General Strategy toward the Tetrahydronaphthalene Skeleton. An Expedient Total Synthesis of Sertraline

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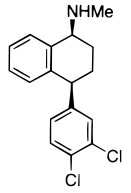
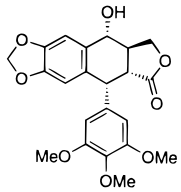
Received June 19, 1997

The enantioselective synthesis of therapeutically important molecules remains a major focus of attention among organic chemists. Particularly appealing is the notion of using asymmetric catalysis to control the absolute stereochemistry of newly generated stereocenters. A large number of bioactive molecules possess a tetrahydronaphthalene core (e.g., the antidepressant sertraline,[1] **1**, and the anticancer agent podophyllotoxin,[2] **2**), and we now report a general method for the enantioselective synthesis of this important skeleton.

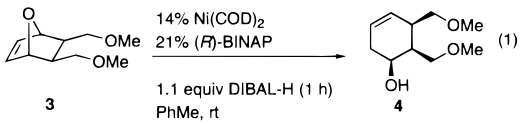


1



2

Recently, we reported that nickel−phosphine complexes catalyze the regioselective and enantioselective reductive ring opening of oxabicyclic alkenes.[4] For example, the reaction of **3** with a DIBAL-H and $Ni(COD)_2$/BINAP system gave the substituted cyclohexenol **4** in 95% yield and 97% ee (eq 1).

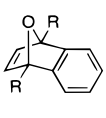
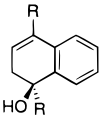
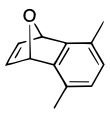
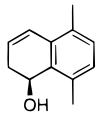
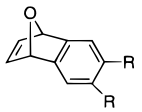
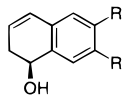


3 **4** (1)

Subjecting **5**[3] to our enantioselective hydrometalation/fragmentation sequence would afford **6**, which has the requisite functionality in place to use as a central template for the synthesis of a variety of substituted tetrahydronaphthalenes.

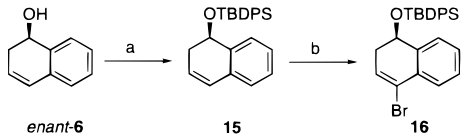
Reacting **5** under the previously described conditions in toluene gave a complex mixture of products including **6** in modest ee, entry 1, Table 1. However, changing the solvent from toluene to THF gave much better results, perhaps because of the reduced Lewis acidity of DIBAL-H in THF, entry 3. Alcohol **6**, a formal hydrate of naphthalene, is surprisingly stable to dehydration[6] and can be purified by column chromatography on silica gel.

Table 1. Enantioselective Ring Opening of Oxabenzonorbornenes

Entry[a]	Subtrate	Solvent	Time[b]	Product	Yield[c]	ee[d]
						
1	**5** R=H	PhMe	1	**6** R=H	33	60
2[e]	**5**	PhMe	24	**6**	70	60
3	**5**	THF	2	**6**	88	98
4	**7** R=Me	THF	16	**8** R=Me	66	73
5						
	9	THF	2	**10**	73	88
6	 **11** R=OCH_2O	THF	3	 **12** R=OCH_2O	58	94
7	**13** R=F	THF	3	**14** R=F	84	96

[a] All reactions were run in the presence of 14 mol % $Ni(COD)_2$ and 21 mol % (*R*)-BINAP at room temperature unless otherwise noted. [b] Addition of DIBAL-H to a solution of $Ni(COD)_2$, (*R*)-BINAP, and the alkene *via* syringe pump. [c] Isolated yield. [d] Measured by capillary GC (Chiraldex G-TA or B-TA column) or chiral HPLC (Chiracel OD or OJ column). [e] Hydroalumination at −40 °C.

Scheme 1[a]



enant-**6** **15** **16**

[a] Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, DMAP, 88%; (b) Br_2, CH_2Cl_2, Et_3N, 0 °C then DBU, PhH, 83%.

In light of the limited methods available for the synthesis of compounds of general structure **6**, the scope of this reaction was investigated. Substituents at the allylic bridgehead position lead to a decrease in enantioselectivity, entry 4, Table 1. However, better enantioselectivity is observed with substrates bearing methyl substituents distal to the olefin as was seen with substrate **9** (88% ee). We also studied the electronic effects of substituents on the aromatic ring. Subjecting the 1,3-dioxolane-substituted oxabicyclic **11** to the reaction conditions leads to **12** in 94% ee. We noticed a drop in chemical yield to 58% for **12**, likely owing to increasing ease of dehydration. Significantly, the presence of two electron-withdrawing fluorine substituents in compound **13** leads to no discernible change in enantioselectivity (96% ee), indicating the reaction is insensitive to electronic effects on the aromatic ring.

In order to illustrate the utility of alcohol **6** in the synthesis of bioactive products, we undertook the total synthesis of the clinically important antidepressant agent sertraline.

To access **1**, we required *enant*-**6**, readily available from **5** using (*S*)-BINAP as the ligand. On a 7.7 mmol scale, the use of 1.9 mol % of $Ni(COD)_2$ and 3.3 mol % of (*S*)-

(1) (a) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508. (b) Williams, M.; Quallich, G. *Chem. Ind. (London)* **1990**, *10*, 315. (c) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239. (d) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (e) Johnson, B. M.; Chang, P.-T. L. *Anal. Profiles Drug Subst.* **1996**, *24*, 443.

(2) Kamal, A.; Gayatri, N. L. *Tetrahedron Lett.* **1996**, *37*, 3359 and references therein.

(3) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599.

(4) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. For an early attempt at asymmetric hydroalumination see: Giacomelli, G.; Bertero, L.; Lardicci, L. *Tetrahedron Lett.* **1981**, *22*, 883.

(5) For a racemic route to **6** from **5**, see: Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 3002. Alcohol **6** has been isolated in high ee from the microbial oxidation of dihydronaphthalene (62% yield). (a) Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P.; Jenkins, R. O. *J. Chem. Soc., Chem. Commun.* **1989**, 339. (b) Boyd, D. R.; Sharma, N. D.; Kerley, N. A.; McMordie, R. A. S.; Sheldrake, G. N.; Williams, P.; Dalton, H.; *J. Chem. Soc., Perkin Trans. 1* **1996**, 67.

(6) For a study of the relative tendencies of some aromatic hydrates to aromatize, see: Rao, S. N.; More O'Ferrall, R. A.; Kelly, S. C.; Boyd, D. R.; Agarwal, R. *J. Am. Chem. Soc.* **1993**, *115*, 5458.

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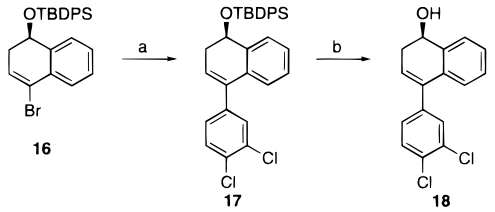
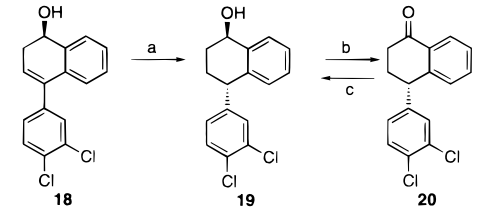
Scheme 2[a]



[a] Reagents and conditions: (a) 5% $(MeCN)_2PdCl_2$, 20% $AsPh_3$, (3,4-diCl)$C_6H_3SnMe_3$, NMP, 80 °C, 1.5 h, 55%; (b) TBAF, THF, AcOH, 3 d, quant.

Scheme 3[a]



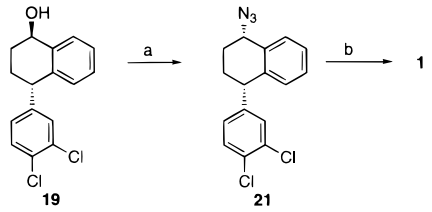
[a] Reagents and conditions: (a) 10 mol % [Ir(COD)pyPCy$_3$]PF_6, H_2 (1000 psi), CH_2Cl_2, 88%, 28:1; (b) activated MnO_2, $CHCl_3$, quant; (c) $NaBH_4$, EtOH, quant, 1.1:1.

BINAP led to an 88% yield of *enant*-**6** with an ee of 91%. Recrystallization of the alcohol from hexanes gave *enant*-**6** in 98% ee. Protection of the alcohol as its silyl ether proceeded in 88% yield using TBDPSCl (TBDPSCl = *tert*-butyl diphenylsilyl chloride) in the presence of imidazole and DMAP, Scheme 1. Treatment of the silyl ether **15** with bromine in CH_2Cl_2 at 0 °C[7] gave the dibromide, which was not isolated but instead immediately treated with an excess of diazabicycloundecene (DBU) to give the vinyl bromide **16** in 83% isolated yield. We found that both **15** and **16** were prone to elimination, so on scale-up, the silylation and bromination/dehydrobromination steps were done without purification of intermediates, giving rise to **16** in 88% isolated yield from the alcohol *enant*-**6**.

The vinyl bromide **16** was subjected to a palladium-catalyzed Stille cross coupling with a suitably substituted arylstannane, Scheme 2. A number of typical Stille coupling conditions were examined, but the best yields were obtained using Farina's conditions (triphenylarsine as ligand and *N*-methylpyrrolidinone (NMP) as solvent).[8] Under these conditions, the coupling proceeded to completion at 80 °C in 1.5 h. Longer reaction times or higher temperatures led to formation of significant amounts of the substituted naphthol arising from dehydrogenation of the product by the palladium catalyst. The product was isolated in only 55% yield due to the extreme sensitivity of the silyl ether **17** to elimination, and in fact, higher yields were realized by treatment of the crude reaction mixture with tetrabutylammonium flouride/acetic acid to give the alcohol **18** in a 64% overall yield from **16**. Acetic acid was an essential additive in order to avoid aromatization via elimination of silanol.

A directed hydrogenation reaction was used in order to control the stereochemistry of the carbon bearing the dichloroaryl group. While significant precedent exists for the rhodium- and iridium-catalyzed directed hydrogenations of substituted cyclohex-3-en-1-ols, the selectivity in a nearly planar system such as **18** was less well documented.[9] Treatment of **18** with Brown's cationic rhodium catalyst (1 mol % [Rh(NBD)dppb]BF_4) in CH_2Cl_2 led to

Scheme 4[a]



[a] Reagents and conditions: (a) dppa, DBU, THF, 88%, 98:2; (b) (i) H_2, Pd−C, EtOH, (ii) $ClCO_2Et$, MeCN, K_2CO_3, (iii) $LiAlH(OMe)_3$, THF, reflux, 40 h, 86%.

complete consumption of the starting material at 1000 psi of hydrogen. A 10:1 mixture of **19** and its epimer was obtained along with a second unidentified side product. Purification by chromatography gave **19** in 74% yield (Scheme 3). Crabtree's catalyst (10 mol % [Ir(COD)py-PCy$_3$]PF_6) gave **19** in better yield (88%) and with higher selectivity (28:1).[10]

Oxidation of **19** with MnO_2 gave tetralone **20** which represented a formal synthesis of sertraline.[11] However, the subsequent reductive amination gave sertraline and its epimer in a 3:1 ratio. Our route, via **19**, provided an opportunity to introduce the amine via a stereoselective displacement reaction using conditions developed by Thompson and co-workers.[12] Reaction of diphenylphosphoryl azide [dppa] in THF followed by the addition of DBU gave the azide **21** in 88% yield and 98:2 selectivity (Scheme 4). The azide was reduced to the free amine, which was then treated with ethyl chloroformate and subsequently reduced with $LiAlH(OMe)_3$ in refluxing THF. This protocol was done without isolation of intermediates and afforded sertraline, **1**, in 86% overall yield from the azide.

In summary, we have illustrated that the oxabenzonorbornadienes are excellent substrates for the nickel-catalyzed hydroalumination reaction, and the products are promising precursors to a wide range of biologically important compounds. We have shown that significantly less catalyst (2 mol %) can be employed than reported in our original disclosure (14 mol %). A total synthesis of the important antidepressant sertraline has been achieved in eight steps with an overall yield of 33% starting from the oxabenzonorbornadiene **5**.

Acknowledgment. The E. W. R. Steacie Memorial Fund and the NSERC of Canada are thanked for financial support. T.R. thanks NSERC for a postgraduate scholarship. We thank Professor R. H. Morris and C. Forde for technical help in the preparation of Crabtree's catalyst and Professor S. V. Ley for first bringing sertraline to our attention.

Supporting Information Available: Experimental procedures and spectral data for all new compounds reported herein (33 pages).

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(7) Willems, A. G. M.; Pandit, U. K.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 389.

(8) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73 and references therein.

(9) For a review on the directed homogeneous hydrogenation, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. For a recent review encompassing directed hydrogenations, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. Following completion of our work, a report appeared in the literature describing the use of the cationic rhodium complex in the directed hydrogenation of a dihydronaphthalenol: Kuroda, T.; Takahashi, M.; Kondo, K.; Iwasaki, T, *J. Org. Chem.* **1996**, *61*, 9560.

(10) For a seminal reference, see: Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. For a synthesis of Crabtree's catalyst, see: Crabtree, R. H.; Morehouse, S. M. *Inorganic Syntheses*; Shreeve, J. M., Ed.; Wiley: New York, 1986; Vol. 24, p 173.

(11) Reduction yielded a 1.1:1 mixture of **19** and *epi*-**19**. Tetralone **20** exhibited spectral data identical to the reported values; see ref 1d above.

(12) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.