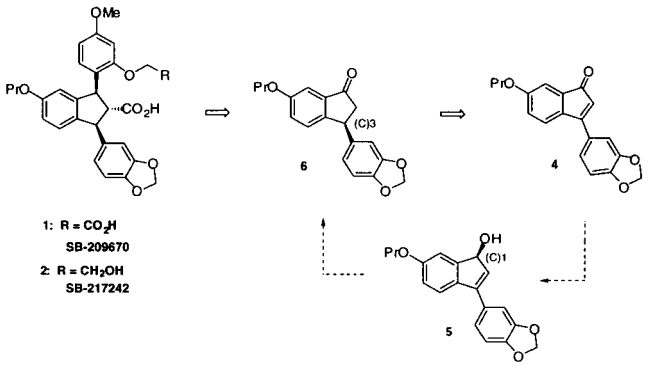
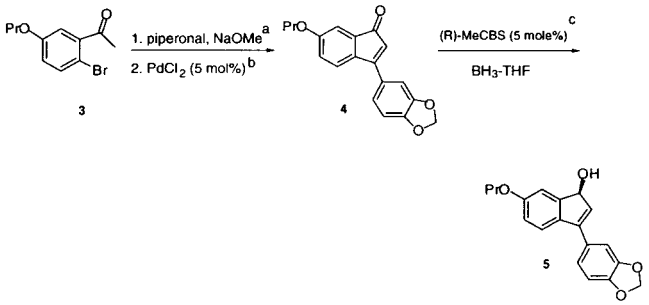
In the pursuit of breakthrough chemotherapeutics, endothelin-1[1] and its isopeptides have garnered a significant amount of attention within the pharmaceutical industry.[2] The 21 amino acid peptide exhibits potent constrictor activity of vascular smooth muscle through its selective binding of the ET_A/ET_B receptors and is believed to play an important role in cardiovascular and pulmonary disease.[3] Recently, SmithKline Beecham discovered two nonpeptide ET_A/ET_B receptor antagonists with nanomolar binding affinity, SB-209670 (**1**) and SB-217242 (**2**), which possess three contiguous stereocenters upon an indan ring framework.[4] During our investigations toward a viable synthesis of **1** and **2** to support clinical development, we discovered and successfully utilized an unusual base-catalyzed highly stereospecific 1,3-hydrogen rearrangement of a chiral 3-arylindenol which is described in this communication.

We were interested in developing a catalytic enantioselective approach to **1** and **2**, and preliminary studies indicated that **4** was a useful substrate for an asymmetric ketone reduction (Scheme 1). Drawing from the seminal work of Itsuno[5a] and Corey,[5b] an oxazoborolidine-catalyzed ketone reduction was determined to deliver the indenol **5** with high enantioselectivity using the (*R*)-MeCBS catalyst. With this discovery, our synthetic strategy turned to the possibility of a stereospecific C(1) → C(3) hydrogen transfer to prepare the indanone **6**. Although suprafacial 1,3-hydrogen transfers are forbidden due to orbital symmetry considerations, Motherwell[6a] has reported that lithium alkoxides of allylic alcohols in the presence of a Ni(II) catalyst can be efficiently isomerized to the carbonyl product, presumably through a nickel hydride addition−elimination pathway. The indenol **5** appeared well suited for this type of transformation since suprafacial hydrogen delivery seemed extremely likely using a transition metal catalyst.[7]

Scheme 1



Scheme 2[a]



[a] Key: (a) EtOH, 25 °C, 3 h (83%); (b) PPh_3 (15 mol %), K_2CO_3 (2 equiv), DMF, 110 °C. 0.5 h (75%); (c) THF, −15 °C, 1 h (90%, 94% ee).

The synthesis of **5** commenced with the condensation of piperonal with 2-bromoacetophenone **3**[8] in preparation for a palladium-catalyzed 5-endo-trig cyclization to furnish the indenone **4** (Scheme 2). Realizing the 5-endo-trig cyclization must overcome significant distortional strain to achieve ring closure, we reasoned the palladium d-orbitals would enable sufficient p-orbital overlap for insertion into the olefinic bond.[9] Therefore, we were gratified to discover that treatment of the bromochalcone with $PdCl_2$ (5 mol %), PPh_3 (15 mol %), and K_2CO_3 in DMF at 110 °C led to a facile cyclization and delivery of **4** in 75% yield. The enantioselective ketone reduction was then performed via addition of **4** to a solution of the (*R*)-MeCBS catalyst and BH_3−THF (1.1 equiv) in THF cooled to −15 °C to complete the synthesis of **5** in 90% yield and 94% ee.

To our delight, **5** underwent a highly efficient and stereoselective hydrogen rearrangement to give the indanone **6** (Table 1). Initially we attempted the reaction with $Pd(PPh_3)_2Cl_2$ and Et_3N which resulted in the formation of **6** in 95% yield with high stereospecificity (90.6% ee) (1). Our early mechanistic assumption of a palladium hydride catalyzed olefin isomerization became uncertain, however, when we observed a slight increase in stereospecificity (92.2% ee) with DABCO as the amine base (2). Due to geometric constraints, DABCO should be incapable of undergoing palladium oxidation, thus negating formation of the palladium hydride catalytic species.[10] The crucial role of the amine base quickly became apparent when **5** was heated for 24 h at 60 °C in THF, resulting in recovered starting material in the

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(2) Lago, M. A.; Luengo, J. I.; Peishoff, C. E.; Elliot, J. D. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic: San Diego, 1996; Vol. 31, p 81.

(3) *Endothelin Receptors: From the Gene to the Human*; Ruffolo, R. R., Jr., Ed.; CRC: Boca Raton, 1995.

(4) Elliot, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; DeBrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R., Jr.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. H. *J. Med. Chem.* **1994**, *37*, 1553.

(5) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551 and references therein.

(6) (a) Motherwell, W. B.; Sandham, D. A. *Tetrahedron Lett.* **1992**, *33*, 6187. For related examples, see (b) Edwards, G. L.; Motherwell, W. B.; Powell, D. M.; Sandham, D. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1399.

(7) Anti β-hydrogen addition and/or elimination pathways are relatively uncommon in nickel and palladium chemistry—a pathway which would lower the stereoselectivity of **5** → **6**; see: Cross, R. J. In *The Chemistry of the Metal−Carbon Bond*; Hartley, S. P. F. R., Ed.; John Wiley: New York, 1985; Vol. 2, p 559.

(8) Bisarya, S. C.; Rao, R. *Synth. Commun.* **1993**, *23*, 779.

(9) To the best of our knowledge, this is the first example of a palladium-catalyzed 5-endo-trig cyclization to form a 2*H*-indenone. For examples of palladium-catalyzed and transition metal based transformations for the synthesis of indenones, see: (a) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579 and references therein.

(10) Chen, C.-Y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676.

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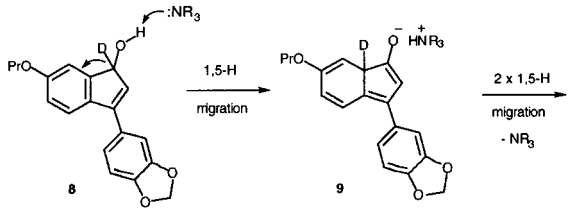
Table 1. Formation of **6** with Base in the Presence and Absence of a Palladium Catalyst

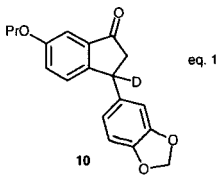
entry	catalyst	base	conditions	% ee[a]	% yield[b]
1	$PdCl_2(PPh_3)_2$ (2.5 mol %)	Et_3N (1.0 equiv)	THF (60 °C), 3.5 h	90.6	95
2	$PdCl_2$(dppe) (2.5 mol %)	DABCO (1.0 equiv)	THF (60 °C), 3.5 h	92.2	92
3	$PdCl_2$(dppe) (2.5 mol %)		THF (60 °C), 24 h		NR
4			THF (60 °C), 24 h		NR
5		DABCO (0.5 equiv)	THF (60 °C), 3.5 h	92.5	95
6		DABCO (0.5 equiv)	THF (25 °C), 23 h	92.8	94
7		DABCO (0.1 equiv)	THF (60 °C), 6.5 h	92.5	91
8		pyridine (0.5 equiv)	THF (60 °C), 20 h		<5
9		$LiN(TMS)_2$ (1.0 equiv)	THF (25 °C), 10 h	41.5	53
10		$KN(TMS)_2$ (1.0 equiv)	THF (−78 °C), < 5 min	4.0	65

[a]The optical purity of **6** determined by chiral HPLC (Daicel Chiralpak AD, 93:7 hexane/IPA, 1 mL/min, 254 nm). [b] Solution yields determined by RP HPLC using analytically pure **6** as standard.

presence and absence of $Pd(dppe)Cl_2$ (3, 4). Subsequently we observed that simply heating **5** with base (DABCO) resulted in a highly efficient and stereoselective hydrogen rearrangement. The reaction is extremely facile, furnishing **6** in 96% yield with 0.1 equiv of DABCO after 6.5 h at 60 °C and is equally effective at 25 °C (6, 7). Interestingly pyridine is not basic enough to catalyze the hydrogen rearrangement, affording **6** in <5% yield (8) whereas the lithium and potassium alkoxides gave **6** in moderate yield but with low stereospecificity (9, 10).[11]

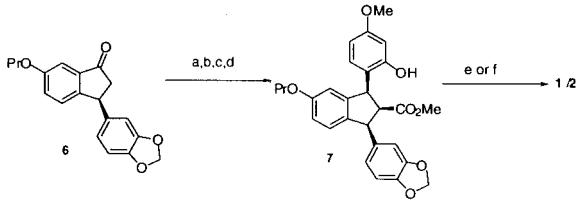
From a mechanistic perspective, a sequence of suprafacial 1,5-sigmatropic hydrogen rearrangements would account for the high stereospecificity and base dependence observed in the formation of **6**.[12,13] In addition the high stereospecificity observed with DABCO and other amine bases[14] also indicates a large preference for counterclockwise 1,5-hydrogen migration relative to clockwise migration which would lead to a loss of stereochemistry. Consistent with this postulate, complete deuterium conservation was observed with **8** using catalytic DABCO in THF at 60 °C, affording **10** in 95% yield (eq 1).[15] A clockwise migration would





have resulted in a reduction of the deuterium label due to the kinetic isotope effect. Interestingly, substituent effects have been reported to influence the direction of 1,5-hydrogen migrations in isoindenes and were correlated with Hückel molecular orbital theory.[16] Similarly with indenol **5**, an increase in the ionic character of the lithium and potassium alkoxide appears to cause sufficient perturbation of the HOMO orbital symmetry to favor clockwise migration, thus resulting in the reduction of the stereochemical fidelity observed in the formation of **6**.

Scheme 3[a]



[a] Key: (a) sodium *tert*-amylate (2.0 equiv), dimethyl carbonate, 25 °C (85%); (b) $(FSO_2)_2O$, NaH (1.5 equiv), $PhCH_3$, O °C (82%); (c) [2-(benzyloxy)-4-methoxyphenyl]boronic acid, $PdCl_2$(dppf) (1 mol %), $PhCH_3/H_2O$ (9:1), K_2CO_3, 70 °C (75%); (d) 20% $Pd(OH)_2/C$, H_2, EtOH, 60 °C (75%, 99.9% ee); (e) methyl bromoacetate, THF, K_2CO_3; LiOH, THF, 60 °C; (f) ethylene carbonate, K_2CO_3, $PhCH_3$, 110 °C; LiOH, THF, 60 °C.

To complete the synthesis of **1** and **2** (Scheme 3), the indanone **6** was then carboxylated with sodium *tert*-amylate (2.0 equiv) in dimethyl carbonate and the resulting enolate sulfonylated with fluorosulfonic anhydride (1.5 equiv) in toluene at 0 °C. A Suzuki coupling with [2-(benzyloxy)-4-methoxyphenyl]boronic acid and $Pd(dppf)Cl_2$ (0.5 mol %) followed by hydrogenolysis and olefin reduction afforded the ester **7** in 75% yield (99.9% ee). Alkylation of **7** with methyl bromoacetate or ethylene carbonate, followed by epimerization and hydrolysis, then completed the synthesis of **1** and **2**.

In conclusion a successful catalytic enantioselective synthesis has been demonstrated for the endothelin receptor antagonists SB-209670 and SB-217242 based on a net stereospecific 1,3-hydrogen transfer of a chiral 3-aryl indenol. Additional investigations are ongoing to develop a better understanding of this interesting reaction.

Acknowledgment. We thank the Analytical and Physical & Structural Chemistry Departments at SmithKline Beecham for the supporting analytical data.

Supporting Information Available: Experimental details and characterization for **4**, **5**, and **6** (2 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) A reduction in the optical purity of **5** (94% ee) was not observed with the potassium alkoxide when quenched with glacial AcOH after 50% conversion. Therefore carbanion formation did not contribute to the dramatic loss of stereochemistry observed in this reaction.

(12) The DABCO-catalyzed rearrangement was equally efficient in the absence of light, ruling out a photochemical rearrangement. For examples of 1,5-sigmatropic migrations of alkenyl and aryl groups of 2,3-phenylindenol and 2,3,4,5-tetraphenylcyclopentenol, see: Battye, P. J.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1984**, 990.

(13) Dramatic rate acceleration of potassium alkoxides on 1,5-hydrogen rearrangements has also been reported: Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.

(14) Using a stoichiometric amount of base, piperidine and tributylamine delivered **6** in 92% yield (88.7% ee) and 90% yield (91.7% ee), respectively.

(15) The percent deuterium incorporation of **8** and **10** was determined by flow injection analysis electrospray ionization mass spectrometry using successive normalization subtraction of the observed ion patterns of the labeled and unlabeled compounds.

(16) Pettit, W. A.; Wilson, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 6372.