# The Enantioselective Synthesis of the Potent Dopamine D1 Agonist (1*R*,3*S*)-3-(1′-Adamantyl)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran (A77636)

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The synthesis of both enantiomers of the title compound is described. The corresponding racemic compound (±)-1 was previously shown to be a highly potent and selective dopamine D1 agonist. Key to the synthesis of the enantiomers was the oxazaborolidine-catalyzed asymmetric reduction of the α-bromomethyl ketone 12 which led to the optically enriched epoxide 7. An aryllithium addition to the epoxide followed by a diastereospecific cyclization to the isochroman system furnished compound 17, which was deprotected to afford (−)-1 with >99.5% optical purity.

In the past few years, the pharmaceutical industry has been under increasing pressure from the FDA to develop enantiomerically pure drugs instead of racemates. Chemists have achieved this goal in the past by relying on an enzymatic or chemical resolution of a racemic intermediate or final product. However, with many recent developments in the arena of asymmetric synthesis and catalysis,[1] the possibility of a commercially viable chiral synthesis has proven to be a reality.[2]

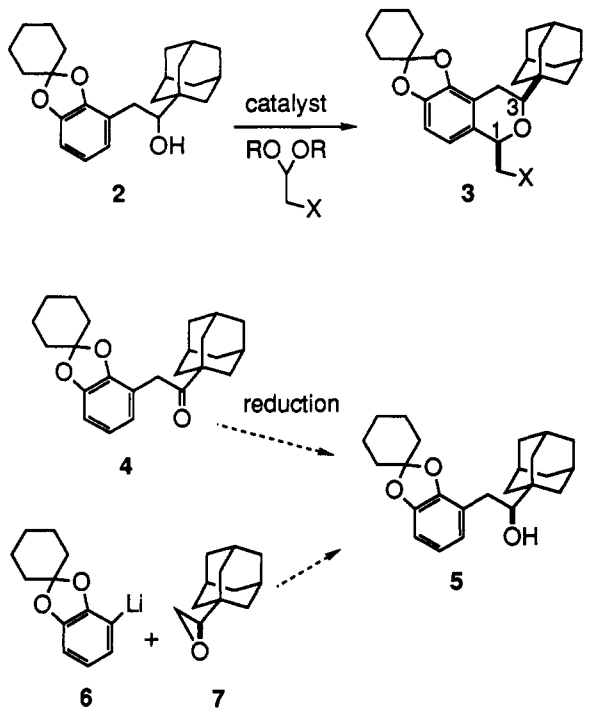
Our group has been focused on the development of selective D1 agonists for the treatment of Parkinson's Disease. We have recently reported on a series of isochroman-based agonists, and one of these, *cis*-3-(1′-adamantyl)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran (1) (Figure 1), was chosen for further development.[3] As part of the development process, an efficient asymmetric synthesis of 1 was desired that could supply multigram quantities of both enantiomers of the drug for further evaluation. This paper describes the results of this effort.

Our earlier work indicated that the cis product 3 is exclusively formed when a reaction between 2 and an aminoacetaldehyde synthon is undertaken (Scheme I).[3c] Thus, an asymmetric synthesis of 1 could be simplified to preparation of enantiomerically pure 2.

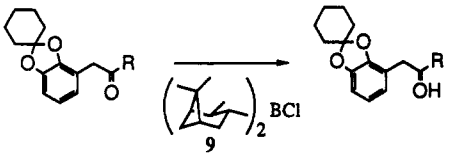
Two approaches were explored in this regard as shown in Scheme I. Alcohol 5 can be prepared either by asymmetric reduction of ketone 4, or by aryllithium addition to chiral epoxide 7. The former method was previously used to synthesize the 3-phenyl analogue, and thus was the first to be examined (Scheme II). Unfortunately, the *B*-chlorodiisopinocampheylborane reducing agent, 9,[4] which proved ideal for the reduction of compound 8,[3c] was unreactive toward the more hindered adamantane ketone 4, under a variety of conditions.[5]

The failure of this approach led us to explore other alternate chiral borane reducing agents on a variety of substrates. After examining the literature, and briefly screening several candidates, we selected the proline-derived oxazaborolidine 13 reported by Corey[5] for further evaluation. The three substrates that we focused on were compound 4 and the α-chloro and α-bromomethyl adamantane ketones 11 and 12 which were potential precursors of the chiral epoxide 7. The results of these studies are shown in Table I. Since the reduction of ketone 4 using catalyst 13 was also sluggish, this approach was abandoned. The reductions of 11 and 12 were both rapid, perhaps owing to the increased electrophilicity of the

**Scheme I**




**Scheme II**




**8** R = Ph
**4** R = 1-Adamantyl

**10** R = Ph, 78%, >95% ee
**5** R = 1-Adamantyl, No Rxn

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(1) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1983–1985; Vols. 1–5.

(2) Crosby, J. *Tetrahedron* **1991**, *47*, 4789.

(3) (a) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1990**, *33*, 2948. (b) DeNinno, M. P.; Schoenleber, R.; MacKenzie, R.; Britton, D. R.; Asin, K. E.; Briggs, C.; Trugman, J. M.; Ackerman, M.; Artman, L.; Bednarz, L.; Bhatt, R.; Curson, P.; Gomez, E.; Stittsworth, J.; Kebabian, J. W. *Eur. J. Pharmacol.* **1991**, *199*, 209. (c) DeNinno, M. P.; Schoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2561.

(4) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

0022-3263/92/1957-7115$03.00/0 

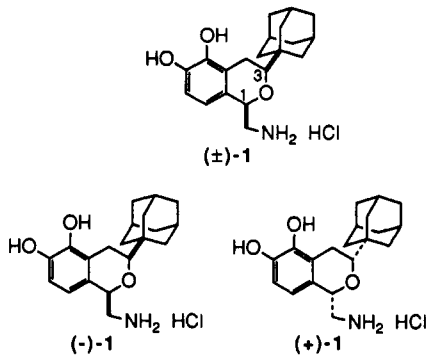
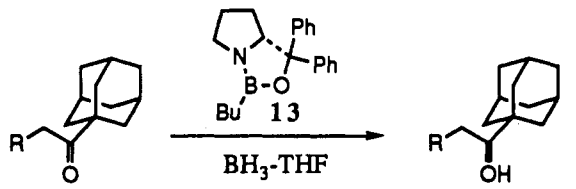
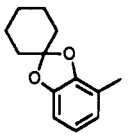



Figure 1.

**Table I. Enantioselective Reductions**[a]



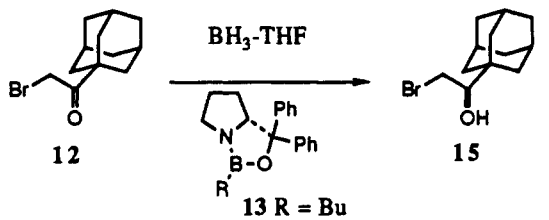

| ketone | R | product | yield (%) | % ee |
|---|---|---|---|---|
| 4 |  | 5 | 46 | 78.2 |
| 11 | Cl | 14 | >95 | 71.0 |
| 12 | Br | 15 | >95 | 89.4 |

[a] All reductions were run using 10 mol % of catalyst and 60 mol % of borane–THF complex in THF at rt.

carbonyl. However, we chose the commercially available bromomethyl ketone **12** for further development because of the higher ee's obtained in its reduction.

To optimize the enantioselectivity of the reduction, the reaction conditions were exhaustively explored. Some of the results of this study are shown in Table II. The variables adjusted in this reaction included catalyst load, temperature, substituent on boron, and solvent. Many of these findings are in concurrence with the results reported by Corey[6] on similar substrates. The less costly catalyst derived from phenylboronic acid (**16**) was also prepared, and it furnished products with slightly higher ee's than the corresponding *B*-butyl catalyst.[7] The optimal conditions for the reduction were 10 mol % of the *B*-phenyl catalyst **16** and 60 mol % of borane at room temperature in THF or toluene solvent. In this manner, the reduction proceeded in quantitative yield and 95% ee, based on HPLC analysis of alcohol product **15**.[8] The reaction ran equally well in THF or toluene which allows for the in situ preparation of the catalyst in toluene. The catalyst precursor, diphenylprolinol, is easily recovered in high yield as the HCl salt by quenching the reaction with ethereal HCl.

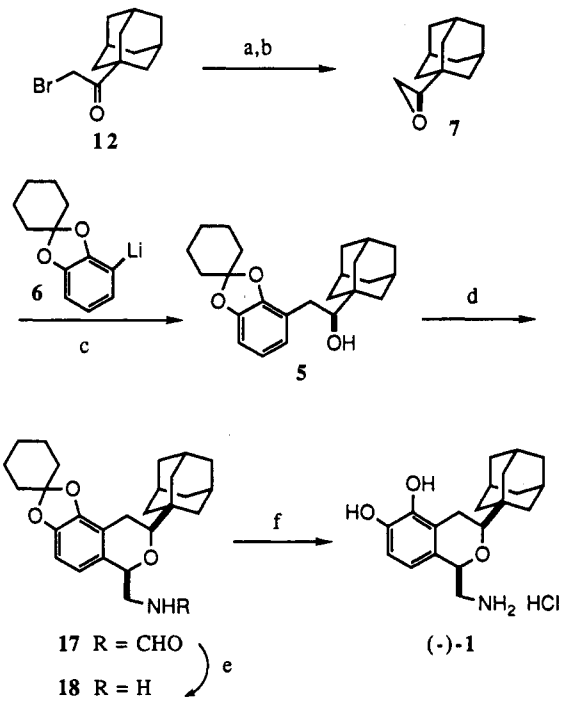
**Table II**[a]




| R | cat. mol % | temp (°C) | solvent | opt. purity % ee |
|---|---|---|---|---|
| butyl | 5 | 25 | THF | 87.5 |
| butyl | 10 | 25 | THF | 89.4 |
| butyl | 25 | 25 | THF | 94.8 |
| butyl | 10 | −20 | THF | 68.8 |
| butyl | 10 | 0 | THF | 82.6 |
| phenyl | 5 | 25 | THF | 89.4 |
| phenyl | 10 | 25 | THF | 94.6 |
| phenyl | 25 | 25 | THF | 96.2 |
| phenyl | 10 | 25 | toluene | 94.0 |

[a] All reactions were complete within 30 min in >95% yield.

**Scheme III**[a]




[a] Key: (a) 10 mol % of **16**, 60 mol % of $BH_3$–THF; (b) 2 N NaOH, $Et_2O$; (c) $BF_3{\cdot}OEt_2$, THF, −78 °C; (d) $(MeO)_2CHCH_2NHCHO$, 5 mol % of TMSOTf, $CH_3CN$; (e) 15% NaOH, THF, MeOH; (f) 5 N HCl in DME/1% $H_2O$.

With the reduction satisfactorily achieved, we addressed the remainder of the synthesis (Scheme III). Bromohydrin **15**, without purification, was partitioned between 2 N NaOH and ether and stirred vigorously for 12 h to effect complete conversion to epoxide **7**. The crude epoxide was added to a solution of the aryllithium derivative **6**[9] at −78 °C and, upon addition of 1 equiv of $BF_3{\cdot}OEt_2$, a rapid reaction ensued. After workup, product **5** was obtained

(5) No product could be observed in the reduction of **4** with **9** even under forcing conditions (i.e., 10 equiv of **9**, neat, 50 °C).

(6) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (d) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (e) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. Abstracts from the 203rd ACS National Meeting, San Francisco, 1992; Division of Organic Chemistry, Abstract No. 85.

(7) (a) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415. (b) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J., Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763.

(8) Bromohydrin **15** was analyzed as the corresponding 1-naphthoate derivative using chiral HPLC. See the Experimental Section for details.

(9) Boeckmann, J.; Schill, G. *Chem. Ber.* **1977**, *110*, 703.

as an oil which was determined to be ~95% ee, indicating that no racemization had occurred. Addition of methanol to the oil initiated crystallization to afford the pure alcohol **5** in 88% yield and 98.8% ee. One recrystallization from methanol (90% recovery) improved the enantiomeric purity to greater than 99.5% (limits of detection).[10]

The cyclization reaction was now investigated. This transformation (**5**–**17**) can be carried out efficiently using [(*N*-formylamino)methyl]acetaldehyde dimethyl acetal and 3 equiv of $BF_3$·$OEt_2$ in ether.[3c] However, the large excess of catalyst needed prompted a search for alternative conditions. The use of acetonitrile as solvent allowed the use of a variety of Lewis acids to effect the cyclization reaction including TMSOTf, $TiCl_4$, and $Zn(OTf)_2$. Furthermore, only 2–10 mol % of the catalyst was required. For the case at hand, a solution of the alcohol and acetal in acetonitrile was treated with five mol % TMSOTf and heated at reflux temperature for 4 h at which time the product began to precipitate. After cooling and filtering, the desired cis product **17** was isolated in 85% yield.

Although it was possible to cleave both the nitrogen and catechol protecting groups in one step using strong acid, we found a stepwise deprotection process to be higher yielding. Thus, the formamide was most efficiently hydrolyzed using base (2 N NaOH/MeOH/THF) to furnish the amine **18** in quantitative yield with no purification necessary. The cyclohexylidene protecting group could now be readily cleaved under acidic conditions (1% $H_2O$:5 N HCl/DME). After precipitation and recrystallization from ethanol/ether, the final product (−)-**1** was isolated in 80% yield. The enantiomeric excess of (−)-**1** was determined to be >99.5% by HPLC of the corresponding Mosher[10] amide. The absolute stereochemistry of the final product, initially inferred by analogy,[5] was verified by single-crystal X-ray analysis. The (1*S*,3*R*) enantiomer of **1** was synthesized in the same manner using the enantiomer of catalyst **16**.

In summary, an efficient enantioselective synthesis of both enantiomers of *cis*-3-(1′-adamantyl)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran has been accomplished. The key step in the synthesis was the chiral reduction of α-bromomethyl adamantane ketone en route to the enantiomerically enriched epoxide **7**. The ability to crystallize compound **5** to apparent enantiomeric purity was also crucial to the effort. The synthesis required six steps (three purifications) and proceeded in 50% overall yield. Nearly 50 g of each enantiomer has been synthesized, and the pharmacological profile of these isomers will be the subject of future publications.

## Experimental Section

**(1*S*)-1-(1′-Adamantyl)-2-[spiro[1,3-benzodioxole-2,1′-cyclohexane]]-1-ethanol (5).** Step 1. **1-Aza-2-boro-3-oxa-1,4,4-triphenylbicyclo[3.3.0]octane (16).** Diphenyl-((2*R*)-2′-pyrrolidinyl)methanol[6b] (7.3 g, 0.029 mol) and phenylboronic acid (3.52 g, 0.029 mol) were taken up in 290 mL of toluene. The reaction mixture was heated at reflux temperature for 4 h under $N_2$ using a Dean-Stark trap filled with 4A molecular sieves to remove water. The reaction was then cooled and concentrated in vacuo to afford the title compound as a colorless oil. The product was carried on to the next step without purification.

Step 2. **(1*R*)-1-(1′-Adamantyl)-2-bromo-1-hydroxyethane (15).** Borane in THF (173 mL of 1.0 M THF solution, 0.173 mol) was added dropwise over 10 min to a solution of 74.3 g (0.29 mol) of 1-adamantyl bromomethyl ketone (Aldrich Chemical Co.) and 1-aza-2-boro-3-oxa-1,4,4-triphenylbicyclo[3.3.0]octane (**16**, 9.8 g, 0.029 mol) in 350 mL of anhydrous THF. The reaction mxiture was stirred for 10 min at rt and then cooled to 0 °C in an ice bath and was quenched by the careful addition of 90 mL of methanol. Diethyl ether saturated with HCl (75 mL) was added, and the solution was allowed to warm to rt. The precipitated salt of the catalyst precursor was collected by filtration for recycling, and the filtrate was concentrated to one-third volume and then poured into 1 L of diethyl ether and 1 L of water. The organic layer was washed with 1 N aqueous HCl solution, aqueous saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 87 g (>100% yield) of the title compound as an oil which was used directly in the next reaction without purification.

Step 3. **(*R*)-(1′-Adamantyl)ethylene Oxide (7).** A 15% aqueous solution of NaOH (1 L) was added to a solution of 87 g (0.29 mol, crude from previous step) of bromohydrin **15**, in 2 L of diethyl ether. The mixture was stirred vigorously at rt for 18 h. The mixture was then diluted with 1 L of diethyl ether and 500 mL of water. The layers were separated, and the aqueous layer was reextracted with 500 mL of diethyl ether. The combined organic layers were washed with 2 × 500 mL of water and 500 mL of brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 52 g of the title compound. The product was carried on to the next step without purification.

Step 4. **(1*S*)-1-(1′-Adamantyl)-2-[spiro[1,3-benzodioxole-2,1′-cyclohexane]]-1-ethanol (5).** *n*-Butyllithium (139 mL of a 2.5 M solution in hexane, 0.348 mol) was added over 10 min to a solution of spiro(1,3-benzodioxole-2,1′-cyclohexane)[9] (66 g, 0.348 mol) in 400 mL of THF at 0 °C. The reaction mixture was allowed to warm to rt over a 0.5-h period and then stirred for 3.5 h at rt. The reaction mixture was cooled to −78 °C, and a solution of 52 g (0.029 mol) of epoxide **7** in 50 mL of THF was added. $BF_3$·$OEt_2$ (42.8 mL, 0.348 mol) was then added dropwise over 10 min. After 30 min, $NaHCO_3$ solution was added (500 mL) followed by 500 mL of ethyl acetate. The reaction mixture was allowed to warm to rt and transferred to a separatory funnel. Ethyl acetate (500 mL) and saturated aqueous $NaHCO_3$ solution (500 mL) were added to the funnel, and the layers were separated. The aqueous layer was reextracted with ethyl acetate. The combined organic layers were washed with 2 × 500 mL of aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to an oil. The crude product was dissolved in 500 mL of methanol, and the solution was cooled to 0 °C. The precipitate was collected by filtration and washed with cold methanol to give 95 g (89% yield) of the desired product. The title compound was recrystallized from methanol to give 85.6 g of the title compound, mp 72–73 °C: $[\alpha]_D$ = −27.75° (*c* 1.63, $CHCl_3$); DCI MS 386 (M + $NH_4$)$^+$; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.9 (q, 0.25 H, *J* = 6 Hz, MeOH solvate), 1.5–2.1 (m, 25 H), 2.5 (dd, 1 H, *J* = 13.5, 10.5 Hz), 2.87 (dd, 1 H, *J* = 13.5, 2.0 Hz), 3.3 (m, 1 H), 3.5 (d, 0.75 H, *J* = 6 Hz, MeOH solvate). Anal. Calcd for $C_{24}H_{32}O_3$+0.25 MeOH: C, 77.35; H, 8.83. Found: C, 77.09; H, 8.77.

**(1*R*,3*S*)-3-(1′-Adamantyl)-5,6-(cyclohexylidenedioxy)-3,4-dihydro-1-[(*N*-formylamino)methyl]-1*H*-2-benzopyran (17).** Trimethylsilyl triflate (2.22 mL, 0.0115 mol) was added to a mixture of 85 g (0.23 mol) of alcohol **5** and (*N*-formylamino)-acetaldehyde dimethyl acetal (46 g, 0.345 mol) in 500 mL of acetonitrile. The reaction mixture was heated at a gentle reflux for 2 h, and an additional 1 mL of trimethylsilyl triflate was added. A precipitate formed, and after 4 h the reaction mixture was cooled to 0 °C. The precipitate was collected by filtration, washed with cold acetonitrile, and dried to afford 86 g (85% yield) of the title compound as colorless crystals, mp 220–221 °C: $[\alpha]_D$ = −33.15° (*c* 1.63, $CHCl_3$); DCI MS 438 (M + H)$^+$; $^1$H NMR (300 MHz, $d_6$-DMSO) δ (140 °C) 1.5–2.05 (m, 25 H), 2.5 (m, 2 H), 2.8 (m, 1 H), 3.1 (dd, 1 H, *J* = 7.5, 3.0 Hz), 3.32 (m, 1 H), 3.71 (br s, 1 H), 4.65 (br s, 1 H), 6.6 (m, 2 H), 8.05 (br s, 1 H). Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.82; H, 8.10; N, 3.14.

**(1*R*,3*S*)-3-(1′-Adamantyl)-1-(aminomethyl)-5,6-(cyclohexylidenedioxy)-3,4-dihydro-1*H*-2-benzopyran (18).** A 15% solution of NaOH in water was added to a solution of formamide **17** (85 g, 0.194 mol) in 900 mL of methanol and 600 mL of THF. The mixture was heated at 50 °C for 3 h and then concentrated in vacuo to ~600 mL. The concentrated mixture was diluted with 1.5 L of EtOAc/$CH_2Cl_2$ (2:1) and 1 L of water. The layers were

(10) Alcohol **5** was analyzed without derivatization using chiral HPLC. See the Experimental Section for details.

(11) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

separated, and the organic layer was washed with 2 × 500 mL of water and 500 mL of brine. The combined aqueous layers were reextracted with EtOAc/$CH_2Cl_2$ (2:1) and discarded. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 79 g of the title compound as a light tan colored solid, mp 153–155 °C: $[\alpha]_D$ = −73.73° (c 1.58, $CHCl_3$); DCI MS 410 $(M + H)^+$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.5–2.05 (m, 25 H), 2.54 (dd, 1 H, J = 16.0, 4.0 Hz), 2.62 (dd, 1 H, J = 16.0, 11.0 Hz), 2.91 (dd, 1 H, J = 13.5, 6.5 Hz), 3.12 (dd, 1 H, J = 10.0, 4.0 Hz), 3.20 (dd, 1 H, J = 13.5, 3.0 Hz), 4.59 (m, 1 H), 6.49 (d, 1 H, J = 7.0 Hz), 6.60 (d, 1 H, J = 7.0 Hz). Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.36; H, 8.57; N, 3.33.

**(1*R*,3*S*)-3-Adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran Hydrochloride (−)-1.** A solution of anhydrous HCl in DME (900 mL of a 5 N solution) and 9 mL of $H_2O$ was added to amine 18 (74 g, 0.181 mol), and the reaction mixture was heated at reflux temperature for 3 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethanol (350 mL), and the product was triturated with ether (2 L). The precipitate was washed with ether and dried and then recrystallized from ethanol/ether to afford 53 g (80%) as colorless crystals, mp 220 °C: $[\alpha]_D$ = −69.4° (c 1.1, MeOH); DCI MS 330 $(M + H)^+$; $^1H$ NMR (300 MHz, $CD_3OD$) δ 1.65–2.05 (m, 15 H), 2.6 (dd, 1 H, J = 16.5, 12.0 Hz), 2.72 (dd, 1 H, J = 16.5, 3.0 Hz), 3.08 (dd, 1 H, J = 12.6, 7.5 Hz), 3.15 (dd, 1 H, J = 12.0, 3.0 Hz), 3.54 (dd, 1 H, J = 12.6, 3.2 Hz), 4.85 (m, 1 H), 6.5 (d, 1 H, J = 8.4 Hz), 6.69 (d, 1 H, J = 8.4 Hz). Anal. Calcd for $C_{20}H_{22}ClNO_3$ + 0.6 EtOH: C, 64.70; H, 8.09; N, 3.56. Found: C, 64.37; H, 7.81; N, 3.63.

**HPLC Separations.** Bromohydrin 15 was analyzed as the corresponding naphthoate ester prepared using 1-naphthoyl chloride and DMAP in $CH_2Cl_2$. The HPLC sample was prepared by preparative TLC (50- × 100- × 0.25-mm plate, 10% hexane/ethyl acetate eluant). The samples were analyzed on a Chiracel OD column using the following parameters: mobile phase, 98% hexane/2-isopropanol with 0.1% diethylamine; flow rate, 0.5 mL/min; UV detection (λ = 293 nM).

Alcohol 5 was analyzed without derivatization using the Chiralcel OD column with the following parameters: mobile phase, 98% hexane/2-propanol with 0.1% diethylamine; flow rate 0.5 mL/min; UV detection (λ = 280 nM).

Compound 1 was analyzed by standard HPLC by the Mosher amide method.[10] The amides were prepared using excess (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride and DMAP in DMF to ensure complete reaction. Without purification, the amides were injected on a C18 Rainin axial compression column under the following conditions: mobile phase, 30:70 (v/v) A:B (A = 0.01 M aqueous ammonium perchlorate, 0.1% trifluoroacetic acid, B = 25% methanol/acetonitrile); flow rate 1.5 mL/min; UV detection (λ = 275 nM).

**Acknowledgment.** We would like to thank Dr. Stephen Spanton of the Abbott Analytical Department for the X-ray crystallographic structure determination of compound (−)-1.

# Enantioselective Construction of Natural (+)-Pallescensin A. A Sigmatropic Pathway to Furanosesquiterpenes

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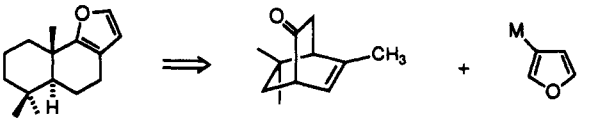
Addition of the cerium reagent derived from 3-lithiofuran and anhydrous $CeCl_3$ to optically pure bicyclic ketone 2 affords alcohol 4 selectively. Anionic oxy-Cope rearrangement of 4 in hot diglyme results in conversion to keto aldehyde 6, a consequence of β-elimination following upon the [3,3]sigmatropic event. Advantage was then taken of chemoselective acetalization and unidirectional introduction of an enone double bond. Regio- and stereoselective epoxidation of 8 was a prelude to formation of the furan ring by $BF_3$-etherate-promoted cyclization. Once the carbonyl group was reduced with alane, catalytic hydrogenation in the presence of diethylamine gave the title compound. An alternative scheme involving silylation of the furan ring as a protective maneuver, while entirely workable, was both less direct and less efficient.

Notwithstanding the extensive use that has been made of the anionic oxy-Cope rearrangement in natural product total synthesis,[1] the adaptation of furan derivatives to the convergent variant of this [3,3] sigmatropic process has been reported only once.[2] The ready availability of many functionalized furans[3] and the richness of the furanosesqui- and diterpene field[4] appeared to us to be factors well suited to amalgamation. The resulting initial thrust is exemplified herein by an enantioselective route to (+)-pallescensin A (1).




1 2 3

This marine metabolite was first isolated in 1975 from the sponge *Disidera pallescens* by Cimino and co-workers.[5] In the intervening years, 1 has been prepared on several occasions as either a racemate[6] or a pure enantiomer.[7,8]

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