Asymmetric Synthesis of Pyrrolidinoindolines. Application for the Practical Total Synthesis of (−)-Phenserine

Audris Huang, Jeremy J. Kodanko, and Larry E. Overman*

Contribution from the Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

Received June 5, 2004; E-mail: leoverma@uci.edu

Abstract: A versatile route to enantiopure 3,3-disubstituted oxindoles and 3a-substituted pyrrolidinoindolines is described in which diastereoselective dialkylation of enantiopure ditriflate **10** with oxindole enolates is the central step. These reactions are rare examples of alkylations of prosterogenic enolates with chiral sp³ electrophiles that proceed with high facial selectivity (10−20:1). The scope of this method is explored, and a model to rationalize the sense of stereoselection is advanced. This dialkylation chemistry was used to synthesize (−)-phenserine on a multigram scale in six steps and 43% overall yield from 5-methoxy-1,3-dimethyloxindole (**27**) and to complete a short formal total synthesis of (−)-physostigmine (**2**).

Introduction

Pyrrolidinoindolines bearing a carbon substituent at C-3a of the hexahydropyrrolo[2,3-*b*]indole ring system (**1**), exemplified by (−)-physostigmine (**2**), (−)-flustramine B (**4**), and (−)-pseudophrynaminol (**5**), have been obtained from a diverse array of natural sources (Figure 1).[1] For example, physostigmine was isolated initially from the seeds of the African Calabar bean *Physostigma venenosum*,[2] whereas flustramine B was found in the marine bryozoan *Flustra foliacea*[3] and (−)-pseudophrynaminol in the skin of an Australian frog, *Pseudophryne coriacea*.[4]

A variety of biological activities are associated with 3a-substituted pyrrolidinoindolines.[1] Physostigmine is a potent reversible inhibitor of acetyl- and butyrylcholinesterase and is employed clinically to treat glaucoma. For almost two decades, physostigmine was evaluated in clinical trials for the symptomatic treatment of Alzheimer's disease.[5] However, its clinical use was compromised by its short duration of action, low bioavailability, and narrow therapeutic window.[6] (−)-Phenserine, a synthetic congener of (−)-physostigmine, is physostigmine's successor in the clinic[5a] because of its more-favorable pharmacological profile[7] and its ability to inhibit both acetylcholinest-
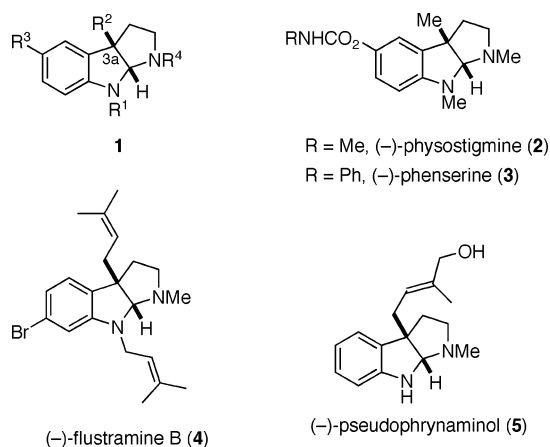
Figure 1. Representative hexahydropyrrolo[2,3-*b*]indole alkaloids with a quaternary center at C-3a.

erase[8] and β-amyloid plaque deposition in the brain.[9] Phenserine was advanced recently to phase III clinical trials.[10]

Several asymmetric methods for preparing hexahydropyrrolo-[2,3-*b*]indoles have been documented,[1b,11] many in the context of total syntheses of (−)-physostigmine (**2**).[12] One common route involves the construction of an enantioenriched oxindole intermediate containing a 2-aminoethyl side chain (or a progeni-

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(10) See Axonyx Home Page, http://www.axonyx.com/pipeline (accessed December 2003), or Senior Citizens Information and News, http://seniorjournal.com/NEWS/Alzheimer's/04-08-02Phenserine.htm (accessed December 2003).
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tor), which subsequently is cyclized under reductive conditions to generate the tricyclic pyrrolidinoindoline ring system.[13] One of the more-notable methods of this type, introduced by scientists at Hoechst-Roussel, involves alkylation of 5-methoxy-1,3-dimethyloxindole with chloroacetonitrile in the presence of a chiral phase-transfer catalyst.[12i] These conditions deliver the 3-cyanomethyl derivative in 78% ee; this intermediate, or the derived amine, is then enriched to a high enantiopurity by classical resolution.[12i,14] An optimized version of this sequence delivers (−)-phenserine in seven steps and 35% overall yield from 5-methoxy-1,3-dimethyloxindole.[12e,15]

Some years ago, we described a catalytic asymmetric construction of (−)- and (+)-physostigmine that utilized an asymmetric intramolecular Heck reaction to assemble oxindole **8** (Scheme 1).[12c,g] In this case, the chiral oxindole aldehyde product is generated in 95% ee and >99% ee after one recrystallization. However, the preparation of Heck cyclization precursor **7** was not straightforward and required the use of the expensive coupling reagent (benzotriazol-1-yloxy)tris(dimethyl-amino)phosphonium hexafluorophosphate (BOP).

Scheme 1

8
(>99% ee after recrystallization)

(−)-physostigmine (**2**)
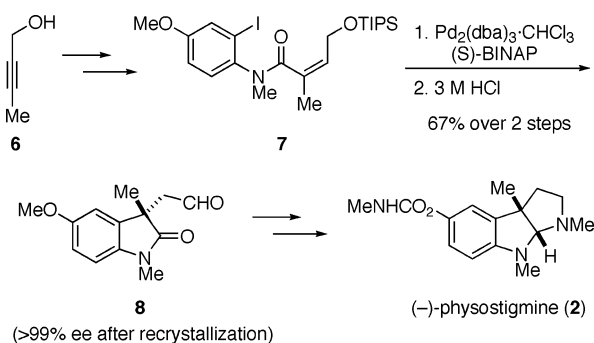
During an exploratory phase of recent investigations in our laboratory directed at the total synthesis of the tris(pyrrolidinoindoline) alkaloid hodgkinsine,[16] a new method for synthesizing pyrrolidinoindolines of high enantiopurity was conceived.[17] The central step in this approach is the dialkylation of enantiopure, tartrate-derived ditriflate **10**[18] with 2 equiv of an

Scheme 2
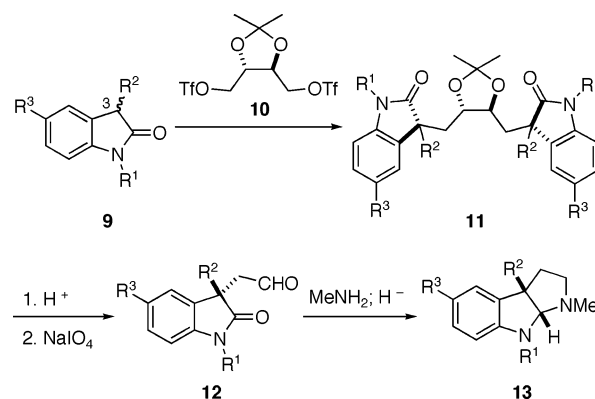
enolate formed from a C3-substituted oxindole **9** (Scheme 2). As dialkylation product **11** encodes 2 equiv of oxindole aldehyde **12**, an attractive route to enantiopure pyrrolidinoindolines **13** appeared possible. Although three stereoisomeric dialkylation products could result from the union of oxindole **9** and ditriflate **10**, our experience with related reactions of this dielectrophile with dienolates[19] suggested that one C_2-symmetric product should predominate. In this paper, we describe the development of this new asymmetric synthesis of 3,3-disubstituted oxindoles and 3a-substituted pyrrolidinoindolines.

Results

A. Synthesis of Oxindole Substrates. Our investigations into the asymmetric dialkylation reaction began with the preparation of a series of oxindoles containing a variety of substituents at N1, C3, and C5. Several different synthetic sequences were employed. The 1-alkyl-3-benzyloxindoles **16**[11c] and **17**[20] were synthesized by aldol condensation of benzaldehyde and oxindole to furnish benzylidene oxindole **15** (Scheme 3).[21] After N-alkylation of this intermediate with benzyl bromide or methyl iodide, reduction of the alkene double bond with zinc under acidic conditions provided oxindoles **16** and **17** in good yields. *N*-Benzyl-3-phenyloxindole (**20**) was prepared by adding phenylmagnesium chloride to *N*-benzylisatin (**18**)[22] and followed by the Lewis acid-promoted reductive deoxygenation[23] of
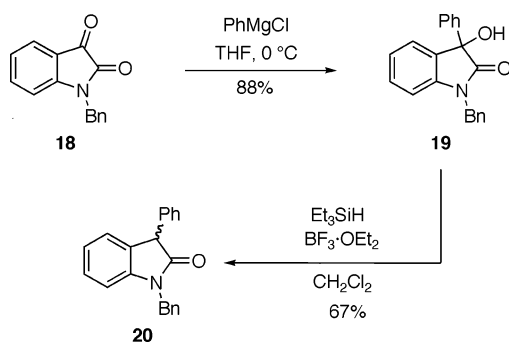
Scheme 3

16 R = Bn, 63% over 2 steps
17 R = Me, 84% over 2 steps
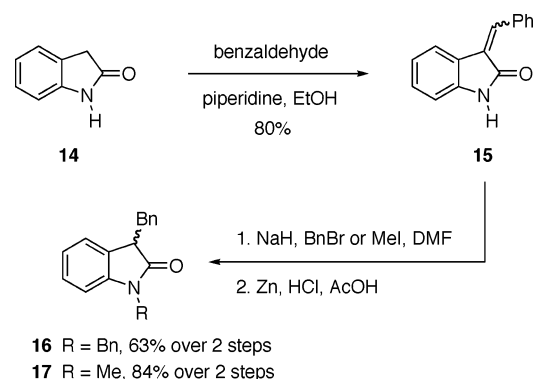
(12) For physostigmine, see: (a) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049−1052. (b) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675−678. (c) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (d) Node, M.; Hao, X.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715−719. (e) Pei, X.-F.; Yu, Q.-S.; Lu, B.-Y.; Greig, N. H.; Brossi, A. *Heterocycles* **1996**, *42*, 229−236. (f) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363−370. (g) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949−6951. (h) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572. (i) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872−875. (j) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982−5984. (k) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705−1707. (l) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411−414. (m) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109−112.

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Scheme 4

alcohol **19**[24] (Scheme 4). Finally, the synthesis of *N*-benzyl-3-isopropyloxindole (**22**) was accomplished in two steps from *N*-benzylisatin (**18**) via a sequential reaction with isopropyl-triphenylphosphorane and hydrogen over Pd/C (Scheme 5).

Scheme 5
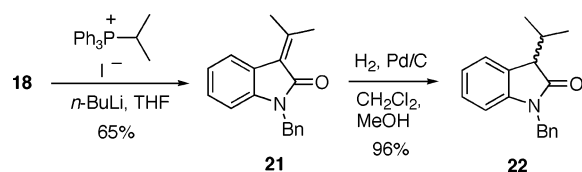
Several oxindoles (Figure 2) were prepared by methods reported in the literature or by straightforward modifications
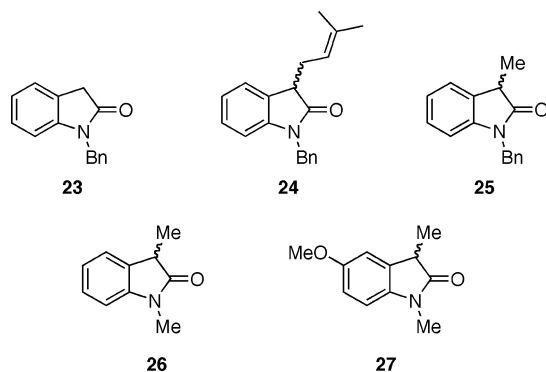

Figure 2. Oxindoles **23**−**27**.

thereof. Wolff−Kishner reduction of *N*-benzylisatin (**18**) furnished *N*-benzyloxindole (**23**).[25] Using a sequence reported by Fuji, appendage of a prenyl group to **23** was accomplished by reacting oxindole **23** with 1-bromo-3-methyl-2-butene to afford isopropylidene derivative **24**.[26] Oxindoles **25**[27] and **26**[28] were synthesized from 3-thiomethyloxindole by the Gassman oxindole synthesis.[29] Finally, 5-methoxy-1,3-dimethyloxindole (**27**) was prepared from commercially available 4-(methylamino)phenol sulfate using the Brossi group's modification of the original Julian synthesis.[13a,30]

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B. Scope of Diastereoselective Dialkylation Reactions. Initial Survey. Reactions of lithium enolates of oxindoles **16**, **17**, **20**−**22**, and **24**−**27** with ditriflate **10** were examined to explore the scope of the dialkylation reaction. The conditions chosen for this initial survey involved adding 2.2 equiv of a 1.0 M THF solution of LHMDS to an equimolar amount of the oxindole at −78 °C in THF containing a small amount of 1,3-dimethyl-3,4,5,6-tetrahydro-1(1*H*)-pyrimidinone (DMPU), leading to a final ratio 98:2 THF/DMPU and an oxindole concentration of 0.15 M. After 15−30 min, ditriflate **10** (1.0 equiv) was added as a solid in one portion, and the solution was allowed to warm to room temperature over an 18−24 h period in a −78 °C CO$_2$/*i*-PrOH bath. The results of these experiments are summarized in Table 1.

Generally, the dialkylation reactions proceeded cleanly to generate a mixture of three stereoisomeric dialkylation products. Stereoisomer ratios were determined by ^{1}H NMR, GC, or HPLC analysis of the crude product mixtures. In all but one instance, one *C*$_2$-symmetric product was formed predominantly; the *C*$_1$-symmetric isomer was produced in smaller amounts, and the second *C*$_2$-symmetric isomer was present in trace amounts only. In cases where stereoselection was good, the crude reaction product was filtered through a short column of silica gel and the resulting mixture of stereoisomeric dialkylation products was crystallized to provide the major isomer in pure form. In the best case (entry 9), diastereoselection was 9:1 (major isomer: sum of the two minor isomers), with the major dialkylation product, **36a**, being isolated in 70% yield as a high-melting crystalline solid. To obtain sufficient amounts of the minor *C*$_2$-symmetric diastereomers for isolation and characterization, most dialkylation reactions were repeated under conditions in which the reaction took place with lower stereoselectivity: 2.2 equiv of NaH, 2.2 equiv of oxindole in THF, and 1.0 equiv ditriflate **10** at 23 °C.

After examining the dialkylation reaction with oxindoles bearing an alkyl or aryl substituent at C3, we explored the possibility of carrying out the dialkylation of **10** with an oxindole enolate lacking substitution at C3. However, reaction of the lithium enolate of *N*-benzyloxindole (**23**) with ditriflate **10** yielded only the spiro-annulated product, **37** (eq 1).
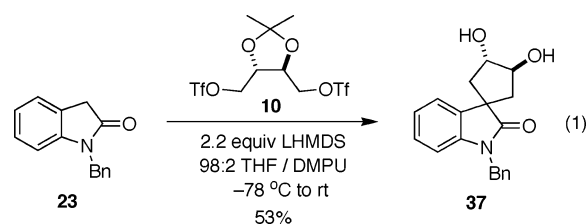
To explore the potential role of oxygens in the dioxolane ring of dielectrophile **10**, the dialkylation reaction of Table 1, entry 9, was repeated using cyclopentyl ditriflate **41** as the chiral dielectrophile. The synthesis of racemic **41** was accomplished from β-ketoester **38**[31] (Scheme 6). Bromination of β-ketoester **38**, followed by a Favorski rearrangement,[31] led to the formation of *trans*-cyclopentanedicarboxylate (**39**).[32] Reduction of this diester with LiAlH$_4$ gave diol **40**, which was triflated to provide

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**Table 1.** Dialkylation of Ditriflate **10** and Oxindole Lithium Enolates
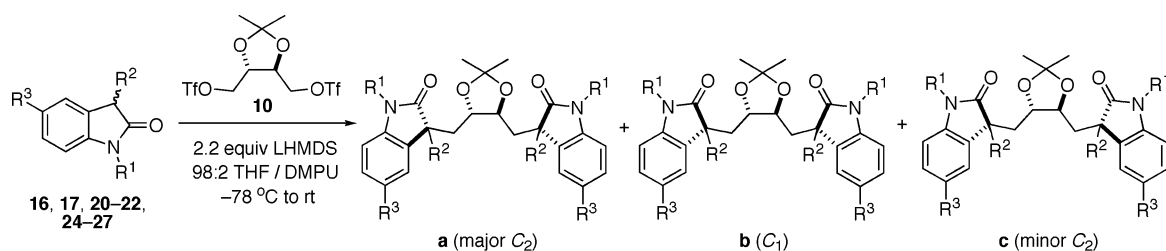
| entry	substrate	R¹ (N1)	R² (C3)	R³ (C5)	product	a:b:c^a	a:b	yield (%)^b a	yield (%)^c a+b+c
1	**16**	Bn	Bn	H	**28**	70:22:8^d	3.2:1	65	
2	**20**	Bn	Ph	H	**29**	55:39:6^d	1.4:1		94
3	**21**	Bn	2-propenyl	H	**30**	47:44:9^e	1.1:1		81
4	**22**	Bn	CH(CH$_3$)$_2$	H	**31**	71:24:5^{e,f}	3.0:1		45
5	**25**	Bn	Me	H	**32**	81:16:3^d	5.0:1	65	
6	**24**	Bn	CH$_2$CH=C(CH$_3$)$_2$	H	**33**	86:13:1^e	6.6:1	41	88
7	**17**	Me	Bn	H	**34**	87:12:1^e	7.3:1	67	
8	**26**	Me	Me	H	**35**	88:11:1^{e,f}	8.0:1		89
9	**27**	Me	Me	OMe	**36**	90:9:1^g	10.0:1	70	

^{a} Duplicate experiments unless otherwise indicated. Mean product ratio reported (±3%). ^{b} Yield of the major C_2-symmetric diastereomer isolated by recrystallization. ^{c} Yield of the mixture of diastereomers. ^{d} Determined by ^{1}H NMR analysis. ^{e} Determined by HPLC analysis. ^{f} Result of one run. ^{g} Determined by GC analysis.

Scheme 6
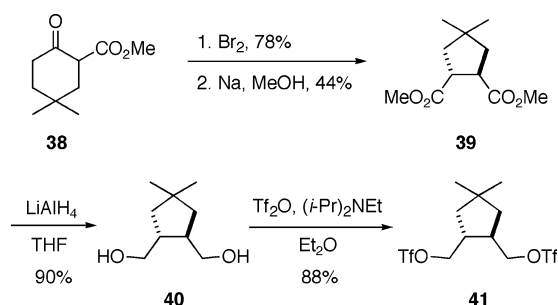
ditriflate **41**. Finally, reaction of 2.2 equiv of the lithium enolate of **27** with ditriflate **41** furnished a mixture of three diastereomeric dialkylation products (**42**–**44**) in a ratio of 69:23:8 (major C_2:C_1:minor C_2; eq 2).
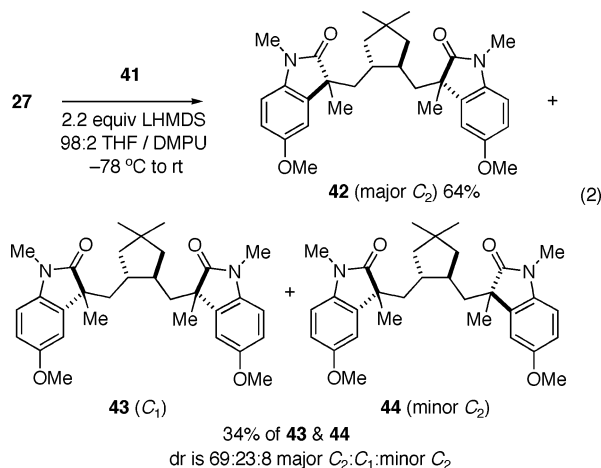
In an effort to gain insight into individual selectivities of the first and second alkylation steps, alkylation of the triflate derivative of glycerol acetonide was examined. Reaction of 1.1 equiv of the lithium enolate of oxindole **27** with triflate **45**[33] in

Scheme 7
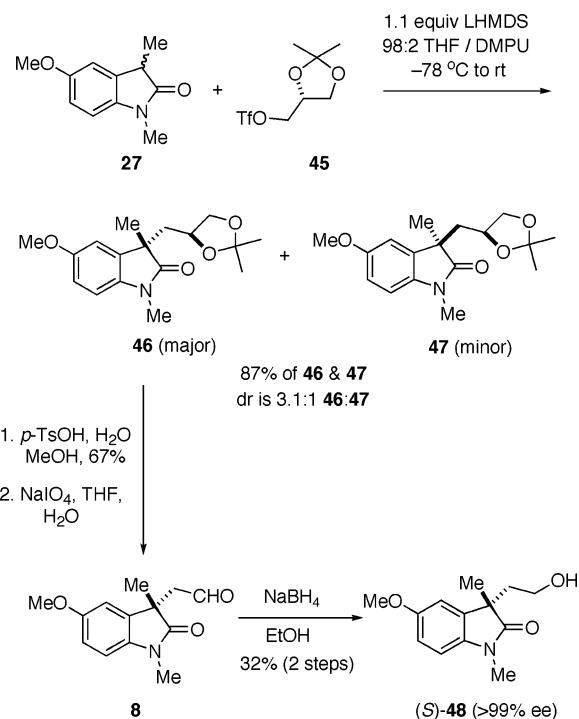
a 98:2 ratio of THF/DMPU (−78 to 23 °C) yielded two alkylation products, **46** and **47**, in a ratio of 3.1:1 (Scheme 7). The absolute configuration of the quaternary stereocenter of oxindole acetal **46** was determined by chemical correlation of this major alkylation product to (*S*)-oxindole aldehyde **8**.[12c] The primary alcohol derivative of oxindole **8** was found to be enantiopure (>99% ee, by HPLC analysis using a chiral stationary phase).
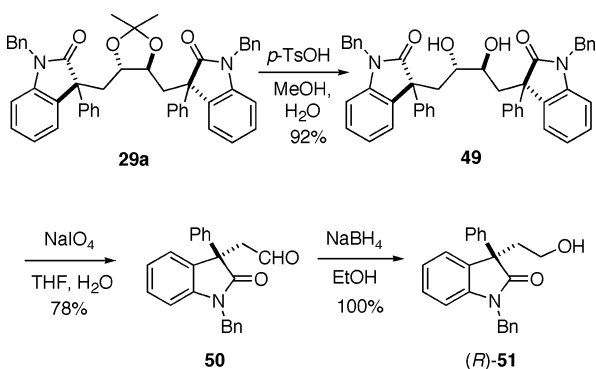
Relative and Absolute Configurations of Dialkylation Products. The relative and absolute configurations of the

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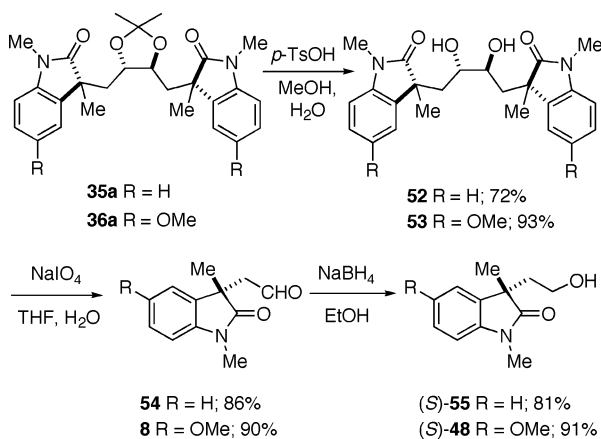
Scheme 8

dialkylation products reported in Table 1 and eq 2 were established in the following manner. Because of its lack of symmetry, the C_1-symmetric dialkylation product, whose quaternary stereocenters have opposite absolute configurations, was recognized readily by its diagnostic ^{1}H and ^{13}C NMR spectra. The configuration of the newly formed quaternary stereocenters of the major C_2-symmetric dialkylation products was established by either chemical correlation or single-crystal X-ray analysis of a heavy atom derivative; the minor C_2-symmetric diastereomers were assigned the opposite absolute configuration at their quaternary stereocenters.

The absolute configurations of the stereogenic quaternary centers of **29a**, **35a**, and **36a** were determined by chemical correlation of these products to the configurations of oxindole alcohols (*R*)-**51**,[34] (*S*)-**55**,[35] and (*S*)-**48**,[12c] whose absolute configurations had been established previously. As summarized in Schemes 8 and 9, these conversions were accomplished in good overall yield by routine three-step sequences that were identical to the sequence employed to form oxindole alcohol (*S*)-**48** from oxindole acetal **46**.
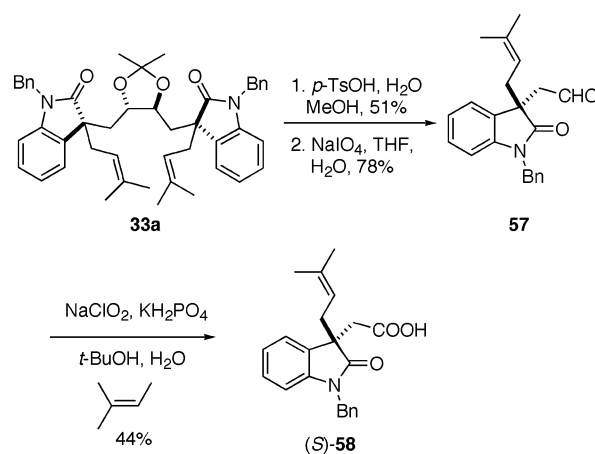
Scheme 9

The absolute configuration of dialkylation product **32a** was assigned by chemical correlation to that of the tetramethyl dialkylation product **35a** (Scheme 10). This correlation was accomplished by cleavage of the benzyl groups of **32a** with Na/NH$_3$, followed by methylation of the oxindole nitrogens, to yield tetramethyl dioxindole **35a**.

Scheme 10
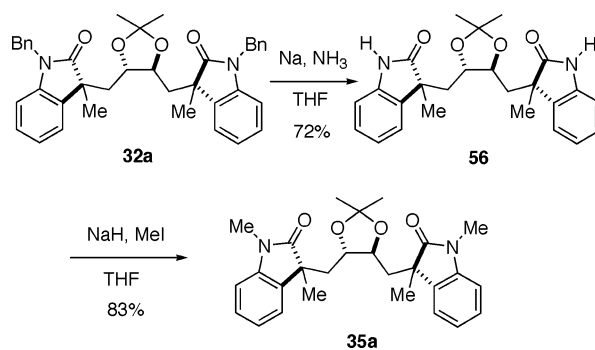
The relative configuration of diprenyl dialkylation product **33a** was established by its chemical correlation to that of oxindole acid (*S*)-**58**[26] (Scheme 11). As in previous cases, this major C_2-symmetric dialkylation product was converted in two steps to oxindole aldehyde **57**. Lindgren oxidation[36] of this intermediate then provided the (*S*)-oxindole acid **58**[26] in moderate yield.

Scheme 11

The relative and absolute configurations of the quaternary stereocenters of C_2-symmetric dialkylation product **28a** were established by X-ray crystallographic analysis of iodopyrrolidinoindoline **61** (Scheme 12). This derivative was accessed by initially transforming **28a** to aldehyde **59**. Conversion of this intermediate to the methylimine analogue, followed by reduction with LiAlH$_4$, provided the corresponding pyrrolidinoindoline.[12c] Removal of the *N*-benzyl substituent of this product by reaction with Na/NH$_3$ gave pyrrolidinoindoline **60**. Installation of an iodine substituent at the 7-position of this intermediate was achieved in three steps by ortho-lithiation−iodination of the *tert*-butoxycarbonyl derivative.[37] Single-crystal X-ray analysis of product **61** then established the absolute configuration of the quaternary stereogenic center as *S*.[38]

The absolute configuration of the quaternary stereocenters of dialkylation product **34a** was established by its chemical

(34) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M.; Ziller, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 6261−6271.

(35) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499.

(36) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176. (b) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.

(37) (a) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008−9009. (b) Iwao, M.; Kuraishi, T. *Org. Synth.* **1996**, *73*, 85−93.

(38) Absolute configuration was assigned by analysis of the anomalous dispersion using Rogers's *η* parameter: Flack, H. D. *Acta Crystallogr.*, *Sect. A* **1983**, *39*, 876−881.

correlation with that of tetrabenzyl dialkylation product **28a**. This correlation was accomplished by removing both benzyl groups, in low yield, by reaction of **28a** with potassium *tert*-butoxide and O$_2$[39] and followed by methylation of the oxindole nitrogens of the resulting product to give **34a** (eq 3).[40]

(3)
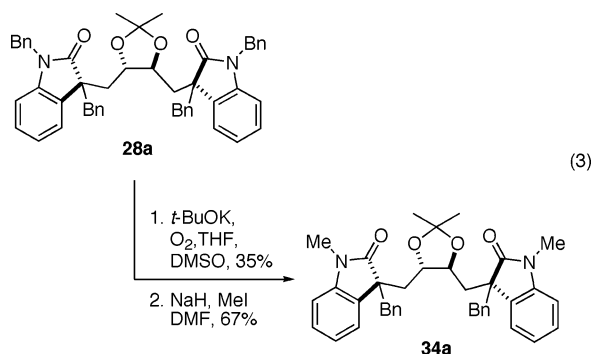
Finally, the relative configuration of the major C_2-symmetric dialkylation product **42**, derived from cyclopentyl ditriflate **41**, was verified by X-ray crystallographic analysis of dibromide derivative **62**. This analogue was accessed, with the tribromination product **63**,[41] by reaction of **42** with 3.3 equiv of bromine in acetic acid at room temperature (eq 4).

(4)

76% of **62** and **63** in a 88:12 ratio
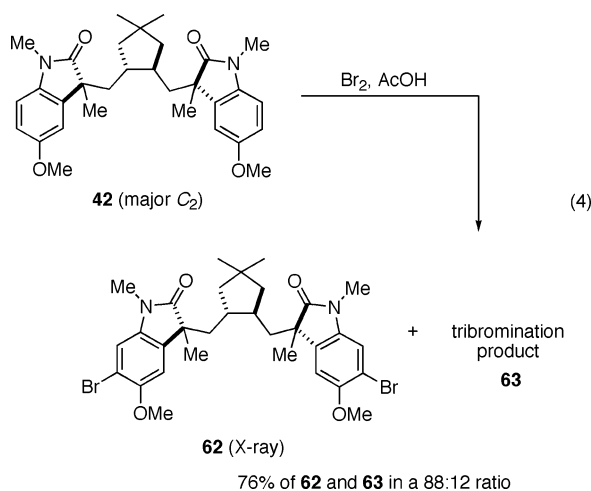
Optimization of the Dialkylation Reaction Conditions. Although the results in Table 1 establish that diastereoselective dialkylations of ditriflate **10** with lithium enolates of 1,3-disubstituted oxindoles have reasonable scope, the reaction conditions remained to be fully optimized. To this end, studies were conducted to optimize the solvent, reaction temperature, and base. The reaction that provided the highest diastereoselectivity, that between 5-methoxy-1,3-dimethyloxindole (**27**) and ditriflate **10**, was chosen for these studies.

First, the effect of the additives DMPU and HMPA on the reaction was examined (Table 2). Compared to the original conditions (entry 2), the addition of more than 2% of DMPU as a cosolvent had a detrimental effect on diastereoselectivity (entries 5 and 6). The highest diastereoselection was realized

(39) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399−402.
(40) The quaternary stereocenters of **30a** and **31a** were assigned the *R* absolute configurations by analogy to the relative and absolute configurations established for compounds **28a**, **29a**, and **32a**−**36a**.
(41) Tentatively assigned from the diagnostic peaks of the ^{1}H and ^{13}C NMR of **63**.

Scheme 12
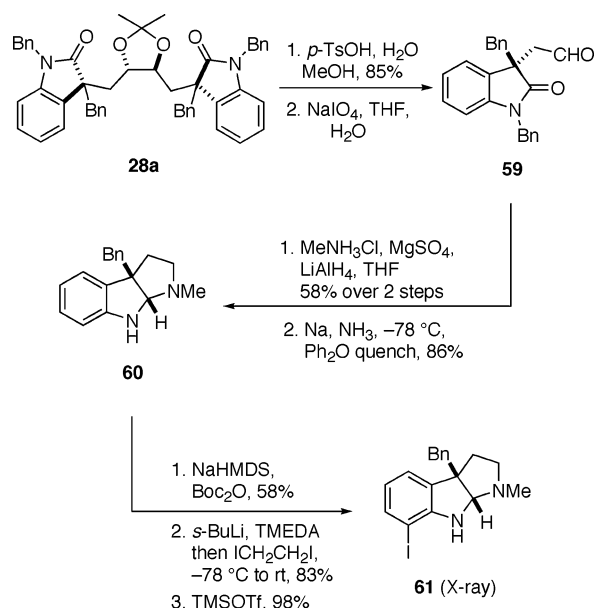
Table 2. Effect of Solvent on the Reaction of the Lithium Enolate of Oxindole **27** with Ditriflate **10**[a]

entry	solvent	36a:36b:36c[b]	36a:36b
1	100% THF	89:11:1	8.1:1
2	98:2 THF/DMPU	90:9:1	10.0:1
3	98:2 THF/HMPA	90:9:1	10.0:1
4	90:10 THF/HMPA	86:14:1	6.1:1
5	90:10 THF/DMPU	84:15:1	5.6:1
6	70:30 THF/DMPU	72:24:4[c]	3.0:1

[a] Conditions: 2.2 equiv of LHMDS, −78 °C to room temperature. [b] Determined by GC analysis of duplicate experiments. Mean product ratio reported (±2%). [c] Result of one run.

Table 3. Effect of Temperature on the Reaction of the Lithium Enolate of Oxindole **27** with Ditriflate **10**[a]

entry	temperature[b]	36a:36b:36c[c]	36a:36b	% conversion
1	−20 °C	76:21:4	3.6:1	100
2	−40 °C	82:16:3	5.1:1	100
3	−60 °C	86:13:1	6.6:1	100
4	−70 °C	88:11:1[d]	8.0:1	95
5	−78 °C	89:10:1	8.9:1	90
6	−78 °C to room temperature	90:9:1	10.0:1	100

[a] Conditions: 2.2 equiv of LHMDS, 98:2 THF/DMPU, 18−24 h. [b] Unless otherwise indicated, reaction mixtures were maintained at this temperature throughout the course of the reaction. [c] Determined by GC analysis of duplicate experiments. Mean product ratio reported (±2%). [d] Result of one run.

using 2% of either HMPA or DMPU (entries 2 and 3). Diastereoselection was slightly lower in the absence of either additive (entry 1). Because of the toxicity of HMPA, the original solvent conditions (98:2 THF/DMPU) were deemed optimal.

The reaction temperature was investigated next (Table 3). As expected, the dialkylation was found to be more stereoselective at lower temperatures, with the highest selectivity being achieved at −78 °C (entry 5). Unfortunately, the reaction of the lithium enolate of oxindole **27** with ditriflate **10** at this temperature was only 90% complete after 24 h.

Other bases were explored to determine whether a more reactive enolate would lead to faster reaction rates without erosion of the stereoselectivity. As summarized in Table 4,

Table 4. Effect of Counterion on the Reaction of the Enolates of Oxindole **27** with Ditriflate **10**[a]

entry	base	36a:36b:36c[b]	36a:36b	% conversion
1	LHMDS	90:9:1	10.0:1	90
2	KHMDS	90:11:<1	8.2:1	100
3	KDA	88:12:<1	7.3:1	100
4	NaHMDS	75:24:2	3.2:1	98

[a] Conditions: 2.2 equiv of base, 98:2 THF/DMPU, −78 °C. [b] Determined by GC analysis of duplicate experiments. Mean product ratio reported (±2%).

Scheme 13

89:11:<1 (major C_2:C_1:minor C_2)

8 (>99% ee)

64

(−)-phenserine (**3**)
obs: $[\alpha]_D$ −73; lit: $[\alpha]_D$ −74
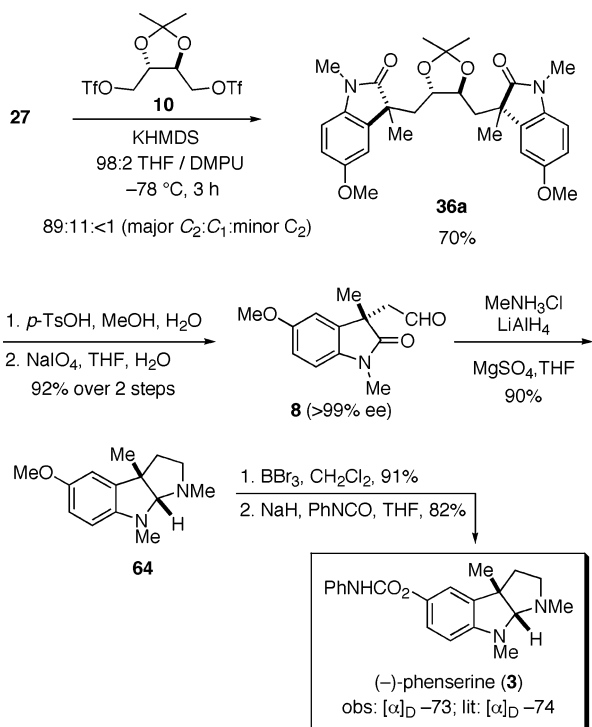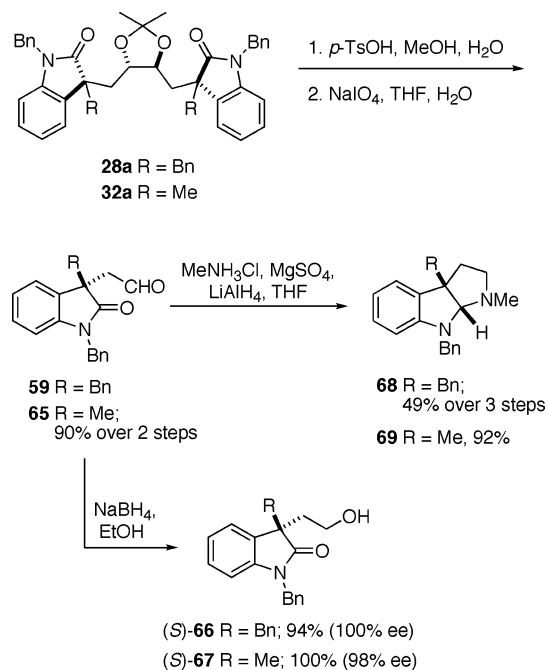
dialkylation of the sodium enolate with ditriflate **10** was less selective,[42] whereas the potassium enolate reacted with **10** with a stereoselectivity only slightly less than that realized with the corresponding lithium enolate (entries 1−4). Using potassium bis(trimethylsilyl)amide (KHMDS) as the base, the reaction of oxindole **27** and ditriflate **10** was complete in <3 h. Although these results indicate that LHMDS produces the most-selective reaction, the long reaction time (18−24 h) and the need to slowly ramp the reaction temperature (−78 °C to room temperature) to realize complete conversion of the starting material, while retaining high stereoselectivity, make this procedure cumbersome for large-scale reactions. For these reasons, KHMDS was chosen as the optimal base for preparative scale applications.

C. Enantioselective Total Synthesis of (−)-Phenserine and Other 3a-Substituted Pyrrolidinoindolines. With the optimal reaction conditions established, a large-scale asymmetric total synthesis of (−)-phenserine (**3**) was undertaken (Scheme 13). The Julian−Brossi procedure for preparing 5-methoxy-1,3-dimethyloxindole (**27**)[13a,30] was readily scaled and used to prepare 80 g of this intermediate from inexpensive, 4-(methyl-

amino)phenol sulfate. The central dialkylation reaction of oxindole **27** and ditriflate **10** was conducted on a 20 g scale using KHMDS as the base to furnish the crystalline C_2-symmetric dialkylation product **36a** in 70% yield after recrystallization. Deprotection of the acetonide of **36a**, followed by oxidative cleavage of the resultant vicinal diol, provided aldehyde **8**,[12c] thus completing a formal total synthesis of (−)-physostigmine. The optical purity of **8** was assayed by reduction of the aldehyde to give alcohol (*S*)-**48**, which was found to be 99% ee by HPLC analysis. Condensation of **8** with methylamine, followed by in situ reduction of the crude imine with LiAlH₄,[12g] provided (−)-esermethole (**64**) in 83% overall yield from dialkylation product **36a**. Finally, using a slight modification of the conditions reported by Brossi,[43] this intermediate was transformed in two steps and 75% yield to (−)-phenserine (**3**): $[\alpha]_D$ −73° (*c* 1.0, CHCl₃); (literature)[44] $[\alpha]_D$ −74° (*c* 1.0, CHCl₃). This total synthesis of enantiopure (−)-phenserine was completed in nine steps and 26% overall yield from commercially available 4-(methylamino)phenol sulfate and in six steps and 43% overall yield from oxindole **27**.

Using an identical sequence, ditriflate dialkylation products **28a** and **32a** were converted in good overall yields to the 3a-substituted pyrrolidinoindolines **68** and **69** (Scheme 14). HPLC

Scheme 14

28a R = Bn
32a R = Me

59 R = Bn
65 R = Me;
90% over 2 steps

68 R = Bn;
49% over 3 steps

69 R = Me, 92%

(*S*)-**66** R = Bn; 94% (100% ee)
(*S*)-**67** R = Me; 100% (98% ee)

analysis of the derived alcohols (*S*)-**66** and (*S*)-**67** confirmed, as in the case of pyrrolidinoindolines **60** and **64**, that these products were formed in high enantiopurity.

Discussion

Synthetic Implications. The dialkylation of tartrate-derived ditriflate **10** with lithium or potassium enolates of oxindoles containing substituents at C3 represents a new method for the

(42) The lower selectivity observed in this reaction using sodium bis(trimethylsilyl)amide (NaHMDS) as the base is not general; stereoselection in the reaction of 3-benzyloxindole (**16**) and ditriflate **10** was 70:22:8 (major C_2: C_1:minor C_2) using either NaHMDS, LHMDS, or KHMDS as the base.

(43) Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745−750.
(44) Brossi, A.; Brzostowska, M.; Rapoport, S.; Greig, N.; He, X. S. Substituted phenserines and phenylcarbamates of (−)-eseroline, (−)-N1-noreseroline, and (−)-N1-benzylnoreseroline; as specific inhibitors of acetylcholinesterase. WO 9306105 A1, April 1, 1993.
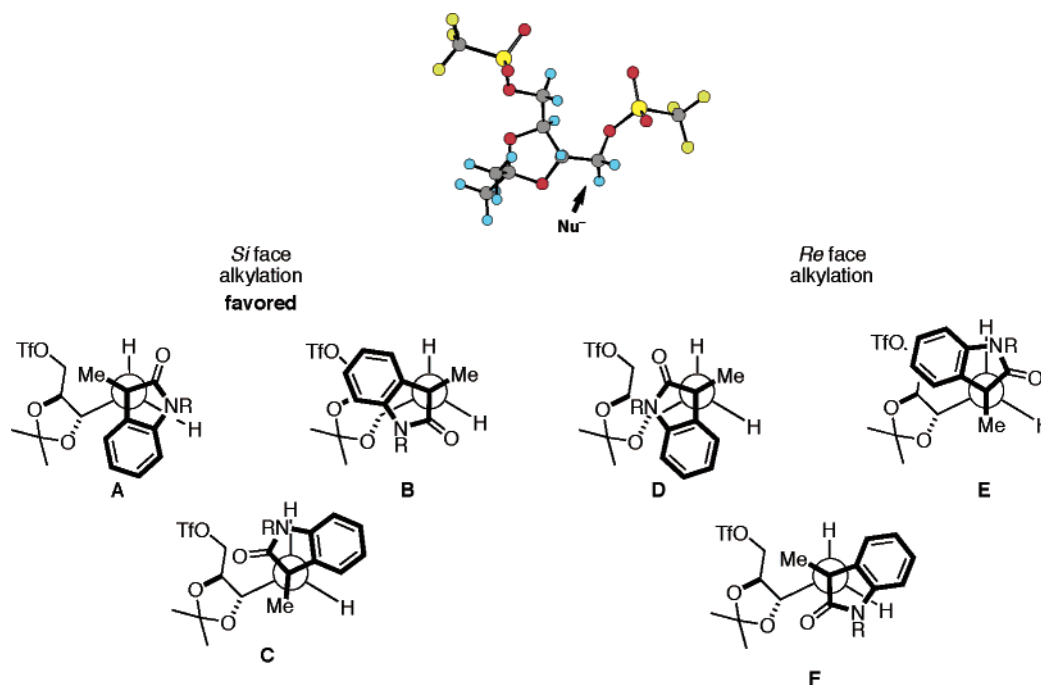
Figure 3. Possible transition structures for the reaction of a 3-methyloxindole enolate with ditriflate **10**. For clarity, the counterion of the enolate nucleophile is omitted.

asymmetric construction of all-carbon quaternary stereocenters.[45] One major C_2-symmetric dialkylation product typically is formed, which in most cases can be isolated in pure form by simple recrystallization. The proclivity to form largely one stereoisomeric product from these reactions is unusual as high stereoselection is rarely seen in the union of prostereogenic enolates with sp³-hybridized chiral electrophiles.[19,46] This method appears limited to the synthesis of oxindoles having alkyl substituents at C3 since diastereoselection is low when this substituent is phenyl or 2-propenyl (Table 1). The substituent on the oxindole nitrogen is of less importance, although diastereoselectivity is slightly higher when this group is methyl rather than benzyl. Although it was not examined in a systematic way, an electron-releasing substituent in the aromatic ring appears to further increase diastereoselection. For example, the highest dialkylation diastereoselectivity observed in this study is seen with enolates derived from 5-methoxy-1,3-dimethyloxindole (9:1, major isomer:sum of minor isomers). To our surprise, the enolate counterion appears to play a minor role, with high diastereoselection being realized with both lithium and potassium oxindole enolates. As the potassium derivative reacts more rapidly, this enolate is preferred for preparative scale applications.

Using a diastereoselective dialkylation as the central step, (−)-esermethole (**64**) was prepared on a multigram scale from readily available 5-methoxy-1,3-dimethyloxindole (**27**) in four steps and 58% overall yield. This sequence is shorter and is accomplished in higher yield than that employed in the asymmetric synthesis of (−)-phenserine reported by Brossi,[12e,15] wherein catalytic asymmetric cyanomethylation of oxindole **27** is the key step.[12i] However, for large-scale synthesis, the cost

of triflic anhydride is a disadvantage of the method reported here. For many other applications, this new route to 3a-substituted pyrrolidinoindolines should be attractive because the highly crystalline alkylated oxindole intermediate is produced in enantiopure form, and either enantiomer will be available depending which enantiomer of tartaric acid is employed.

Alkylation Diastereoselection. Obtaining high diastereoselection in the reaction of prostereogenic enolates and chiral sp³ electrophiles is rare;[46] thus, it is important to consider the possible origin of the diastereoselection realized in this study. Since diastereoselectivity was nearly identical with lithium and potassium enolates in 98:2 THF/DMPU, we believe open transition states are involved. Moreover, stereoselection observed in the dialkylation of the former nucleophile is only slightly eroded by increasing the amount of HMPA or DMPU to 10%. Another observation that influences our thinking is the stereoselectivity (69:23:8) seen in the dialkylation of cyclopentyl ditriflate **41** with the lithium enolate of oxindole **27**, which is lower than that realized in the identical reaction of tartrate-derived ditriflate **10** (90:9:1). We conclude that the oxygens of the dioxolane ring of **10** are not involved in chelation; however, they do play a role in organizing the transition state.

Any discussion of possible origins of diastereoselection in the two alkylation steps must be speculative in the absence of information regarding the orientation of the conformationally flexible electrophiles during the alkylation events. One possible arrangement would involve the enolate nucleophile approaching the triflatomethyl group in a staggered arrangement in which the C1−C2 σ-bond of the electrophile is oriented to position the largest substituent at C2 anti to the approaching nucleophile. This orientation, depicted in Figure 3 for the first alkylation step, should be favored by stereoelectronic factors as it places the electron-releasing C2−C3 σ-bond coplanar to the p orbital of a trigonal bipyramidal S_N2 transition structure.[47,48] The six possible transition structures possessing this arrangement are

(45) For recent reviews of asymmetric synthesis of quaternary carbon centers, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

depicted in Figure 3: transition structures A−C arising from the reaction of the enolate *Si* face and transition structures D−F from the reaction of the *Re* face. Steric considerations would appear to favor structures C and F by placing the largest substituent of the nucleophile, the oxindole aryl group, between the two hydrogens. Of these two transition structures, C should have lower energy because F would be destabilized by interactions (electrostatic or dipole) between the oxygen of the enolate and the proximal oxygen of the dioxolane ring of the electrophile. Alternatively, if minimizing repulsion between the dipoles of the enolate and the C2−O σ-bond is of primary importance, conformations A and D would be the two to consider. Of these, A should be favored as the two dipoles directly oppose each other. Both of these models predict alkylation from the *Si* face of the enolate, as observed.[49]

If both alkylation steps took place with a *Si*:*Re* facial preference of *n*:1, the three diastereomeric dialkylation products would be produced in a ratio of n^2:2*n*:1 (major C_2-symmetric isomer:C_1-symmetric isomer:minor C_2-symmetric isomer). In this scenario, the ratio of the major C_2-symmetric isomer:C_1-symmetric isomer observed in the most-selective dialkylation reactions (entries 7−9 of Table 1) would arise from *Si*:*Re* selectivities of 15, 16, and 20, respectively. This analysis predicts that the minor C_2-symmetric isomer would have been produced in somewhat lower amounts (<0.3%) than observed (∼1.0% in the reactions of 7−9 of Table 1), although this difference is close to the error in measuring the amount of this minor product. The spectator trifloxymethyl substituent of electrophile **10** must contribute to the high facial diastereoselection observed in reactions of this electrophile with oxindole enolates since low diastereoselection was observed in the alkylation of glycidol acetonide monotriflate **45** with the lithium enolate of oxindole **27** (3.1:1, Scheme 7).[50,51]

(46) (a) A recent survey of stereoselective C−C bond-formation cites no examples of alkylation reactions with chiral electrophiles: *Methoden Org. Chem.* (*Houben−Weyl*), *4th Ed.*, 1996; Vol. E21−E22, pp 1077−1118 (Workbook Edition). (b) For examples of selectivity in the range of 7−10:1 in alkylations of lactate triflates, see: Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814.

(47) (a) The rate of S_N2 reactions is typically diminished by the incorporation of electron-withdrawing substituents at the β-carbon;[48] in the case at hand, the electron-withdrawing substituent would be oxygen. This deactivation should have the stereoelectronic component we propose, although we are unaware of specific discussions of this issue as it pertains to S_N2 reactions. (b) Conformations that place the electron-releasing C−H σ-bond coplanar to the p orbital of the trigonal bipyramidal S_N2 transition structure would be favored also by this stereoelectronic feature.

(48) Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; pp 16−20.

(49) The erosion of stereoselection observed in the reaction of the lithium enolate of oxindole **27** with ditriflate **10** as the DMPU content of the solvent is increased from 2 to 30% (Table 2) would be consistent with the importance of electrostatic or dipole interactions in organizing the alkylation transition state.

(50) If *Si*:*Re* selectivity in the first step was indeed 3.1:1 and the second alkylation occurred exclusively from the *Si* face, the major C_2-symmetric isomer and the C_1-symmetric isomer would be produced in a 3.1:1 ratio; if selectivity in the second step was also 3.1:1, this ratio would be only 1.6:1. To realize the observed 9:1 ratio of the major C_2-symmetric isomer: C_1-symmetric isomer, the major monoalkylation product would have to react with high *Si* selectivity and the minor monoalkylation product would have to partition in the alternate sense (i.e., react preferentially from the *Re* face). However, this scenario is not consistent with the observed results as it would lead to the formation of significant amounts of the second (minor) C_2-symmetric isomer.

(51) It is not surprising that this substituent would effect diastereoselection in the initial alkylation step and the oxindolemethyl substituent in the second. Interactions of these groups with the triflate leaving group could modulate the alignment of the C1−C2 σ-bond of the electrophile and/or the conformation of the dioxolane ring, with the latter orienting the dimethyl group in a way that influences the approach of the nucleophile.

Conclusion

Dialkylation of enantiopure ditriflate **10** with oxindole enolates, having alkyl substituents at C3, occurs with high diastereoselection to give largely one C_2-symmetric dialkylation product. This product is readily cleaved to give 2 equiv of the corresponding enantiopure 3-alkyl-3-(2-oxoethyl)oxindole, which, in one double reductive amination step, can be converted to enantiopure 3a-substituted pyrrolidinoindolines. Using this dialkylation chemistry, enantiopure (−)-phenserine was prepared on a multigram scale in six steps and 43% overall yield from 5-methoxy-1,3-dimethyloxindole (**27**). A model that rationalizes the observed preference for alkylation to occur preferentially on the *Si* face of the oxindole enolate is advanced. The alkylation reactions that are the subject of this account are atypical examples of prostereogenic enolates reacting with high facial selectivity (10−20:1) with chiral sp^3 electrophiles.

Experimental Section[52,53]

General Procedure for Dialkylation of Lithium Oxindole Enolates with Ditriflate 10. Preparation of 32a−c. A solution of **25** (1.50 g, 6.33 mmol), DMPU (0.85 mL), and THF (41.7 mL) was cooled to −78 °C in a dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 30 min. A 1 M solution of LHMDS in THF (6.3 mL, 6.3 mmol) was added dropwise. After 20 min, ditriflate **10** (1.23 g, 2.88 mmol) was added as a solid. The reaction mixture was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction mixture was quenched with saturated aqueous NH₄Cl (23 mL) and diluted with 20 mL of 1:1 benzene/EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford an orange residue. Purification of this residue by silica gel chromatography (eluant, 10% EtOAc/toluene−100% EtOAc) yielded a residue consisting of a mixture of three diastereomers. Recrystallization from hot EtOH afforded the major C_2-symmetric product **32a** as a colorless solid (1.12 g, 65%). The mother liquor was concentrated to yield a colorless solid. A small portion of this solid was purified further by HPLC [Phenomenex, Luna C-18 (2), 5 μm, 250 × 21.2 mm, column temperature 23 °C, 75% MeOH in H₂O, flow rate 16 mL/min, UV detection at 254 nm, t_r = 46 min (major C_2), 62 min (C_1), and 71 min (minor C_2)] to afford pure analytical samples of the C_1-symmetric product **32b** (7.0 mg) and the minor C_2-symmetric product **32c** (1.3 mg).

Major C_2-symmetric product, **32a**: [α]²⁷₅₈₉ −55°, [α]²⁷₅₇₇ −57°, [α]²⁷₅₄₆ −65°, [α]²⁷₄₃₅ −103°, [α]²⁷₄₀₅ −117°; mp 147−149 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.33−7.23 (m, 10H), 7.15−7.12 (m, 4H), 7.02 (t, 2H, *J* = 7.6 Hz), 6.65 (d, 2H, *J* = 7.7 Hz), 4.99 (d, 2H, *J* = 15.9 Hz), 4.74 (d, 2H, *J* = 15.8 Hz), 3.31 (m, 2H), 2.09 (dd, 2H, *J* = 14.4, 9.6 Hz), 1.75 (d, 2H, *J* = 12.5 Hz), 1.37 (s, 6H), 1.09 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 180.3, 142.7, 136.2, 133.0, 128.6, 127.8, 127.4, 127.2, 122.8, 122.2, 109.2, 108.9, 77.7, 46.6, 43.9, 40.5, 26.9, 25.2; IR (thin film) 3056, 2968, 2929, 1711, 1611, 1490, 1372, 754 cm⁻¹; HRMS (ESI) *m/z* calcd for C₃₉H₄₀N₂O₄ (M + Na)⁺ 623.2886, found 623.2885. Anal. Calcd for C₃₉H₄₀N₂O₄: C, 77.97; H, 6.71; N, 4.66. Found: C, 78.02; H, 6.71; N, 4.78.

C_1-Symmetric product, **32b**: [α]²⁷₅₈₉ +10°, [α]²⁷₅₇₇ +13°, [α]²⁷₅₄₆ +16°, [α]²⁷₄₃₅ +41°, [α]²⁷₄₀₅ +56°; ¹H NMR (500 MHz, CDCl₃) δ 7.34−7.24 (m, 10H), 7.16 (t, 2H, *J* = 6.5 Hz), 7.12 (app t, 2H, *J* = 7.7 Hz), 7.01 (ddd, 1H, *J* = 7.6, 7.6, 1.0 Hz), 6.96 (ddd, 1H, *J* = 7.6, 7.6, 1.0 Hz), 6.71 (d, 1H, *J* = 7.8 Hz), 6.63 (d, 1H, *J* = 7.8 Hz), 5.03

(52) General experimental details have been described: Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387.

(53) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication: CCDC-241957 (**61**) and CCDC-241958 (**62**).

(d, 1H, J = 15.8 Hz), 4.95 (d, 1H, J = 15.8 Hz), 4.91 (m, 1H), 4.70 (d, 1H, J = 15.9 Hz), 3.45 (ddd, 1H, J = 8.3, 8.3, 3.0 Hz), 3.26 (ddd, 1H, J = 10.1, 7.9, 2.2 Hz), 2.11 (dd, 1H, J = 14.2, 10.1 Hz), 1.95 (dd, 1H, J = 14.3, 8.6 Hz), 1.85 (ddd, 2H, J = 14.0, 9.7, 3.0 Hz), 1.39 (d, 6H, J = 16.5 Hz), 1.10 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.6, 180.3, 142.7, 142.0, 136.2, 136.0, 133.6, 133.0, 128.8, 128.6, 127.7, 127.6, 127.5, 127.3, 127.2, 123.7, 122.9, 122.3, 122.2, 109.1, 108.9 (2), 78.1, 78.0, 47.2, 46.7, 43.9, 43.7, 40.5, 39.7, 26.9, 26.8, 25.4, 24.8; IR (thin film) 3056, 2968, 2927, 1710, 1611, 1488, 1372, 1179, 753 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{39}$H$_{40}$N$_2$O$_4$ (M + Na)$^+$ 623.2886, found 623.2876.

Minor C_2-symmetric product, **32c**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31−7.24 (m, 10H), 7.19 (app d, 2H, J = 7.4 Hz), 7.10 (ddd, 2H, J = 7.8, 7.8, 1.3 Hz), 6.97 (ddd, 2H, J = 7.6, 7.6, 1.0 Hz), 6.67 (d, 2H, J = 7.4 Hz), 4.88 (d, 2H, J = 15.7 Hz), 4.81 (d, 2H, J = 16.0 Hz), 3.53 (m, 2H), 1.95 (dd, 2H, J = 14.2, 8.7 Hz), 1.85 (dd, 2H, J = 14.4, 2.4 Hz), 1.42 (s, 6H), 1.02 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.5, 142.0, 136.1, 133.8, 128.7, 127.5, 127.2, 123.7, 122.2, 108.9 (2), 78.4, 47.1, 43.6, 39.7, 29.7, 27.0, 24.6; IR (thin film) 3047, 2917, 1711, 1613, 1490, 1378, 1181, 741 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{39}$H$_{40}$N$_2$O$_4$ (M + Na)$^+$ 623.2886, found 623.2882.

(3*S*)-5-Methoxy-3-[((4*S*,5*S*)-5-{[(3*S*)-5-methoxy-1,3-dimethyl-2-oxo-1,3-dihydro-2*H*-indol-3-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (36a). A solution of oxindole **27** (20.0 g, 105 mmol), DMPU (14.2 mL), and THF (700 mL) was cooled to −78 °C in a cooling bath and deoxygenated by vigorously sparging with argon for 60 min. Solid KHMDS (22.0 g, 105 mmol) was added in one portion. After 70 min, a solution of ditriflate **10** (22.3 g, 52.3 mmol) and THF (50 mL) was added dropwise over 100 min with a syringe pump, being careful to keep the reaction mixture temperature below −74 °C. The reaction mixture was maintained at −78 °C for 100 min and then allowed to warm to room temperature. A solution of 3% acetic acid in THF (100 mL) was added. After 20 min, EtOAc (800 mL) and H$_2$O (800 mL) were added, and the layers were separated. The aqueous phase was extracted with EtOAc (1 × 800 mL and 1 × 300 mL). The combined organic layers were washed with a solution of saturated aqueous NaHCO$_3$ (1 × 500 mL) and a solution of saturated aqueous NH$_4$Cl (1 × 500 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to afford a yellow solid. Recrystallization of this solid from hot ethanol (8 mL/1 g) yielded **36a** as colorless crystals. The mother liquor was concentrated, and the resulting solid was taken up in Et$_2$O and filtered to remove residual DMPU. The filtered solid was recrystallized from hot ethanol to afford two additional crops (total yield of 18.7 g, 70%): $[\alpha]^{27}_{589}$ −33°, $[\alpha]^{27}_{577}$ −35°, $[\alpha]^{27}_{546}$ −38°, $[\alpha]^{27}_{435}$ −51°, $[\alpha]^{27}_{405}$ −50°; mp 209−211 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.81, 6.77, 6.69, 3.80, 3.22, 3.10, 1.92, 1.64, 1.31, 1.04; ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.1, 155.7, 137.2, 134.7, 111.8, 110.9, 108.1, 108.0, 77.6, 55.8, 47.0, 40.3, 26.8, 26.3, 23.8; IR (thin film) 3058, 2933, 1708, 1495, 1293, 1040, 803 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{29}$H$_{36}$N$_2$O$_6$ (M + Na)$^+$ 531.2471, found 531.2478. Anal. Calcd for C$_{29}$H$_{36}$N$_2$O$_6$: C, 68.48; H, 7.13; N, 5.51. Found: C, 68.59; H, 7.12; N, 5.58.

Isolation of Minor Dialkylation Products 36b and 36c. A solution of oxindole **27** (300 mg, 1.57 mmol) and THF (10.4 mL) was cooled to 0 °C and deoxygenated by vigorously sparging with argon for 50 min. A 60% dispersion of NaH (62.8 mg, 1.57 mmol) was added to this solution. After 15 min, ditriflate **10** (304 mg, 0.714 mmol) was added as a solid, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH$_4$Cl (12 mL) and diluted with EtOAc (16 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 16 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated to yield a yellow residue. Purification of this residue by silica gel chromatography (eluant, 60−80% EtOAc/hexanes) afforded a solid consisting of a mixture of three diastereomers. A small amount of this

mixture was purified further by HPLC [Alltech, Altima silica, 5 mm, 250 × 21.2 mm, column temperature 23 °C, 5% IPA/hexanes, flow rate 10−12 mL/min, UV detection at 254 nm, t_r = 39 min (C_1), 45 min (major C_2), and 53 min (minor C_2)] to afford pure analytical samples of the C_1-symmetric diastereomer **36b** (1 mg) and the minor C_2-symmetric diastereomer **36c** (1 mg).

C_1-Symmetric product, **36b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.84 (dd, 2H, J = 10.8, 2.4 Hz), 6.78 (ddd, 2H, J = 8.5, 6.1, 2.5 Hz), 6.73 (d, 1H, J = 8.4 Hz), 6.69 (d, 1H, J = 8.4 Hz), 3.79 (d, 6H, J = 12.5 Hz), 3.34 (ddd, 1H, J = 8.0, 8.0, 3.4 Hz), 3.27 (m, 1H), 3.20 (s, 3H), 3.10 (s, 3H), 1.91 (d, 1H, J = 14.2 Hz), 1.89 (dd, 1H, J = 14.2, 1.5 Hz), 1.71 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 1.14 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.2 (2), 155.9, 155.7, 137.1, 136.4, 134.6, 134.5, 112.1 (2), 111.3, 110.6, 108.3, 108.2, 108.0, 78.1, 77.8, 55.8, 55.8, 47.5, 47.0, 40.3, 39.5, 26.9 (2), 26.3, 24.3, 23.9; IR (thin film) 3054, 2933, 1702, 1600, 1495, 1291, 1036, 803 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{29}$H$_{36}$N$_2$O$_6$ (M + Na)$^+$ 531.2471, found 531.2465.

Minor C_2-symmetric product, **36c**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.83 (d, 2H, J = 2.5 Hz), 6.77 (dd, 2H, J = 8.4, 2.5 Hz), 6.69 (d, 2H, J = 8.4 Hz), 3.78 (s, 6H), 3.49 (m, 2H), 3.12 (s, 6H), 1.88 (dd, 2H, J = 14.3, 8.8 Hz), 1.66 (dd, 2H, J = 14.2, 2.4 Hz), 1.35 (s, 6H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.2, 155.9, 136.5, 134.7, 112.1, 111.5, 108.7, 108.1, 78.3, 55.8, 47.4, 39.3, 27.1, 26.2, 24.0; IR (thin film) 2933, 1706, 1497, 1291, 1119, 1040, 805 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{29}$H$_{36}$N$_2$O$_6$ (M + Na)$^+$ 531.2471, found 531.2487.

(*S*)-3-(2-Oxoethyl)-1,2-dihydro-5-methoxy-1,3-dimethyl-2-oxo-[3*H*]indole ((*S*)-8). *p*-Toluenesulfonic acid monohydrate (25.1 g, 132 mmol) and H$_2$O (50 mL) were added to a stirred solution of **36a** (17.5 g, 34.4 mmol) and MeOH (403 mL). The reaction mixture was heated at reflux for 21 h and then allowed to cool to room temperature. Saturated aqueous NaHCO$_3$ (130 mL) was added; the mixture was concentrated to remove the organic solvent, and EtOAc (300 mL) and saturated aqueous NaHCO$_3$ (130 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (8 × 200 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated to afford a yellow solid. Recrystallization of this solid from hot EtOH (13 mL/1 g) gave the corresponding diol as colorless crystals (9.62 g). An additional crop (6.49 g) was obtained by concentrating the mother liquor and purifying the residual solid by silica gel chromatography (2−10% MeOH in CH$_2$Cl$_2$). The two crops were combined and carried forward.

A mixture of this diol, NaIO$_4$ (110 g, 513 mmol), THF (370 mL), and H$_2$O (193 mL) was stirred at room temperature for 22 h and then concentrated to remove the THF. The resulting mixture was filtered, and the filter cake was washed with Et$_2$O (1 L). Water (500 mL) was added to the filtrate, and the layers were separated. The aqueous phase was extracted with Et$_2$O (14 × 450 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated to afford (*S*)-**8** as an orange solid (14.7 g, 92% over two steps). Spectral data for this product were consistent with those previously reported.[12c]

(−)-Phenserine (3). A slight modification of Brossi's procedure was employed.[43] Boron tribromide (3.0 g, 12.9 mmol) was added dropwise over 15 min to a stirred solution of (−)-esermethole (**64**) (3.0 g, 12.9 mmol) and CH$_2$Cl$_2$ (57 mL). The reaction mixture was maintained at room temperature for 3 h, and then the reaction mixture was concentrated to afford a foam. This foam was cooled to 0 °C and dissolved in dry MeOH (50 mL); the resulting solution was stirred for 10 min, and the solution was concentrated. This step was repeated one time. The resulting residue was dissolved in H$_2$O (60 mL), basified with saturated aqueous NaHCO$_3$ (40 mL), and extracted with Et$_2$O (15 × 200 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered, and concentrated to afford (3a*S*,8a*R*)-1,3a,8-trimethyl-1,2,3,-3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-ol as a light orange solid (2.56 g, 91%), which was carried forward without further purification.

A 60% dispersion of NaH (46.8 mg, 1.17 mmol) was added to a solution of (3a*S*,8a*R*)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo-

[2,3-*b*]indol-5-ol (2.56 g, 11.7 mmol) and THF (229 mL). This mixture was stirred for 10 min at room temperature, and then phenyl isocyanate (1.53 mL, 14.0 mmol) was added. After 4.5 h, the solution was concentrated. EtOAc (170 mL) and saturated aqueous NaHCO$_3$ (170 mL) were added; the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 170 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant, 1−10% MeOH in CH$_2$Cl$_2$) furnished (−)-phenserine (**3**) as a pink foam (3.22 g, 82%): $[\alpha]^{27}_{589}$ −73.4°, $[\alpha]^{27}_{577}$ −76.4°, $[\alpha]^{27}_{546}$ −85.2°, $[\alpha]^{27}_{435}$ −141°, $[\alpha]^{27}_{405}$ −162°; mp 151−152 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, 2H, J = 7.8 Hz), 7.34−7.31 (m, 2H), 7.09 (t, 1H, J = 7.4 Hz), 6.87 (dd, 2H, J = 8.4, 2.4 Hz), 6.82 (d, 1H, J = 2.4 Hz), 6.36 (d, 1H, J = 8.4 Hz), 4.13 (s, 1H), 2.93 (s, 3H), 2.74−2.71 (m, 1H), 2.68−2.63 (m, 1H), 2.55 (s, 3H), 1.98−1.94 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 152.5, 149.8, 142.5, 137.6 (2), 129.1, 123.7, 120.4, 118.6, 116.1, 106.5, 98.0, 53.2, 52.6, 40.8, 38.4, 36.9, 27.2; IR (thin film) 2960, 1721, 1602, 1495, 1198, 1009 cm^{-1}. Anal. Calcd for C$_{20}$H$_{23}$N$_3$O$_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.02; H, 6.95; N, 12.36.

Supporting Information Available: Experimental procedures for the preparation of **15**−**17**, **19**−**22**, **24**−**26**, **28a**−**c**, **29a**−**c**, **30a**−**c**, **31a**−**c**, **33a**−**c**, **34a**−**c**, **35a**−**c**, **37**, **39**, **41**−**44**, **46**−**63**, and **65**−**69**; copies of ^{1}H and ^{13}C NMR spectra for **21**, **22**, **28b,c**, **29a**−**c**, **30a**−**c**, **31a**−**c**, **32b,c**, **33a**−**c**, **34a**−**c**, **35a**−**c**, **36b,c**, **37**, **41**−**44**, **46**, **47**, **49**−**57**, **59**, **62**, **63**, **65**−**67**, and **69**; HPLC traces used to determine the enantiopurity of **48**, **66**, and **67**; and CIF files for single-crystal X-ray analyses of **61** and **62**. This material is available free of charge via the Internet at http://pubs.acs.org.

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