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Synthesis of Diverse 2,3-Dihydroindoles, 1,2,3,4-Tetrahydroquinolines, and Benzo-Fused Azepines by Formal Radical Cyclization onto Aromatic Rings

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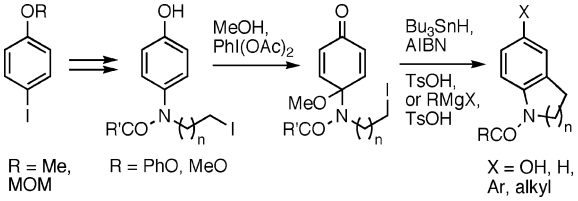
Received December 10, 2007



2,3-Dihydroindoles, 1,2,3,4-tetrahydroquinolines, and 2,3,4,5-tetrahydrobenzo[*b*]azepines are available by a process that represents formal radical cyclization onto aromatic rings. Optically pure benzo-fused heterocycles are also accessible by this method. *p*-Iodophenols, especially those with the phenolic oxygen protected as a MOM-ether, can be coupled with amino alcohols to produce *N*-aryl amino alcohols, which can be converted into the corresponding alkyl iodides in which the nitrogen is protected as a carbamate. These compounds give cross-conjugated ketones after removal of the phenolic protecting group and oxidation with $PhI(OAc)_2$ in the presence of MeOH. The ketones undergo 5-, 6- or 7-*exo*-trigonal radical cyclization, and then exposure to acid, or sequential treatment with a Grignard reagent and then acid, effects rearomatization to produce the benzo-fused nitrogen heterocycles.

Introduction

A number of benzo-fused nitrogen heterocyclic systems, such as 2,3-dihydroindoles and 1,2,3,4-tetrahydroquinolines, are of considerable interest as potential pharmaceutical agents because of their activity as various enzyme inhibitors, receptor ligands, and hormone release promotors.[1,2] We describe here a general method for the synthesis of such compounds, including optically pure materials, by a route that formally constitutes an oxidative radical cyclization onto a benzene ring.[3] A broad range of derivatives is available by simple modification of this route.

While the cyclization of sp^3 and sp^2 carbon radicals onto double and triple bonds is an integral part of synthetic methodology, radical cyclization onto benzene rings along the lines summarized in Scheme 1 is a far less developed subject, notwithstanding the fact that it can be useful in preparing important benzo-fused compounds. Examples where the acceptor aromatic ring is a heterocycle are fairly well-known[4] and, for benzene rings, there are a growing number of reports[5,6] in which the attacking radical is sp^2 hybridized. However, there does not appear to be a general method to deal with direct closure of sp^3-hybridized carbon onto carbocyclic aromatic rings. Although some examples of this type are indeed known, the mechanism for the rearomatization (cf. **2** → **3**) is poorly understood.[7] The

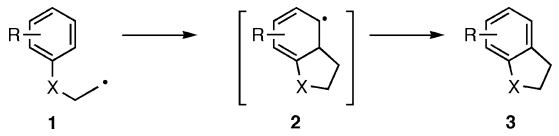
(1) See, for example: Kinase inhibitors: Adams, J. L.; Bryan, D. L.; Kasparec, J.; King, F. D.; Takle, A. K.; Wilson, D. M.; Goodman, S. N. WO 2004043379, 2004. Histamine H3 receptor antagonists: Beavers, L. S.; Finley, D. R.; Gadski, R. A.; Hipskind, P. A.; Jesudason, C. D.; Pickard, R. T.; Stevens, F. C. WO 2004026837, 2004. 2,3-Oxidosqualene-lanosterol cyclase inhibitors: Aebi, J.; Ackermann, J.; Chucholowski, A.; Dehmlow, H.; Morand, O.; Wallbaum, S.; Weller, T.; Panday, N. WO 2002050041, 2002. Growth hormone release promoters: Tokunaga, T.; Nagata, T. JP 11292894, 1999. Treatment for dementia: Greig, N. H.; Shaw, K. T. Y.; Yu, Q.-S.; Holloway, H. W.; Utsuki, T.; Soncrant, T. T.; Ingram, D. S.; Brossi, A.; Giordano, A.; Powers, G.; Davidson, D.; Sturgess, M. WO 2002048150, 2002. Dopamine D4 receptor ligands: Perregaard, J. K.; Bang-Andersen, B.; Pedersen, H.; Mikkelsen, I.; Dancer, R. WO 9828293, 1998. Estrogen receptor modulators: Wallace, O. B. WO 2002094788, 2002.

(2) For recent advances in the preparation of indolines, see, for example: (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776−5777. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264−14265. For recent advances in the preparation of tetrahydroquinolines, see, for example: (c) Legros, J.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899−1902. (d) Nagarajan, R.; Magesh, C. J.; Perumal, P. T. *Synthesis* **2004**, 69−74. (e) Jia, X.; Lin, H.; Huo, C.; Zhang, W.; Lü, J.; Yang, L.; Zhao, G.; Liu, Z.-L. *Synlett* **2003**, 1707−1709.

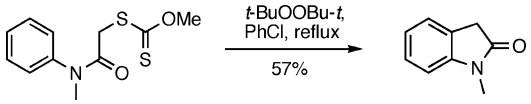
(3) Preliminary communication: Fletcher, S. P.; Clive, D. L. J.; Peng, J.; Wingert, D. A. *Org. Lett.* **2005**, *7*, 23−26.

10.1021/jo7026307 CCC: $40.75
Published on Web 02/16/2008

SCHEME 1. Radical Cyclization onto a Benzene Ring

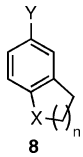


SCHEME 2. Xanthate Method for Radical Cyclization onto a Benzene Ring



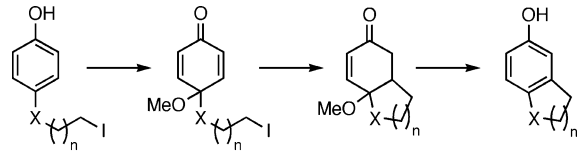
most effective procedure is the use of xanthates (see Scheme 2).[8−10] This powerful method relies on the formation of a radical that is more stable than Me• (or Et•, if an ethyl xanthate is used).[8i]

Several years ago, an indirect but general method for achieving the overall transformation shown in Scheme 1 was developed in this laboratory along the lines shown in Scheme 3.[11] The essential steps involve conversion of a phenol into a cross-conjugated ketone (**4** → **5**), which readily undergoes classical radical closure. The product is then rearomatized by treatment with acid (**6** → **7**).

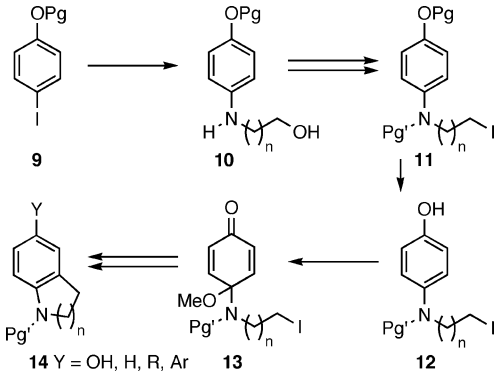


A noteworthy feature of this approach is the fact that the intermediate enone **6** can be reduced with $NaBH_4$ or treated with a Grignard reagent so as to form, after the rearomatization step, aromatic systems of type **8**, where Y = H, alkyl, or aryl. These possibilities greatly extend the types of compound that can be made and more than offset the requirement that the starting material be a phenol.

SCHEME 3. Indirect Radical Cyclization onto a Benzene Ring



SCHEME 4. Formation of Benzo-Fused Nitrogen Heterocycles



The principles summarized in Scheme 3 were applied to the formation of benzo-fused oxygen[11] and nitrogen[3] heterocycles, and have recently been extended[12] in a modified form to the generation of benzo-fused carbocycles. The required radicals are generated from iodides, and we have used the radical cyclization to produce five-, six-, and seven-membered rings. Full details and applications of this method for making oxygen heterocycles have been published,[11] and we describe here our work on the more valuable nitrogen case, which affords, among other compound types, derivatives of dihydroindoles and tetrahydroquinolines. As indicated above, some compounds of type **8**, where X = N, have potentially valuable biological properties.[1,2]

Results and Discussion

To extend our original studies on oxygen heterocycles to the nitrogen series, we had to identify a reliable method for making the amino phenols **12** (Scheme 4) as well as the derived cross-conjugated ketones **13**. This task entailed a good deal of exploratory work since the route had to satisfy a number of closely linked requirements in a mutually compatible way. Access to the cross-conjugated ketones requires the preparation of *p*-amino phenols **12** carrying on nitrogen both a protecting

(4) Typical examples of alkyl radical cyclization onto heteroaromatic rings: (a) Murphy, J. A.; Sherborn, M. S. *Tetrahedron* **1991**, *47*, 4077−4088. (b) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639−2643. (c) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111−8128. (d) Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett.* **2000**, *41*, 381−384. (e) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181−10184. (f) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (g) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191−4193. (h) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345−4348. (i) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671−3674. (j) Storey, J. M. D.; Ladwa, M. M. *Tetrahedron Lett.* **2006**, *47*, 381−383. (k) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875−1878.

(5) Leading references to cyclization of aryl radicals onto aromatic rings: Clyne, M. A.; Aldabbagh, F. *Org. Biomol. Chem.* **2006**, *4*, 268−277.

(6) Examples of cyclization of vinyl radicals onto aromatic rings: (a) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765−1768. (b) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 3105−3108. (c) Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615−10618.

(7) (a) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98. (c) Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706−13707.

(8) (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719−1722. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759−1762. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295−7298. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125−2126. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533−2536. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731−733. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 1692−1693. (h) Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 2306−2307. (i) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663−668.

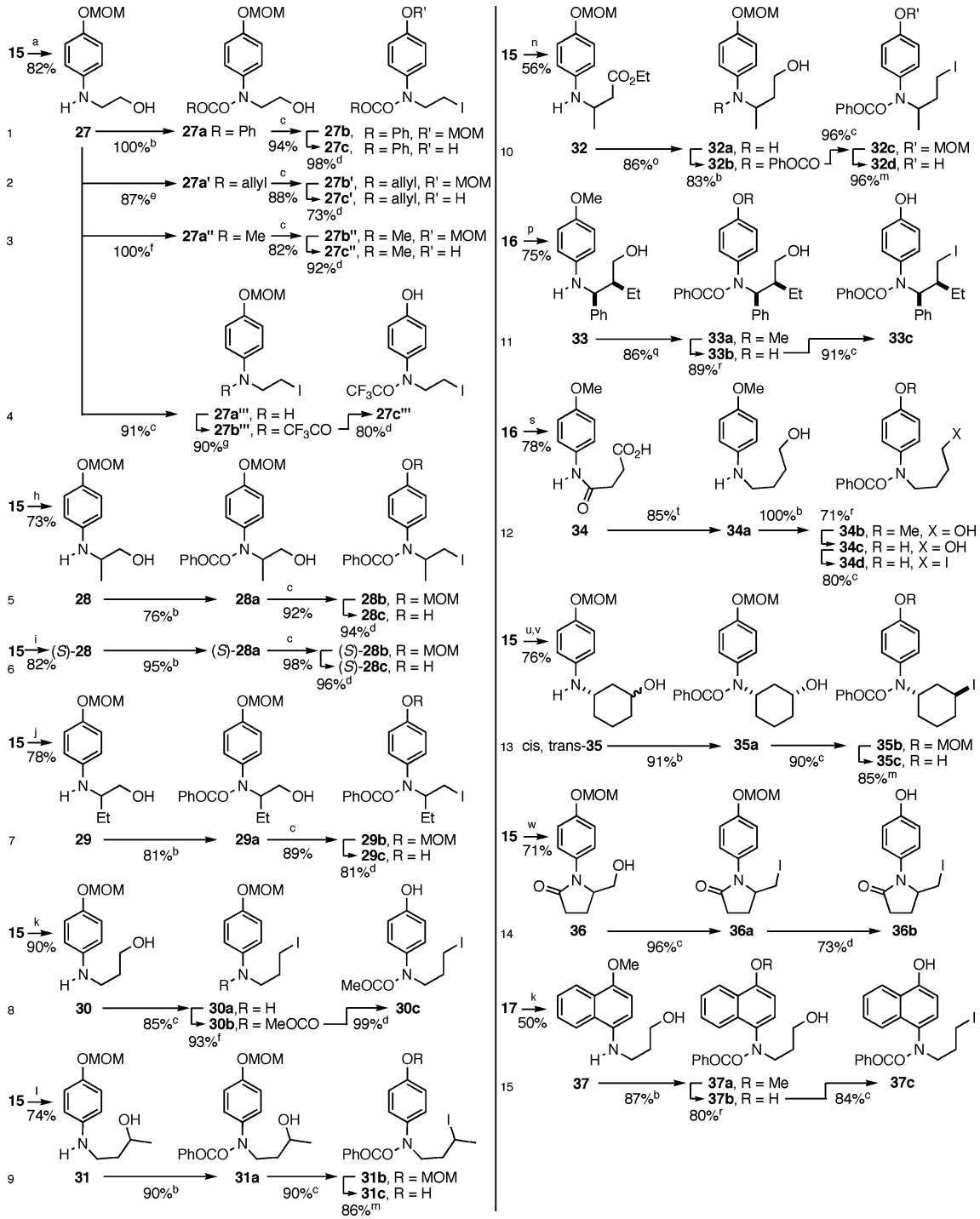
(9) For cyclizations of β-dicarbonyl compounds see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363.

(10) For methods that do not involve xanthates see: (a) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781−1784. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (c) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977−978.

(11) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282−3293.

(12) Clive, D. L. J.; Sunasee, R. *Org. Lett.* **2007**, *9*, 2677−2680.

TABLE 1. Preparation of Iodides from Protected Phenols, with and without *N*-Protection before Introducing Iodine

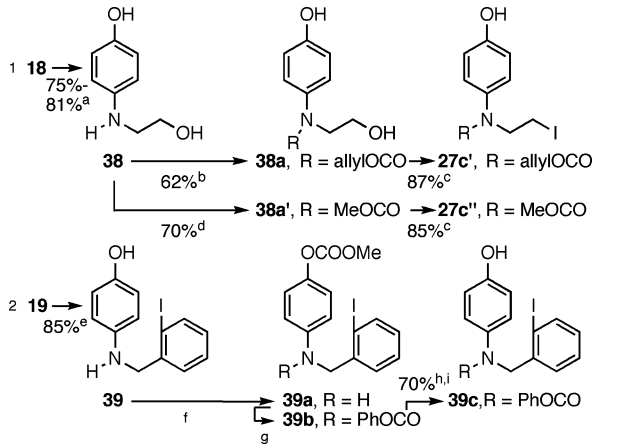


[a] K_2CO_3, CuI, L-proline, ethanolamine, DMSO. [b] PhOCOCl, *i*-Pr_2NEt. [c] Ph_3P, imidazole, I_2. [d] Me_3SiBr. [e] allylOCOCl, *i*-Pr_2NEt. [f] MeOCOCl, *i*-Pr_2NEt. [g] $(CF_3CO)_2O$, *i*-Pr_2NEt. [h] K_2CO_3, CuI, L-proline, (±)-**21**, DMSO. [i] K_2CO_3, CuI, L-proline, (*S*)-**21**, DMSO. [j] K_2CO_3, CuI, L-proline, 2-amino-1-butanol, DMSO. [k] K_2CO_3, CuI, L-proline, 1,3-propanolamine, DMSO. [l] K_2CO_3, CuI, L-proline, 4-amino-2-butanol, DMSO. [m] $BCl_3.SMe_2$, CH_2Cl_2. [n] K_2CO_3, CuI, L-proline, ethyl 3-aminobutyrate, DMSO. [o] $LiAlH_4$. [p] PhCHO, **16**, L-proline, *N*-methyl-2-pyrrolidinone, PrCHO; then $NaBH_4$, MeOH. [q] PhOCOCl, *i*-Pr_2NEt, DMAP. [r] BBr_3, CH_2Cl_2. [s] Succinic anhydride. [t] BH_3·SMe_2. [u] K_2CO_3, CuI, L-proline, 3-aminocyclohexanol (cis/trans mixture), DMSO. [v] Yield of cis and trans isomers 76%; only cis isomer (64%) was carried forward. [w] **15**, (±)-pyroglutaminol, Cs_2CO_3, CuI, *N*,*N*′-dimethylethylenediamine, DMF.

group and an alkyl chain terminating in an iodine atom. Our approach was designed very largely around a cross-coupling strategy involving an aryl iodide and a suitably functionalized amine (see **9** → **10**), because we felt that such a route would be more flexible and efficient than *N*-monoalkylation of a para-oxygenated aniline. However, we did demonstrate in three specific cases (see Table 1, entries 11 and 12; Table 2, entry 2) that para-oxygenated anilines (*p*-$ROC_6H_4NH_2$, R = H, Me) are also very convenient starting materials.

We decided to make the alkyl iodide segment from the corresponding alcohol **10** (Scheme 4). For this conversion of C−OH to C−I, the choice of nitrogen protecting group turned

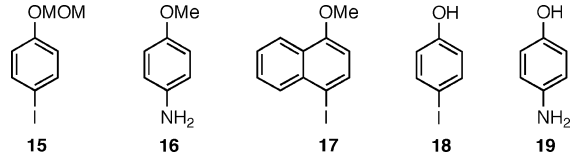
TABLE 2. Preparation of Iodides with Unprotected Phenols



[a] K_2CO_3, CuI, L-proline, ethanolamine, DMSO. [b] allylOCOCl, *i*-Pr_2NEt. [c] Ph_3P, imidazole, I_2. [d] MeOCOCl, *i*-Pr_2NEt. [e] 2-iodobenzaldehyde; then $NaBH_4$, MeOH. [f] MeOCOCl, Et_3N. [g] PhOCOCl, *i*-Pr_2NEt. [h] K_2CO_3, MeOH. [i] Overall yield from **39**.

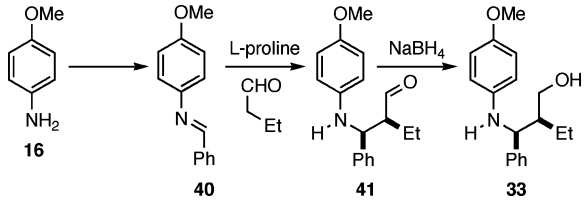
out to be crucial and, in the event, its nature also determined the ease of oxidation of the aromatic ring into the cross-conjugated ketone (**12** → **13**). We evaluated a number of nitrogen protecting groups, as described below, and eventually discovered that carbamates, especially phenyl carbamates (Scheme 4, Pg′ = PhOCO), are very satisfactory and that the subsequent oxidation is then also straightforward. The suitability of phenyl carbamates was a key finding, which allowed us to use the process of Scheme 4 to prepare a wide range of benzo-fused nitrogen heterocycles. According to our understanding, the method can produce compounds that would be difficult to make by any other approach.

Preparation of the Starting Amino (and Amido) Alcohols. As indicated above, we generally prepared our *N*-aryl amino alcohols (and in one case, an amido alcohol) from aromatic iodides, but have sometimes used anilines (*p*-$ROC_6H_4NH_2$, R = Me, H). We examined the five starting materials **15**,[13] **16**, **17**,[14] **18**, and **19**. In the case of the iodides, we found that the

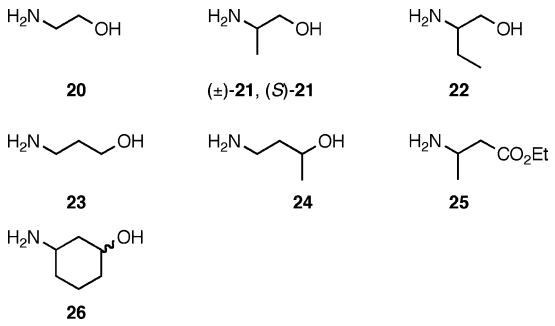


coupling procedure of Ma, Cai, and Zhang[15] is very effective for converting them into the requisite *N*-(β-hydroxyethyl)- or *N*-(γ-hydroxypropyl)anilines. As shown in Table 1 (entries 1−10, 13, and 15), this coupling method generally gives the products in 70−80% yields. It is also not essential to protect the hydroxyl group of the iodophenol used in the coupling step, since we found that an unprotected phenol (**18**) reacts with an amino alcohol (Table 2, entry 1), but our experience is that the use of protected phenols is more dependable and gives a cleaner

SCHEME 5. Formation of Single Enantiomers



coupling product. We also find that the subsequent transformations (*N*-protection and iodide formation) generally work better if the original phenolic oxygen is protected. The Ma procedure is easy to carry out and involves adding CuI, L-proline, K_2CO_3, and the amino alcohol to a solution of the *O*-protected iodophenol in DMSO. The mixture is then stirred for 12 h at 85 °C under Ar. We have performed many such reactions satisfactorily on a small scale (1−4 mmol of iodide), using amines **20**−**26**.[16]



For the aryl iodide−amide coupling with racemic pyroglutaminol (Table 1, entry 14) we used the amidation procedure (CuI, *N*,*N*-dimethylethylenediamine, Cs_2CO_3, DMF, 80 °C) developed[17] by the Buchwald group. This example (Table 1, entry 14) is noteworthy because no nitrogen protection step is subsequently needed.

The aliphatic carbon bearing the amino group can carry a simple substituent (e.g., Me, Et), but bulky groups such as *i*-Pr and *t*-Bu cause problems, either at the coupling stage (*t*-Bu, ca. 20% yield) or at the *N*-protection stage (*i*-Pr, poor chemoselectivity between OH and NH).

When starting with **16**, it is possible to form suitable *N*-substituted anilines by acylation, and this approach was used in converting **16** into **34** (Table 1, entry 12) by treatment with succinic anhydride. Both the amide and the carboxyl were then reduced in the same reaction to afford **34a**, the actual amine substrate for our purpose. We also used amine **19** for reductive amination of 2-iodobenzaldehyde to afford phenol **39** (Table 2, entry 2).

Another way of using amines directly is shown by the formation of **33** (Scheme 5 and Table 1, entry 11), which was generated from **16** by an asymmetric Mannich condensation, exactly according to a literature[18] procedure (Scheme 5). The

(13) Takatori, K.; Nishihara, M.; Nishiyama, Y.; Kajiwara, M. *Tetrahedron* **1998**, *54*, 15861−15869.

(14) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett*. **2002**, *43*, 5047−5048.

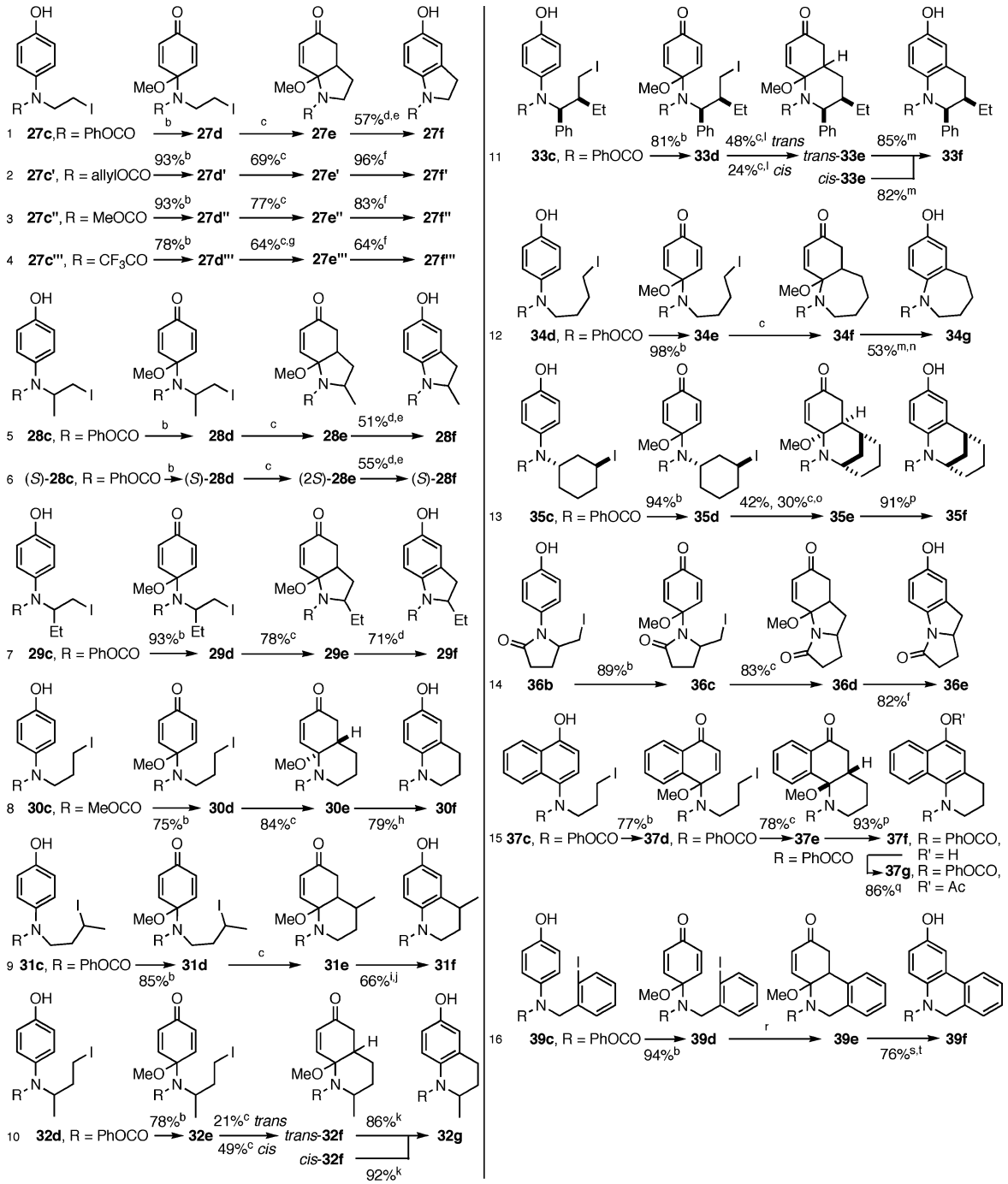
(15) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett*. **2003**, *5*, 2453−2455. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem*. **2005**, *70*, 5164−5173. (c) Cf.: Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 3490−3491.

(16) All are commercially available, although we prepared **26** ourselves: Greenhill, J. V.; Ramli, M.; Tomassini, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 588−591.

(17) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421−7428.

(18) (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 3677−3680. (b) We assign the indicated absolute configuration by analogy to an example for which the absolute configuration was determined by X-ray methods (see ref 18a).

TABLE 3. Oxidation, Cyclization, and Aromatization[a]

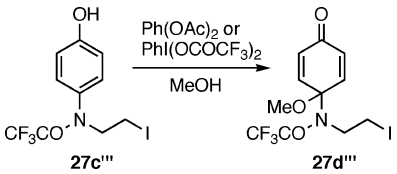


[a] All compounds are racemic, except those of entries 6 and 11. Cis and trans refer to ring fusion stereochemistry. [b] $PhI(OAc)_2$, MeOH. [c] Bu_3SnH, AIBN, PhMe, 85 °C. [d] $TsOH.H_2O$, 4 Å molecular sieves, $CHCl_3$. [e] Over three steps from the iodophenol. [f] $TsOH.H_2O$, 4 Å molecular sieves, CH_2Cl_2. [g] Corrected for recovered **27d'''**; without correction, 54%. [h] $TsOH.H_2O$, CH_2Cl_2. [i] HCl, PhMe. [j] Over two steps from **31d**. [k] $TsOH.H_2O$, THF. [l] Both the trans and cis ring-fused compounds were single isomers. [m] HCl, $CHCl_3$. [n] Over two steps from **34e**. [o] Yield of **35e** is 42%; **35f** is also formed (30%); ring fusion in **35e** is cis, but relative stereochemistry to bridgehead is a tentative assignment. [p] $TsOH.H_2O$, $CHCl_3$. [q] Ac_2O, Et_3N. [r] Bu_3SnH, AIBN, PhH, 85 °C. [s] HCl, PhH. [t] Over two steps from **39d**.

ee value reported for **33** is 97% and, although our own experience of this process is limited to a single example, we consider the method to be an excellent and convenient way of applying our radical cyclization to make optically active benzo-fused nitrogen heterocycles. Entry 6 of Table 1 summarizes a route to an optically active product via our standard aryl iodide−amine coupling procedure and, in principle, use of optically pure pyroglutaminol (Table 1, entry 14; Table 3, entry 14) would likewise give a single enantiomer.

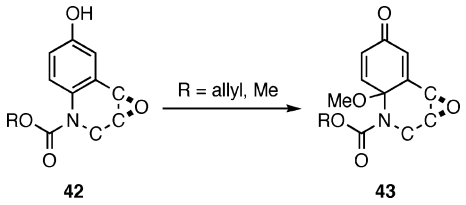
Protection of Nitrogen and Formation of the Iodides for Radical Closure. As indicated earlier, the choice of nitrogen protecting group is crucial. Apart from the obvious requirement that installation and removal should be easy, the group must allow replacement of the alcoholic hydroxyl by iodine and then

SCHEME 6. Evaluation of *N*-Trifluoroacetate

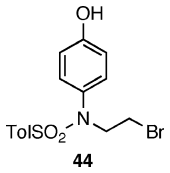


oxidation of the phenol to the cross-conjugated ketone. Ease of installation requires that the reagent used to attach the *N*-protecting group should be highly selective for nitrogen versus hydroxyl.

Precedent for the desired type of oxidation was available in synthetic work on dynemycin A[19,20] in which the substructure **42** was converted into substructure **43**. Nonetheless, our first

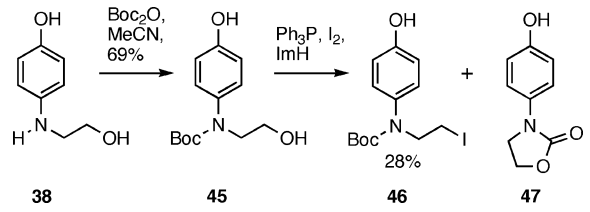


test of a nitrogen protecting group was to examine a toluenesulfonyl group but, with **44** and the corresponding iodide as substrates, we were unable to effect oxidation in the required sense (cf. **12** → **13**), using DDQ, CAN, $Pb(OAc)_4$, or $Tl(NO_3)_3$.

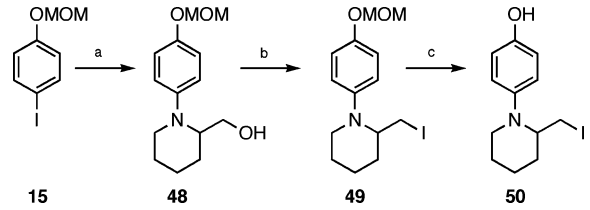


The trifluoroacetyl group was chosen as the next candidate, mainly because of its ease of removal. When we examined the *N*-trifluoroacetate **27c‴** (Scheme 6), oxidation occurred slowly with $PhI(OAc)_2$ (2 days, 78%) but more rapidly with $PhI(OCOCF_3)_2$ (30 min, 53%). The subsequent radical cyclization and rearomatization were also successful, but the trifluoroacetyl group was not ideal because yields in the latter part of the sequence were modest. Consequently, it was decided to continue the search for a better protecting group, and so we turned our attention to carbamates. To this end, amino alcohol **38** was treated with Boc_2O and we then attempted to convert the product **45** into the corresponding iodide **46**. Although this iodide was formed, the yield was poor (28%) and the compound was accompanied by the cyclic carbamate **47**. Moreover, phenol **46** was not oxidized by $PhI(OAc)_2$ or by $PhI(OCOCF_3)_2$. The formation of **47** suggested that other carbamates, less liable to fragment by way of a stable carbonium ion,[21] ought to be examined, and so allyloxy, methyl, and phenyl carbamates were evaluated in that order. It quickly emerged that, while our sequence of *N*-acylation, phenol oxidation, radical closure, and rearomatization could be made to work with all of them, the phenyl carbamate was clearly the best in terms of ease of

SCHEME 7. Evaluation of *N*-Boc Derivative

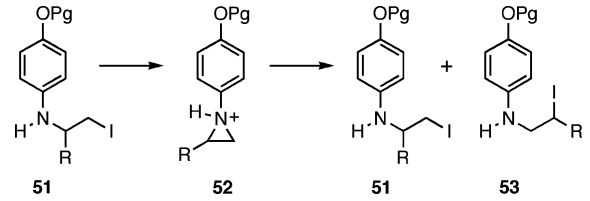


SCHEME 8. Evaluation of *N,N*-Dialkyl Groups[a]



[a] Reagents and conditions. (a) K_2CO_3, CuI, L-proline, 2-piperidinemethanol, DMSO, 80 °C, 26 h, 28%. (b) Ph_3P, imidazole, I_2, THF, 45 min. (c) Me_3SiBr, CH_2Cl_2, 15 min, 41% from **48**.

SCHEME 9. Mechanism for Potential Scrambling of Regiochemistry



installation and yields in the subsequent steps. Even when the position α to the nitrogen carries a substituent (Me, Et), use of a phenyl carbamate did not lead to the generation of a heterocycle during formation of the iodide (cf. **45** → **47** Scheme 7), as sometimes occurred with methyl and allyl carbamates. Consequently, most of our work has been based on phenyl carbamates.

We also examined briefly the possibility of *N*-alkyl protection. The phenol **50** was prepared as shown in Scheme 8, but we were unable to oxidize it to the desired cross-conjugated ketone with either $PhI(OAc)_2$ or PhIO.

Finally, we should mention that we encountered a minor practical inconvenience associated with using carbamates: slow C(O)−N bond rotation often severely broadens the NMR signals.

Experimentally, our amino alcohols were converted into phenyl carbamates by reaction with PhOCOCl in the presence of a base, and yields were generally in the range 80−90%, as indicated in Table 1. When the position α to nitrogen carries an isopropyl group, however, acylation with PhOCOCl was not sufficiently selective for nitrogen over oxygen.

In a few cases (see Table 2, preparation of **38a** and **38a′**) we obtained much better results if the acylating agent (0.6 equiv), Hünig's base (0.6 equiv), and then a second portion of acylating agent (0.6 equiv) were added in that order.

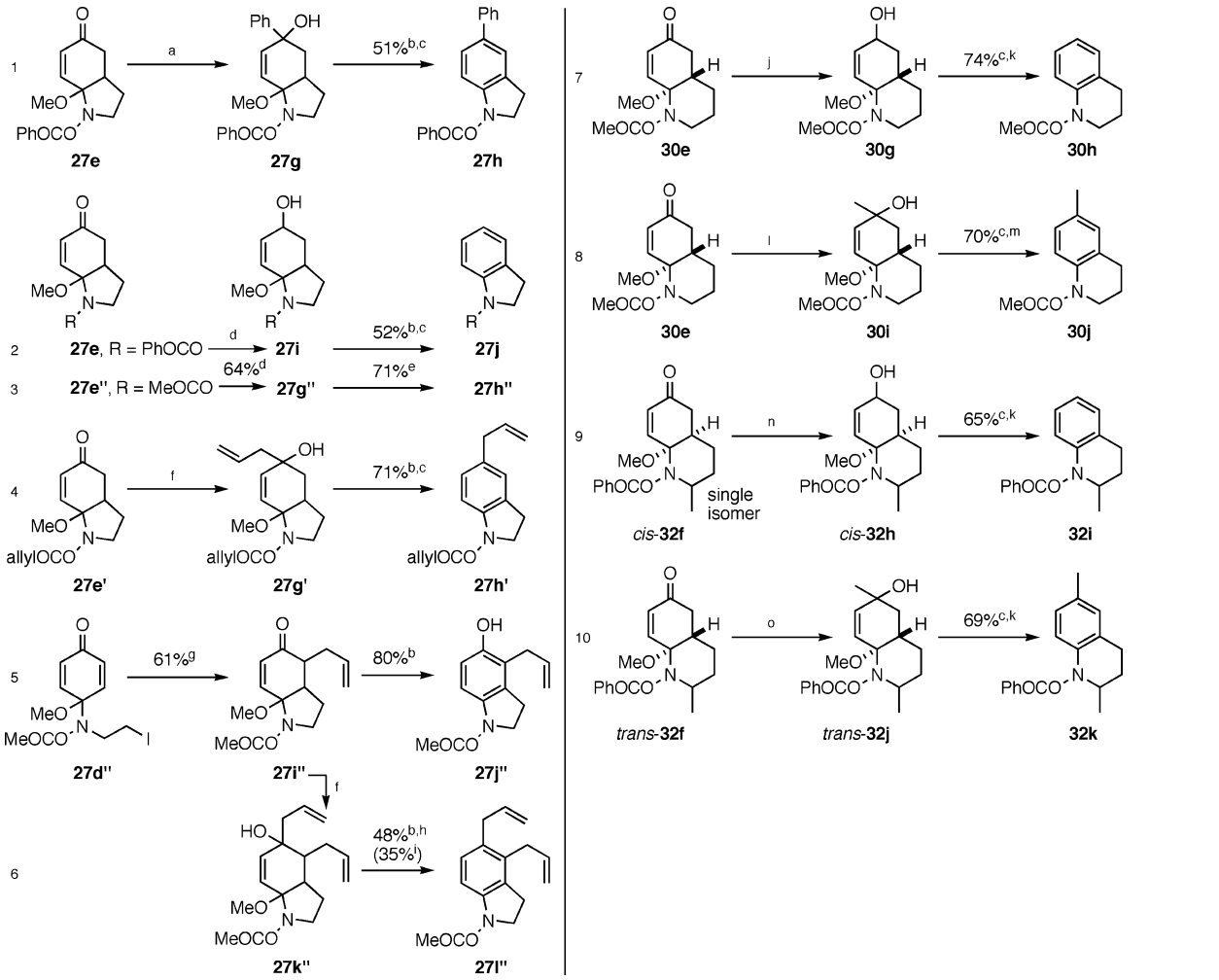
Table 1 also shows some of the results we obtained in our search for an ideal protecting group. That phase of the work involved not only the use of different forms of *N*-protection but also experiments in which the alcohol was converted into an iodide *before N*-protection. Entry 4 of Table 1 shows the formation of a trifluoroacetamide in which iodine is already in place, and entry 8, the formation of a methyl carbamate, again

(19) (a) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16−43. (b) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509−9525.

(20) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072−6094.

(21) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: Hoboken, NJ, 2007; p 244.

TABLE 4. Further Modifications



[a] PhMgCl, THF. [b] $TsOH.H_2O$, 4 Å molecular sieves, CH_2Cl_2. [c] Over two steps, from enone. [d] $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH. [e] $TsOH.H_2O$, 4 Å molecular sieves, $CHCl_3$. [f] allylMgBr, THF. [g] allyltributyltin, AIBN, PhMe, reflux. [h] Yield of **27l″**. [i] **27j″** also isolated (35%) after the two-step process as a result of incomplete reaction of **27i″** with allylMgBr (experiment done only once). [j] $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH. [k] $TsOH.H_2O$, $CHCl_3$. [l] MeMgBr, Et_2O. [m] $TsOH.H_2O$, Et_2O. [n] $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF. [o] MeMgBr, THF.

starting with an iodide. However, we did not put extensive effort into studying the sequence in which the iodine is introduced *before* acylation of the nitrogen because amino iodide **27a‴** was not very stable (it should be used the same day it is made) and we were concerned about the ease of formation of aziridinium ions from such amino iodides. If aziridinium ions were to form, the regiochemical integrity of the starting materials might be compromised by the rearrangement (**51** → **52** → **51** + **53**) shown in Scheme 9.

The pyroglutaminol-derived compound **36** (see Table 1) is internally protected on nitrogen, and the amine **39** (Table 2) already has the iodine in place.

In preparing iodides from our *N*-protected amines we favor the standard Ph_3P-imidazole$-I_2$ procedure[22] as it gave the desired products, often in yields above 90%.

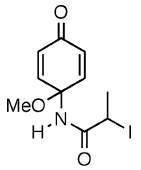
Phenol Deprotection and Formation of Cross-Conjugated Ketones. As is clear from Table 1, we usually worked with MOM-protected phenols, from which the protecting group was readily removed by treatment with Me_3SiBr at room temperature, generally in yields of about 85%. In three cases (**31b** → **31c**, **32c** → **32d**, **35b** → **35c**) $BCl_3 \cdot SMe_2$was used in an equally efficient process. In those few examples (**33a** → **33b**, **34b** → **34c**, **37a** → **37b**) where the original phenol had been protected as a methyl ether, removal was effected with BBr_3 in satisfactory yield (71−89%).

As indicated above, our search for suitable *N*-protecting groups was undertaken bearing in mind that oxidation would be done with $PhI(OAc)_2$ in MeOH, since this system had been uniformly successful in our earlier work on the oxygen series of Scheme 2 (X = O).[11] Our exploratory studies in the present instance had identified phenolic *N*-protected amino iodides as satisfactory candidates for this type of oxidation, and we found that the $PhI(OAc)_2$ oxidation method worked satisfactorily for most of our examples (Table 3). Yields were often above 90%, but a few of the cross-conjugated ketones appeared to decompose when their solutions were concentrated to dryness. In these cases the material obtained from flash chromatography was not evaporated completely and the eluent was displaced by multiple partial evaporations after adding portions of dry PhMe. PhIO was also tested as an oxidant: with **27c′** it gave the cross-conjugated ketone in 84% yield. Compound **27c‴** was oxidized

(22) Cf.: Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681−683.

with $PhI(OCOCF_3)_2$, but the yield was lower (53%) than that with $PhI(OAc)_2$ (78%).

The cross-conjugated ketone **54**,[23] where the nitrogen has an acidic hydrogen, was not sufficiently stable to survive even the mild conditions used for radical cyclization.



54

Radical Cyclization and Rearomatization. With the exception of compound **54**, the radical cyclization step proceeded without incident under standard conditions that involved slow addition of a solution of Bu_3SnH and AIBN in PhMe to a hot solution of the cross-conjugated ketone in the same solvent. The only complication we met was the tendency for some of the cyclization products to aromatize during handling. In most cases, aromatization was actually the desired next step, and in those where it was not, the radical cyclization product was processed promptly (see later).

We examined the formation in the radical step of five-, six-, and seven-membered rings but did not explore beyond this range.

When five-membered rings are generated in the radical cyclization, we obtain only a single ring-fusion geometry, presumably[24] cis, in the bicyclic product. When six-membered rings are formed, we sometimes observed mixtures of both the cis and trans ring-fused products. However, the production of such isomer mixtures is of no consequence as the asymmetric centers involved are subsequently converted to sp^2 hybridization.

In all cases, the rearomatization was effected by adding a small amount of an acid to a solution of the radical cyclization product. Usually $TsOH\cdot H_2O$ was used, most often in the presence of 4 Å molecular sieves, with CH_2Cl_2 or $CHCl_3$ as solvents. In a few cases, a small amount of concentrated hydrochloric acid was added to a solution of the substrate in PhH, $CHCl_3$, or PhMe. Reaction mixtures were left for 15 min to 12 h, but all the aromatizations were probably complete within minutes. The use of molecular sieves was based on observations made in the aromatization of **27e‴**, because in this case complete selectivity for aromatization by loss of the MeO group, as opposed to opening of the heterocycle, was observed only in the presence of sieves.

We suspect that the MeO−C bond overlaps better with the enone π system than the endocyclic C−N bond, and this situation causes aromatization to occur preferentially by loss of the MeO group (as MeOH).

Manipulation of the Radical Cyclization Products. All the above rearomatizations generate phenols, but the sequence is easily modified so as to provide other compound types.

Reduction of the intermediate α,β-unsaturated ketones gives secondary alcohols (see Table 4, entries 2, 3, 7, and 9) that also undergo the rearomatization, giving products in which the original phenolic hydroxyl is now replaced by hydrogen. Similarly, when the intermediate α,β-unsaturated ketones are treated with a Grignard reagent, rearomatization in the presence of acid gives products carrying an additional alkyl, allyl, or aryl group (Table 4, entries 1, 4, 8, and 10).

The examples of Table 4, entries 5 and 6, represent a more sophisticated diversion from the normal pathway. In this case the α-keto radical produced by the cyclization was trapped by Keck allylation[25] and the resulting ketone was treated with allylmagnesium bromide. The bis-allylic product formed in this way was rearomatized in the normal manner (**27k″** → **27l″**).

Conclusions

The final products shown in Tables 3 and 4 firmly establish that the present method is general and can be used to construct a wide range of substances including linearly fused, angularly fused, and bridged systems. Ring sizes accessible in the radical closure step cover the range 5−7. Although most of the final aromatized compounds that are chiral were prepared in racemic form, optically active substances are also accessible. A very useful feature of the route is the opportunity it provides for incorporating additional substituents, especially at the location of the original phenolic hydroxyl, and the method can provide access to compounds that would be difficult to make by other routes.

Experimental Section

2-[[4-(Methoxymethoxy)phenyl]amino]ethanol (27). Ethanolamine (1.13 mL, 18 mmol) was injected into an oven-dried round-bottomed flask containing **15**[13] (990.0 mg, 3.75 mmol) (Ar atmosphere). Oven-dried K_2CO_3 (2.58 g, 18 mmol), CuI (178 mg, 0.94 mmol), and L-proline (215 mg, 1.87 mmol) were tipped in. Dry DMSO (5 mL) was added and the flask was lowered into an oil bath preset at 85 °C. The mixture was stirred for 45 min, cooled to room temperature, and partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with water (twice) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.6 × 18 cm), using EtOAc−hexane mixtures from 0% to 100% EtOAc, gave **27** (609 mg, 82%) as an oil: FTIR ($CHCl_3$ cast) 3381, 2944, 1512, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90−3.18 (br s, 2 H), 3.27 (t, J = 5.5 Hz, 2 H), 3.48 (s, 3 H), 3.82 (t, J = 5.0 Hz, 2 H), 5.08 (s, 2 H), 6.62 (apparent d, J = 8.9 Hz, 2 H), 6.93 (apparent d, J = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.0 (t), 55.8 (q), 61.3 (t), 95.6 (t), 114.5 (d), 118.0 (d), 143.4 (s), 149.9 (s); exact mass m/z calcd for $C_{10}H_{15}NO_3$ 197.10519, found 197.10390.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (27a). PhOCOCl (0.213 mL, 1.695 mmol) was injected rapidly (3−4 s) into a stirred and cooled (−30 °C) solution of **27** (298.5 mg, 1.513 mmol) and *i*-Pr_2NEt (0.295 mL, 1.695 mmol) in CH_2Cl_2 (10 mL). After 30 min, the cold bath was removed and stirring was continued for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 18 cm), using EtOAc−hexane mixtures from 10% to 50% EtOAc, gave **27a** (480.3 mg, 100%) as an oil: FTIR ($CDCl_3$ cast) 3468, 2950, 1720, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.5−2.7 (br s, 1 H), 3.49 (s, 3 H), 3.86 [dd (one appears as a broad signal), J = 4.5 Hz, 4 H], 5.18 (s, 2 H), 7.06−7.07 (m, 4 H), 7.18 (t, J = 7 Hz, 1 H), 7.26−7.28 (m, 2 H), 7.33 (t, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.6 (t), 56.1 (q), 61.0 (t), 94.5 (t), 116.8 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d),

(23) For preparation, see the Supporting Information.

(24) Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353−355.

(25) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829−5831.

135.5 (q), 151.3 (q), 156.3 (q); exact mass *m*/*z* calcd for $C_{17}H_{19}NO_5$ 317.12631, found 317.12644.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (27b). Imidazole (264.0 mg, 3.880 mmol), Ph_3P (723.0 mg, 2.757 mmol), and I_2 (674.0 mg, 2.655 mmol) were added in that order to a stirred and cooled (0 °C) solution of **27a** (324.0 mg, 1.021 mmol) in dry THF (20 mL). After 1 h, the cold bath was removed and stirring was continued for 12 h. The mixture was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ (12 mL) and brine (12 mL). The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 18 cm), using EtOAc−hexane mixtures from 2% to 20% EtOAc, gave **27b** (410.2 mg, 94%) as an oil: FTIR ($CDCl_3$ cast) 2954, 1720, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.30 (t, J = 7.3 Hz, 2 H), 3.49 (s, 3 H), 3.98−4.26 (br m, 2 H), 5.18 (s, 2 H), 7.08 (apparent d, J = 8.9 Hz, 3.5 H), 7.13−7.24 (br s, 1.3 H), 7.27 (apparent d, J = 8.9 Hz, 2.2 H), 7.30−7.40 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.8 (t), 52.9 (t), 56.1 (q), 94.5 (t), 116.9 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d), 134.4 (s), 151.2 (s), 153.9 (s), 156.5 (s); exact mass *m*/*z* calcd for $C_{17}H_{18}INO_4$ 427.02805, found 427.02809.

(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Phenyl Ester (27c). Me_3SiBr (1.070 mL, 8.089 mmol) was injected at a fast dropwise rate into a stirred solution of **27b** (288.0 mg, 0.6741 mmol) in dry CH_2Cl_2 (23 mL). Stirring was continued for 22 h, and the mixture was then quenched with water (30 mL) and extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 17 cm), using EtOAc−hexane mixtures from 2% to 25% EtOAc, gave **27c** as a white solid (253.2 mg, 98%): mp 123−126 °C with trace amounts not melting until 149−160 °C; FTIR ($CDCl_3$ cast) 3367, 1694, 1596, 1515, 1398 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 3.18−3.35 (apparent br m, 2 H), 3.92−4.20 (br m, 2 H), 6.83 (apparent d, J = 8.8 Hz, 2 H), 7.02 (d, J = 7.6 Hz, 1 H), 7.11−7.26 (m, 3.9 H), 7.26−7.43 (m, 2.1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.2 (t), 53.0 (t), 116.2 (d), 121.5 (d), 125.5 (d), 128.8 (d), 129.3 (d), 133.0 (s), 151.2 (s), 154.3 (s), 155.3 (s); exact mass *m*/*z* calcd for $C_{15}H_{14}INNaO_3$ 405.99107, found 405.99067.

(2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (27d). $PhI(OAc)_2$ (163.0 mg, 0.4958 mmol) was added to a stirred and cooled (0 °C) solution of **27c** (152.0 mg, 0.3970 mmol) in dry MeOH (26 mL). After 20 min the cold bath was removed, stirring was continued for 4.5 h, and the mixture was quenched with a mixture of aqueous $Na_2S_2O_3$ (1 M, 35 mL) and saturated aqueous $NaHCO_3$ (35 mL). The aqueous phase was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm), using EtOAc−hexane mixtures from 2% to 20% EtOAc, gave **27d**. The compound decomposes on concentration of its solutions and satisfactory ^1H and ^{13}C NMR could not be obtained. Crude material: FTIR (microscope) 3044, 2937, 2850, 2835, 1726, 1673, 1633, 1494, 1455, 1385 cm^{-1}; exact mass *m*/*z* calcd for $C_{16}H_{16}INO_4$ 413.01186, found 413.01181.

7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester (27e). A solution of Bu_3SnH (0.158 mL, 0.5945 mmol) and AIBN (43.0 mg, 0.2616 mmol) in dry PhMe (10 mL) was added over 2.5 h by syringe pump to a stirred and heated (85 °C) solution of **27d** [assumed to contain 163.0 mg (0.3964 mmol) of **27d**] in dry PhMe (34 mL). Heating at 85 °C was continued for 14.5 h after the addition and the mixture was then cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF−silica gel (10% w/w KF) (2 × 20 cm), using EtOAc−hexane mixtures from 2% to 50% EtOAc, gave **27e** as an oil. The compound partially aromatizes on attempts at further purification and satisfactory ^1H and ^{13}C NMR could not be obtained. Crude material: FTIR (microscope) 3066, 2955, 2901, 2833, 1726, 1687, 1493, 1456, 1370 cm^{-1}; exact mass *m*/*z* calcd for $C_{16}H_{17}NO_4$ 287.11575, found 287.11588.

5-Hydroxy-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester (27f). $TsOH{\cdot}H_2O$ (60.0 mg, 0.3154 mmol) was added to a stirred mixture of the above crude **27e** [assumed to contain 113.0 mg (0.3933 mmol) of **27e**] and 4 Å molecular sieves (ca. 60 mg) in $CHCl_3$ (20 mL). Stirring was continued for 2.5 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using EtOAc−hexane mixtures from 0% to 50% EtOAc, gave **27f** (57.4 mg, 57% over three steps) as an oil: FTIR (microscope) 3390, 2923, 1693, 1601, 1490, 1416, 1336 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.13 (t, J = 8.2 Hz, 3 H), 3.96−4.12 (apparent s, 0.5 H), 4.19 (t, J = 8.2 Hz, 1.5 H), 6.60 (d, J = 8.0 Hz, 1.0 H), 6.68 (s, 0.9 H), 6.79−6.85 (m, 0.1 H), 6.95−7.08 (apparent s, 0.1 H), 7.18 (d, J = 7.6 Hz, 2 H), 7.23 (t, J = 7.1 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 2.2 H), 7.56 (d, J = 8.5 Hz, 0.7 H); ^{13}C NMR (CD_3OD, 125 MHz) (one signal appears to be obscured by the solvent peak) δ 28.7 (t), 113.3 (d), 114.6 (d), 116.5 (d), 123.0 (d), 126.8 (d), 130.4 (d), 134.4 (s), 135.7 (s), 152.4 (s), 152.9 (s), 155.1 (s); exact mass *m*/*z* calcd for $C_{15}H_{13}NO_3$ 255.08954, found 255.08943.

5-Phenyl-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester (27h). Dry THF (3 mL) was added to **27e** (0.1171 g, 0.408 mmol) and the solution was cooled to −78 °C. PhMgCl (0.51 mL, 1.02 mmol) was then added dropwise, and stirring was continued for 5 min after the addition. The cooling bath was removed and stirring was continued for 1 h. The mixture was quenched with water (1 mL) and partitioned between water and EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material was dissolved in dry CH_2Cl_2 (2 mL), and 4 Å molecular sieves (ca. 72 mg) and $TsOH.H_2O$ (0.0057 g, 0.048 mmol) were added. Stirring was continued for 5 min. The liquid contents of the flask were transferred to another flask, using $CHCl_3$ as a rinse, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 2.5:10 EtOAc−hexanes, gave **27h** (0.0659 g, 51%) as a white solid: mp 174−177 °C; FTIR ($CHCl_3$ cast) 3031, 1723, 1598, 1509 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ 3.24 (t, J = 9 Hz, 2 H), 4.32 (t, J = 9.5 Hz, 2 H), 7.22−7.98 (m, 13 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.8 (t), 48.1 (t), 115.2 (d), 121.7 (d), 123.4 (d), 125.6 (d), 126.6 (d), 126.8 (d), 128.7 (d), 129.3 (d), 131.7 (s), 136.3 (s), 140.8 (s), 141.6 (s), 150.7 (s), 151.1 (s), 192.2 (s); exact mass *m*/*z* calcd for $C_{21}H_{17}NO_2$ 315.12592, found 315.12596.

2,3-Dihydroindole-1-carboxylic Acid Phenyl Ester (27j). Dry MeOH was added to **27e** (0.0715 g, 0.25 mmol) and the solution was stirred and cooled to −78 °C. $CeCl_3{\cdot}7H_2O$ (0.0927 g, 0.25 mmol) and then $NaBH_4$ (0.0283 g, 0.75 mmol) were tipped in. Stirring was continued for 5 min, the cooling bath was removed, and stirring was continued for 1 h. The mixture was partitioned between EtOAc and brine, and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in dry CH_2Cl_2 (2 mL), and 4 Å molecular sieves (ca. 72 mg) and $TsOH.H_2O$ (0.0047 g, 0.025 mmol) were tipped in. Stirring was continued for 5 min. The liquid contents of the flask were transferred to another flask, using $CHCl_3$ as a rinse, and the solution was evaporated. Flash chromatography of the residue over silica gel (1 × 25 cm), using 1:5 EtOAc−hexanes, gave **27j** (0.0309 g, 52%) as a white solid: mp 129−132 °C; FTIR ($CDCl_3$ cast) 3053, 3027, 2669, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 65 °C) δ 3.21 (t, J = 9 Hz, 2 H), 4.25 (t, J = 9.0 Hz, 2 H), 7.05−7.88 (m, 9 H); ^{13}C NMR ($CDCl_3$, 125.3 MHz, 75 °C) δ 27.9 (t), 48.3 (t), 115.5 (d), 121.8 (d), 123.3 (d), 124.9 (d), 125.6 (d), 127.8 (d), 129.4 (d), 151.4 (s), (several signals are missing, but comparison with an authentic sample made from indoline showed the same effect); exact mass *m*/*z* calcd for $C_{15}H_{13}NO_2$ 239.09464, found 239.09474.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Allyl Ester (27a′). AllylOCOCl (0.052 mL, 0.487 mmol, 0.6 equiv) was injected at a fast dropwise rate into a stirred and cooled (−40 °C) solution of **27** (160 mg, 0.8112 mmol) in dry MeCN (8 mL) (Ar atmosphere). Stirring was continued for 5 min, and the cooling bath was removed. After an additional 7 min, dry *i*-Pr_2NEt (0.085

mL, 0.487 mmol, 0.6 equiv) was injected rapidly and stirring was continued for 2 min. The mixture was recooled to −40 °C and a second portion of allylOCOCl (0.052 mL, 0.487 mmol, 0.6 equiv) was injected. Stirring was continued for 5 min, and the cold bath was removed. Stirring was continued for 15 min, and water (5 mL) was added. The mixture was concentrated under water pump vacuum (rotary evaporator) to remove most of the organic solvent, and the residue was partitioned between $CHCl_3$ and brine. The aqueous phase was extracted with $CHCl_3$ (7 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 35 cm), using EtOAc−hexane mixtures from 0% to 100% EtOAc, gave **27a′** (204 mg, 87%) as an oil: FTIR (CH_2Cl_2 cast) 3457, 2948, 1701, 1511, 1445, 1402, 1295 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.48 (s, 3 H), 3.78 (m, 4 H), 4.58 (br d, J = 3.3 Hz, 2 H), 5.18 (m, 4 H), 5.85 (br s, 1 H), 7.02 (apparent d, J = 9.0 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.4 (t), 56.0 (q), 61.3 (t), 66.4 (t), 94.5 (t), 116.7 (d), 117.2 (t), 128.5 (d), 132.6 (d), 135.8 (s), 156.0 (s); exact mass m/z calcd for $C_{14}H_{19}NO_5$ 281.12631, found 281.12614.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Allyl Ester (27b′). Imidazole (160.7 mg, 2.361 mmol), Ph_3P (440.1 mg, 1.678 mmol), and I_2 (410.1 mg, 1.616 mmol) were added in that order to a stirred solution of **27a′** (174.8 mg, 0.6214 mmol) in dry THF (14 mL), and stirring was continued for 12 h. The mixture was quenched with a 1:1:1:4 mixture of saturated aqueous $Na_2S_2O_3$, brine, saturated aqueous $NaHCO_3$, and water. The aqueous phase was extracted with $CHCl_3$ (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.7 × 21 cm), using EtOAc−hexane mixtures from 2% to 50% EtOAc, gave **27b′** (214.4 mg, 88%) as an oil: FTIR (CH_2Cl_2 cast) 2952, 2897, 2825, 1705, 1511, 1396, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.22 (t, J = 8.0 Hz, 2 H), 3.49 (s, 3 H), 3.98 (t, J = 7.3 Hz, 2 H), 4.59 (br apparent s, 2 H), 5.18 (apparent s, 4 H), 5.86 (br s, 1 H), 7.03 (apparent d, J = 9.0 Hz, 2 H), 7.14 (br d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ 0.9 (t), 45.8 (t), 53.0 (t), 56.0 (q), 61.2 (t), 66.4 (t), 94.9 (t), 117.1 (d), 117.4 (s), 128.6 (d), 132.7 (d), 135.1 (s), 155.2 (s), 156.4 (s); exact mass m/z calcd for $C_{14}H_{18}INO_4$ 391.02805, found 391.02724.

(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Allyl Ester (27c′). Me_3SiBr (0.444 mL, 3.364 mmol) was injected at a fast dropwise rate into a stirred solution of **27b′** (137.0 mg, 0.3364 mmol) in dry CH_2Cl_2 (12 mL). Stirring was continued for 19 h, and the mixture was quenched with water (10 mL) and extracted with $CHCl_3$ (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 22 cm), using EtOAc−hexane mixtures from 2% to 25% EtOAc, gave **27c′** as a semisolid (89.3 mg, 73%): FTIR (CH_2Cl_2 cast) 3340, 2947, 1674, 1515, 1450, 1408, 1264 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.21 (t, J = 7.0 Hz, 2 H), 3.93 (br t, J = 5.9 Hz, 2 H), 4.43−4.75 (br m, 2 H), 5.00−5.45 (br m, 2 H), 5.75−6.08 (br m, 1 H), 6.78 (d, J = 8.5 Hz, 2 H), 7.08 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (CD_3OD, 100 MHz, 60 °C) (mixture of rotamers) δ 1.4 (t), 47.6 (t), 53.9 (t), 63.2 (t), 67.3 (t), 116.7 (d), 117.6 (t), 122.8 (d), 131.7 (s), 133.8 (s), 133.9 (d), 155.8 (s), 157.2 (s), 157.8 (s); exact mass m/z calcd for $C_{12}H_{14}INO_3$ 347.00183, found 347.00146.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Methyl Ester (27a″). MeOCOCl (0.032 mL, 0.415 mmol, 0.6 equiv) was injected at a fast dropwise rate into a stirred and cooled (−30 °C) solution of **27** (136.4 mg, 0.6916 mmol) in dry MeCN (10 mL) (Ar atmosphere). Stirring was continued for 25 min, dry *i*-Pr_2NEt (0.072 mL, 0.415 mmol, 0.6 equiv) was injected rapidly, and the cooling bath was removed. After an additional 20 min, the mixture was recooled to −30 °C and a second portion of MeOCOCl (0.032 mL, 0.415 mmol, 0.6 equiv) was injected. The cold bath was left in place but not recharged and stirring was continued for 5.5 h. The mixture was quenched with brine (10 mL) and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 19 cm), using EtOAc−hexane mixtures from 2% to 80% EtOAc, gave **27a″** (176.5 mg, 100%) as an oil: FTIR ($CHCl_3$ cast) 3455, 2954, 1703, 1511, 1455, 1387, 1295 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.20−3.04 (br s, 1 H), 3.48 (s, 3H), 3.67 (s, 3 H), 3.78 (m, 4 H), 5.17 (s, 2 H), 7.02 (apparent d, J = 8.8 Hz, 2 H), 7.13 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.2 (q), 53.4 (t), 56.1 (q), 61.2 (t), 94.5 (t), 116.8 (d), 128.5 (d), 135.8 (s), 156.1 (s), 157.6 (s); exact mass m/z calcd for $C_{12}H_{17}NO_5$ 255.11067, found 255.10998.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Methyl Ester (27b″). Imidazole (142 mg, 2.083 mmol), Ph_3P (388 mg, 1.480 mmol), and I_2 (362 mg, 1.425 mmol) were added in that order to a stirred solution of **27a″** (140 mg, 0.5481 mmol) in dry THF (12 mL), and stirring was continued for 20 h. The mixture was quenched with a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and brine. The aqueous phase was extracted with $CHCl_3$ (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.7 × 21 cm), using EtOAc−hexane mixtures from 2% to 10% EtOAc, gave **27b″** as an oil (165.2 mg, 82%): FTIR (CH_2Cl_2 cast) 2953, 2899, 2825, 1709, 1511, 1449, 1381, 1292 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.20 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.66 (br s, 3 H), 3.95 (t, J = 7.3, 2 H), 5.15 (s, 2 H), 7.03 (apparent d, J = 9.0 Hz, 2 H), 7.13 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.2 (t), 52.8 (t), 53.1 (q), 56.1 (q), 94.5 (t), 116.8 (d), 128.6 (d), 134.7 (s) 155.9 (s), 156.2 (s); exact mass m/z calcd for $C_{12}H_{16}INO_4$ 365.01242, found 365.01305.

(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Methyl Ester (27c″). Me_3SiBr (0.668 mL, 5.061 mmol) was injected at a fast dropwise rate into a stirred solution of **27b″** (154 mg, 0.4217 mmol) in dry CH_2Cl_2 (14 mL). Stirring was continued for 19 h, and the mixture was then quenched with water (15 mL) and extracted with $CHCl_3$ (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using EtOAc−hexane mixtures from 2% to 25% EtOAc, gave **27c″** (125.6 mg, 92%) as a semisolid: FTIR (CH_2Cl_2 cast) 3331, 2954, 1675, 1515, 1457, 1389, 1264 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 3.19 (t, J = 7.5 Hz, 2 H), 3.47−3.86 (br m, 3 H), 3.91 (t, J = 7.3 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 7.05 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 1.7 (t), 53.6 (q), 53.9 (t), 116.8 (d), 130.0 (d), 133.5 (s), 157.9 (s), 158.1 (s); exact mass m/z calcd for $C_{10}H_{12}INO_3$ 320.98621, found 320.98589.

(2*S*)-2-[[4-(Methoxymethoxy)phenyl]amino]propan-1-ol [(*S*)-28]. Amine (*S*)-**21** (0.322 g, 4.287 mmol), CuI (41 mg, 0.2144 mmol), L-proline (0.0492 g, 0.427 mmol), and oven-dried K_2CO_3 (0.296 g, 0.536 mmol) where added in that order to **15** (0.283 g, 1.072 mmol) contained in a dry, nitrogen-flushed, round-bottomed flask fitted with a condenser. Dry DMSO (1 mL) was then added and the mixture was heated at 80 °C for 17 h, cooled to room temperature, and partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 28 cm), using EtOAc−hexane mixtures from 0% to 50% EtOAc, gave (*S*)-**28** (186.0 mg, 82%) as an oil: FTIR (CH_2Cl_2 cast) 3380, 2932, 1511, 1227, 1196 cm^{-1}; $[\alpha]_D$ 45.5 (*c* 0.82, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, J = 6.4 Hz, 3 H), 2.70−2.91 (br s, 2 H), 3.41−3.47 (m and s, 4 H), 3.47−3.54 (m, 1 H), 3.65 (dd, J = 10.3, 4.0 Hz, 1 H), 5.04 (s, 2 H), 6.59 (apparent d, J = 8.9 Hz, 2 H), 6.88 (apparent d, J = 9.0, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (q), 51.7 (d), 55.8 (q), 66.1 (t), 95.5 (t), 115.3 (d), 118.0 (d), 142.6 (s), 149.9 (s); exact mass m/z calcd for $C_{11}H_{17}NO_3$ 211.12085, found 211.12104.

(*S*)-(2-Hydroxy-1-methylethyl)[4-(methoxymethoxy)phenyl]-carbamic Acid Phenyl Ester [(*S*)-28a]. PhOCOCl (0.510 mL, 4.06 mmol) was injected rapidly (3−4 s) into a stirred and cooled

(−30 °C) solution of (*S*)-**28** (0.7661 g, 3.626 mmol) and *i*-Pr_2NEt (0.708 mL, 4.06 mmol) in CH_2Cl_2 (18.5 mL). After 30 min, the cold bath was removed and stirring was continued for 3.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using EtOAc−hexane mixtures from 10% to 50% EtOAc, gave (*S*)-**28a** (1.142 g, 95%) as an oil: FTIR (CH_2Cl_2 cast) 3468, 2935, 1718, 1593, 1511, 1456, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 7.0 Hz, 3 H), 2.97 (br s, 1 H), 3.50 (s, 3 H), 3.56 (apparent dd, J = 11.3, 9.5 Hz, 1 H), 3.68 (apparent dd, J = 11.6, 4.1 Hz, 1 H), 4.49−4.59 (m, 1 H), 5.18 (s, 2 H), 7.06 (apparent d, J = 8.9 Hz, 3 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.24 (apparent d, J = 8.9 Hz, 2 H), 7.30 (t, J = 7.8, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2 (q), 56.0 (q), 56.1 (d), 64.5 (t), 94.5 (t), 116.5 (d), 121.7 (d), 125.2 (d), 129.1 (d), 130.6 (d), 131.7 (s), 151.4 (s), 155.4 (s), 156.7 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}NO_5$ 331.14197, found 331.14143.

(*S*)-(2-Iodo-1-methylethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester [(*S*)-28b]. Imidazole (306.0 mg, 4.495 mmol), Ph_3P (838.0 mg, 3.194 mmol), and I_2 (781.0 mg, 3.076 mmol) were added in that order to a stirred and cooled (0 °C) solution of (*S*)-**28a** (392.0 mg, 1.183 mmol) in dry THF (24 mL). After 1 h, the cold bath was removed and stirring was continued for 3 h. The mixture was quenched with a mixture of saturated aqueous $Na_2S_2O_3$ (15 mL) and brine (15 mL). The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 22 cm), using EtOAc−hexane mixtures from 2% to 10% EtOAc, gave (*S*)-**28b** (511.6 mg, 98%) as an oil: FTIR (CH_2Cl_2 cast) 2956, 1720, 1593, 1511, 1495, 1455, 1394, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, J = 6.8 Hz, 3 H), 3.26 (apparent dd, J = 10.1, 6.3 Hz, 1 H), 3.38 (apparent t, J = 9.5 Hz, 1 H), 3.50 (s, 3 H), 4.55−4.75 (apparent br s, 1 H), 5.20 (s, 2 H), 7.01−7.11 (m, 3 H), 7.16 (apparent t, J = 8.8 Hz, 1 H), 7.27−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6 (t), 18.9 (q), 56.1 (q), 56.1 (d), 94.5 (d), 116.6 (d), 121.6 (d), 125.3 (d), 129.1 (d), 130.3 (d), 131.6 (s), 151.3 (s), 154.0 (s), 156.9 (s); exact mass *m*/*z* calcd for $C_{18}H_{20}INO_4$ 441.04370, found 441.04347.

(*S*)-(4-Hydroxyphenyl)(2-iodo-1-methylethyl)carbamic Acid Phenyl Ester [(*S*)-28c]. Me_3SiBr (0.930 mL, 7.048 mmol) was injected at a fast dropwise rate into a stirred solution of (*S*)-**28b** (311.0 mg, 0.7048 mmol) in dry CH_2Cl_2 (24 mL). Stirring was continued for 9 h, and the mixture was then quenched with water (40 mL) and extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 23 cm), using EtOAc−hexane mixtures from 2% to 25% EtOAc, gave (*S*)-**28c** (270.0 mg, 96%) as a yellow solid: mp 124−128 °C; FTIR (CH_2Cl_2 cast) 3359, 2977, 1717, 1689, 1611, 1594, 1514, 1494, 1446, 1399, 1336 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.29 (d, J = 6.5 Hz, 3 H), 3.20−3.40 (br m, 2 H), 4.50−4.82 (br m, 1 H), 6.84 (apparent d, J = 8.9 Hz, 3 H), 6.94−7.07 (br m, 1.2 H), 7.10−7.43 (br m, 4.8 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 8.7 (t), 19.1 (q), 57.5 (d), 116.7 (d), 122.7 (d), 126.5 (d), 130.1 (s), 130.3 (d), 131.7 (d), 152.8 (s), 156.2 (s), 158.7 (s); exact mass *m*/*z* calcd for $C_{16}H_{16}INO_3$ 397.01749, found 397.01780.

(*S*)-(2-Iodo-1-methylethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester [(*S*)-28d]. $PhI(OAc)_2$ (87.0 mg, 0.271 mmol) was added to a stirred and cooled (0 °C) solution of (*S*)-**28c** (86.0 mg, 0.217 mmol) in dry MeOH (18.6 mL). After 20 min the cold bath was removed, stirring was continued for 1.5 h, and the mixture was quenched with a mixture of aqueous $Na_2S_2O_3$ (1 M, 15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 29 cm), using EtOAc−hexane mixtures from 0% to 20% EtOAc, gave (*S*)-**28d**, which was used directly for the next step. The compound decomposes on concentration of its solutions and satisfactory ^1H and ^{13}C NMR could not be obtained. Crude material: FTIR ($CHCl_3$ cast) 3337, 2973, 2834, 1721, 1625, 1594, 1493, 1453 cm^{-1}; exact mass *m*/*z* calcd for $C_{17}H_{18}INNaO_4$ (M + Na) 450.01728, found 450.01700.

(2*S*)-7a-Methoxy-2-methyl-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester [(*S*)-28e]. A solution of Bu_3SnH (0.080 mL, 0.303 mmol) and AIBN (19.0 mg, 0.1157 mmol) in dry PhMe (8.4 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of the above crude (*S*)-**28d** [assumed to contain 92.5 mg (0.217 mmol) of (*S*)-**28d**] in dry PhMe (16.8 mL). Heating at 85 °C was continued for 10 h after the addition, and the mixture was then cooled and evaporated. Flash chromatography of the residue over finely ground KF-flash chromatography silica gel (10% w/w KF) (1.5 × 25 cm), using EtOAc−hexane mixtures from 2% to 50% EtOAc, gave crude (*S*)-**28e** as an oil, which was used directly for the next step. The compound partially aromatizes on attempts at further purification and satisfactory ^1H and ^{13}C NMR could not be obtained. Crude material: FTIR (CH_2Cl_2 cast) 3400, 2965, 2832, 1721, 1686, 1594, 1511, 1494, 1456, 1366 cm^{-1}; exact mass *m*/*z* calcd for $C_{17}H_{19}NO_4$ 301.13141, found 301.13153.

(2*S*)-5-Hydroxy-2-methyl-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester [(*S*)-28f]. $TsOH.H_2O$ (18.0 mg, 0.0955 mmol) was added to a stirred mixture of the above crude (*S*)-**28e** [assumed to contain 36.0 mg (0.119 mmol) of (*S*)-**28e**] and 4 Å molecular sieves (ca. 60 mg) in $CHCl_3$ (5 mL). Stirring was continued for 30 min, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 × 27 cm), using EtOAc−hexane mixtures from 0% to 50% EtOAc, gave (*S*)-**28f** (32.4 mg, 55% over three steps) as an oil: FTIR (CH_2Cl_2 cast) 3387, 1716, 1694, 1652, 1605, 1490, 1456, 1409 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.40 (apparent d, J = 5.5 Hz, 3 H), 2.66 (apparent d, J = 16.1 Hz, 1 H), 3.40 (apparent dd, J = 10.6, 8.0 Hz, 1 H), 4.45−4.81 (br m, 1 H), 6.61 (apparent d, J = 8.5 Hz, 1 H), 6.67−6.71 (m, 0.9 H), 6.82 (apparent d, J = 8.7 Hz, 0.1 H), 6.87−7.02 (br m, 0.1 H), 7.07 (apparent d, J = 8.7 Hz, 0.1 H), 7.18 (d, J = 7.8 Hz, 2 H), 7.24 (t, J = 7.5 Hz, 1.0 H), 7.40 (apparent t, J = 7.8 Hz, 2.2 H), 7.49−7.59 (br d, J = 8.2 Hz, 0.6 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 21.6 (q), 37.0 (t), 57.4 (d), 113.5 (d), 113.6 (d), 117.1 (d), 122.9 (d), 126.7 (d), 130.5 (d), 133.3 (s), 134.6 (s), 152.4 (s), 152.7 (s), 155.3 (s); exact mass *m*/*z* calcd for $C_{16}H_{15}NO_3$ 269.10519, found 269.10529.

4-[[(4-Methoxymethoxy)phenyl]amino]butan-2-ol (31). CuI (23.3 mg, 0.12 mmol), L-proline (28.2 mg, 0.24 mmol), K_2CO_3 (339 mg, 2.45 mmol), and 4-amino-2-butanol (229 mg, 2.45 mmol) were added in that order to a solution of iodide **15** (323 mg, 1.22 mmol) in DMSO (4 mL). The mixture was stirred for 12 h at 85 °C (Ar atmosphere), cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using EtOAc, gave **31** (203 mg, 74%) as an oil: FTIR (CH_2Cl_2 cast) 3379, 2963, 2930, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 6.2 Hz, 3 H), 1.66−1.83 (m, 2 H), 3.19−3.31 (m, 2 H), 2.90 (br s, 2 H), 3.48 (s, 3 H), 4.02 (dqd, J = 8.4, 6.3, 3.8 Hz, 1 H), 5.08 (s, 2 H), 6.60−6.65 (m, 2 H), 6.90−6.94 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9 (q), 38.0 (t), 43.1 (t), 55.8 (q), 67.8 (d), 95.5 (t), 114.7 (d), 117.9 (d), 143.4 (s), 150.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{20}NO_3$ [M + H] 226.14377, found 226.14374.

(3-Hydroxybutyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (31a). *i*-Pr_2NEt (0.36 mL, 2.06 mmol) was added to a stirred and cooled (−78 °C) solution of **31** (385.8 mg, 1.71 mmol) in CH_2Cl_2 (8 mL). PhOCOCl (0.26 mL, 2.06 mmol) was then added at a fast dropwise rate, and stirring was continued for 1 h (Ar atmosphere). The mixture was diluted with $CHCl_3$, washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica, using 1:1 to 2:1 EtOAc−hexane, gave **31a** (543 mg, 90%) as a pale yellow oil: FTIR (CH_2Cl_2 cast)

3433, 2963, 1719, 1594 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, $J = 6.3$ Hz, 3 H), 1.56 (br m, 1 H), 1.76 (br m, 1 H), 2.80 (br s, 1 H), 3.50 (s, 3 H), 3.54 (br m, 1 H), 3.95 (dqd, $J = 9.5$, 6.3, 3.2 Hz, 1 H), 4.20 (br m, 1 H), 5.19 (s, 2 H), 7.05−7.10 (m, 4 H), 7.16−7.22 (m, 3 H), 7.33 (t, $J = 7.8$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (q), 37.3 (t), 48.0 (t), 56.1 (q), 64.1 (q), 94.5 (t), 116.8 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d), 134.9 (s), 151.2 (s), 155.3 (s), 156.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{23}NNaO_5$ [M + Na] 368.14864, found 368.14690.

(3-Iodobutyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (31b). Imidazole (206 mg, 3.03 mmol) and Ph_3P (794 mg, 3.03 mmol) were added in that order to a stirred and cooled (−40 °C) solution of **31a** (523 mg, 1.51 mmol) in THF (8 mL). A solution of I_2 (576.5 mg, 3.03 mmol) in THF (2 mL) was added at a fast dropwise rate. After 30 min, the cold bath was removed, and stirring was continued for 40 min. Water was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous Na_2SO_3 and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **31b** (620 mg, 90%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2955, 1721, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95 (d, $J = 6.8$ Hz, 3 H), 2.05 (dddd, $J =$ 14.2, 9.0, 5.6, 5.2 Hz, 1 H), 2.18 (dddd, $J = 14.3$, 8.7, 8.7, 5.6 Hz, 1 H), 3.50 (s, 3 H), 3.79 (br m, 1 H), 3.88 (br m, 1 H), 4.16 (dqd, $J = 8.6$, 6.8, 5.2 Hz, 1 H), 5.19 (s, 2 H), 7.04−7.10 (m, 4 H), 7.15−7.24 (m, 3 H), 7.33 (t, $J = 7.4$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7 (d), 28.9 (q), 40.8 (t), 51.4 (t), 56.1 (q), 94.5 (t), 116.8 (d), 121.6 (d), 125.3 (d), 128.3 (d), 129.2 (d), 135.2 (s), 151.3 (s), 154.1 (s), 156.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{23}INO_4$ [M + H] 456.06664, found 456.06683.

(4-Hydroxyphenyl)(3-iodobutyl)carbamic Acid Phenyl Ester (31c). $BCl_3{\cdot}SMe_2$ (0.80 mL, 2 M, 1.60 mmol) was added dropwise to a stirred solution of **31b** (604.5 mg, 1.33 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). After 105 min, the mixture was quenched with water and extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 3:7 EtOAc−hexane, gave **31c** (468 mg, 86%) as a white solid: mp 112−114 °C; FTIR (CH_2Cl_2 cast) 3356, 2922, 1717, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (d, $J = 6.8$ Hz, 3 H), 2.03 (dddd, $J = 14.4$, 9.0, 7.2, 5.4 Hz, 1 H), 2.10−2.23 (m, 1 H), 3.66−4.00 (m, 2 H), 4.15 (dqd, $J = 8.6$, 6.8, 5.0 Hz, 1 H), 5.29 (s, 1 H), 6.63−6.87 (m, 3 H), 7.00−7.22 (m, 4 H), 7.33 (br, m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6 (d), 28.9 (q), 40.8 (t), 51.5 (t), 116.1 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d), 134.0 (s), 151.2 (s), 154.3 (s), 154.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{18}INNaO_3$ [M + Na] 434.02237, found 434.02254.

(3-Iodobutyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (31d). $PhI(OAc)_2$ (436 mg, 1.32 mmol) was added in portions to a stirred solution of **31c** (453 mg, 1.10 mmol) in MeOH (11 mL). After 30 min, the solvent was evaporated at room temperature. Flash chromatography of the residue over silica gel, using 3:7 EtOAc−hexane, gave **31d** (414 mg, 85%) as an oil: FTIR (CH_2Cl_2 cast) 2960, 1724, 1673, 1633, 1593 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.61 (d, $J = 6.7$ Hz, 3 H), 1.88 (dddd, $J =$ 14.1, 9.7, 5.0, 5.0 Hz, 1 H), 2.08 (dddd, $J = 14.0$, 10.0, 9.0, 5.0 Hz, 1 H), 2.71 (s, 3 H), 3.42 (ddd, $J = 14.1$, 10.0, 5.2 Hz, 1 H), 3.60 (ddd, $J = 14.1$, 9.8, 5.1 Hz, 1 H), 3.77 (dqd, $J = 8.9$, 6.8, 4.5 Hz, 1 H), 6.06−6.16 (m, 4 H), 6.88 (tt, $J = 7.2$, 1.3 Hz, 1 H), 7.00−7.10 (m, 4 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 25.4 (d), 29.0 (q), 43.5 (d), 44.7 (d), 50.7 (q), 83.4 (s), 121.6 (d), 125.5 (d), 129.4 (d), 130.5 (d), 143.7 (d), 151.4 (s), 152.3 (s), 184.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{20}INNaO_4$ [M + Na] 464.03293, found 464.03264.

6-Hydroxy-4-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (31f). A solution of Bu_3SnH (0.06 mL, 0.21 mmol) and AIBN (6.3 mg, 0.04 mmol) in PhMe (4 mL) was added over 4 h (syringe pump) to a stirred and heated (85 °C) solution of **31d** (85.5 mg, 0.19 mmol) in PhMe (10 mL) (N_2 atmosphere). After the addition, heating was continued for 4 h. The mixture was cooled to room temperature, concentrated hydrochloric acid (1 drop) was added, and the mixture was stirred for 2 h. Evaporation of the solvent and flash chromatography of residue over silica gel, using 1:5 EtOAc−hexane, gave **31f** (32.8 mg, 66%) as a solid: mp 131−133 °C; FTIR (CH_2Cl_2 cast) 3369, 2959, 1689, 1613, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32 (d, $J = 7.0$ Hz, 3 H), 1.66 (dddd, $J = 13.7$, 7.6, 7.6, 7.6 Hz, 1 H), 2.14 (dddd, $J = 13.3$, 5.7, 5.7, 5.7 Hz, 1 H), 2.88 (apparent sextets, $J = 7.0$ Hz, 1 H), 3.85−3.93 (br m, 2 H), 4.81 (s, 1 H), 6.61 (dd, $J = 8.8$, 2.8 Hz, 1 H), 6.67 (d, $J = 2.8$ Hz, 1 H), 7.15−7.19 (m, 2 H), 7.21 (tt, $J = 7.3$, 1.1 Hz, 1 H), 7.38−7.41 (m, 2 H), 7.58 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 31.1 (d), 31.8 (t), 43.6 (t), 113.3 (d), 113.4 (d), 121.7 (d), 125.2 (d), 125.5 (d), 129.3 (d), 130.1 (s), 137.1 (s), 151.2 (s), 152.5 (s), 153.5 (s); exact mass *m*/*z* calcd for $C_{17}H_{17}NO_3$ 283.12085, found 283.12080.

(β*S*,γ*R*)-β-Ethyl-γ-[(4-methoxyphenyl)amino]benzenepropanol (33).[18] A solution of PhCHO (0.96 mL, 9.42 mmol), *p*-anisidine (**16**) (1.28 g, 10.36 mmol), and L-proline (0.18 g, 0.94 mmol) in *N*-methyl-2-pyrrolidinone (8 mL) was stirred at room temperature for 5 h and then cooled to −20 °C. PrCHO (2.55 mL, 28.27 mmol) was added dropwise and stirring was continued for 24 h. The mixture was quenched with aqueous pH 7.0 buffer and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (12 mL) and $NaBH_4$ (1.07 g, 28.27 mmol) was added to the resulting solution, which was stirred at 0 °C for 1 h. The cooling bath was removed and stirring was continued for 7 h. Aqueous pH 7 buffer was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **33**[18] (2.01 g, 75%) as a white solid.

(1*S*,2*S*)-[(2-Hydroxymethyl)-1-phenylbutyl](4-methoxyphenyl)carbamic Acid Phenyl Ester (33a). *i*-Pr_2NEt (0.20 mL, 1.15 mmol), PhOCOCl (0.14 mL, 1.15 mmol), and DMAP (2 mg) were added in that order to a stirred solution of **33** (272 mg, 0.95 mmol) in THF (10 mL). After 2 h, EtOAc was added and the solution was washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc−hexane, gave **33a** (333 mg, 86%) as a solid, which was used directly in the next step. The material appeared (^1H NMR) to contain ca. 6% of a diastereoisomer.

(1*S*,2*S*)-[2-(Hydroxymethyl)-1-phenylbutyl](4-hydroxyphenyl)carbamic Acid Phenyl Ester (33b). BBr_3 (1 M in CH_2Cl_2, 2.47 mL, 2.47 mmol) was added dropwise to a stirred solution of **33a** (333 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). After 4 h, the mixture was quenched with water and extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc−hexane, gave **33b** (286 mg, 89%) as a solid, which was used directly in the next step.

(1*S*,2*S*)-(4-Hydroxyphenyl)[(2-iodomethyl)-1-phenylbutyl]carbamic Acid Phenyl Ester (33c). Imidazole (86 mg, 1.27 mmol) and Ph_3P (333 mg, 1.27 mmol) were added in that order to a stirred solution of **33b** (248 mg, 0.63 mmol) in THF (8 mL). Solid I_2 (322 mg, 1.27 mmol) was added in one portion. After 5 min, EtOAc and water were added, and the organic phase was washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:10 EtOAc−hexane to 1:2 EtOAc−hexane, gave **33c** (290 mg, 91%) as an oil. The compound was not characterized, as it contains a small amount (100:12) of a diastereoisomer that is removed at the next stage.

(1*S*,2*S*)-(2-Iodomethyl-1-phenylbutyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (33d). $PhI(OAc)_2$ (223 mg, 0.69 mmol) was added in portions to a stirred solution of **33c** (290 mg, 0.58 mmol) in MeOH (9 mL). After 25 min, water was added and the mixture was extracted with EtOAc. The

combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **33d** (249 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2964, 1720, 1674, 1493 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 1.00 (t, J = 7.4 Hz, 3 H), 1.39−1.43 (m, 1 H), 1.82−1.89 (m, 1 H), 2.39−2.43 (m, 1 H), 2.95−3.02 (m, 1 H), 3.35 (br s, 3 H), 3.52 (dd, J = 10.6, 2.9 Hz, 1 H), 5.10−5.40 (br s, 1 H), 6.22 (dd, J = 10.0, 1.5 Hz, 1 H), 6.20−6.28 (br s, 1 H), 6.58−6.62 (br s, 1 H), 6.99 (br s, 2 H), 7.18 (tt, J = 7.5, 1.0 Hz, 1 H), 7.29−7.44 (m, 6 H), 7.68 (d, J = 6.9 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 11.1 (q), 16.6 (t), 24.7 (t), 40.2 (d), 51.1 (q), 61.9 (d), 84.4 (s), 121.7 (d), 125.6 (d), 128.4 (d), 128.9 (d), 129.5 (d), 129.9 (d), 130.5 (d), 140.5 (s), 144.6 (d), 150.9 (s), 152.4 (s), 184.3 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{26}INNaO_4$ [M + Na] 554.07988 found 554.07956.

(2*S*,3*R*,4a*R*,8a*R*)-3-Ethyl-8a-methoxy-6-oxo-2-phenyl-3,4,4a,5,6,-8a-hexahydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (*trans*-33e) and (2*S*,3*R*,4a*R*,8a*S*)-3-Ethyl-8a-methoxy-6-oxo-2-phenyl-3,4,4a,5,6,8a-hexahydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (*cis*-33e). A solution of Bu_3SnH (0.04 mL, 0.14 mmol) and AIBN (4 mg, 0.02 mmol) in PhH (2 mL) was added over 4 h (syringe pump) to a stirred and heated (85 °C) solution of **33d** (64 mg, 0.12 mmol) in PhH (6 mL) (N_2 atmosphere). After the addition, heating was continued for 4 h. Evaporation of the solvent and flash chromatography of residue over silica gel, using 1:10 to 1:4 EtOAc−hexane, gave *trans*-**33e** (23.3 mg, 48%) and *cis*-**33e** (11.8 mg, 24%) as oils. *trans*-**33e**: FTIR (CH_2Cl_2 cast) 2961, 2933, 1718, 1683, 1495 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.60 (t, J = 7.4 Hz, 3 H), 0.77 (sextet, J = 7.4 Hz, 1 H), 0.94 (sextet, J = 7.4 Hz, 1 H), 1.00 (ddd, J = 13.8, 4.4, 3.3 Hz, 1 H), 1.78 (ddddd, J = 13.8, 7.4, 7.4, 6.9, 4.4 Hz, 1 H), 2.00−2.11 (m, 2 H), 2.40 (dddd, J = 12.6, 4.9, 3.3, 3.3 Hz, 1 H), 2.55 (dd, J = 16.4, 12.6 Hz, 1 H), 5.45 (d, J = 6.9 Hz, 1 H), 2.82 (s, 3 H), 5.91 (dd, J = 10.4, 1.1 Hz, 1 H), 6.86−6.91 (m, 1 H), 6.93−6.97 (m, 2 H), 6.99−7.04 (m, 2 H), 7.09−7.14 (m, 3 H), 7.42 (d, J = 10.4 Hz, 1 H), 7.63−7.67 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 11.7 (q), 26.4 (t), 27.3 (t), 35.0 (d), 40.2 (t), 41.2 (d), 50.3 (q), 61.1 (d), 86.4 (s), 122.2 (d), 125.4 (d), 125.7 (d), 128.1 (d), 128.3 (d), 129.5 (d), 131.4 (d), 139.0 (s), 147.3 (d), 151.7 (s), 155.6 (s), 197.8 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{28}NO_4$ [M + H] 406.20128, found 406.20115.

cis-**33e**: FTIR (CH_2Cl_2 cast) 2932, 1725, 1687, 1494 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.30 (br m, 1 H), 0.59 (t, J = 7.5 Hz, 3 H), 0.88 (br m, 1 H), 1.09−1.30 (br m, 2 H), 1.76 (br m, 1 H), 2.15−2.30 (m, 2 H), 2.72 (dd, J = 16.0, 5.8 Hz, 1 H), 3.17 (s, 3 H), 5.98 (d, J = 6.7 Hz, 1 H), 6.03 (d, J = 10.4 Hz, 1 H), 6.63−6.69 (m, 2 H), 6.78−6.86 (m, 2 H), 6.90−7.00 (m, 3 H), 7.00−7.12 (m, 3 H), 7.37 (d, J = 10.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 11.8 (q), 25.9 (t), 27.3 (t), 40.2 (d), 41.5 (d), 41.7 (t), 50.7 (d), 65.2 (q), 88.1 (s), 122.1 (d), 125.5 (d), 127.4 (d), 128.3 (d), 128.4 (d), 129.0 (d), 129.3 (d), 141.4 (s), 145.6 (d), 151.6 (s), 154.2 (s), 196.3 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{28}NO_4$ [M + H] 406.20128, found 406.20137. NOEs were observed between the OC**H**$_3$ group and both the C**H**(Ph) and ring-fusion hydrogen, thus establishing the stereochemistry shown for *cis*-**33e**. Corresponding NOEs were not observed for *trans*-**33e**.

(2*S*,3*R*)-3-Ethyl-6-hydroxy-2-phenyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid Phenyl Ester (33f). Concentrated hydrochloric acid (one drop) was added to a stirred solution of *trans*-**33e** (20.0 mg, 0.049 mmol) in $CHCl_3$ (3 mL). Stirring was continued for 3 min, and the solvent was then evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **33f** (15.6 mg, 85%) as a solid: mp 170−171 °C.

cis-**33e** was subjected to the same conditions. Concentrated hydrochloric acid (one drop) was added to a stirred solution of *cis*-**33e** (11.0 mg, 0.027 mmol) in $CHCl_3$ (3 mL). Stirring was continued for 3 min, and the solvent was then evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **33f** (8.3 mg, 82%) as a solid: mp 170−171 °C; FTIR ($CHCl_3$ cast) 3380, 2961, 1691, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95−1.05 (m, 4 H), 1.25−1.39 (m, 1 H), 2.25−2.35 (br m, 1 H), 2.52 (dd, J = 16.5, 11.4 Hz, 1 H), 2.84 (dd, J = 16.5, 5.0 Hz, 1 H), 4.74 (s, 1 H), 5.71 (d, J = 5.0 Hz, 1 H), 6.65 (d, J = 3.0 Hz, 1 H), 6.69 (dd, J = 9.0, 3.0 Hz, 1 H), 6.92 (br d, J = 7.2 Hz, 2 H), 7.10−7.14 (m, 2 H), 7.17 (tt, J = 7.5, 1.1 Hz, 1 H), 7.24−7.28 (m, 3 H), 7.31 (tt, J = 7.9, 2.0 Hz, 2 H), 7.95 (br m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7 (q), 25.1 (t), 29.9 (t), 39.5 (d), 61.8 (d), 113.9 (d), 115.1 (d), 121.7 (d), 125.4 (d), 127.3 (d), 127.8 (d), 128.2 (d), 129.2 (d), 130.1 (s), 130.6 (s), 139.2 (s), 151.1 (s), 151.7 (s), 153.4 (s), (apparently, two aromatic signals overlap); exact mass m/z calcd for $C_{24}H_{23}NO_3$ 373.16779, found 373.16811.

***cis*-3-[(4-Methoxymethoxy)phenyl]amino]cyclohexanol (*cis*-35) and *trans*-3-[(4-Methoxymethoxy)phenyl]amino]cyclohexanol (*trans*-35).** CuI (35.8 mg, 0.19 mmol), L-proline (43.3 mg, 0.38 mmol), K_2CO_3 (520.0 mg, 3.76 mmol), and 3-aminocyclohexanol (cis/trans mixture, 325 mg, 2.82 mmol) were added in that order to a solution of iodide **15** (499 mg, 1.88 mmol) in DMSO (8 mL). The mixture was stirred for 12 h at 85 °C (Ar atmosphere), cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc−hexane, gave *cis*-**35** (303 mg, 64%) and *trans*-**35** (57 mg, 12%) as oils. *trans*-**35**: FTIR (CH_2Cl_2 cast) 3383, 2932, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.31 (m, 1 H), 1.46−1.63 (m, 4 H), 1.74−1.81 (br m, 1 H), 1.94−2.00 (br m, 2 H), 2.55 (br s, 2 H), 3.47 (s, 3 H), 3.66 (dddd, J = 8.6, 8.6, 3.7, 3.7 Hz, 1 H), 4.10 (br m, 1 H), 5.06 (s, 2 H), 6.53−6.58 (m, 2 H), 6.86−6.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4 (t), 32.2 (t), 33.2 (t), 39.9 (t), 48.1 (d), 55.8 (d), 66.9 (q), 95.6 (t), 114.5 (d), 118.0 (d), 142.5 (s), 149.2 (s); exact mass m/z calcd for $C_{14}H_{21}NO_3$ 251.15215, found 251.15243. We observed no NOE between C**H**(OH) and C**H**(N); consequently the amino and hydroxy groups are trans.

Major isomer (*cis*-**35**): FTIR (CH_2Cl_2 cast) 3365, 2932, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00−1.44 (m, 4 H), 1.79−1.87 (m, 1 H), 1.89−2.02 (m, 2 H), 2.28 (br d, J = 12.2 Hz, 1 H), 2.56 (br s, 2 H), 3.26 (dddd, J = 10.0, 10.0, 3.7, 3.7 Hz, 1 H), 3.47 (s, 3 H), 3.74 (dddd, J = 8.5, 8.5, 4.0, 4.0 Hz, 1 H), 5.08 (s, 2 H), 6.53−6.58 (m, 2 H), 6.87−6.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.2 (t), 34.8 (t), 41.9 (t), 51.2 (d), 55.8 (d), 69.2 (q), 95.6 (t), 114.7 (d), 118.0 (d), 142.4 (s), 149.5 (s), 21.0 (t); exact mass m/z calcd for $C_{14}H_{21}NO_3$ 251.15215, found 251.15191. A TROESY spectrum showed an NOE between C**H**N and C**H**OH, suggesting that this isomer has the amino and hydroxy groups cis.

***cis*-(3-Hydroxycyclohexyl)[(4-methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (35a).** *i*-Pr_2NEt (0.24 mL, 1.40 mmol) and PhOCOCl (0.18 mL, 1.40 mmol) were added in that order to a stirred solution of *cis*-**35** (major isomer) (294 mg, 1.18 mmol) in CH_2Cl_2 (6 mL). Stirring was continued for 5 h, water was then added, and the mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 3:7 EtOAc−hexane, gave **35a** (397 mg, 91%) as an oil: FTIR (CH_2Cl_2 cast) 3430, 2934, 1716, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (qd, J = 12.4, 3.5 Hz, 1 H), 1.12−1.32 (m, 2 H), 1.37 (dt, J = 13.4, 3.2 Hz, 1 H), 1.80 (dq, J = 13.4, 3.3 Hz, 1 H), 1.92 (br m, 2 H), 2.26 (br d, J = 11.7 Hz, 1 H), 3.51 (s, 3 H), 3.72 (dddd, J = 10.5, 10.5. 4.1, 4.1 Hz, 1 H), 4.28 (tt, J = 12.2, 3.5 Hz, 1 H), 5.19 (s, 2 H), 6.98−7.09 (m, 4 H), 7.09−7.18 (m, 3 H), 7.30 (t, J = 7.4 Hz, 2 H) (OH signal not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (t), 30.3 (t), 34.4 (t), 40.7 (t), 56.1 (d), 54.9 (d), 69.5 (q), 94.4 (t), 116.3 (d), 121.6 (d), 125.2 (d), 129.1 (d), 130.8 (d), 131.5 (s), 151.4 (s), 154.2 (s), 156.7 (s); exact mass m/z calcd for $C_{21}H_{25}NO_5$ 371.17328, found 371.17418.

(*trans*-3-Iodocyclohexyl)[(4-methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (35b). Imidazole (106 mg, 1.56 mmol), Ph_3P (410 mg, 1.56 mmol), and I_2 (396 mg, 1.56 mmol) were added in that order to a stirred solution of **35a** (290 mg, 0.78 mmol) in THF

(5 mL). After 10 min, water was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:9 EtOAc−hexane, gave **35b** (338 mg, 90%) as an oil: FTIR (CH_2Cl_2 cast) 2933, 1717, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (br t, J = 14.8 Hz, 1 H), 1.42 (qd, J = 12.3, 2.7 Hz, 1 H), 1.63 (td, J = 12.6, 3.2 Hz, 1 H), 1.71 (dt, J = 14.7, 3.2 Hz, 1 H), 1.90−2.07 (m, 3 H), 2.33 (br d, J = 13.6 Hz, 1 H), 3.50 (s, 3 H), 4.78 (br t, J = 12.0 Hz, 1 H), 4.84 (s, 1 H), 5.19 (s, 2 H), 7.02−7.18 (m, 7 H), 7.31 (t, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 31.0 (t), 33.2 (d), 35.1 (t), 40.7 (t), 54.9 (d), 56.2 (q), 94.5 (t), 116.4 (d), 121.7 (d), 125.2 (d), 129.1 (d), 130.5 (d), 132.4 (s), 151.4 (s), 153.9 (s), 156.7 (s); exact mass m/z calcd for $C_{21}H_{24}INO_4$ 481.07501, found 481.074378. The chemical shift for C**H**(I) suggests[26] that the halogen is axial.

(4-Hydroxyphenyl)(*trans*-3-iodocyclohexyl)carbamic Acid Phenyl Ester (35c). BCl_3·SMe_2 (2 M in CH_2Cl_2, 0.39 mL, 0.77 mmol) was added dropwise to a stirred solution of **35b** (310 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) (Ar atmosphere). After 5 min, the mixture was quenched with water and extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **35c** (240 mg, 85%) as a white solid: mp 101−103 °C; FTIR (CH_2Cl_2 cast) 3350, 2936, 1717, 1684, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (br t, J = 12.8 Hz, 1 H), 1.36−1.42 (br m, 1 H), 1.56 (br t, J = 12.1 Hz, 1 H), 1.69 (br d, J = 13.7 Hz, 1 H), 1.87−2.06 (m, 3 H), 2.31 (br d, J = 12.1 Hz, 1 H), 4.76−4.82 (br m, 1 H), 4.84 (br s, 1 H), 6.27 (s, 1 H), 6.47−6.80 (br m, 2 H), 6.83−7.08 (br m, 3 H), 7.15−7.21 (br m, 2 H), 7.31−7.42 (br m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3 (t), 31.1 (t), 33.1 (d), 35.1 (t), 40.7 (t), 54.8 (q), 115.9 (d), 121.6 (d), 125.4 (d), 128.6 (s), 129.2 (d), 130.4 (d), 151.2 (s), 154.5 (s), 155.8 (s); exact mass m/z calcd for $C_{19}H_{20}INO_3$ 437.04880, found 437.04821.

5-Hydroxymethyl-1-[4-(methoxymethoxy)phenyl]pyrrolidin-2-one (36). DMF (3 mL) was injected into an oven-dried, round-bottomed flask containing **15** (606.1 mg, 2.296 mmol) and (±)-pyroglutaminol (0.80 g, 6.9 mmol) (Ar atmosphere). Cs_2CO_3 (1.496 g, 4.592 mmol) and CuI (87.2 mg, 0.459 mmol) were tipped in, and *N*,*N*′-dimethylethylenediamine (0.10 mL, 0.92 mmol) was injected. The mixture was lowered into an oil bath (80 °C) and stirred for 30 h. The mixture was cooled to room temperature and filtered through a pad of silica gel (2 × 3 cm^2), using 20% MeOH−EtOAc (100 mL) as a rinse. The filtrate was evaporated and the residue was kept overnight under oil pump vacuum. Flash chromatography of the residue over silica gel (2.6 × 28 cm), using MeOH−EtOAc mixtures from 0% to 10% MeOH, gave **36** (411.1 mg, 71%) as an oil: FTIR (CH_2Cl_2 cast) 3391, 2950, 1668, 1607, 1511, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.04−2.12 (m, 1 H), 2.15−2.25 (m, 1 H), 2.38−2.46 (m, 1 H), 2.60 (ddd, J = 17.1, 10.1, 7.6 Hz, 1 H), 3.08 (br s, 1 H), 3.43 (s, 3 H), 3.44−3.56 (m, 2 H), 4.05−4.12 (m, 1 H), 5.11 (AB q, J = 6.9 Hz, $\Delta\nu_{AB}$ = 4.4 Hz, 2 H), 7.00 (apparent d, J = 9.0 Hz, 2 H), 7.21 (apparent d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (t), 31.3 (t), 55.9 (q), 61.8 (d), 62.0 (t), 94.5 (t), 116.8 (d), 126.2 (d), 131.2 (s), 155.5 (s), 175.5 (s); exact mass m/z calcd for $C_{13}H_{17}NO_4$ 251.11575, found 251.11562.

5-Iodomethyl-1-[4-(methoxymethoxy)phenyl]pyrrolidin-2-one (36a). Imidazole (104.8 mg, 1.542 mmol), Ph_3P (262.6 mg, 1.002 mmol), and I_2 (254.5 mg, 1.002 mmol) were added in that order to a stirred solution of **36** (193.5 mg, 0.7710 mmol) in dry THF (10 mL) (Ar atmosphere). Stirring was continued for 1.5 h, and the mixture was quenched with water (5 mL). Saturated aqueous $Na_2S_2O_3$ was added and the mixture was partitioned between brine and $CHCl_3$. The aqueous phase was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 × 28 cm), using first 50% EtOAc−hexane and then EtOAc, gave **36a** (267.2 mg, 96%) as an oil: FTIR ($CHCl_3$ cast) 2953, 1694, 1510, 1392, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.92−2.00 (m, 1 H), 2.35−2.43 (m, 1 H), 2.50−2.58 (m, 1 H), 2.73 (tt, J = 10.6, 6.7 Hz, 1 H), 3.16 (dd, J = 10.5, 6.5 Hz, 1 H), 3.31 (dd, J = 10.5, 2.5 Hz, 1 H), 3.47 (s, 3 H), 4.12 (tt, J = 4.7, 4.1 Hz, 1 H), 5.16 (AB q, J = 6.9 Hz, $\Delta\nu_{AB}$ = 4.4 Hz, 2 H), 7.07 (apparent d, J = 9.0 Hz, 2 H), 7.26 (apparent d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.2 (t), 24.6 (t), 30.5 (t), 55.9 (q), 59.5 (d), 90.4 (t), 116.9 (d), 126.4 (d), 130.3 (s), 155.7 (s), 174.1 (s); exact mass m/z calcd for $C_{13}H_{16}INO_3$ 361.01749, found 361.01839.

1-(4-Hydoxyphenyl)-5-(iodomethyl)pyrrolidin-2-one (36b). Me_3SiBr (0.22 mL, 1.7 mmol) was injected at a fast dropwise rate into a stirred solution of **36a** (264.1 mg, 0.7316 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued for 30 min, and the mixture was quenched with water (10 mL). The aqueous phase was extracted three times with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 26 cm), using EtOAc and then 5% MeOH−EtOAc, gave **36b** (170.1 mg, 73%) as an oil: FTIR (microscope) 3057, 2981, 2815, 1639, 1595, 1509 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.69−1.77 (m, 1 H), 2.21−2.29 (m, 1 H), 2.38 (quintet, J = 1.8 Hz, 1 H), 2.48−2.55 (m, 1 H), 3.20 (dd, J = 10.6, 5.6 Hz, 1 H), 3.35 (dd, J = 10.6, 2.3 Hz, 1 H), 4.11−4.16 (m, 1 H), 6.77 (apparent d, J = 8.9 Hz, 2 H), 7.16 (apparent d, J = 8.9 Hz, 2 H), 9.42 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 13.9 (t), 23.7 (t), 30.0 (t), 58.1 (d), 115.2 (d), 126.2 (d), 127.9 (s), 155.3 (s), 172.9 (s); exact mass m/z calcd for $C_{11}H_{12}INO_2$ 316.99127, found 316.99091.

5-Iodomethyl-1-(1-methoxy-4-oxocyclohexa-2,5-dienyl)pyrrolidin-2-one (36c). $PhI(OAc)_2$ (112.5 mg, 0.3494 mmol) was tipped into a stirred solution of **36b** (97.0 mg, 0.2795 mmol) in dry MeOH (10 mL). Stirring was continued for 30 min, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 × 26 cm), using first 50% EtOAc−hexane and then EtOAc, gave **36c** (86.4 mg, 89%) as an oil: FTIR ($CHCl_3$ cast) 2939, 1697, 1672, 1634, 1456, 1386 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.00 (apparent t, J = 9.5 Hz, 1 H), 2.18−2.28 (m, 2 H), 2.57−2.67 (m, 1 H), 3.22 (two overlapping s, 3 H), 3.37 (dd, J = 10.0, 7.7 Hz, 1 H), 3.49 (dd, J = 10.0, 2.4 Hz, 1 H), 4.17 (tm, J = 8.5 Hz, 1 H), 6.39 (apparent d, J = 10.3, 1.0 Hz, 2 H), 6.58 (dm, J = 9.2 Hz, 1 H), 6.76 (dm, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3 (t), 25.2 (t), 30.3 (t), 50.9 (q), 57.3 (d), 82.1 (s), 131.1 (d), 131.4 (d), 143.1 (d), 143.8 (d), 173.9 (s), 184.6 (s); exact mass m/z calcd for $C_{12}H_{14}INO_3$ 347.00183, found 347.00228.

3b-Methoxy-1,2,7,7a,8,8a-hexahydro-3b*H*-3a-azacyclopenta[*a*]indene-3,6-dione (36d). A solution of Bu_3SnH (0.08 mL, 0.28 mmol) and AIBN (10 mg, 0.06 mmol) in PhMe (5 mL) was added over 4 h by syringe pump to a stirred and heated (85 °C) solution of **36c** (80.8 mg, 0.233 mmol) in PhMe (15 mL). Heating at 85 °C was continued for 8 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.6 × 30 cm), using EtOAc, gave **36d** (42.9 mg, 83%) as an oil: FTIR (CH_2Cl_2 cast) 2938, 1694, 1457, 1390, 1346, 1326 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34 (td, J = 11.9, 9.3 Hz, 1 H), 1.64−1.73 (m, 1 H), 2.23 (quintet, J = 6.3 Hz, 1 H), 2.26−2.32 (m, 1 H), 2.41 (dd, J = 12.7, 4.1, 1 H), 2.43−2.49 (m, 1 H), 2.68−2.76 (m, 1 H), 2.75 (dd, J = 16.7, 6.5 Hz, 1 H), 2.98−2.34 (m, 1 H), 3.49 (s, 3 H), 4.20 (tt, J = 9.4, 6.0 Hz, 1 H), 6.05 (apparent d, J = 10.5 Hz, 1 H), 7.66 (dm, J = 10.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.9 (t), 35.9 (t), 36.9 (t), 38.7 (t), 46.4 (d), 52.0 (q), 61.4 (d), 87.6 (s), 128.6 (d), 140.8 (d), 174.5 (s), 196.9 (s); exact mass m/z calcd for $C_{12}H_{15}NO_3$ 221.10519, found 221.10554.

6-Hydroxy-1,2,8,8a-tetrahydro-3a-azacyclopenta[*a*]inden-3-one (36e). TsOH·H_2O (4.3 mg) was added to a stirred mixture of **36d** (29.3 mg, 0.132 mmol) and 4 Å molecular sieves (ca. 20 mg)

(26) Pretsch, E.; Bühlmann, P.; Affoter, C. *Structure Determination of Organic Compounds. Tables of Spectral Data*; Springer: Heidelberg, Germany, 2000; p 201.

in CH_2Cl_2 (10 mL), and stirring was continued for 40 min. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 × 29 cm), using EtOAc, gave **36e** (20.5 mg, 82%) as a white solid: FTIR (microscope) 3203, 2975, 1651, 1610, 1500, 1453 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.94−2.02 (m, 1 H), 2.44 (quintet of m, J = 7.3 Hz, 1 H), 2.50 (ddd, J = 16.6, 8.6, 0.7 Hz, 1 H), 2.79−2.90 (m, 2 H), 3.10 (dd, J = 15.7, 8.2 Hz, 1 H), 4.64 (tdd, J = 9.8, 8.3, 6.2 Hz, 1 H), 6.60 (dd, J = 8.4, 2.5 Hz, 1 H), 6.67−6.69 (m, 1 H), 7.29 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.8 (t), 36.7 (t), 37.2 (t), 65.4 (d), 113.8 (d), 114.5 (d), 116.2 (d), 132.6 (s), 138.0 (s), 156.1 (s) (carbonyl signal not observed); exact mass m/z calcd for $C_{11}H_{11}NO_2$ 189.07898, found 189.07917.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support. S.P.F. held an NSERC Graduate Fellowship.

Supporting Information Available: Experimental procedures for **27c′** (from **38a**), **27d′**, **27e′**, **27f′**, **27h′**, **27c″** (from **38a**), **27d″**, **27e″**, **27f″**, **27g″**, **27h″**, **27i″**, **27j″**, **27l″**, **27a‴**, **27b‴**, **27c‴**, **27d‴**, **27e‴**, **27f‴**, **28**, **28a**, **28b**, **28c**, **28d**, **28e**, **28f**, **29**, **29a**, **29b**, **29c**, **29d**, **29e**, **29f**, **30**, **30a**, **30b**, **30c**, **30d**, **30e**, **30f**, **30h**, **30j**, **32**, **32a**, **32b**, **32c**, **32d**, **32e**, *trans*-**32f**, *cis*-**32f**, **32g**, **32i**, **32k**, **34a**, **34b**, **34c**, **34d**, **34e**, **34g**, **35d**, **35e**, **35f**, **37**, **37a**, **37b**, **37c**, **37d**, **37e**, **37f**, **37g**, **38**, **38a**, **38a′**, **39**, **39c**, **39d**, **39f**, and **54**, and NMR spectra of **15**, **27**, **27a**, **27a′**, **27a″**, **27a‴**, **27b**, **27b′**, **27b″**, **27b‴**, **27c**, **27c′**, **27c″**, **27c‴**, **27d**, **27d′**, **27d″**, **27d‴**, **27e′**, **27e″**, **27e‴**, **27f**, **27f′**, **27f″**, **27f‴**, **27h**, **27h′**, **27h″**, **27j**, **27j″**, **27l″**, **28**, **28a**, **28b**, **28c**, **28f**, (*S*)-**28**, (*S*)-**28a**, (*S*)-**28b**, (*S*)-**28c**, (*S*)-**28f**, **29**, **29a**, **29b**, **29c**, **29f**, **30**, **30a**, **30b**, **30c**, **30d**, **30e**, **30f**, **30h**, **30j**, **31**, **31a**, **31b**, **31c**, **31d**, **31f**, **32**, **32a**, **32b**, **32c**, **32d**, **32e**, *cis*-**32f**, *trans*-**32f**, **32g**, **32i**, **32k**, **33d**, *cis*-**33e**, *trans*-**33e**, **33f**, **34a**, **34b**, **34c**, **34d**, **34e**, **34g**, *cis*-**35**, *trans*-**35**, **35a**, **35b**, **35c**, **35d**, **35e**, **35f**, **36**, **36a**, **36b**, **36c**, **36d**, **36e**, **37**, **37a**, **37b**, **37c**, **37d**, **37e**, **37g**, **38a**, **38a′**, **39**, **39c**, **39d**, and **39f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7026307