Zr-Catalyzed Kinetic Resolution of Allylic Ethers and Mo-Catalyzed Chromene Formation in Synthesis. Enantioselective Total Synthesis of the Antihypertensive Agent (*S*,*R*,*R*,*R*)-Nebivolol

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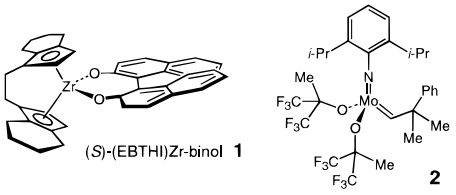
Abstract: The first enantioselective total synthesis of the antihypertensive agent (*S*,*R*,*R*,*R*)-nebivolol (**3**) is described. The synthesis includes the efficient (EBTHI)Zr-catalyzed kinetic resolutions of cycloheptenyl styrenyl ethers **8** and **16**, which are subsequently treated with 4 mol % Mo(CHCMe$_2$Ph)(N(2,6-(*i*-Pr)$_2$C$_6$H$_3$))(OCMe(CF$_3$)$_2$)$_2$ to afford chiral nonracemic 2-substituted chromenes (*R*,*R*)-**9** and (*S*,*R*)-**17**. Since the present retrosynthetic analysis dissects the molecule into two chromene fragments, both the (*R*) and (*S*) antipodes of (EBTHI)Zr catalyst are required. Accordingly, Buchwald's efficient resolution process is used to resolve *rac*-(EBTHI)ZrCl$_2$ (from catalytic hydrogenation of commercially available *rac*-(EBI)ZrCl$_2$), such that the two requisite transition metal chiral catalysts are obtained by a single process. Other noteworthy features of the synthesis include a highly efficient, regio- and stereoselective Pd-catalyzed opening of cyclic allylic epoxide **7** with diaryloxystannane **15** and a photochemical modification of the C2 chromane side chain (e.g., **10** → **11**).

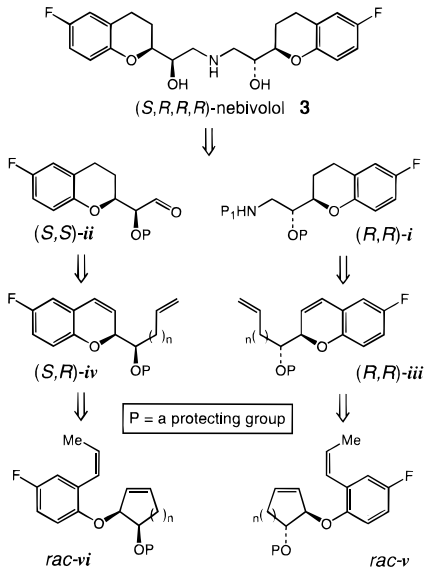
Introduction

An important aspect of research at the interface of inorganic and organic chemistry is the development of metal-catalyzed transformations that allow for the efficient and enantioselective preparation of organic molecules. In this context, we recently reported the total synthesis of the antifungal agent Sch 38516 (fluvirucin B$_1$),[1] where a number of metal-catalyzed processes were used to control the regio- and stereochemical outcome of key bond forming events. The Zr-catalyzed asymmetric alkylation of an unsaturated heterocycle (promoted by **1**)[2] and the Mo-catalyzed formation of a 14-membered lactam (promoted by **2**)[3] were two of the noteworthy reactions. These catalytic



operations transpired efficiently and stereoselectively and contributed significantly to the brevity of the synthesis route.

Scheme 1



After the above studies, the medicinal significance of chromane systems[4] and the inability of our Zr-catalyzed protocol to resolve 2-substituted chromenes efficiently led us to initiate the study of a number of additional metal-catalyzed transformations.[5]

(*S*,*R*,*R*,*R*)-Nebivolol (**3**, Scheme 1) is one of a multitude of therapeutically important agents that bear a chromane unit.[6] In 1990, researchers at the Janssen Research Foundation and R. W. Johnson Pharmaceutical Research Institute reported the

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(3) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1836. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(4) For a Mn-catalyzed kinetic resolution of 2,2-disubstituted chromenes, see: Vander Velde, S. L.; Jacobsen, E. N. *J. Org. Chem.* **1995**, *60*, 5380−5381.

(5) (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (b) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

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structure and pharmacological properties of this β_1-adrenergic antagonist, which was first prepared in the racemic form. Various enantiomers were subsequently obtained optically pure through separation procedures involving chiral HPLC.[6b] In clinical studies with hypertensive patients, (*S*,*R*,*R*,*R*)- or *d*-nebivolol has proved to be a potent β_1-adrenergic receptor blocker that has caused reduction of heart rate and blood pressure and improved left ventricle function.[7] Although one of the other enantiomeric forms, (*R*,*S*,*S*,*S*)- or *l*-nebivolol, is inactive, it has a significant synergistic effect on the antihypertensive efficiency of the (*S*,*R*,*R*,*R*) isomer.[8] In addition, *l*-nebivolol has a positive influence on the antihypertensive properties of related β_1-blockers propanolol, atenolol, and metoprolol.[9]

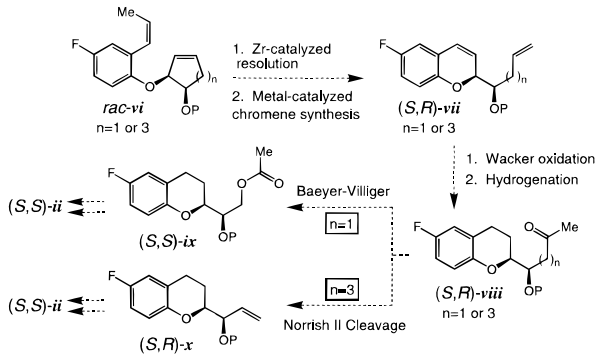
Herein, we disclose the first enantioselective total synthesis of (*S*,*R*,*R*,*R*)-nebivolol (**3**). Zr-catalyzed kinetic resolution of cyclic allylic styrenyl ethers[10] and their Mo-catalyzed ring-opening and ring-closing metathesis[5] play a pivotal role in this convergent total synthesis. The present study for the first time challenges and demonstrates the synthetic utility of the above two classes of catalytic reactions.

Synthesis Plan

The general retrosynthetic analysis that was adopted is illustrated in Scheme 1. According to this plan, fragments ***i*** and ***ii*** would be joined through a reductive amination. The requisite chiral chromanes would be derived from nonracemic chromenes (*R*,*R*)-***iii*** and (*S*,*R*)-***iv***, which would, in turn, be obtained from the metal-catalyzed ring-opening and ring-closing transformations of optically pure (*R*,*R*)-***v*** and (*S*,*R*)-***vi***. We would access enantiomerically pure styrenyl ethers ***v*** and ***vi*** through Zr-catalyzed kinetic resolution.[10] Such a strategy thus requires efficient and selective catalytic resolution of cyclic styrenyl ethers. It would be therefore imperative that the alkenyl side chain in (*R*,*R*)-***iii*** and (*S*,*R*)-***iv*** be amenable to functionalization necessary to readily reach (*R*,*R*)-***i*** and (*S*,*S*)-***ii***.

As illustrated in Scheme 2, we were particularly interested in utilizing cyclopentenyl and cycloheptenyl substrates ***vi*** (n = 1 and 3). With the smaller ring system (n = 1), we planned to modify the side chain of the derived chromene ***vii*** by the regioselective catalytic oxidation of the terminal olefin by a Wacker-type process,[11] followed by hydrogenation of the

Scheme 2



derived ketone to obtain (*S*,*R*)-***viii***; a regioselective Baeyer−Villiger oxidation[12] would then give (*S*,*S*)-***ix***. A related pathway would involve cycloheptenyl ***v*** (n = 3) as the starting material. As such, we intended to examine the utility of the Norrish type II cleavage process (→(*S*,*R*)-***x***),[13] a transformation that has scarcely been used in synthesis.

It is worthy of note that, although the general plan presented in Scheme 2 necessitates at least two steps in order to truncate the C2 side chain, we judged that this approach remained optimal, since (i) the requisite carbocyclic starting materials would be readily prepared from commercially available cyclic dienes (see below), and (ii) the relative stereochemistry could be efficiently controlled at the early stages of the total synthesis by taking advantage of the rigid framework of the cyclic starting materials. An important feature of the proposed route is that, while catalytic resolution of one segment ((*R*,*R*)-***i***) would require the use of the (*R*)-(EBTHI)Zr system, the *S* complex could be used to reach (*S*,*S*)-***ii***.[4] We found this attribute of the synthesis plan economically attractive, since we could use Chin and Buchwald's recently reported procedure[14] to obtain *both* chiral metallocene antipodes upon the resolution of *rac*-(EBTHI)$ZrCl_2$, which is easily accessed by catalytic hydrogenation of the commercially available *rac*-(EBI)$ZrCl_2$.[15]

Enantioselective Synthesis of the (*R*,*R*)-Chromane Fragment (*i*). We began our studies by examining the Zr-catalyzed kinetic resolution of cyclopentenyl styrenyl ethers. As shown in eq 1, these substrates can be readily prepared by the regio- and stereoselective nucleophilic opening of allylic epoxide **4** (obtained from oxidation of cyclopentadiene) with styrenylphenol **5**[16] to afford the parent alcohol **6a**. We established that, whereas **6a** and triethylsilyl (TES) ether **6b** undergo 20−30% uncatalyzed alkylation within 2 h, there is <2% background reaction for *tert*-butyldimethylsilyl ether **6c** and *tert*-butyldiphenylsilyl ether **6d** when these substrates (Table 1) are treated with EtMgCl (5 equiv in THF, 70 °C). Despite the promising initial results obtained for **6c** and **6d**, these substrates, as well as those that undergo uncatalyzed reaction (**6a** and **6b**), resolved with inferior levels of enantioselectivity ($k_{rel} \leq 4$).[17]

(6) (a) For receptor binding and activity of various stereoisomers of nebivolol, see: Pauwells, P. J.; Gommeren, W.; Van Lommen, G.; Janssen, P. A. J.; Leysen, J. E. *Mol. Pharm.* **1988**, *34*, 843−851. (b) Synthesis and pharmacological properties: Van Lommen, G.; De Bruyn, M.; Schroven, M. *J. Pharm. Belg.* **1990**, *45*, 355−360. (c) Crystal structure: Peeters, O. M.; Blaton, N. M.; De Ranter, C. J. *Acta Crystallogr.* **1993**, *C49*, 2154−2157. (d) For related synthetic studies, see: Zheng, H.-C.; Costanzo, M. J.; Maryanoff, B. E. *Tetrahedron Lett.* **1994**, *35*, 4891−4894.

(7) (a) De Cree, J.; Geukens, H.; Leempoels, J.; Verhaegen, H. *Drug Dev. Res.* **1986**, *8*, 109−117. (b) De Cree, J.; Geukens, H.; Cobo, C.; Verhaegen, H. *Angiology* **1987**, *38*, 440−448. (c) Van de Water, A.; Janssens, W.; Van Nueten, J.; Xhonneux, R.; De Cree, J.; Verhaegen, H.; Reneman, R. S.; Janssen, P. A. J. *J. Cardiovasc. Pharmacol.* **1988**, *11*, 552−563.

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(10) Visser, M. S.;. Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779−3780.

(11) For a review of Wacker-type oxidations, see: Tsuji, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp 449−468.

(12) For a review of the Baeyer−Villiger oxidation, see: Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp 671−688.

(13) (a) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168−177. (b) Encinas, M. V.; Wagner, P. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 1357−1360. (c) Scaiano, J. C. *Acc. Chem. Res.* **1982**, *15*, 252−255.

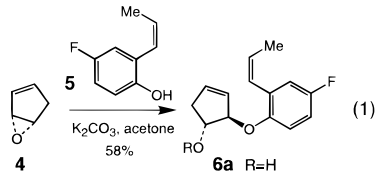
(14) Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650−5651.

(15) Waymouth, R. M.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911−4914.

(16) Phenol **5** was prepared on the basis of procedures reported by Corey and Christensen. (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237. (b) Christensen, H. *Synth. Commun.* **1975**, *5*, 65−78.

(17) The value for k_{rel} is calculated by the equation reported by Kagan and Fiaud. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *53*, 708−710. For a recent comprehensive review of metal-catalyzed kinetic resolution, see: Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.*, in press.

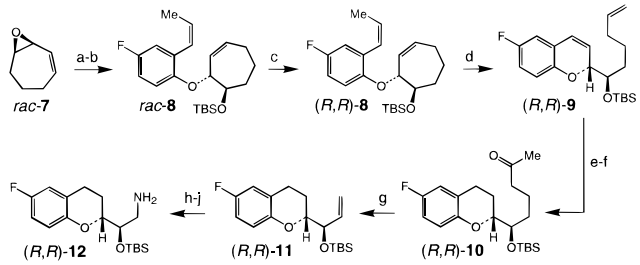
Table 1. Zr-Catalyzed Kinetic Resolution of Cyclopentenyl Styrenyl Ethers[a]



substrate	R	k_{rel}[b]
6a	H	2.4
6b	Et_3Si	3.7
6c	*t*-$BuMe_2Si$	3.3
6d	*t*-$BuPh_2Si$	1.9

[a] Conditions: 10 mol % (*R*)-**1**, 5 equiv of EtMgCl, 70 °C, THF, 2−4 h. [b] Selectivities determined by chiral HPLC analysis (Chiralpak AD) of the derived parent alcohols (**6a**).

Scheme 3[a]

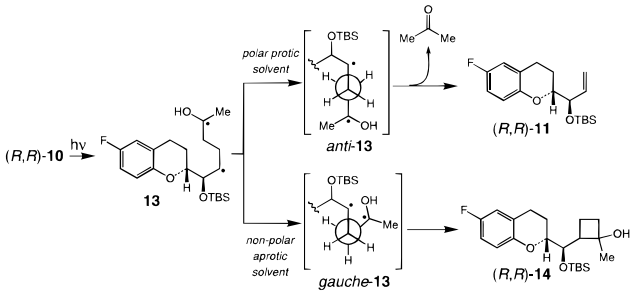


[a] Conditions: (a) 1.0 equiv of **5**, 1.5 equiv of K_2CO_3, acetone, 12 h, 80%. (b) 1.1 equiv of TBSOTf, 2 equiv of 2,6-lutidine, CH_2Cl_2, 4 h, 93%. (c) 10 mol % (*R*)-(EBTHI)Zr-binol, 5 equiv of EtMgCl, 70 °C, THF, 3 h, 44%. (d) 4 mol % **2**, 1 atm ethylene, C_6H_6, 24 h, 97%. (e) 25 mol % $PdCl_2$, 25 mol % CuCl, 1 atm O_2, DMF, H_2O, 4 h, 87%. (f) 10% (by weight) Pd/C, 1 atm H_2, 30 min, 98%. (g) *hν*, Vycor filter, 1 mol % Et_3N, MeOH, 2.5 h, 58% (90% based on recovered starting material). (h) O_3, CH_2Cl_2/MeOH (5:1), 10 min, −78 °C; 3 equiv of $NaBH_4$, 22 °C, 1.5 h, 91%. (i) 1.5 equiv of ADDP, 1.5 equiv of Bu_3P, 1.5 equiv of phthalimide, C_6H_6, 20 h, 85%. (j) H_4N_2, EtOH, 70 °C, 4 h, 68%.

We therefore turned our attention to the possibility of utilizing cycloheptenyl systems as the starting materials. As before (cf. eq 1), and as shown in Scheme 3, the regio- and stereoselective nucleophilic opening of allylic epoxide *rac*-**7** with styrenylphenol **5** proceeded smoothly (>98% regioselectivity, 80%). Protection of the resulting secondary carbinol delivered *rac*-**8** in 93% yield.[18] Treatment of *rac*-**8** with 5 equiv of EtMgCl and 10 mol % (*R*)-(EBTHI)Zr-binol at 70 °C (THF) resulted in the isolation of the recovered starting material (*R*,*R*)-**8** in >98% ee and 44% yield ($k_{rel} \geq 25$). In the presence of 4 mol % $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$ (**2**)[19] and under an atmosphere of ethylene (C_6H_6, 22 °C, 24 h), (*R*,*R*)-**8** was converted to unsaturated chromene (*R*,*R*)-**9** in 97% yield after silica gel chromatography.[5]

The two alkene sites in the relatively unstable 2-substituted chromene[20] were differentiated through an efficient Pd-catalyzed "Wacker" oxidation of the terminal olefin (*R*,*R*)-**9** to afford the derived methyl ketone in 87% isolated yield; subsequent catalytic hydrogenation delivered (*R*,*R*)-**10** (98%). We next

Scheme 4



turned our attention to the adjustment of the length of the chromane side chain by a photochemical Norrish type II cleavage. We were aware of previous mechanistic studies indicating that such transformations have higher quantum efficiency[21] and afford larger amounts of cleavage products when more polar solvents are used. It has been suggested that, with polar solvents, the corresponding 1,4-biradical intermediate (**13**, Scheme 4) adopts a transoid conformation (*anti*-**13**) to favor the generation of cleavage products. In contrast, in nonpolar media, the cisoid orientation (*gauche*-**13**) is significantly populated, leading to the formation of cyclobutenyl adducts.[22] Indeed, our attempts to effect the conversion of (*R*,*R*)-**10** to (*R*,*R*)-**11** in C_6H_6, Et_2O, or THF (Vycor or Corex) resulted in either low conversion (~10% with C_6H_6) or substantial formation of unidentified byproducts, including diastereomeric cyclobutanols (**14**). Reaction efficiency improved noticeably upon irradiation of (*R*,*R*)-**10** for 2.5 h in MeOH at 22 °C (Vycor), affording (*R*,*R*)-**11** in 38% isolated yield. When photolysis was performed at −10 °C, the desired product was obtained in 58% yield, along with 36% of the recovered starting material after chromatography (90% yield based on the recovered starting material); longer reaction times led to lower yields due to product decomposition.[23] The addition of 1 mol % Et_3N proved to be necessary to avoid concomitant removal of the silyl protecting group.

Synthesis of the amine segment (*R*,*R*)-**12** was effected in a three-step process. An ozonolytic cleavage−reduction sequence performed on the monosubstituted olefin of (*R*,*R*)-**11** was followed by conversion of the resulting primary alcohol to a primary amine. The latter operation involved a modified Mitsonobu procedure (85%)[24] and a hydrazine-mediated deprotection to afford (*R*,*R*)-**12** in 58% overall yield.

Enantioselective Synthesis of the (*S*,*S*)-Chromane Fragment (*ii*). The (*S*,*S*)-chromene segment also called for the opening of the oxirane ring in *rac*-**7** with regio- and stereochemical control (Scheme 5). In this case, however, cleavage of the allylic epoxide with syn stereochemistry was required. To address this issue, we took note of an elegant study by Trost and Tengalia,[25] regarding a directed[26] Pd-catalyzed coupling of allylic epoxides with various cyclic tin alkoxides; reactions were reported to occur in a 1,2-syn fashion (vs 1,4-allylic substitu-

(18) Epoxide **7** was prepared by oxidation (peracetic acid) of the commercially available cycloheptadiene. The overall yield for the three steps (from cycloheptadiene to *rac*-**8**) is 72%.

(19) (a) Fox, H. H.; Yap, K. B.; Jennifer, R.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287−2289. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; Oregan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(20) 2-Substituted chromenes undergo significant decomposition at 22 °C within 24 h.

(21) Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898−5901.

(22) (a) Sciano, J. C. *Tetrahedron* **1982**, *38*, 819−824. (b) Reddy, G. D.; Jayasree, B.; Ramamurthy, V. *J. Org. Chem.* **1987**, *52*, 3107−3113.

(23) Alternatively, the aldehyde derived from oxidation of the terminal alkene in (*R*,*R*)-**9** could be subjected to Norrish type II cleavage. However, preliminary studies indicated that such photochemical processes are significantly less efficient. This observation is consistent with the proposal that the less substituted biradical intermediates derived from an aldehyde are shorter lived than those derived from ketone substrates.

(24) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Tsunada, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

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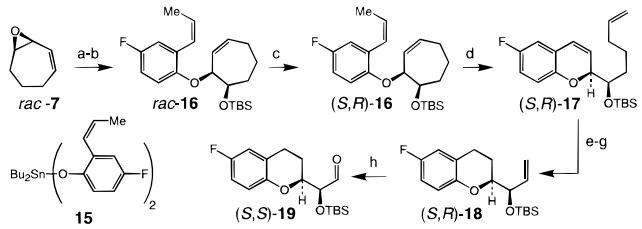
(26) For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

Scheme 5[a]



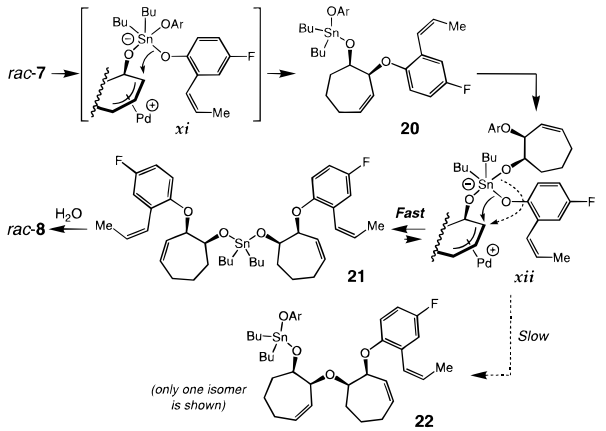
[a] Conditions: (a) 2.5 mol % $Pd(PPh_3)_4$, 0.5 equiv of **15**, 4-Å molecular seives (powder), THF, 10 min, 84%. (b) 1.1 equiv of TBSOTf, 2 equiv of 2,6-lutidine, CH_2Cl_2, 4 h, 93%. (c) 10 mol % (*S*)-(EBTHI)Zr-biphen, 5 equiv of EtMgCl, 70 °C, THF, 3 h, 40%. (d) 4 mol % **2**, 1 atm ethylene, C_6H_6, 24 h, 97%. (e) 25 mol % $PdCl_2$, 25 mol % CuCl, 1 atm O_2, DMF, H_2O, 4 h, 87%. (f) 10% (by weight) Pd/C, 1 atm H_2, 30 min, 98%. (g) *hν*, Vycor filter, 1 mol % Et_3N, MeOH, 2.5 h, 58% (90% based on recovered starting material). (h) O_3, CH_2Cl_2/MeOH (5:1), −78 °C; Me_2S, 22 °C, 10 min, 91%.

tion). We argued that, under similar conditions, dialkylstannylbis(phenoxide) **15** might add to *rac*-**7** to afford *rac*-**16**. However, the feasibility of this plan was less than certain, since all the successful cases in the Trost report involved the use of 1 equiv of a *cyclic* di*alkoxy* stannane. Nonetheless, after extensive experimentation, we established that treatment of *rac*-**7** with 0.5 equiv of **15** (Scheme 5) in the presence of 2.5 mol % $Pd(PPh_3)_4$ (THF, 10 min) leads to the formation of *rac*-**7** with >98% regio- and stereoselectivity in 84% yield after chromatography.

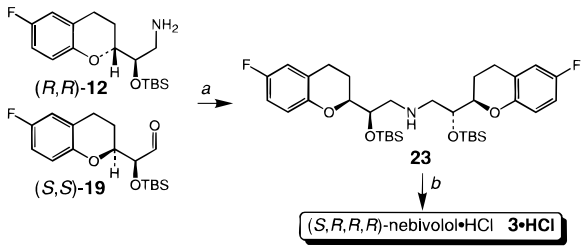
Origin of the Regio- and Stereoselective Pd-Catalyzed Epoxide Opening. Although the exact reason for this highly selective transfer is not clear at present, a plausible reaction pathway can be put forward (Scheme 6). Directed transfer of the first phenoxide unit may proceed via stannate ***xi***, as proposed initially.[25] The group-selective transfer of the second phenoxy unit (**20** → **21** through ***xii***) is noteworthy, however (<2% transfer of the alkoxy group in ***xii*** is observed). Additional experiments indicated that prolonged reaction times (2 h) lead to the formation of the product derived from the alkoxy transfer (**22**); when the reaction was quenched after 10 min, <2% **22** was detected.[27] Presumably, under extended reaction times, allylic phenoxide **21** reacts with the active Pd(0) catalyst to regenerate ***xii***, to result in the formation of the undesired bicyclic ether.

As illustrated in Scheme 5, conversion of *rac*-**16** to (*S*,*S*)-**19** was carried out efficiently and in a fashion similar to that adopted for the synthesis of (*R*,*R*)-**12** (Scheme 3). Importantly, the Zr-catalyzed resolution, with (*S*)-(EBTHI)Zr-biphen (obtained from the same resolution operation that afforded the *R*

Scheme 6



Scheme 7[a]



[a] Conditions: (a) 1.4 equiv of $NaBH(OAc)_3$, 1,2-dichloroethane, 2 h, 91%. (b) 10% HCl, MeOH, 30 min, 97%.

antipode) proceeded with excellent selectivity ($k_{rel} \geq 25$). The subsequent Mo-catalyzed chromene synthesis ((*S*,*R*)-**16** → (*S*,*R*)-**17**) transpired efficiently and in high yield.

Union of the Chromane Fragments and Completion of the Synthesis. The total synthesis was completed by the two reactions illustrated in Scheme 7. Coupling of (*R*,*R*)-**12** and (*S*,*S*)-**19** by reductive amination ($NaBH(OAc)_3$, →**23**, 91%), followed by the removal of the silyl ether protecting groups (10% HCl, MeOH), afforded (*S*,*R*,*R*,*R*)-nebivolol (HCl salt; 88% yield for the two-step sequence).[28] The synthetic material proved identical with an authentic sample by ^1H NMR, ^{13}C NMR, TLC, IR, and HRMS analysis, optical rotation, and elemental analysis.

Conclusions

In brief, we present an efficient and convergent enantioselective total synthesis of (*S*,*R*,*R*,*R*)-nebivolol in the optically pure form in 10.9% overall yield. The Zr-catalyzed kinetic resolution of cyclic aryl ethers and their subsequent Mo-catalyzed conversion to the 2-substituted chromenes serve a pivotal function. The present work demonstrates that the resulting 2-alkenylchromene can be functionalized to afford myriad chiral nonracemic heterocycles. Resolution of *rac*-(EBTHI)$ZrCl_2$ affords the *R* and *S* enantiomers, which are both utilized in the asymmetric synthesis of the two requisite subtargets; accordingly, the overall plan is rendered more efficient and cost-effective. However, future developments are required for the identification of a more efficient chiral Zr catalyst, such that lower levels of catalyst loading (<10 mol %) are required. In addition to the Zr- and Mo-catalyzed transformations discussed above, the efficient and selective Pd-catalyzed addition of aryloxystannes to allylic epoxides further highlight the utility of organometallic chemistry in the design and execution of efficient and stereoselective synthesis routes to various biologically important target molecules.

Experimental Section

General Information. Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on a Varian Unity 300 (300 MHz) or Varian GN-400 (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q =

(27) For example, after 2 h, hydrolysis product derived from **22** is isolated in 53% yield along with 11% of **21**. These data suggest that, although **21** is the kinetically favored product, the thermodynamic selectivity is not as high.

(28) Our attempts toward reductive coupling of benzylamine derived from (*S*,*S*)-**12** and (*R*,*R*)-**19** under a variety of conditions resulted in the formation of unidentified products. We therefore selected to carry out the coupling with the unmasked primary amine.

quartet, br = broad, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Varian Unity 300 (75 MHz) or Varian GN-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$, δ 77.0 ppm). Electronic spectra were collected on a Cary 1E UV/vis spectrophotometer. An Alltech Associates DB-1 capillary column (30 m × 0.32 mm) was used to determine conversions. Enantiomer ratios were determined by chiral HPLC with either a Chiralcel OB/H column or a Chiralpak AD column or by analysis of the derived (*R*)-MPTA ester. Microanalyses were performed by Robertson Microlit Laboratories (Madison, NJ). High-resolution mass spectrometry was performed by University of Illinois Mass Spectrometry Laboratories. Photolyses were carried out using a 450-W medium-pressure Hanovia lamp. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

All reactions were conducted in oven-dried (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl, and dichloromethane was distilled from calcium hydride. All Grignard reagents were prepared from the appropriate alkyl halide purchased from Aldrich and used without further purification. Mg turnings (Strem) were washed with 5% HCl in MeOH, and then with Et_2O and THF, and were subsequently flame-dried. Mo(CHCMe$_2$Ph)(N(2,6-(*i*-Pr)$_2$C$_6$H$_3$))(OMe(CF$_3$)$_2$)$_2$ was purchased from Strem and recrystallized from pentanes prior to use or prepared by the method of Schrock et al.[19] 1,1′-(Azodicarbonyl)dipiperidine (ADDP), diethyl azodicarboxylate (DEAD), 2-cyclohexen-1-ol, (ethyl)triphenyl phosphonium bromide, 2-bromo-4-fluorophenol, cycloheptadiene, 2,6-lutidine, and potassium *tert*-butoxide were used as received from Aldrich. *tert*-Butyldimethylsilyl triflate was prepared by the method of Corey.[29] Copper chloride, palladium chloride, and tetrakis(triphenylphosphine)palladium were used as received from Strem.

Fluorsalicylaldehyde. To 4-fluorophenol (30.0 g, 268 mmol) in 180 mL of H_2O was added NaOH (70.7 g, 1.77 mol). The reaction was heated to 55 °C, after which $CHCl_3$ (46.8 mL, 589 mmol) was slowly added dropwise. The reaction was subsequently heated to 70 °C for 1 h. The mixture was cooled to 22 °C, diluted with 50 mL of H_2O, and acidified with concentrated HCl (20 mL). The resulting solution was washed three times with 50-mL portions of CH_2Cl_2, and the organic layers were dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded a red oil, which was purified by silica gel chromatography (100:1 hexanes/EtOAc) to afford 8.3 g (59 mmol, 22%) of a white solid (mp 82−84 °C; R_f = 0.67 in 3:1 hexanes/EtOAc). IR (KBr): 3055 (w), 2892 (w), 1665 (m), 1488 (s), 1281 (s), 1149 (s), 877 (m) cm^{-1}. ^{1}H NMR: δ 10.79 (1H, s, CHO), 9.85 (1H, s, OH), 7.27 (1H, m, aromatic CH), 6.97 (1H, m, aromatic CH). ^{13}C NMR: δ 195.4, 157.9, 156.8, 154.5, 124.8 (d, J = 23.5), 119.2 (d, J = 6.8), 118.1 (d, J = 22.7).

Fluorsalicylaldehyde (Alternative and Higher Yielding Method). 2-Bromo-4-fluorophenol (5.0 g, 26 mmol) was dissolved in 400 mL of THF, and the resulting solution was cooled to −60 °C. At this point, the mixture was charged with *n*-BuLi (27.2 mL of a 2.5 M in hexanes, 68 mmol) in a dropwise fashion. The reaction temperature was maintained at −60 °C for 1 h. Dimethylformamide (2.4 mL, 31 mmol) was then added slowly in a dropwise manner (at −60 °C), after which the mixture was stirred for an additional 5 min. The mixture was subsequently allowed to warm to 22 °C, diluted with 50 mL of a saturated solution of aqueous NH_4Cl, and washed with 5 × 75 mL of Et_2O. The resulting organic layers were dried over anhydrous $MgSO_4$. Removal of organic solvents in vacuo afforded a red oil, which was purified by silica gel chromatography (25:1 hexanes/EtOAc) to afford 2.97 g (21.2 mmol) of a white solid (81% yield).

2-Propenyl-4-fluorophenol (5). To ethyltriphenylphosphonium bromide (5.83 g, 15.7 mmol) in 100 mL of toluene was added potassium *tert*-butoxide (1.76 g, 15.7 mmol) in 24 mL of THF in a dropwise manner. The resulting cloudy red solution was stirred at 22 °C for 4 h. The mixture was subsequently cooled to −78 °C, and the aromatic aldehyde (1.00 g, 7.14 mmol), dissolved in 16 mL of toluene, was added dropwise. The resulting solution was allowed to slowly warm to 22 °C, and stirring was allowed to continue for 14 h. At this point, the reaction was quenched by dropwise addition of 50 mL of a saturated solution of NH_4Cl. The resulting mixture was diluted with 50 mL of H_2O and washed three times with 50 mL portions of Et_2O; organic layers were dried over anhydrous $MgSO_4$. The solution containing the unpurified reaction product was absorbed onto silica gel (∼25 g), and the solvent was subsequently removed in vacuo to afford a pale yellow silica gel−product mixture which was directly dry-packed on a chromatography column and eluted with 20:1 mixture solution of hexanes/EtOAc. Silica gel chromatography afforded 1.02 g (6.71 mmol, 94%) of a yellow oil as a 9:1 mixture of *Z:E* olefin isomers (as determined by analysis of the 400-MHz ^{1}H NMR spectrum) (R_f = 0.53 in 3:1 hexanes/EtOAc). IR (KBr): 3446 (br), 3031 (m), 2943 (w), 2917 (w), 1495 (s), 1187 (s), 771 (m). ^{1}H NMR: δ 6.85 (3H, m, aromatic CH), 6.73 (2H, m, aromatic CH), 6.34 (1H, dd, J = 11.2, 1.6, vinylic CH), 4.96 (1H, s, ArO*H*), 1.73 (3H, dd, J = 6.96, 1.83, CH_3). ^{13}C NMR: δ 157.7, 155.4, 148.7 (d, J = 2.3), 131.9, 123.3 (d, J = 1.5), 115.9 (d, J = 29.6), 115.8, 114.9 (d, J = 22.7), 158.4, 156.1, 148.2, 129.3, 124.5 (d, J = 2.3), 116.5 (d, J = 8.3), 114.2 (d, J = 23.5), 113.2 (d, J = 22.7), 18.8.

1,2-Epoxy-3-cycloheptene (*rac*-7). Cycloheptadiene (5.0 g, 55 mmol) and Na_2CO_3 (23.4 g, 220 mmol) were suspended in 90 mL of CH_2Cl_2, and the resulting mixture was cooled to 0 °C and charged in a dropwise fashion with 11.3 mL of peracetic acid (54 mmol) dissolved in 20 mL of CH_2Cl_2. The mixture was allowed to warm to 22 °C and stirred for 14 h, after which filtration was carried out to remove Na_2CO_3. The resulting solution was diluted with 100 mL of a saturated solution of $Na_2S_2O_3$ and washed three times with 75-mL portions of CH_2Cl_2; organic layers were subsequently dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded 5.9 g (53 mmol, 97%) of a colorless oil. IR (KBr): 3024 (w), 2936 (s), 2873 (w), 2841 (w), 1444 (s), 935 (s), 733 (m). ^{1}H NMR: δ 5.89 (1H, m, vinylic CH), 5.78 (1H, m, vinylic CH), 3.42 (1H, m, allylic CHOC*H*), 3.22 (1H, dd, J = 4.7, 4.4, C*H*OCH), 2.24 (2H, m, allylic CH), 1.98 (2H, m, aliphatic CH), 1.60 (2H, m, aliphatic CH). ^{13}C NMR: δ 138.5, 123.8, 60.7, 53.6, 31.4, 29.7, 22.1.

***anti*-2-(2-(1′-Propenyl)-4-fluorophenoxy)-3-cyclohepten-1-ol.** Styrenylphenol **5** (0.50 g, 3.3 mmol) was dissolved in 2.75 mL of acetone, and the resulting solution was treated with K_2CO_3 (0.76 g, 5.5 mmol) and allowed to stir for 10 additional minutes. Cycloheptadiene oxide (0.30 g, 2.7 mmol) was then added dropwise, and the mixture was heated to 55 °C in an oil bath for 24 h. The reaction was allowed to cool to 22 °C and filtered to remove excess K_2CO_3. Evaporation of organic solvents in vacuo afforded a yellow oil, which was purified by silica gel chromatography (40:1 hexanes/EtOAc) to afford 0.47 g of the desired styrenyl ether (1.8 mmol, 80%) (R_f = 0.19 in 10:1 hexanes/EtOAc). IR (KBr): 3478 (br), 3031 (m), 2943 (s), 2861 (s), 1596 (m), 1426 (m), 1243 (s), 1035 (m), 809 (m) cm^{-1}. ^{1}H NMR: δ 6.99 (1H, dd, J = 9.2, 3.1, aromatic CH), 6.88−6.75 (2H, m, aromatic CH), 6.48 (1H, dd, J = 11.5, 1.3, vinylic ArC*H*CH), 6.05−5.85 (2H, m, vinylic CH), 5.58 (1H, dt, J = 11.7, 2.7, vinylic CH), 4.66 (1H, d, J = 8.1, CHOAr), 3.72 (1H, dt, J = 3.5, 9.5, C*H*OH), 2.98 (1H, s, OH), 2.95 (1H, s, OH), 2.28 (2H, m, allylic CH), 2.05 (2H, m, aliphatic CH), 1.80 (3H, dd, J = 8.9, 1.8, CH_3), 1.78−1.39 (2H, m, aliphatic CH). ^{13}C NMR: δ 158.0, 155.7, 151.1, 132.9, 130.9, 128.7, 124.3, 116.7 (d, J = 22.8), 114.6 (d, J = 8.4), 113.8 (d, J = 22.8), 83.1, 70.9, 36.0, 28.0, 14.6. HRMS calcd for $C_{16}H_{19}FO_2$: 262.1369. Found: 262.1370. Anal. Calcd for $C_{16}H_{19}FO$: C, 73.26; H, 7.30. Found: C, 73.40; H, 7.53.

***anti*-2(*R*)-(2-(1′-Propenyl)-4-fluorophenoxy)-1(*R*)-*tert*-butyldimethylsiloxy-3-cycloheptene ((*R,R*)-8).** Styrenyl alcohol, prepared according to the procedure described above (0.85 g, 3.2 mmol), was dissolved in 16 mL of CH_2Cl_2, and the resulting solution was treated with 8.2 mL of 2,6-lutidine (7.1 mmol). The mixture was then cooled to −78 °C and charged with 1.48 mL of TBSOTf (6.44 mmol) in a dropwise manner; the reaction temperature was maintained at −78 °C for 4 h. The reaction was quenched by the addition of ∼10 mL of a saturated solution of $NaHCO_3$; the resulting mixture was allowed to warm to 22 °C, diluted with 50 mL of H_2O, and washed three times with 50-mL portions of Et_2O. Organic layers were dried over anhydrous

(29) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

$MgSO_4$. Removal of volatiles in vacuo afforded a yellow oil, which was purified by silica gel chromatography (200:1 hexanes/Et_2O) to afford 1.16 g of *rac*-**8** (3.06 mmol, 95%) as a yellow oil. ($R_f = 0.53$ in 10:1 hexanes/EtOAc). *rac*-**8** (100 mg, 0.27 mmol) was dissolved in 0.75 mL of THF, followed by the addition of 0.58 mL of a 2.29 M solution of EtMgCl in THF. To the stirred solution was added 17.3 mg of (*R*)-(EBTHI)Zr-biphenol (0.03 mmol) in one portion, and the reaction vessel was equipped with a reflux condenser and submerged into a preheated 70 °C oil bath. The solution was allowed to stir at this temperature for 3 h; the flask was then removed from the oil bath and cooled to 0 °C. At this point, the solution was quenched by the addition of 1 mL of wet ether, followed by 2 mL of H_2O, and then 2 mL of a 2 M solution of HCl. The solution was washed three times with 5-mL portions of Et_2O, and the organic layers were dried over anhydrous $MgSO_4$. Removal of volatiles in vacuo afforded a yellow oil, which was purified by silica gel chromatography (hexanes to obtain product with $R_f = 0.37$ in 20:1 hexanes/EtOAc, followed by 100:1 heaxanes/EtOAc to obtain unreacted starting material with $R_f = 0.26$ in 20:1 hexanes/EtOAc) to afford 40.2 mg of (*R*,*R*)-**8** (0.11 mmol) as a clear oil (40%). Enantiomeric excess was determined by analysis of the ^{1}H NMR (400 MHz) spectrum of the derived (*R*)-MTPA ester. IR (KBr): 2929 (s), 2886 (w), 2856 (m), 1486 (s), 1249 (m), 1197 (m), 1086 (m), 837 (m) cm^{-1}. ^{1}H NMR: δ 6.98 (1H, d, $J = 9.0$, aromatic CH), 6.82 (2H, m, aromatic CH), 6.56 (1H, d, $J = 11.7$, vinylic CH), 5.85 (2H, m, vinylic CH), 5.58 (1H, d, $J = 11.9$, vinylic CH), 4.74 (1H, m, ArOC*H*), 3.89 (1H, m, C*H*OTBS), 2.12 (2H, m, allylic CH), 1.83 (3H, dd, $J = 6.6$, 1.6, CH_3), 1.78−1.44 (2H, m, aliphatic CH), 0.83 (9H, s, $(CH_3)_3$CSi), 0.07 (3H, s, CH_3Si), −0.08 (3H, s, CH_3Si). ^{13}C NMR: δ 157.5, 155.1, 151.9 (d, $J = 2.3$), 132.6, 130.4, 127.1, 116.5 (d, $J = 22.8$), 114.8 (d, $J = 8.3$), 113.5 (d, $J = 22.0$), 81.3, 72.2, 36.9, 28.3, 25.8, 22.8, 18.1, 14.5, −4.7, −5.0. HRMS calcd for $C_{22}H_{33}FO_2Si$ (M − H): 375.2155. Found: 375.2156. Anal. Calcd for $C_{16}H_{19}FO$: C, 70.17; H, 8.83; F, 5.04. Found: C, 70.01; H, 8.85; F, 4.95. $[\alpha]^{22}_{589} = -6.32$ (THF, $c = 0.1$).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-5-hexenyl)-6-fluoro-2*H*-benzopyran ((*R*,*R*)-9). Molybdenum alkylidene **2** (35.0 mg, 0.04 mmol) was added to a solution of (*R*,*R*)-**8** (0.34 g, 0.90 mmol) dissolved in 9 mL of benzene. The reaction vessel was fitted with a balloon of ethylene and purged three times with ethylene, and the mixture was allowed to stir at 22 °C for 20 h. Addition of ethyl vinyl ether or MeOH to quench the alkylidene catalyst, followed by the removal of volatile solvents in vacuo, afforded a black oil, which was purified by silica gel chromatography (200:1 hexanes/EtOAc) to afford 0.32 g (0.88 mmol) of a colorless oil (97%) ($R_f = 0.75$ in 10:1 hexanes/EtOAc). IR (KBr): 2964 (m), 2928 (s), 2885 (w), 2856 (s), 1488 (s), 1251 (m), 1214 (m), 776 (m) cm^{-1}. ^{1}H NMR: δ 6.78−6.63 (3H, m, aromatic CH), 6.38 (1H, dd, $J = 10.1$, 1.6, vinylic CH), 5.82 (1H, m, vinylic CH), 5.00 (1H, dd, $J = 17.1$, 1.5, trans vinylic CHCH_2), 4.94 (1H, d, $J = 10.3$, cis vinylic CH), 4.84 (1H, m, ArOC*H*), 3.86 (1H, m, C*H*OTBS), 2.05 (2H, m, allylic CH), 1.70−1.38 (4H, m, aliphatic CH), 0.87 (9H, s, $(CH_3)_3$CSi), 0.06 (6H, s, CH_3Si). ^{13}C NMR: δ 158.3, 156.0, 149.6, 138.7, 124.3, 123.9, 116.2 (d, $J = 8.4$), 114.9 (d, $J = 22.8$), 114.5 (d, $J = 23.5$), 78.0, 73.4, 33.8, 31.9, 25.8, 24.9, 18.0, −4.4, −4.6. HRMS calcd for $C_{21}H_{31}FO_2Si$ (M − H): 361.1998. Found: 361.1996. Anal. Calcd for $C_{21}H_{31}FO_2Si$: C, 69.57; H, 8.62; F, 5.24. Found: C, 69.71; H, 8.71; F, 5.19. $[\alpha]^{22}_{589} = +174.40$ (THF, $c = 0.1$).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-5-oxohexyl)-6-fluoro-2*H*-benzopyran. $PdCl_2$ (37 mg, 0.21), CuCl (29 mg, 0.29 mmol), and H_2O (0.250 mL, 14.1 mmol) were added to 5 mL of DMF, and the resulting mixture was stirred under an atmosphere of O_2 for 1 h. Benzopyran (*R*,*R*)-**9** (0.30 g, 0.83 mmol) in 3.3 mL of DMF was added to the mixture, and stirring was continued under an O_2 atmosphere at 22 °C for 12 h. The reaction was quenched by the dropwise addition of 50 mL of a saturated solution of NH_4Cl. The mixture was subsequently diluted with 25 mL of H_2O and washed three times with 50-mL portions of Et_2O. The resulting solution was dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded a yellow oil, which was purified by silica gel chromatography (20:1 hexanes/EtOAc) to afford 0.22 g (0.60 mmol) of a colorless oil (87%) ($R_f = 0.23$ in 10:1 hexanes/EtOAc). IR (KBr): 2954 (m), 2928 (m), 2895 (w), 2856 (m), 1717 (s), 1488 (s), 1252 (m), 836 (m) cm^{-1}. ^{1}H NMR: δ 6.78−6.62 (3H, m, aromatic CH), 6.36 (1H, dd, $J = 9.9$, 1.8, vinyl CH), 5.82 (1H, dd, $J = 10.1$, 2.2, vinyl CH), 4.85 (1H, m, ArOC*H*), 3.86 (1H, m, C*H*OTBS), 2.44 (2H, m, $CH_2C(O)CH_3$), 2.12 (3H, s, $CH_2C(O)CH_3$), 1.79−1.38 (4H, m, aliphatic CH), 0.87 (9H, s, $(CH_3)_3$CSi), 0.08 (6H, s, CH_3Si). ^{13}C NMR: δ 208.7, 158.6, 155.9, 149.5, 124.3, 123.8, 116.2 (d, $J = 8.4$), 115.0 (d, $J = 31.9$), 112.8 (d, $J = 23.5$), 77.9, 73.2, 43.7, 31.9, 29.8, 25.8, 20.0, 18.0, −4.4, −4.7. HRMS calcd for $C_{21}H_{31}FO_3Si$ (M − H): 377.1947. Found: 377.1950. Anal. Calcd for $C_{21}H_{31}FO_3Si$: C, 66.63; H, 8.25; F, 5.02. Found: C, 66.82; H, 8.41; F, 5.09. $[\alpha]^{22}_{589} = +180.79$ (THF, $c = 0.1$).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-5-oxohexyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran ((*R*,*R*)-10). Chromene ketone, prepared according to the procedure described above (0.20 g, 0.53 mmol), was dissolved in 1.5 mL of EtOH, and 10 mg of Pd/C was added (5 wt %). The reaction was allowed to stir under an atmosphere of H_2 at 22 °C for 30 min. Removal of the catalyst by filtration through a pad of Celite, residue wash with (twice) 30-mL portions of Et_2O, and removal of the solvent in vacuo affored a colorless oil. When necessary, purification was accomplished by silica gel chromatography with 20:1 hexanes/EtOAc to afford 0.18 g (0.46 mmol) of the desired ketone as a colorless oil (98%) ($R_f = 0.36$ in 10:1 hexanes/EtOAc). IR (KBr): 2954 (s), 2928 (s), 2883 (w), 2855 (m), 1718 (m), 1493 (s), 1219 (s), 836 (m) cm^{-1}. ^{1}H NMR: δ 6.74 (3H, m, aromatic CH), 3.86 (2H, m, ArOC*H*, C*H*OTBS), 2.46 (2H, m, CH_2C(O)CH_3), 2.18 (3H, s, CH_2C(O)CH_3), 2.02−1.38 (6H, m, aliphatic CH), 0.90 (9H, s, $(CH_3)_3$CSi), 0.1 (6H, s, CH_3Si). ^{13}C NMR: δ 208.8, 157.7, 155.4, 150.9, 117.4 (d, $J = 7.5$), 115.3 (d, $J = 22.0$), 113.8 (d, $J = 22.7$), 78.7, 73.5, 43.8, 31.5, 29.9, 25.9, 25.3, 21.8, 20.0, 18.2, −4.3, −4.6. UV−vis (Et_2O, λ_{max}, nm): 278. HRMS calcd for $C_{21}H_{33}FO_3Si$: 380.2183. Found: 380.2183. Anal. Calcd for $C_{21}H_{33}FO_3Si$: C, 66.28; H, 8.74; F, 4.99. Found: C, 66.12; H, 8.80; F, 5.17. $[\alpha]^{22}_{589} = -38.11$ (THF, $c = 0.1$).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-2-propenyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran ((*R*,*R*)-11). Chromane ketone (*R*,*R*)-**10** (0.06 g, 0.15 mmol) was dissolved in MeOH (3.7 mL, distilled over Mg and degassed by three freeze−pump−thaw cycles) in a quartz test tube. The mixture was cooled to 0 °C, after which 37 μL of Et_3N (1 vol %) was added. The mixture was irradiated through a Vycor filter with a 450-W medium-pressure mercury lamp for 2 h 20 min. Subsequent removal of solvent in vacuo afforded a colorless oil. Purification by silica gel chromatography with 50:1 hexanes/EtOAc afforded 0.03 g of (*R*,*R*)-**11** (0.09 mmol) as a colorless oil (58%) ($R_f = 0.59$ in 10:1 hexanes/EtOAc). IR (KBr): 2968 (w), 2927 (s), 2854 (m), 1494 (s), 1218 (s), 777 (m) cm^{-1}.^{1}H NMR: δ 6.75 (3H, m, aromatic CH), 5.93 (1H, M, vinyl CH), 5.36 (1H, dt, $J = 17.2$, 1.83, trans vinyl CHCH_2), 5.22 (1H, dt, $J = 10.6$, 1.6, cis vinyl CHCH_2), 4.35 (1H, m, ArOC*H*), 3.89 (1H, ddd, $J = 10.8$, 5.7, 2.2, C*H*OTBS), 2.75 (2H, m, benzylic CH), 2.03−1.55 (2H, m, aliphatic CH), 0.93 (9H, s, $(CH_3)_3$CSi), 0.11 (3H, s, CH_3Si), 0.08 (3H, s, CH_3Si). ^{13}C NMR: δ 157.8, 155.4, 150.8, 136.8 117.4 (d, $J = 7.5$), 116.2, 115.3 (d, $J = 22.0$), 78.9, 74.8, 25.8, 24.9, 22.0, 18.3, −4.7, −4.8. HRMS calcd for $C_{18}H_{27}FO_2Si$ (M + H): 323.1843. Found: 323.1847. $[\alpha]^{22}_{589} = -0.621$ (THF, $c = 0.031$).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-2-hydroxyethyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran. Allylic silyl ether (*R*,*R*)-**11** (19 mg, 0.16 mmol) was placed in a 10-mL round-bottom flask and dissolved in 2 mL of a 4:1 CH_2Cl_2/MeOH solution mixture. The mixture was then charged with $NaHCO_3$ (3.5 mg, 0.25 equiv) and cooled to −78 °C. At this point, O_3 was introduced into the mixture (ozone is passed through a plug of Drierite) for 10−15 min. Reaction progress was monitored by TLC analysis (R_f product = 0.42 in 3:1 hexanes/EtOAc). Upon disappearance of the starting material, $NaBH_4$ (10 mg, 0.18 mmol) was added (at −78 °C), and the mixture was allowed to warm slowly to 23 °C over 1 h; stirring continued for an additional 1.5 h. The reaction was quenched by the addition of 2 mL of a saturated solution of $NaHCO_3$ and washed three times with 5-mL portions of CH_2Cl_2. Purification was accomplished by silica gel chromatography (6:1 hexanes/EtOAc) to provide 17.5 mg of the desired alcohol (0.054 mmol, 91%) as a colorless oil. IR (KBr): 3450 (w, br), 2967 (m), 2926 (m), 2892 (w), 2857 (m), 1511 (s), 1269 (m) 1217 (s), 1108 (m), 832 (m). ^{1}H NMR: δ 6.70−6.81 (3H, m, aromatic CH), 3.98−4.04 (1H, ddd, OC*H*CHOSi, $J = 11.17$, 5.67, 2.01), 3.89−3.94 (1H, dd, $J = 10.1$,

5.5, C*H*OSi), 3.74−3.80 (1H, dd, J = 11.2, 4.2, C*H*HNH$_2$), 3.66−3.71 (1H, dd, J = 11.3, 4.6, CH*H*NH$_2$), 2.70−2.88 (2H, m, ArC*H*$_2$-CH$_2$), 2.00−2.08 (1H, m, Ar CH$_2$*H*H), 1.70−1.82 (1H, m, ArCH$_2$CH*H*), 0.92 (9H, s, *t*-BuSi), 0.6 (3H, s, C*H*$_3$SiMe), 0.4 (3H, s, MeSiC*H*$_3$). ^{13}C NMR: δ 157.9, 153.0 (d, J = 488.4), 123.1 (d, J = 6.9), 117.4 (d, J = 8.4), 115.2 (d, J = 22.8), 113.8 (d, J = 23.5), 77.6, 74.1, 63.4, 25.8, 25.0, 22.5, 18.2, −4.4, −4.7. HRMS calcd for $C_{17}H_{27}FO_3Si$: 327.1792. Found: 327.1793. $[\alpha]^{22}_{589}$ = −0.744 (THF, c = 0.015).

2(*R*)-(1(*R*)-*tert*-Butyldimethylsiloxy-2-ethanphthalimidyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran. The silyl alcohol (25.4 mg, 0.080 mmol) was weighed into a 5-mL round-bottom flask and dissolved in 0.26 mL of benzene; the mixture was cooled to 0 °C, and Bu$_3$P (0.039 mL, 0.150 mmol) and phthalimide (23 mg, 0.16 mmol) were added subsequently. The mixture was then charged with azadicarbonyldipiperidine (ADDP; recrystallized from benzene/hexanes; 34.9 mg, 0.156 mmol) in one portion to produce a yellow solution which turned clear after 5 min. The mixture was allowed to warm to 23 °C and stirred for 20 h. The reaction was quenched by adding ∼10 mL of hexanes, at which point excess ADDP crashed out of solution and was removed by filtration through a plug of Celite. After removal of hexanes in vacuo, purification was accomplished by silica gel chromatography (10:1 hexanes/EtOAc) to provide 30.4 mg of the desired phthalimide (0.07 mmol, 85%) as a colorless oil (R_f = 0.60 in 3:1 hexanes/EtOAc). IR (KBr): 2962 (w), 2949 (w), 2869 (w), 1717(s), 1491 (w), 1408 (w), 1233 (w) cm^{-1}. ^{1}H NMR: δ 7.80−7.77 (2H, dd, J = 5.5, 3.1, NCOCC*H*), 7.68−7.65 (2H, dd, J = 5.5, 2.9, NCHOCCHC*H*), 6.75−6.50 (3H, m, aromatic CH), 4.37−4.31 (1H, dt, J = 7.7, 5.5, ArCOC*H*), 3.94−3.87 (2H, m, ArCOCHC*H*OTBS, C*H*HN), 3.83−3.76 (1H, m, J = 13.5, 7.7, CH*H*N), 2.79−2.70 (2H, m, ArC*H*$_2$), 2.11−2.05 (1H, m, ArCH$_2$C*H*H), 1.95−1.82 (1H, m, ArCH$_2$CH*H*), 0.77 (9H, s, *t*-BuSi), 0.01 (3H, s, C*H*$_3$SiCH$_3$), −0.14 (3H, s, CH$_3$SiC*H*$_3$). ^{13}C NMR: δ 168.3, 157.9, 153 (d, J = 478), 133.9, 132.2, 123.2, 117.4 (d, J = 8.3), 115.2 (d, J = 22.0), 113.7 (d, J = 22.8), 77.7, 69.8, 39.8, 25.6, 25.2, 21.4, 17.9, −4.7, −4.9. HRMS calcd for $C_{25}H_{30}FNO_4Si$ (M + H): 456.2007. Found: 456.2008.

2(*R*)-(2-*tert*-Butyldimethylsiloxy-3-aminopropyl)-6-fluoro-4(*R*)-dihydrobenzopyran ((*R*,*R*)-12). The protected amine−phthalimide, prepared as described above (30.0 mg, 0.066 mmol), was weighed into a reaction flask equipped with a coldfinger and dissolved in 0.66 mL of EtOH; the solution was then charged with H_2NNH_2 (7 μL, 0.1 mmol). The reaction tube was submerged into a preheated 75 °C oil bath and left to stir for 6 h. The solvent was removed in vacuo to obtain a white solid, which was passed through a plug of Celite eluted with CH_2Cl_2. Purification of the clear oil residue was accomplished by silica gel chromatography (10:1 CH_2Cl_2/MeOH) to provide 16 mg (0.05 mmol, 74%) of a colorless oil (R_f = 0.39 in 10:1 CH_2Cl_2/MeOH). IR (KBr): 3408 (w), 2974 (w), 2942 (w), 2873 (w), 1501 (w), 1262 (w), 1224 (w), 1117 (w) cm^{-1}. ^{1}H NMR: δ 6.70 (3H, m, aromatic CH), 3.98 (1H, dd, J = 11.2, 5.5, 3.8, SiOC*H*) (1H, dt, J = 10.8, 5.7, OC*H*COSi), 2.96 (1H, dd, J = 13.2, 3.6, ArC*H*HCH$_2$), 2.70−2.85 (3H, m, ArCH*H*CH$_2$, H$_2$NC*H*$_2$), 1.96−2.04 (1H, m, ArCH$_2$C*H*H), 1.60−1.78 (3H, m, ArCH$_2$C*H*H, CH$_2$N*H*$_2$), 0.92 (9H, s, *t*-BuSi), 0.14 (3H, s, C*H*$_3$SiMe), 0.12 (3H, s, MeSiC*H*$_3$). ^{13}C NMR: δ 157.8, 153 (d, J = 461.0), 123.1, 117.4 (d, J = 8.4), 115.2 (d, J = 22.7), 113.8 (d, J = 23.5), 78.0, 75.5, 44.0, 25.9, 25.2, 22.4, 18.2, −4.3, −4.5. HRMS calcd for $C_{17}H_{28}FNO_2Si$ (M + H): 326.1952. Found: 326.1950. $[\alpha]^{22}_{589}$ = −0.468 (THF, c = 0.010).

***syn*-2-(2-(1′-Propenyl)-4-fluorophenoxy)-3-cyclohepten-1-ol.** Phenol **5** (1.0 g, 6.6 mmol) was dissolved in 50 mL of benzene containing 800 mg of 4-Å molecular sieves. To this mixture was added *n*-Bu$_2$Sn(OMe)$_2$ (0.75 mL, 3.3 mmol) in a dropwise fashion. The reaction was stirred for 14 h at 22 °C. Filtration through a Schlenck tube to remove molecluar sieves and removal of solvent in vacuo afforded the purported phenoxystannane as a yellow oil which was used without further purification. *n*-Bu$_2$Sn(OAr)$_2$ was then dissolved in 10 mL of THF, and to this solution was added PPh$_3$ (0.17 g, 0.66 mmol) and Pd$_2$(dba)$_3$ (0.15 g, 0.16 mmol). In a separate flask, *rac*-**7** (0.74 g, 6.6 mmol) was dissolved in 24 mL of THF; the latter solution was added to the Pd-containing original mixture, cooled to 0 °C, in a dropwise manner over a period of 1.5 h. TLC analysis indicated that the reaction was complete immediately after addition of *rac*-**7**. The reaction mixture was then diluted with three 30-mL portions of 1.0 N HCl and washed with 3 × 75 mL of Et$_2$O. The resulting solution was dried over anhydrous MgSO$_4$. Removal of solvent in vacuo afforded a yellow oil. Silica gel chromatography (13:1 hexanes/EtOAc) afforded 0.99 g of the alcohol as a colorless oil (2.7 mmol, 83%).

Alternative One-Pot Procedure for the Synthesis of *syn*-2-(2-(1′-Propenyl)-4-fluorophenoxy)-3-cyclohepten-1-ol. Phenol **5** (217 mg, 1.42 mmol) was dissolved in 10 mL of THF, and *n*-Bu$_2$Sn(OMe)$_2$ was subsequently added to this solution (214 mg, 0.720 mmol). At this point, 100 mg of activated 4-Å molecular sieves (flame dried) was added, and the mixture was allowed to stir under an Ar atmosphere for 3 h. At this time, Pd(Ph$_3$)$_4$ (0.025 mmol) was added, resulting in a red solution. The mixture was then immediately charged with a THF solution of epoxide **7** (1.4 mmol in 5 mL of THF). Residual *rac*-**7** was added with an additional wash with 1 mL of THF. After 10 min, TLC analysis indicated complete consumption of the starting material. The reaction was quenched with 5 mL of H$_2$O, followed by 5 mL of a 2 M solution of HCl. The insoluble salts were removed by filtration, followed by wash with 5 mL of Et$_2$O. The aqueous layer was washed with three 5-mL portions of Et$_2$O, and the organics were dried over anhydrous MgSO$_4$, which was removed by subsequent filtration. Removal of solvents in vacuo afforded the desired phenyl ether as a yellow oil. Purification was accomplished by silica gel chromatography (13:1 hexanes/EtOAc) to afford 280 mg (1.07 mmol, 74%) of the alcohol as a colorless oil. IR (KBr): 3421 (br), 3037 (w), 2936 (s), 2873 (w), 1495 (s), 1262 (m), 1199 (s) 878 (m) cm^{-1}. ^{1}H NMR: δ 6.98 (1H, dd, J = 9.3, 2.9, aromatic CH), 6.89−6.70 (2H, m, aromatic CH), 6.55 (1H, dd, J = 11.7, 1.3, vinyl CH), 6.04 (1H, m, vinyl CH), 5.86, (1H, m, vinyl CH), 5.62 (1H, m, vinyl CH), 4.86 (1H, m, C*H*OAr), 4.08 (1H, m, C*H*OH), 2.34−2.02 (3H, m, aliphatic CH), 1.83 (3H, dd, J = 5.5, 1.8, CHC*H*$_3$), 1.84−1.50 (3H, m, aliphatic CH). ^{13}C NMR: δ 158.0, 155.6, 151.0 (d, J = 2.1), 134.1, 129.1, 128.1, 124.5, 116.8 (d, J = 22.8), 115.4 (d, J = 8.3), 113.8 (d, J = 22.8), 81.3, 70.0, 34.4, 28.3, 20.9, 14.6. HRMS calcd for $C_{16}H_{19}FO_2$: 262.1369. Found: 262.1372. Anal. Calcd for $C_{16}H_{19}FO_2$: C, 73.26; H, 7.30; F, 7.24. Found: C, 72.90; H, 7.65; F, 6.99.

***syn*-2(*S*)-(2-(1′-Propenyl)-4-fluorophenoxy)-1(*R*)-*tert*-butyldimethylsiloxy-3-cycloheptene ((*S*,*R*)-16).** Racemic phenyl ether **16** (101 mg, 0.27 mmol) was dissolved in 0.2 mL of THF, followed by the addition of 1.14 mL of a 1.18 M solution of EtMgCl in THF. The mixture was subsequently charged with (*S*)-(EBTHI)Zr-binol (17.1 mg, 0.027 mmol), and the reaction vessel was equipped with a reflux condenser and submerged into a preheated 70 °C oil bath. The solution was stirred at this temperature for 1.5 h, removed from the oil bath, and cooled to 0 °C. At this point, the reaction was quenched by the addition of 1 mL of wet ether, followed by 2 mL of H$_2$O, and then 2 mL of a 2 M solution of HCl. The solution was then washed three times with 5-mL portions of Et$_2$O, and the organic layers were dried over anhydrous MgSO$_4$. Removal of volatiles in vacuo afforded a yellow oil, which was purified by silica gel chromatography (pretreated with 10 wt % AgNO$_3$; hexanes; R_f = 0.48 (20:1 hexanes/EtOAc)), and the solvent was removed in vacuo to afford 44.3 mg optically pure ((*S*,*R*)-**16**) (0.12 mmol, 44%) of a clear oil. Enantiomeric excess was determined by analysis of the ^{1}H NMR (400 MHz) spectrum of the derived MTPA ester. IR (KBr): 3034 (m), 2930 (s), 2855 (s), 1483 (s), 1250 (s), 1193 (s), 841 (m) cm^{-1}. ^{1}H NMR: δ 6.98 (1H, dd, J = 9.3, 3.1, aromatic CH), 6.85−6.67 (2H, m, aromatic CH), 6.59 (1H, d, J = 11.7, vinylic CH), 5.92 (1H, m, vinylic CH), 5.80 (1H, m, vinyl CH), 5.36 (1H, d, J = 11.2, vinylic CH), 4.78 (1H, m, ArOC*H*), 4.2 (1H, d, 5.7, C*H*OTBS), 4.16 (1H, d, J = 5.7, C*H*OTBS), 2.31−2.03 (2H, m, allylic CH) 1.83 (3H, dd, J = 6.9, 1.8, CH$_3$), 1.80−1.45 (2H, m, aliphatic CH), 0.88 (9H, s, (C*H*$_3$)$_3$CSi), 0.07 (3H, s, CH$_3$Si), 0.04 (3H, s, CH$_3$-Si). ^{13}C NMR: δ 157.5, 155.2, 151.9, 131.3, 131.1, 127.1, 125.3, 116.7 (d, J = 23.5), 114.0 (d, J = 8.3), 113.4 (d, J = 22.7), 81.4, 70.6, 36.2, 28.3, 25.8, 20.6, 14.6, −4.7, −4.8. HRMS calcd for $C_{22}H_{33}FO_2Si$ (M − H): 375.2155. Found: 375.2156. Anal. Calcd for $C_{22}H_{33}FO_2Si$: C, 70.17; H, 8.83; F, 5.04. Found: C, 70.22; H, 8.66; F, 5.34. $[\alpha]^{22}_{589}$ = +18.27 (THF, c = 0.1).

2(*S*)-(2′-*tert*-Butyldimethylsiloxy-5-hexenyl)-6-fluoro-2*H*-benzopyran ((*S*,*R*)-17). IR (KBr): 2961 (m), 2936 (m), 2854 (m), 1501 (s), 1262 (m), 1224 (m), 840 (m) cm^{-1}. ^{1}H NMR δ 6.80−6.65 (3H, m,

aromatic CH), 6.35 (1H, dd, J = 10.06, 1.83, ArC*H*), 5.90−5.77 (2H, m, vinylic CH, ArCHC*H*), 5.0 (1H, dd, J = 17.2, 1.6, trans vinyl), 4.97 (1H, dd, J = 10.2, 0.9, cis vinyl CH), 4.73 (1H, m, ArOC*H*), 3.92 (1H, m, C*H*OTBS), 2.08 (2H, m, allylic CH), 1.70−1.44 (4H, m, aliphatic), 0.86 (9H, s, *t*-*Bu*SiMe$_2$) 0.06 (3H, s, CH_3Si), −0.02 (3H, s, CH_3Si). ^{13}C NMR: δ 158.1 (d, J = 238.04), 150.3, 139.5, 125.5, 124.5, 123.5 (d, J = 8.4), 117 (d, J = 6.9), 115.5 (d, J = 23.6), 115.4, 113.2 (d, J = 23.6), 78.3, 74.4, 34, 33, 26, 24.2, 18.3, −4.4, −4.5. HRMS calcd for $C_{21}H_{31}FO_2Si$ (M − H): 361.1998. Found: 361.1999. Anal. Calcd for $C_{21}H_{31}FO_2Si$: C, 69.57; H, 8.62; F, 5.24. Found: C, 66.94; H, 8.66; F, 5.35. $[\alpha]^{22}_{589}$ = −9.700 (THF, c = 0.066).

2(*S*)-(1(*R*)-*tert*-Butyldimethylsiloxy-5-oxohexyl)-6-fluoro-2*H*-benzopyran. IR (KBr): 2952 (m), 2928 (m), 2855 (m), 2898 (w), 1717 (s), 1487 (s), 1252 (m), 1218 (m), 837 (m) cm^{-1}. ^{1}H NMR: δ 6.79−6.62 (3H, m, aromatic CH), 6.36 (1H, d, J = 10.2, ArC*H*), 5.82 (1H, dd, J = 9.9, 3.1, vinyl CH), 4.72 (1H, m, ArOC*H*), 3.85 (1H, dt, J = 10.2, 5.1, C*H*OTBS), 2.45 (2H, t, J = 7.2, CH_2COCH$_3$), 2.14 (3H, s, CH$_2$COCH_3), 1.78−1.48 (4H, m, aliphatic CH), 0.84 (9H, s, *t*-BuSi), 0.40 (3H, s, CH_3Si), −0.20 (3H, s, CH_3Si). ^{13}C NMR: δ 208.7, 157.6 (d, J = 150), 149.3, 124.6, 124.1, 123.9, 122.7 (d, J = 8.4), 116.3 (d, J = 7.6), 112.7 (d, J = 23.5), 72.5, 73.7, 43.7, 32.7, 29.7, 25.9, 19.1, 18.1, −4.5. $[\alpha]^{23}_{589}$ = −6.770 (THF, c = 0.0502). Anal. Calcd for $C_{21}H_{31}FO_3Si$: C, 66.63; H, 8.25; F, 5.02. Found: C, 66.39; H, 8.09; F, 5.15.

2(*S*)-(1(*R*)-*tert*-Butyldimethylsiloxy-5-oxohexyl)-6-fluoro-3,4-dihydro-2(*H*)-benzopyran. IR (KBr): 2966 (m), 2937 (m), 2902 (w), 2856 (m), 1730 (m), 1497 (s), 1224 (m), 1097 (m), 836 (m), 783 (m) cm^{-1}. ^{1}H NMR: δ 6.80−6.67 (3H, m, aromatic CH), 3.91−3.80 (2H, m, ArOC*H*, C*H*OTBS), 2.86−2.68 (2H, m, ArCH$_2$), 2.46 (2H, t, J = 6.9, CH$_3$COCH$_2$), 2.15 (3H, s, CH_3O), 1.98 (1H, m, ArCH$_2$C*H*H), 1.42−1.83 (5H, m, ArCH$_2$CH*H*, alkyl), 0.88 (9H, s, *t*-BuSi), 0.10 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si). ^{13}C NMR: δ 208.7, 157.7, 153.1 (d, J = 452), 123.2 (d, J = 6.8), 117.3 (d, J = 8.4), 115.1 (d, J = 22.8), 113.7 (d, 23.5), 78.4, 73.5, 43.7, 33.1, 29.8, 25.9, 24.9, 21.5, 19.5, 18.2, −4.2, −4.6. $[\alpha]^{22}_{589}$ = +3.170 (THF, c = 0.077). Anal. Calcd for $C_{21}H_{33}FO_3Si$: C, 66.28; H, 8.74; F, 4.99. Found: C, 66.23; H, 8.73; F, 5.01.

2(*S*)-(1(*R*)-*tert*-Butyldimethylsiloxy-2-propenyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran ((*S*,*R*)-18). IR (KBr): 2955 (m), 2929 ((m), 2892 (w), 2856 (m), 1494 (m) 1255 (m), 1217 (m) 847 (m). ^{1}H NMR: δ 6.80−6.68 (3H, m, aromatic CH), 5.91 (1H, ddd, J = 17.2, 10.6, 5.3, vinyl CH), 5.36 (1H, dt, J = 17.2, 1.6, trans vinyl CH), 5.20 (1H, dt, J = 10.6, 1.6, cis vinyl), 4.39 (1H, dd, J = 4.9, 4.2, C*H*OTBS), 3.85 (1H, dq J = 10.4, 4.2, ArOCH), 2.68−2.82 (2H, m, ArCH$_2$), 2.20−1.94 (1H, m, ArCH$_2$C*H*H), 1.88−1.78 (1H, m, ArCH$_2$CH*H*), 0.89 (9H, s, *t*-BuSi), 0.08 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si). ^{13}C NMR: δ 157.7, 155.3−150.9 (d, J = 435.2), 137.8, 123.3, 117.2 (d, J = 8.3), 113.7 (d, J = 22.8), 78.9, 74.9, 29.7, 25.8, 24.7, 20.9, 18.3, −4.61, −4.68. HRMS calcd for $C_{18}H_{27}FO_2$ (M + H): 323.1843. Found: 323.1841. $[\alpha]^{22}_{589}$ = +0.990 (THF, c = 0.016).

2(*S*)-(1(*S*)-*tert*-Butyldimethylsiloxy-2-oxoethyl)-6-fluoro-3,4-dihydro-2*H*-benzopyran ((*S*,*S*)-19). IR (KBr): 2961 (m), 2930 (m), 2886 (m), 2857 (m), 1737.90 (m), 1494 (m) 1258 (w), 1216 (m), 916 (w), 841 (w) cm^{-1}. ^{1}H NMR: δ 9.78 (1H, s, CHO), 6.80−6.68 (3H, m, aromatic CH), 4.28−4.22 (2H, m, C*H*OTBS, ArOC*H*), 2.89−2.70 (2H, m, ArCH$_2$), 1.99−1.87 (2H, m, ArCH$_2$CH_2), 0.92 (9H, s, *t*-*Bu*Si), 0.14 (3H, s, SiCH$_3$), 0.09 (3H, s, SiCH$_3$). ^{13}C NMR: δ 202.4, 158.0, 155.6−150.3 (d, J = 237.0), 122.7 (d, J = 6.8), 117.4 (d, J = 7.5), 115.2 (d, J = 22.8), 114.1 (d, J = 22.8), 79.4, 76.3, 29.7, 25.7, 24.4, 22.1, −4.75, −4.84. $[\alpha]^{22}_{589}$ = +0.398 (THF, c = 0.0129). Anal. Calcd for $C_{17}H_{25}FO_2Si$: C, 67.04; H, 8.44; F, 5.89. Found: C, 67.28; H, 8.56; F, 6.14.

(−)-[*S*,*R*,*R*,*R*]-α,α′-[Iminobis(methylene)bis[6-fluoro-3,4-dihydro-2*H*,1-benzopyran-2-*tert*-butyldimethylsiloxymethyl] (23). Terminal amine (*R*,*R*)-**12** (9.0 mg, 0.03 mmol) was dissolved in 0.5 mL of freshly distilled 1,2-dichloroethane. In a separate flask, aldehyde (*S*,*S*)-**19** (12 mg, 0.04 mmol) was dissolved in 0.5 mL of THF, and the mixture was transferred into the original flask by cannula (flask was rinsed with 0.5 mL of solvent to ensure complete transfer). NaBH(OAc)$_3$ (8.3 mg, 0.04 mmol) was added in one portion, and the reaction was allowed to stir at 23 °C; TLC analysis after 3 h indicated that the reaction was complete (R_f product = 0.50 in 10:1 CH_2Cl_2/MeOH). At this point, the mixture was diluted with 2 mL of aqueous $NaHCO_3$ and washed three times with 5-mL portions of CH_2Cl_2. Organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo to obtain a yellow oil. Purification was accomplished by silica gel chromatography (5:1 hexanes/EtOAc) to obtain 16.2 mg of the desired dialkylamine as a clear oil (0.025 mmol, 91%). IR (KBr): 2962 (w), 2928 (w), 2899 (w), 2867 (w), 1494 (m), 1269 (w), 1218 (w) 836 (w) cm^{-1}. ^{1}H NMR: δ 6.80−6.64 (8H, m, aromatic CH), 4.05−3.91 (4H, m, ArCOC*H*, ArCOCHC*H*OSi), 2.92−2.67 (8H, m, CH_2N, ArCH_2), 2.08−1.98 (2H, m, ArCH$_2$C*H*H), 1.84−1.65 (2H, m, ArCH$_2$CH*H*), 0.85 (9H, s, *t*-*Bu*Si), 0.83 (9H, s, *t*-*Bu*Si), 0.12 (3H, s, CH_3SiCH$_3$), 0.10 (6H, s, CH_3SiCH_3), 0.06 (3H, s, CH$_3$SiCH_3). ^{13}C NMR: δ 156.6 (d, J = 236.8), 156.5 (d, J = 238.9), 155.4 (d, J = 6.8), 150.9 (d, J = 15.1), 123.2 (d, J = 7.6), 117.4 (d, J = 9.1), 117.3 (d, J = 8.3), 115.2 (d, J = 22.0), 113.7 (d, J = 22.8), 78.1, 77.2, 73.9, 73.8, 52.9, 52.1, 29.7, 25.9, 25.2, 24.8, 22.4, 22.2, 18.2, −4.3, −4.4, −4.5. HRMS calcd for $C_{34}H_{53}F_2NO_4Si$ (M + H): 634.3560. Found: 634.3562. $[\alpha]^{22}_{589}$ = −0.740 (THF, c = 0.0108).

(+)-[*S*,*R*,*R*,*R*]-α,α′-[Iminobis(methylene)bis[6-fluoro-3,4-dihydro-2H,1-benzopyran-2-methanol] Hydrochloride (3·HCl). Bis(silyl ether) **23** (10.5 mg, 0.16 mmol) was placed in a 5-mL round-bottom flask and dissolved in 1 mL of anhydrous 10% HCl in MeOH. After 5 min, a white precipitate formed. TLC analysis showed the reaction to be complete after 12 h. The mixture was concentrated in vacuo to afford a yellowish oil and a white solid, which was rinsed with $CHCl_3$ and filtered through a microfilter to obtain 7 mg (0.05 mmol) of nebivolol·HCl salt as a white solid (0.05 mmol, 99%) (R_f = 0.26 in 10:1 CH_2Cl_2/MeOH). IR (KBr): 3332 (br), 3181 (br), 2942 (w, br), 2848 (w), 1501 (m) 1438 (w), 1230 (m), 1149 (w), 1073 (w), 803 (w) cm^{-1}. ^{1}H NMR: δ 6.85−6.75 (6H, m, aromatic CH), 4.13−4.07 (1H, m, OC*H*CHOH), 4.04−3.97 (2H, m, OCHC*H*OH), 3.94−3.89 (1H, m, OC*H*CHOH), 3.53−3.20 (4H, m, CHOHCH_2N), 2.96−2.77 (4H, m, ArCH_2), 2.28−2.20 (1H, m, ArCH$_2$C*H*H), 2.22−1.86 (2H, m, ArCH$_2$CH_2), 1.83−1.72 (1H, m, ArCH$_2$CH*H*). ^{13}C NMR: δ 158.5 (d, J = 235.6), 158.4 (d, J = 235.6), 153.2 (d, J = 61.1), 151.8 (d, J = 38.8), 125.0 (d, J = 7.7), 124.8 (d, J = 7.68), 118.8 (d, J = 8.4), 118.7 (d, J = 7.6), 116.5 (d, J = 6.9), 116.3 (d, J = 6.8), 115.0 (d, J = 5.9), 114.8 (d, J = 6.1), 79.1, 78.8, 69.5, 69.4, 51.6, 51.4, 25.9, 25.4, 24.6, 24.2. HRMS calcd for $C_{22}H_{25}F_4NO_4$ (M + H) = 406.1831. Found: 406.1830. $[\alpha]^{22}_{589}$ = +0.040 (MeOH, c = 0.0027). Anal. Calcd for $C_{22}H_{26}ClF_2NO_4$: C, 59.80; H, 5.93; N, 3.17; F, 8.60. Found: C, 59.64; H, 5.82; N, 2.94; F, 8.36.

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Supporting Information Available: Spectral data for all reaction products (39 pages). See any current masthead page for ordering information and Web access instructions.

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