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Selective Functionalization of 1,2-Dihydronaphthalenols Leads to a Concise, Stereoselective Synthesis of Sertraline.

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Abstract: Asymmetric reductive ring opening of oxabenzonorbornadiene provides dihydronaphthalenols in high ee and good yield. Functionality present in this system can be used to elaborate the core towards a number of targets. As an illustration, a concise stereoselective synthesis of the important antidepressant sertraline is described.

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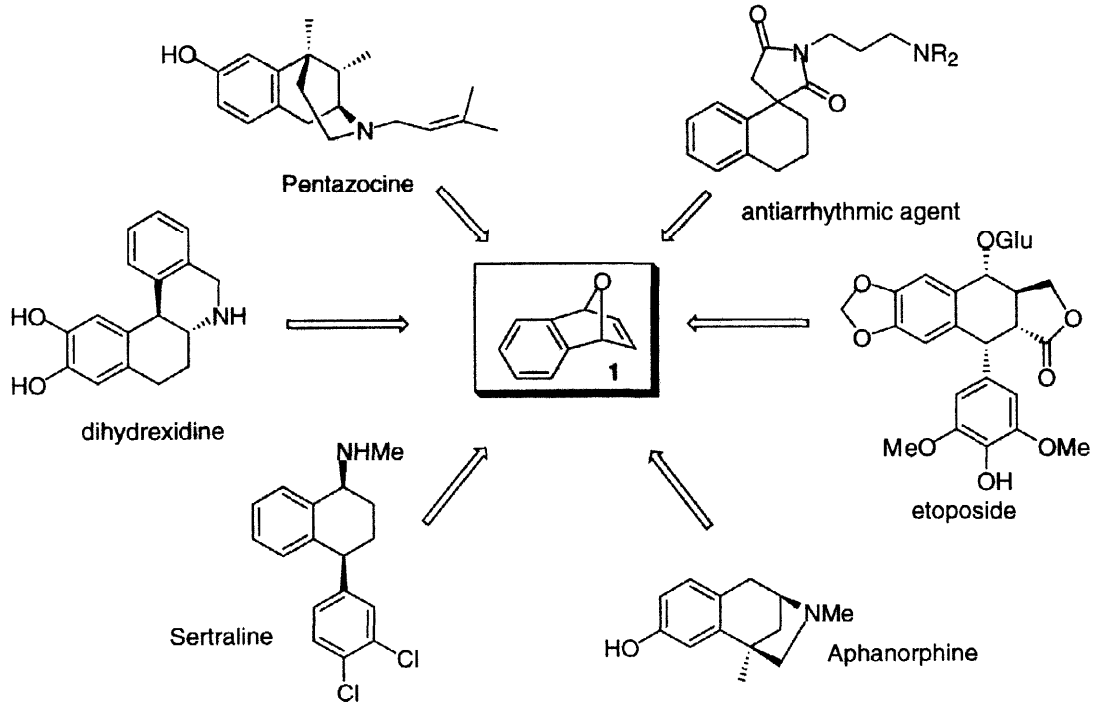
Among the myriad of structural motifs reported in the literature over the past fifty years, there are certain core skeletons which have more than their proportional share of useful biological activity and have been described as "privileged" structures.[1] Privileged structures are particularly important to the pharmaceutical industry and the drug discovery process and often represent a starting point in identifying lead compounds for evaluation. Examples of privileged structures include molecules containing diazepines, isoquinolines and dihydropyridines, as well as a host of others. The tetrahydronaphthalene motif is found in a



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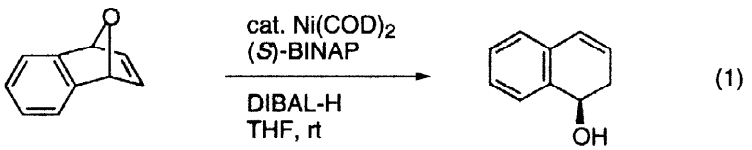
number of biologically active molecules whose functions range from various central nervous system agents[2] to antibiotics[3], immunoregulatory agents[4], and antitumor agents.[5] Thus a concise and rapid approach to a suitably functionalized core that can be elaborated into any of these agents is an attractive goal.

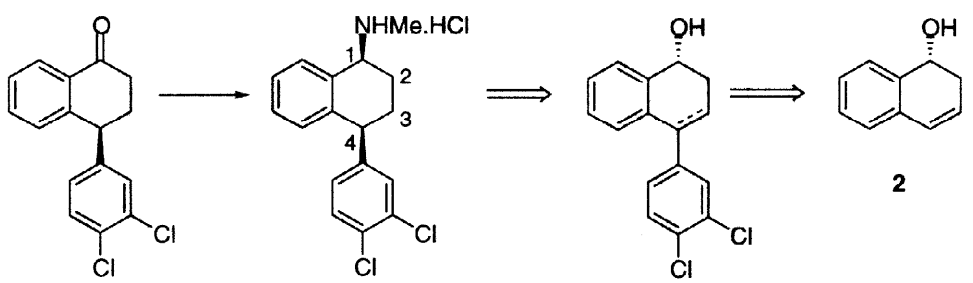
We have previously reported that a number of oxabicyclo[2.2.1]heptenes and oxabicyclo[3.2.1]octenes undergo highly enantioselective reductive ring opening in the presence of $Ni(COD)_2$/BINAP and DIBAL.[6] Oxabenzonorbornadiene **1** is an excellent substrate for this reaction, providing the dihydronaphthalenol **2** in 88% yield and 98% ee, eq. 1. In the context of developing a general route to suitable intermediates in the synthesis of enantiomerically pure tetrahydronaphthalenes, we envisioned that this dihydronaphthalenol possessed the appropriate functionality needed to introduce additional substituents in a stereocontrolled manner.



(1)

1 **2** 88%, 98% ee

Our initial goal was the development of a rapid approach to the total synthesis of the antidepressant sertraline, a commercially important selective serotonin re-uptake inhibitor (SSRI)[7] containing a functionalized tetrahydronaphthalene core. Previous syntheses proceeded through a common intermediate **A**, Scheme 1; however, the subsequent reductive amination was reported to be moderately selective, yielding sertraline and *epi*-sertraline in a 3:1 ratio. We envisioned a route to sertraline that would take advantage of functionality already present in the core to dictate the course of future stereochemical processes, and thus, hoped to avoid the ketone **A** and the reductive amination step.

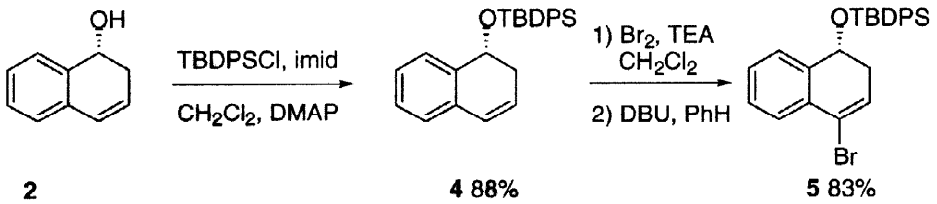


A Sertraline, **3**

Scheme 1

A key consideration at the design stage was to identify reactions which would introduce the aryl group into the dihydronaphthalenol core. Our first approach was to examine the Heck reaction[8] between an aryl halide and the olefin. Model studies with dihydronaphthalene[9] were encouraging but the stereoselectivity of the reaction could not be easily predicted. Electrophilic additions occur on the opposite face of the olefin relative to the stereocentre but no data were available on palladation reactions.[10] Unfortunately all attempts to promote the Heck reaction between **2** or **4** and **7** (Pd_2dba_3, PPh_3, LiCl, DMF 100 °C; $Pd(OAc)_2$, phen., TEA, DMF, 80 °C;[11] $Pd(OAc)_2$, LiCl, LiOAc, Bu_4NCl, DMF, 100 °C[12]), gave no reaction, dehydration or dehydrogenation of the starting material. Subjecting the TBS ether to the reaction conditions above resulted in no reaction.

The failure of the direct coupling approach led us to introduce a halide in order to carry out the C-C bond forming reaction. Subjecting the dihydronaphthalenol **2** to a bromination/dehydrobromination protocol first described by Willems and coworkers[13] gave the bromo alcohol in very low yield (<5%). However when the alcohol was protected as a silyl ether, treatment with bromine in CH_2Cl_2 in the presence of 0.5 equivalents of triethylamine gave the dibromide cleanly. The solvent was removed *in vacuo* at room temperature and benzene was added, followed by DBU. After six hours at room temperature, the dehydrobromination was complete. Upon aqueous workup, the vinyl bromide **5** was isolated in 83% yield.

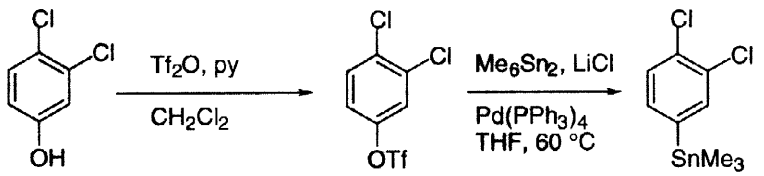


2 **4** 88% **5** 83%

Scheme 2

The choice of DBU as the base was critical to the success of the reaction. The use of anionic bases (NaHMDS) at lower temperatures or weaker amine bases (TEA) at higher temperatures led to significant debromination to regenerate the starting material. A number of mechanistic possibilities may be invoked to account for this observation. It is possible that initial alkylation of the base by the benzylic bromide, through solvolysis or nucleophilic displacement, precedes a bromide ion induced elimination. Alternatively, two successive single electron transfers may account for the observed results.[14] Furthermore, the use of benzene as solvent for the elimination step was essential. More polar solvents, including CH_2Cl_2, led to significant regeneration of starting material.

Two successful coupling strategies were found to introduce the aryl group. The aryltrimethylstannane was readily available from triflate **7** using a Stille reaction with hexamethylditin as nucleophile, Scheme 3.[15]

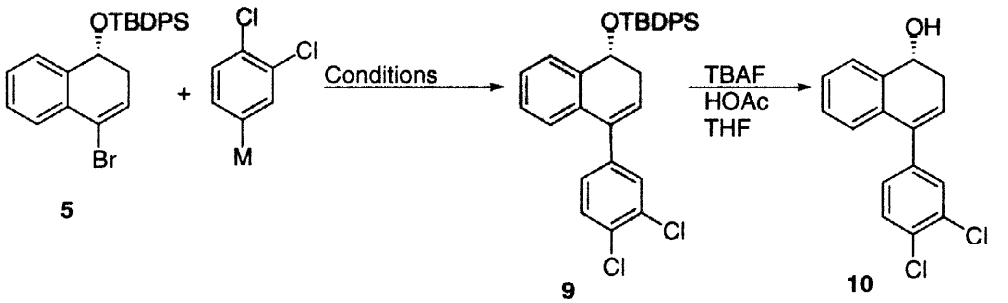


6 **7** 88% **8** 49%

Scheme 3

Subjecting the vinyl bromide and arylstannane **8** to typical Stille coupling conditions ($Pd(PPh_3)_4$, PhMe, 110 °C) resulted in low yields of the desired product. Instead, arylnaphthalene and arylnaphthol arising from coupling and dehydration or dehydrogenation were obtained. It is possible that the high temperatures and prolonged reaction times were responsible for the decomposition of product and/or starting material since reaction of the vinyl bromide **5** and the arylstannane **8** under the Farina coupling conditions[16] led to complete reaction at 80 °C in 1.5 hours, Scheme 4. Initially we obtained poor yields from all the Stille reactions but later found that the product was highly susceptible to elimination of silanol as evidenced by the formation of aryl naphthalene as a side product. Similarly, when the desilylation step was carried out using TBAF in THF,

a 55% yield of the alcohol **10** was obtained accompanied by significant amounts of arylnaphthalene. However, TBAF buffered with HOAc in THF gave **10** in quantitative yield after 3 days at room temperature.



5 **9** **10**

M	Conditions	Yield
$SnMe_3$	$Pd(PPh_3)_4$, PhMe, 110 °C, 3 h	35%
	$(MeCN)_2PdCl_2$, $AsPh_3$, NMP 80 °C, 1.5 h	55%
$B(OH)_2$	$Pd(PPh_3)_4$, NaOEt, PhH, 85 °C, 3 h	33%
	$Pd(PPh_3)_4$, KF, PhMe, H_2O, 100 °C, 3 h	32%
	$PdCl_2$dppf, 3M NaOH, THF, 60 °C, 3 h	53%

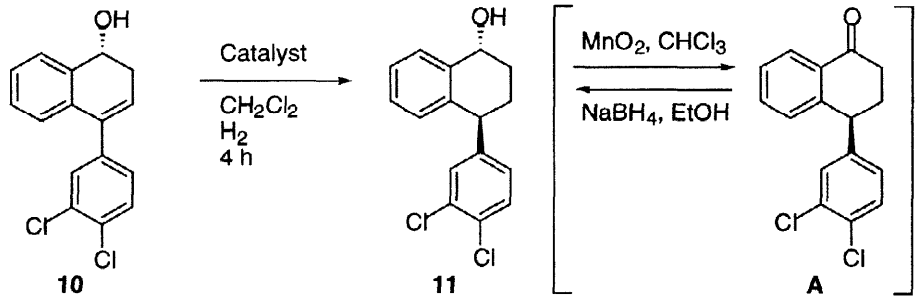
Scheme 4

We also investigated the Suzuki coupling of the vinyl bromide **5** and the corresponding arylboronic acid in order to avoid the use of stannanes. Numerous methods have been published for the Suzuki coupling using a wide variety of bases and catalyst precursors.[17] $Pd(PPh_3)_4$ and NaOEt in benzene at 85 °C consumed only 33% of the starting material as judged by ^1H NMR of the crude reaction mixture. The use of fluoride in the Suzuki reaction as a base-substitute has been reported but under these conditions ($Pd(PPh_3)_4$, KF, PhMe, H_2O, 100 °C), the coupling was accompanied by dehydrogenation of the substrate.[18] After desilylation, the alcohol was isolated in only 32% yield over two steps. It is interesting to note that no desilylation occurred prior to addition of TBAF. The use of dppf as a ligand in the Suzuki reaction gave the best results with this substrate. In the presence of 3M NaOH in refluxing THF, the reaction was complete in three hours.[19] Desilylation of the crude mixture gave the alcohol in 53% yield over two steps, Scheme 4.

With a satisfactory route to the carbon skeleton in sertraline, a selective reduction of the olefin followed by the introduction of the nitrogen functionality in place of the benzylic alcohol was required. Given that the second step would best be executed using an inversion approach and cognizant of the need for a *cis* relationship in sertraline, the reduction of the olefin had to occur *syn* to the hydroxyl. The directed hydrogenation using cationic rhodium ([Rh(NBD)dppb]BF_4) and iridium ([Ir(COD)(py)PCy_3]PF_6) catalysts is well established in substituted cyclohex-3-en-1-ols and was considered the most efficient approach.[20,21] However dihydronaphthalenol **2** is a nearly planar system with four sp^2 carbons so it was difficult to predict the level of selectivity which would be obtained.

Treatment of dihydronaphthalenol **10** with one atmosphere of hydrogen gas in the presence of a catalytic amount of [Rh(NBD)dppb]BF_4 resulted in complete recovery of starting material and the use of [Ir(COD)(py)PCy_3]PF_6 as catalyst resulted in only partial reaction. However, increasing the pressure of hydrogen to 1000 psi led to complete consumption of the starting material with both catalysts. Selectivities were better with the iridium catalyst which gave the alcohol **11** in 88% yield and 28:1 selectivity, Scheme 5.

Decreasing the amount of iridium catalyst resulted in incomplete reaction[18b] whereas as little as 1 mol% of the cationic rhodium catalyst gave the product in good yield and selectivity but an impurity whose structure could not be determined was also present. The diastereomeric ratio of the alcohol was determined by 400 MHz ^{1}H NMR by comparison to a mixture of epimers (cis and trans) obtained by oxidation of the alcohol followed by $NaBH_4$ reduction. The reduction yielded the two epimers of **11** in a 1.1:1 ratio.



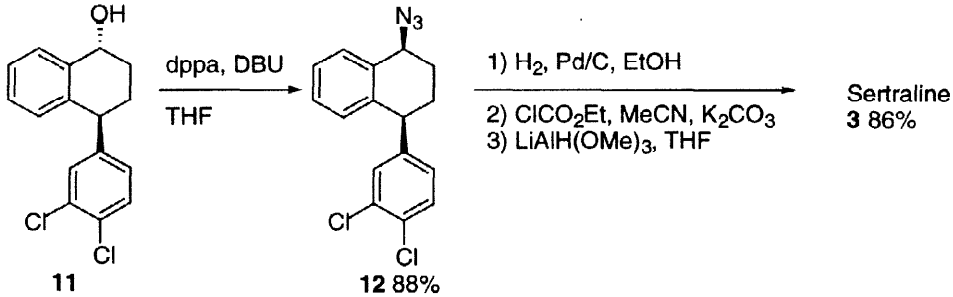
Catalyst	H_2 Pressure	Yield	Selectivity
10 mol% [Ir(COD)pyPCy$_3$]PF$_6$	1 atm	50%*	nd
	1000 psi	88%	28:1
1 mol% [Rh(NBD)dppb]BF$_4$	1 atm	NR	
	1000 psi	73%	10:1

*conversion as judged by ^{1}H NMR of the crude reaction mixture

Scheme 5

The preparation of tetralone **A** represented the completion of a formal synthesis of sertraline as all previous approaches proceeded through **A** as their penultimate intermediate. However, we were interested in controlling the stereochemistry of the amine moiety introduced in the subsequent step by taking advantage of the stereochemistry already present in the alcohol **11**, and could thus avoid the reductive amination step used in previous approaches to sertraline.

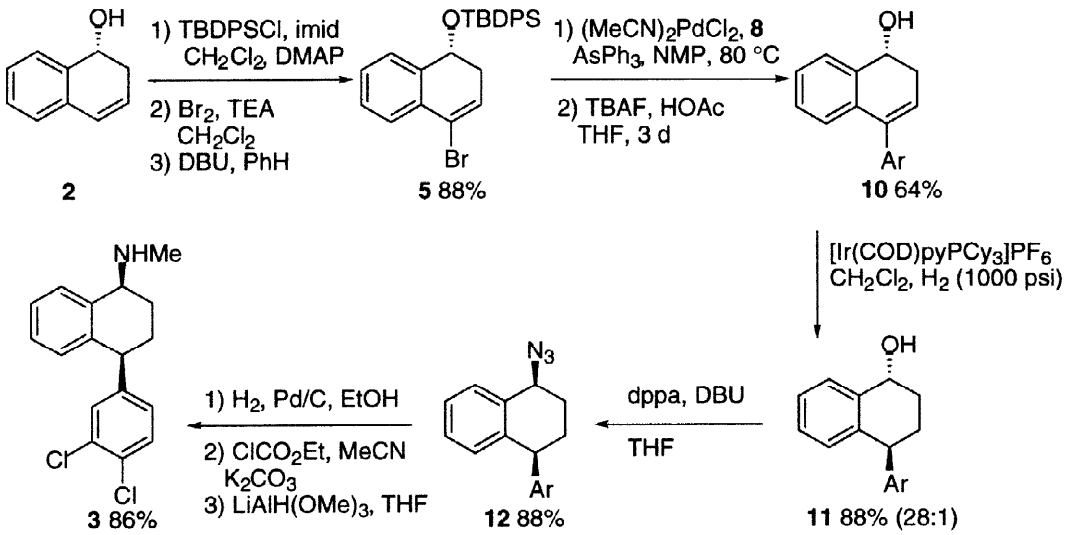
Thompson and coworkers devised an efficient solution to the problem of substituting benzylic alcohols by a nitrogen functionality.[22] They note that classic Mitsunobu conditions (PPh_3, DEAD, HN_3) typically lead to significant epimerization of the stereocentre particularly with electron rich aromatic systems. By using diphenylphosphoryl azide (dppa) in the presence of DBU, a variety of benzylic alcohols can be activated and displaced by azide with inversion of stereochemistry, with selectivities ranging from 99:1 to 94:6 for electron rich aromatic systems. Subjecting the alcohol **11** to these conditions gave the azide **12** in 88% isolated yield and 98:2 selectivity, Scheme 6.



Scheme 6

With the desired substitution pattern in place, all that remained was to reduce the azide and methylate the resulting amine. Reduction of the azide was cleanly effected by hydrogen gas mediated by Pd on charcoal and subsequent treatment of the amine with ethyl chloroformate yielded the carbamate.[23] Reduction of the carbamate proved to be problematic since $LiAlH_4$ also partially reduced the aromatic chlorides to give a mixture of products.[24] The problem was circumvented by using $LiAlH(OMe)_3$ in refluxing THF for 40 hours, which gave sertraline in 86% yield from the azide **12**.

Throughout the synthesis we found that a number of intermediates were sensitive to the workup and purification procedures. In an attempt to improve the efficiency of our route, we avoided several purifications and found that overall yields improved greatly, Scheme 7. Whereas silylation of alcohol **2**, purification, bromination/dehydrobromination and purification yielded the bromide **5** in 73% overall, avoiding the initial purification gave **5** in 88% yield from **2**. Similarly, we found that desilylation of the crude coupling product **9** gave a 64% isolated yield of the alcohol **10**, an improvement on the 55% for coupling alone. Using this sequence, the synthesis of sertraline was completed in nine steps from the dihydronaphthalenol **2** with an overall yield of 38%.



Scheme 7

In summary we have demonstrated that the enantioselective reductive opening of an oxabenzonorbornadiene generates a hydroxydihydronaphthalene which can be readily converted into the commercially important SSRI, sertraline. Since the reductive opening is general for a variety of substituted derivatives bearing electron withdrawing or donating groups it should be possible to adapt this modular route to the preparation of novel sertraline analogues and examine their efficacy.

Experimental

The following includes experimental procedures, specific details for representative reactions, isolation and spectroscopic information for the prepared compounds. All procedures were carried out under strictly anaerobic conditions using freshly distilled solvents. Toluene, benzene and THF were distilled from sodium

benzophenone ketyl before use. Pyridine was distilled and stored over KOH pellets. CH_2Cl_2 and triethylamine were distilled over CaH_2 before use. NMP was obtained from Aldrich and degassed with an argon purge before use but otherwise used as received. $Pd(PPh_3)_4$, 3,4-dichlorophenol, hexamethylditin, triflic anhydride, triphenylarsine, DBU, $PdCl_2(MeCN)_2$, TBDPSCl, DMAP, TBAF and diphenylphosphoryl azide were obtained from Aldrich and used as received. LiCl was dried under high vacuum at 60 °C for 4 hours before use. Crabtree's catalyst ($[Ir(COD)(py)(PCy_3)]PF_6$)was prepared according to the published procedure.[25]

(*R*)-1-*tert*butyldiphenylsiloxy-1,2-dihydro-naphthalene (4). In a flame-dried round bottomed flask, **2** (340 mg, 2.33 mmol), imidazole (390 mg, 5.73 mmol) and DMAP (20 mg, 0.16 mmol) were dissolved in 10 mL of CH_2Cl_2. TBDPSCl (640 mg, 2.33 mmol) in CH_2Cl_2 (4 mL) was added to the solution *via cannula*. After 3 h at rt, the solvent was removed *in vacuo* and the residue immediately purified by flash chromatography on silica gel (hexanes) to yield **4** (770 mg, 86%), a colourless oil. R_f = 0.22 on silica gel (100% hexanes); $[\alpha]^{25}_D$= 57.5° (c= 1.3, PhH); IR (neat) 3065, 2960, 2931, 2854, 1581, 1462, 1420, 1370, 1110, 892, 815, 702 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.80 (2H, m), 7.70 (2H, m), 7.52 (1H, m), 7.10-7.24 (6H, m), 7.06 (2H, m), 6.89 (1H, m), 6.32 (1H, d, *J* = 9.9 Hz), 5.60 (1H, ddd, *J* = 9.2, 4.7, 4.4 Hz), 5.06 (1H, dd, *J* = 9.0, 6.0 Hz), 2.41 (1H, dddd, *J* = 16.8, 9.1, 4.0, 1.8 Hz), 2.09 (1H, dddd, *J* = 16.8, 5.9, 4.4, 1.4 Hz), 1.17 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.9, 135.8, 134.5, 133.6, 133.4, 129.6, 129.6, 127.5, 127.5, 127.4, 127.1, 125.9, 125.8, 125.6, 69.8, 32.8,. 27.0, 19.5; HRMS calcd for $C_{26}H_{28}OSi$ $(M)^+$: 384.1909. Found: 384.1907.

(*R*)-4-bromo-1-*tert*butyldiphenylsiloxy-1,2-dihydro-naphthalene (5). At 0 °C, to **4** (510 mg, 1.33 mmol) dissolved in CH_2Cl_2 (4 mL) was added triethylamine (0.10 mL, 0.72 mmol). A solution of bromine (350 mg, 2.19 mmol) in 2 mL of CH_2Cl_2 was added dropwise until the red colour persisted after an extended period of time. TLC indicated that **4** was consumed and a new spot had formed. The solvent and volatiles were removed *in vacuo* at room temperature and the residue was dissolved in 5 mL of benzene, to which was then added 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU, 0.40 mL, 2.7 mmol). The solution was allowed to stir at rt overnight, during which time it turned red and a precipitate began forming. Distilled water was added (20 mL) and the organics were extracted with hexanes three times, washed with brine and dried over Na_2SO_4. Concentration of the organics *in vacuo* yielded a paste which was immediately purified on silica gel, using hexanes:Et_3N (99:1) as the eluent. Chromatography yielded **5** (510 mg, 83%), a colourless oil. R_f = 0.37 on silica gel (100% hexanes); $[\alpha]^{25}_D$= 19.7° (c= 1.1, $CHCl_3$); IR (neat) 3079, 2931, 2861, 1961, 1623, 1595, 1469 1427, 1384, 1363, 1110, 934, 829, 709 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.73 (2H, m), 7.66 (1H, m), 7.64 (2H, m), 7.10-7.22 (6H, m), 7.03 (2H, m), 5.90 (1H, dd, *J* = 4.9, 4.9 Hz), 4.92 (1H, dd, *J* = 9.3, 5.7 Hz), 2.23 (1H, ddd, *J* = 16.4, 9.3, 4.0 Hz), 1.89 (1H, ddd, *J* = 16.4, 5.5, 5.5 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 138.5, 136.2, 136.0, 135.8, 134.6, 133.8, 132.7, 130.1, 130.0, 128.8, 128.2, 128.1, 127.0, 125.8, 121.0, 69.6, 35.1, 27.2, 19.7; HRMS calcd for $C_{26}H_{27}OSiBr$ $(M\text{-}C_4H_9)^+$: 405.0310. Found: 405.0322.

3,4-dichloro-1-trifluoromethanesulfonyloxybenzene (7). To a solution of 3,4-dichlorophenol (1.44 g, 8.83 mmol) and pyridine (3 mL) in CH_2Cl_2 (10 mL) at 0 °C was added triflic anhydride (2.0 mL, 11.9 mmol) *via* syringe. After 3 h, NaOH (5 M) was added and the organic layer was separated. The aqueous layer was extracted 3 times with hexanes, and the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. Bulb to bulb distillation afforded **7** (2.3 g, 88%), a colourless oil. R_f = 0.40 on silica gel (100% hexanes); IR (neat) 3101, 1578, 1466, 1431, 1218, 1141, 1038, 917, 821, 587 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.52 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 2.9 Hz), 7.15 (1H, dd, J = 8.8, 2.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 134.0, 133.0, 131.5, 123.6, 120.8, 118.6 (q, J^{C-F} = 320.8 Hz).

3,4-dichlorophenyltrimethyltin (8). To LiCl (2.1 g, 50 mmol) was added a solution of **7** (2.20 g, 7.45 mmol) in THF (5 mL), hexamethylditin (2.7 g, 8.2 mmol) in THF (5 mL), and $Pd(PPh_3)_4$ (160 mg, 0.150 mmol) in THF (5 mL). The solution was heated to reflux for 4 d. Upon cooling, phosphate buffer is added (pH 7, 40 mL) and the organic layer was separated. The slurry was extracted 3 times with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Chromatography on silica gel yielded **8** (1.14 g, 49%), a colourless oil. R_f = 0.67 on silica gel (100% hexanes); IR (neat) 2981, 1460, 1356, 1130, 1031, 775, 721, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, dt, J = 20.5[Sn-H], 8.8 Hz), 7.37 (1H, dt, J = 7.7, 4.4[Sn-H] Hz), 7.25 (1H, dd, J = 7.7, 1.1 Hz), 0.30 (9H, t, J = 16.7[Sn-H] Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 137.1 (t, J^{Sn-C} = 19.8 Hz), 134.7 (t, J^{Sn-C} = 17.6 Hz), 132.4, 132.4, 129.9 (t, J^{Sn-C} = 23.3 Hz), -9.3; HRMS calcd for $C_8H_9SnCl_2$ $(M-CH_3)^+$: 294.9103. Found: 294.9090.

(*R*)-1-*tert*butyldiphenylsiloxy-4-(3,4-dichloro-phenyl)-1,2-dihydro-naphthalene (9). A flame dried round bottomed flask fitted with a condenser was charged with $(MeCN)_2PdCl_2$ (6.7 mg, 0.026 mmol) and $AsPh_3$ (31.0 mg, 0.101 mmol). Degassed NMP (2 mL) was added and the solution was stirred at rt. A solution of **5** (197 mg, 0.485 mmol) and **8** (160 mg, 0.517 mmol) in degassed NMP (2 mL) was added *via* cannula. The solution was heated at 80 °C in an oil bath for 1.5 h, allowed to cool, and partitioned between saturated K_2CO_3 in water and hexanes. The organic layer was separated and the aqueous layer was extracted three times with hexanes. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Chromatography on silica gel using hexanes yielded **9** (135 mg, 55%), a colourless oil. R_f = 0.25 on silica gel (100% hexanes); $[\alpha]^{25}_D$ = 15.2° (c= 4.2, PhH); IR (neat) 3060, 2942, 2856, 2277, 1586, 1471, 1430, 1389, 1360, 1196, 1106, 1029, 946, 820, 741, 700 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.81 (2H, m), 7.76 (2H, m), 7.68 (1H, d, J = 17.3 Hz), 7.38 (1H, m), 7.16-7.24 (7H, m), 7.04 (2H, m), 6.85 (1H, dd, J = 7.7, 1.1 Hz), 6.69 (1H, dd, J = 8.2, 2.0 Hz), 5.33 (1H, dd, J = 5.3, 3.8 Hz), 5.08 (1H, dd, J = 10.3, 5.7 Hz), 2.36 (1H, ddd, J = 16.5, 10.3, 4.0 Hz), 2.09 (1H, ddd, J = 16.5, 5.5, 5.5 Hz), 1.21 (9H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 140.6, 139.1, 137.9, 136.2, 136.1, 135.8, 134.8, 134.0, 133.7, 132.7, 131.4, 130.8, 130.4, 130.2, 130.1, 128.1, 127.9, 127.8, 125.9, 125.6, 70.3, 33.3, 27.3, 19.8; HRMS calcd for $C_{28}H_{21}OSiCl_2$ $(M-C_4H_9)^+$: 471.0739. Found: 471.0739.

(*R*)-4-(3,4-dichloro-phenyl)-1,2-dihydro-naphthalen-1-ol (10). A flame-dried round bottomed flask was charged with **9** (48 mg, 0.091 mmol), and THF (1 mL). Tetrabutylammonium fluoride hydrate (36 mg, 0.13 mmol), premixed with glacial acetic acid (5.5 mg, 0.092 mmol), in THF (1 mL) was added to **9** *via* cannula. The reaction was stirred at 0 °C and allowed to warm to rt over 1 h, then left to stir for 3 d. The reaction was partitioned between Et_2O and saturated K_2CO_3 and the aqueous layer was extracted three times with Et_2O. The organic layers were combined, washed with brine, and dried over Na_2SO_4. Removal of solvent and chromatography on silica gel using hexanes:EtOAc (4:1) gave **10** (26 mg, 98%). Recrystallization from ether/pentane gives a white solid. R_f = 0.23 on silica gel (hexanes:EtOAc 4 : 1); mp 107-109°C (Et_2O/pentane); $[\alpha]^{25}_D$= 43.2° (c= 1.3, $CHCl_3$); IR (neat) 3352, 2928, 2360, 1652, 1558, 1470, 1457, 1114, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.48 (3H, m), 7.30 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 7.24 (1H, ddd, J = 7.5, 7.5, 1.4 Hz), 7.18 (1H, dd, J = 8.2, 2.0 Hz), 7.01 (1H, dd, J = 7.7, 1.2 Hz), 6.01 (1H, dd, J = 4.5, 4.5 Hz), 4.83 (1H, m), 2.68 (1H, m), 2.68 (1H, m), 1.87 (1H, d, J = 6.2 Hz, disappears with D_2O); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 140.1, 137.5, 137.5, 132.7, 132.4, 131.4, 130.6, 130.3, 128.3, 128.2, 128.1, 126.7, 125.6, 125.2, 67.8, 32.8; HRMS calcd for $C_{16}H_{12}OCl_2$: $(M)^+$: 290.0265. Found: 290.0267.

(*1R, 4S*)-4-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-ol (11). To a flame-dried round bottomed flask was transferred $[Ir(COD)(py)PCy_3]PF_6$ (6.0 mg, 0.0065 mmol) under an inert atmosphere. A second flame-dried round bottomed flask was charged with **10** (19 mg, 0.065 mmol) and then 0.5 mL of freshly distilled degassed CH_2Cl_2. This solution was transferred *via* cannula to the flask containing the catalyst and the resulting orange solution was transferred *via* cannula to a sleeve in the hydrogenation bomb and 1000 psi of hydrogen was applied. After 3 h, the solvent was removed *in vacuo*, the residue dissolved in ether and filtered through a pad of silica. Chromatography on silica gel using hexanes:EtOAc (4:1) yielded **11** (16.8 mg, 88%). R_f = 0.23 on silica gel (hexanes:EtOAc 4 : 1); $[\alpha]^{25}_D$= 5.0° (c= 0.5, $CHCl_3$); IR (KBr) 3359, 2933, 1468, 1395, 1130, 1038, 965, 820, 764, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 7.3 Hz), 7.31 (1H, d, *J* = 8.4 Hz), 7.26 (1H, m), 7.16 (1H, ddd, *J* = 7.6, 7.4, 1.1 Hz), 7.10 (1H, d, *J* = 2.2 Hz), 6.81-6.85 (2H, m), 4.88 (1H, m), 4.13 (1H, t, *J* = 6.2 Hz), 2.35 (1H, m), 2.11 (1H, m), 1.73-1.83 (3H, m, reduced to 2H with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.6, 137.7, 132.3, 130.5, 130.2, 130.1, 129.9, 128.1, 128.0, 127.9, 127.2, 68.2, 44.5, 30.0, 28.9; HRMS calcd for $C_{16}H_{14}OCl_2$ $(M)^+$: 274.0316 Found: 274.0313.

(*1S, 4S*)-1-azido-4-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalene (12). To a flame-dried round bottomed flask containing **11** (135 mg, 0.460 mmol) was added diphenylphosphorylazide (170 mg, 0.618 mmol) in 1 mL THF, followed by a 0.5 mL wash. The reaction was stirred 5 min and cooled to 0 °C. DBU (0.09 mL, 0.620 mmol) was added *via* syringe and the reaction was allowed to warm to rt overnight. The reaction was partitioned between distilled water and ether and the aqueous layer was extracted three times with ether. The organic layers were combined and washed with brine, dried over Na_2SO_4 and concentrated. Chromatography on silica gel using pentane:ether (4:1) yielded **12** (129 mg, 88%). R_f = 0.37 on silica gel (pentane:Et_2O 4:1); $[\alpha]^{25}_D$= -22.9° (c= 0.7, $CHCl_3$); IR (KBr) 2942, 2096, 1471, 1395, 1238, 1131, 1030, 822, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 8.0 Hz), 7.32 (1H, dd, *J* = 7.7, 1.4 Hz), 7.23-7.28 (2H, m), 7.19 (1H, ddd, *J* = 7.7, 7.3, 1.8 Hz), 6.93 (1H, dd, *J* = 8.4, 2.2 Hz), 6.83 (1H, d, *J* = 8.0 Hz), 4.64 (1H, br s), 3.99 (1H, dd, *J* = 6.6, 6.2 Hz), 1.97 - 2.14 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 138.7, 132.9, 132.4, 130.6, 130.6, 130.5, 130.1, 129.4, 128.7, 128.0, 126.9, 59.5, 44.9, 28.7, 27.9; HRMS calcd for $C_{16}H_{13}NCl_2$ $(M\text{-}N_2)^+$: 289.0425 Found: 289.0435.

(*1S, 4S*)-1-(N-methylamino)-4-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalene (3). A flame dried round bottomed flask was charged with 10% palladium on carbon (5 mg, 0.004 mmol) to which was added **12** (12 mg, 0.038 mmol) dissolved in EtOH (2 mL) *via* cannula. A hydrogen balloon was attached and the reaction allowed to stir for 1 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude mixture was dissolved in acetonitrile (2 mL) and transferred to a flask containing K_2CO_3 (60 mg, 0.434 mmol). Ethyl chloroformate (0.05 mL, 0.52 mmol) was added *via* syringe and the reaction was heated to reflux for two hours. After cooling, the reaction mixture was partitioned between Et_2O and water and the aqueous layer extracted three times with Et_2O. The organic layers were combined, washed with brine and dried over Na_2SO_4. Concentration *in vacuo* gave a crude oil which was dissolved in THF and added to a solution of $LiAlH(OMe)_3$, preformed from $LiAlH_4$ (20 mg, 0.53 mmol) and MeOH (50 mg, 1.58 mmol). The solution was heated at reflux for 40 h. After cooling, the reaction was quenched (inverse addition at 0 °C) into saturated

K_2CO_3 and Et_2O and the aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by column chromatography on silica gel using acetone as eluent, giving **3** (10 mg, 87%). The optical rotation was: $[\alpha]^{25}D$= +39.7° (c= 0.3, CH_3OH/HCl) (literature value: +40.2°) and all other spectral data was identical in all other respects with the reported data.[26]

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