Catalytic Asymmetric Synthesis of Either Enantiomer of Physostigmine. Formation of Quaternary Carbon Centers with High Enantioselection by Intramolecular Heck Reactions of (*Z*)-2-Butenanilides

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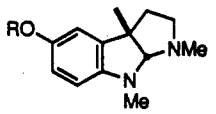
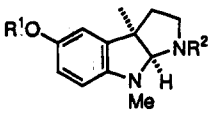
Summary: A practical method for preparing either enantiomer of physostigmine and congeners is reported. The *Z* stereochemistry of the butenanilide cyclization substrate is required to obtain high enantioselection (95% ee) in the key asymmetric Heck insertion.

(−)-Physostigmine (1), a naturally occurring alkaloid found in the seeds of African Calabar beans, is a powerful inhibitor of acetylcholinesterase and is employed clinically to treat glaucoma and myasthenia gravis.[2,3] The phenolic metabolite of physostigmine, (−)-eseroline (2), and other eseroline analogs display potent morphine-like analgesic effects.[3a] Under clinical investigation also is the use of



(−)-physostigmine (1)
R = CONHMe
(−)-eseroline (2); R = H
(−)-esermethole (3) R = Me

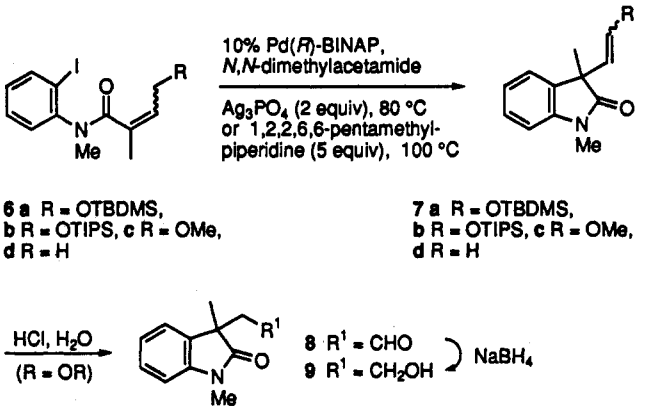


(+)-physostigmine (4)
R^1 = CONHMe, R^2 = Me
(±)-N^1-noresermethole (5)
R^1 = Me, R^2 = H;

(−)-physostigmine and congeners as therapeutic agents for treating Alzheimer's disease.[3b] As is typically the case, biological activity in this series is highly dependent upon absolute configuration. For example, (+)-physostigmine (4) has little effect on acetylcholinesterase in vitro and is a weak centrally acting cholinergic agonist.[3] Although several asymmetric total syntheses of physostigmine have been described,[2,4] convenient access to both enantiomers in this series is at present realized only by resolution of (±)-1-N^1-noresermethole (5).[5]

We report herein a practical method for preparing either enantiomer of physostigmine and congeners by transition metal-catalyzed asymmetric catalysis. The pivotal conversion is the palladium-catalyzed cyclization of a (*Z*)-4-siloxy-2-methyl-2-butenanilide to form an enantioenriched 3,3-disubstituted 2-oxindole,[6] a step that establishes the critical quaternary carbon center of the hexahydropyrrolo-[2,3-*b*]indole ring system of physostigmine with excellent enantioselectivity (95% ee).[7,8] We also describe experiments that demonstrate the importance of the alkene stereochemistry in achieving high enantioselection in the formation of chiral 3,3-disubstituted 2-oxindoles by intramolecular Heck reactions.

Scheme I



6 a R = OTBDMS, b R = OTIPS, c R = OMe, d R = H

7 a R = OTBDMS, b R = OTIPS, c R = OMe, d R = H

8 R^1 = CHO
9 R^1 = CH_2OH

We initially examined Heck cyclizations of both stereoisomers of the TBDMS-protected 4-hydroxy-2-methyl-2-butenanilides **6a**[9] with Pd–(*R*)-BINAP[10] (Scheme I). Consistent with our earlier studies of related enantioselective Heck reactions of cyclic alkenes,[6c] the sense of asymmetric induction in Pd–(*R*)-BINAP-catalyzed cyclizations of the *E* stereoisomer of **6a** was a function of the HI scavenger employed. Cyclization of (*E*)-**6a** in the presence of Ag_3PO_4 gave, after hydrolysis of the enoxysilanes **7a**, the *S* enantiomer of oxindole aldehyde **8**, while cyclization in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) provided (*R*)-**8**, albeit both with low asymmetric induction (Table I, entries 1 and 2). However,

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(1) On leave from (a) Green Cross Corporation, Osaka, Japan, and (b) Shionogi & Co., Ltd., Osaka Japan.

(2) For a review of alkaloids of the Calabar bean, see: Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225–251.

(3) For recent reviews of pharmacology, see: (a) Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311. (b) Sano, M.; Bell, K.; Marder, K.; Stricks, L. *Clinical Pharm.* **1993**, *16*, 61.

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(6) For our previous studies of forming 3,3-disubstituted 2-oxindoles by intramolecular Heck reactions, see: (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785. (c) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (d) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859.

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(9) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binapthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(10) Prepared by a sequence similar to that depicted in Scheme II.

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Table I. Pd-(*R*)-BINAP-Catalyzed Cyclizations of Butenanilides 6

	anilide 6a–d			7	oxindole aldehyde 8		
entry	stereochem	R	cycln condns[a]	*E*:*Z*	yield,[b] %	config[c]	ee,[d] %
1	*E*	OTBDMS	A	*e*	80	*S*	38
2	*E*	OTBDMS	B	77:23	85	*R*	45
3	*Z*	OTBDMS	A	*e*	53	*R*	78
4	*Z*	OTBDMS	B	96:4	81	*R*	92
5	*Z*	OTIPS	A	*e*	73	*R*	80
6	*Z*	OTIPS	B	97:3	87	*R*	90
7	*Z*	OMe	A	4:1	72	*R*	78
8	*Z*	OMe	B	9:1	76	*R*	88
9	*E*	H	B	**7d** (25% ee)[f]			
10	*Z*	H	B	**7d** (84% ee)[g]			

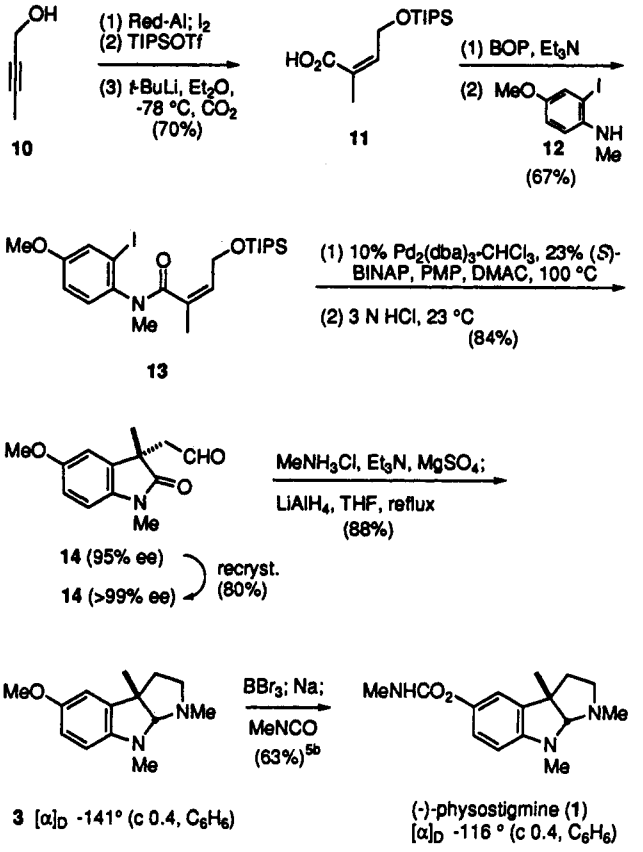
[a] (A) Ag_3PO_4 (2 equiv). (B) 1,2,2,6,6-Pentamethylpiperidine (5 equiv). [b] Overall yield from **6**. [c] Assigned in analogy with the established absolute configuration of (+)- and (−)-14. [d] By HPLC analysis (Chiracel OJ or OB-H, 9:1 hexane/2-propanol) of **9**. [e] A mixture of (*E*)-7, (*Z*)-7 and 8 was formed. [f] By ^1H NMR analysis using Yb(yfc)$_3$.[6c] [g] By HPLC analysis after conversion to **9** (9-BBN; H_2O_2, KOH).

identical cyclizations of (*Z*)-**6a** proceeded with excellent enantioselection (92% in the presence of PMP), and both cyclization conditions provided the *R* enantiomer of oxindole aldehyde **8** (Table I, entries 3 and 4). The size of the oxygen-protecting group plays only a minor role, since similar cyclizations of the TIPS- and methyl-protected *Z* anilides **6b** and **6c** also afforded (*R*)-**8** with high enantioselection in cyclizations carried out in the presence of PMP (Table I, entries 5–8).[11] That the Z alkene stereochemistry, rather than the presence of the γ-oxygen, is critical to obtaining high asymmetric induction is apparent in the results of Pd-(*R*)-BINAP-catalyzed cyclizations of (*E*)- and (*Z*)-**6d** (Table I, entries 9 and 10).

The (*Z*)-2-butenanilide cyclization substrate **13** required for the synthesis of physostigmine was prepared from commercially available 2-butyn-1-ol (**10**) and *N*-methyl-*p*-anisidine as summarized in Scheme II. Using standard methods, **10** was reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) and the resulting vinylalanate iodinated to give (*Z*)-3-iodo-2-buten-1-ol;[12] this latter intermediate was then protected and carboxylated to afford the (*Z*)-acid **11** in 70% overall yield from **6**. Coupling of this intermediate with 2-iodo-*N*-methyl-*p*-anisidine (**12**), which is readily available in a one-pot sequence from *N*-methyl-*p*-anisidine,[13] was not easily accomplished. However, the desired amide **13** could be obtained in good yield by first condensing **11** with the BOP reagent[14] in CH_2Cl_2, followed by heating the resulting activated ester with aniline **12** at 60 °C. Using this somewhat unconventional procedure, stereoisomerically pure butenoylanilide **13** could be obtained in 67% yield.

Asymmetric Heck cyclization of **13** with 20% Pd-(*S*)-BINAP (formed in situ from 10% $Pd_2(dba)_3$·$CHCl_3$ and 23% (*S*)-BINAP, excess (*S*)-BINAP being employed to assure complete complexation of Pd) afforded predominantly (98:2) the (*E*)-enoxysilane stereoisomer of the oxindole product. This intermediate was isolated by chromatography on silica gel and hydrolyzed to provide

Scheme II



the (*S*)-oxindole aldehyde **14** in 84% yield. Borohydride reduction of **14** and analysis of the derived alcohol by chiral HPLC (Chiracel OD) established that **14** was formed with excellent enantioselection (95% ee).[15] A single recrystallization from ethyl acetate–hexane provided enantiopure **14** in 67% overall yield from anilide **13**.[15] Sequential reaction of **14** with methylamine and $LiAlH_4$ afforded enantiomerically pure[15] (−)-esermethole (**3**), $[\alpha]^{25}_D$ −141° (*c* = 0.4, C_6H_6) (lit.[4a] $[\alpha]^{34}_D$ −134° (*c* = 0.3, C_6H_6)), in 88% yield. Using conditions optimized by Brossi,[5b] this intermediate was transformed in two steps to enantiopure[15] natural (−)-physostigmine (**1**); mp 103–104 °C, $[\alpha]^{25}_D$ −116° (*c* = 0.4, C_6H_6); salicylate salt $[\alpha]^{25}_D$ −75° (*c* = 0.5, EtOH).[16] Identical cyclization of **13** with Pd-(*R*)-BINAP lead to enantiopure[15] (+)-esermethole,

(11) Not surprisingly, the two enoxysilane stereoisomers of **7a** and **7b** (but not **7c**) were formed with different enantiomeric purities (determined by separation on silica gel, conversion to **9**, and HPLC analysis), reflecting diasteroselectivity in the β-hydride elimination step: (*E*)-**7a**, 92% ee, and (*Z*)-**7a**, 88% ee; (*E*)-**7b**, 91% ee, and (*Z*)-**7b**, 73% ee.

(12) Denmark, S. E.; Jones T. K. *J. Org. Chem.* **1982**, *47*, 4595. Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamuta, T. *J. Org. Chem.* **1989**, *54*, 2817.

(13) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3047. Katritzky, A. R.; Fan, W.-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027.

(14) BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate: Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219.

(15) Base line resolution of enantiomers was obtained on a Chiracel OD column using hexane/2-propanol as eluent: 9:1 for the alcohol derived from **14**; 99:1 for **1** and **3**. Copies of actual chromatograms are provided as supplementary material.

$[\alpha]^{25}_D$ +137° (c = 0.4, C_6H_6), in 55% overall yield. Subsequent elaboration of this intermediate[5b] provided enantiopure[15] (+)-physostigmine (4): $[\alpha]^{25}_D$ +108° (c = 0.4, C_6H_6); salicylate salt $[\alpha]^{25}_D$ +76° (c = 0.5, EtOH).

The synthesis summarized in Scheme II constitutes a practical method for preparing either enantiomer of physostigmine: 15–20% overall yield from commercially available 2-butyn-l-ol and *N*-methyl-*p*-anisidine. Related sequences should allow direct access to either enantiomer of a wide variety of physostigmine analogs. The investigations outlined here establish that quaternary carbon centers can be formed directly in up to 95% ee by intramolecular Heck insertions and highlight the importance of alkene stereochemistry in achieving high levels of asymmetric induction.

(16) Comparison data for authentic (−)-physostigmine obtained from Aldrich Chemical Co., Inc. were as follows: mp 104–105 °C; $[\alpha]^{25}_D$ −117° (c = 0.4, C_6H_6). A rotation of $[\alpha]_D$ +75° (c = 0.5, EtOH) has been reported for the salicylate salt of (+)-physostigmine.[5b]

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Supplementary Material Available: Experimental details and characterization data for compounds indicated in Scheme II and HPLC traces used to determine % ee of crude and pure 14, (+)-and (−)-(3), and (+)- and (−)-1 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.