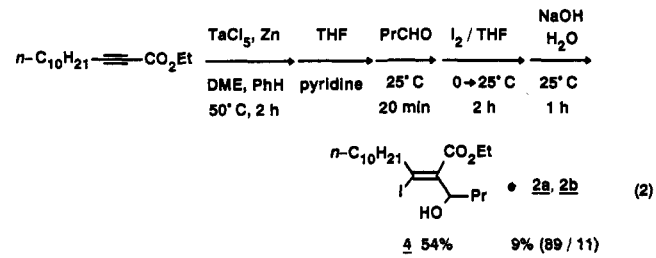
aldehydes was low. The observed reactivities and the β-selectivity could be attributed to the coordination of the nitrogen of amide to tantalum.[13]

Quenching the reaction mixture of a tantalum–ethyl tridecenoate complex and butanal with iodine in THF at 0 °C for 15 min and 25 °C for 2 h afforded β-iodo-α,β-unsaturated ester **4** in 54% yield[14] along with untrapped allylic alcohols **2a** and **2b** in 9% combined yields (**2a**/**2b** = 89/11, eq 2). None of the α-iodo unsaturated ester was obtained. The carbon(sp²)–iodine bond of **4** is a clue to develop further transformations.[15]



(2)

Supplementary Material Available: Experimental procedures and spectral data for all new compounds (13 pages). Ordering information is given on any current masthead page.

(13) When an acetylenic amide was added to the mixture of low-valent tantalum, the color of the mixture changed from greenish dark blue to ultramarine. Similar color change was observed after the addition of TMEDA to the low-valent tantalum.

(14) Reduction of β-iodo ester **4** with $Et_3NH^+HCO_2^-$ under palladium catalysis ($Pd(PPh_3)_4$) produced **2a** in 87% yield. The following method was modified: Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(15) For some examples, see: (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (b) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926. (c) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

Enantiocontrolled Total Syntheses of (−)-Physovenine and (−)-Physostigmine

Seiichi Takano,* Minoru Moriya, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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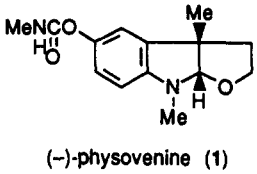
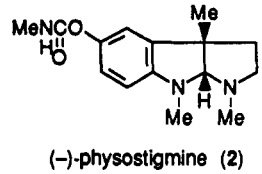
Summary: Enantiocontrolled total syntheses of the Calabar bean alkaloid (−)-physovenine (**1**) and (−)-physostigmine (**2**) have been achieved in a concise manner starting from the optically active tricyclic enone **3** employing a Fischer indolization reaction under nonacidic conditions as the key step.

There is currently considerable interest in compounds having central stimulatory activity such as the anti-cholinergic Calabar bean alkaloids[1] due to their therapeutic potential in Alzheimer's disease[1] and cholinergic disorders.[2,3] We report here the first total syntheses of (−)-physovenine (**1**) and a formal total synthesis of (−)-physostigmine (**2**), both members of the alkaloids of current interest, based on a new strategy exploiting a structurally biased polycyclic ketone **4** as a stereochemical control element in the key Fischer indolization step.



(−)-physovenine (**1**)



(−)-physostigmine (**2**)

Alkylation of the optically active (−)-tricyclic enone[4] **3**, prepared from racemic dicyclopentadiene in a four-step sequence of reactions including lipase-mediated resolution,[5] afforded the monomethyl ketone **4** in 86% yield as a mixture of epimers. When this compound was refluxed with *p*-methoxyphenylhydrazine hydrochloride in aqueous pyridine[6] (1:10), a facile diastereoselective reaction occurred to furnish the carbinol amine **7**, mp 109–111 °C, $[\alpha]^{28}_D$ −144.6° (*c* 1.95, $CHCl_3$), as a single product, in 82% yield. This compound is presumably generated via [3,3]-sigmatropic rearrangement of the diaza-1,5-diene intermediate **5** to afford the imine **6** via introduction of the aryl group from the convex face of the molecule. The imine **6** is then hydrolyzed under the reaction conditions to give the carbinolamine **7** instead of giving the pentacyclic indolenine.

On acetylation followed by methylation, **7** afforded the tertiary amide **9**, $[\alpha]^{29}_D$ −147.1° (*c* 1.21, $CHCl_3$), in 86% overall yield via **8**, mp 163–164 °C, $[\alpha]^{27}_D$ −100.3° (*c* 1.19, $CHCl_3$). Compound **9** was refluxed in *o*-dichlorobenzene to initiate a retro-Diels–Alder reaction to give the cyclopentenone **10**, $[\alpha]^{31}_D$ −64.6° (*c* 1.41; $CHCl_3$), in 66% yield. The enone **10**, on sequential one-flask ozonolysis, borohydride reduction, and periodate cleavage, furnished the lactol **14** in 62% yield via **11**–**13**. Refluxing **14** in methanol containing a trace of hydrochloric acid caused concomitant deacetylation and cyclization to give the tricyclic amino acetal[7] **15**, $[\alpha]^{32}_D$ − 96.2° (*c* 0.35, $CHCl_3$), in 71% yield. Treatment of **15** with boron tribromide[3a] followed by carbamoylation of the resulting phenol **16** afforded (−)-physovenine[7] (**1**), mp 126–127.5 °C, $[\alpha]^{30D}$ −90.0° (*c* 0.09,

(1) A recent review: Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 36, p 225.

(2) Cf. Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311.

(3) Enantiocontrolled syntheses: (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641. (b) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109. (c) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411. (d) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872. (e) Node, M.; Hao, X.-j.; Fuji, K. *Chem. Lett.* **1991**, 57.

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(7) Enantiomeric excess was determined to be ≥97% by HPLC [CHIRACEL OJ, ^{i}PrOH–hexane (1:9)]. Spectral data (IR, ^{1}H NMR, and MS) of **15** were identical with those of racemic material: Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007.

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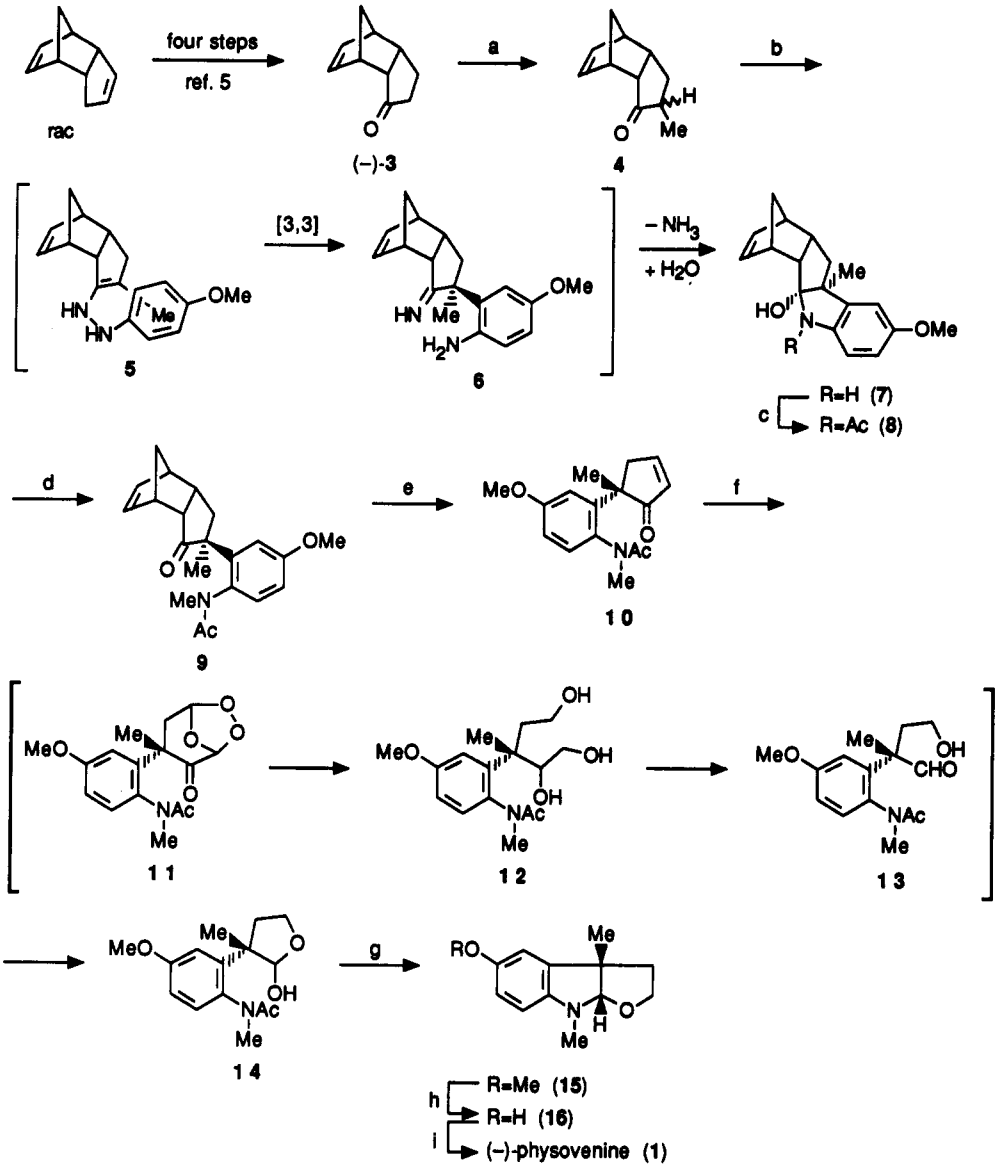
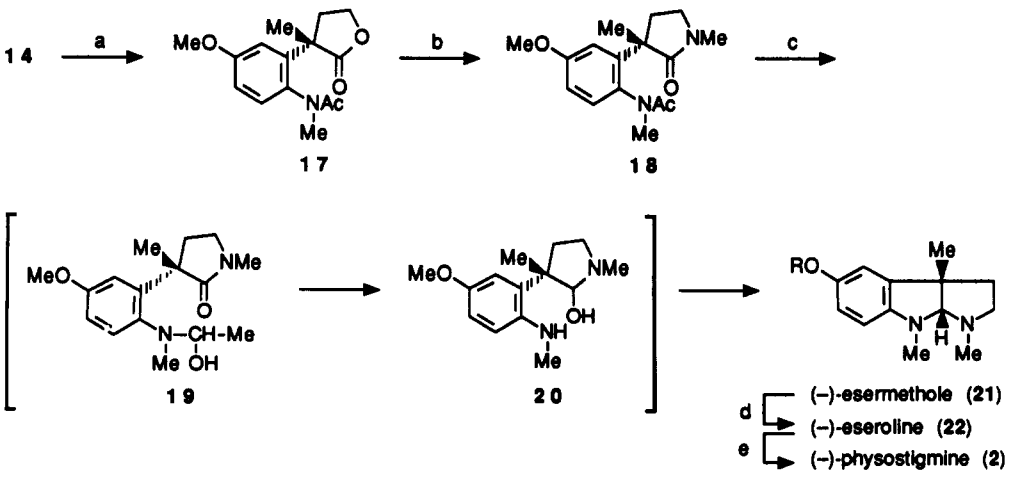
Scheme I[a]



[a] Key: (a) LDA, MeI, THF, −30 °C; (b) 4-methoxyphenylhydrazine hydrochloride, aqueous pyridine (1:10), reflux, 35 min; (c) Ac_2O, pyridine; (d) NaH, MeI, DMF–THF (1:1); (e) *o*-dichlorobenzene, reflux, 11 h; (f) O_3, MeOH, −78 °C, then $NaBH_4$, −78 °C → rt, 10% HCl (neutralize) then $NaIO_4$; (g) 35% HCl (cat.), MeOH, reflux; (h) BBr_3, CH_2Cl_2, 0 °C → rt; (i) NaH (cat.), MeNCO, THF.

Scheme II[a]



[a] Key: (a) Ag_2CO_3 on Celite, benzene, reflux; (b) 40% aqueous $MeNH_2$, sealed tube 180 °C; (c) i, $^iBu_2AlH$, CH_2Cl_2, −78 °C then NH_4OH, ii, LAH, THF, reflux; (d) BBr_3, CH_2Cl_2, 0 °C → rt; (e) NaH (cat.), MeNCO, THF.

EtOH) [natural:[8] mp 124-125 °C, $[\alpha]^{22.5}_D$ -92° (EtOH)], in 84% overall yield. This route constitutes the first enantiocontrolled synthesis of the natural product.

On the other hand, oxidation of the lactol **14** by silver carbonate on Celite[9] gave the lactone **17**, $[\alpha]^{32}_D$ -69.9° (*c* 0.30, $CHCl_3$), in 88% yield, which was transformed into lactam **18**, $[\alpha]^{31}_D$ -72.4° (*c* 1.47, $CHCl_3$), in 76% yield on heating at 180 °C with aqueous methylamine in a sealed tube. Upon exposure to diisobutylaluminum hydride at -78 °C followed by lithium aluminum hydride in refluxing THF, 18 furnished (-)-esermethole[1,10] (**21**), $[\alpha]^{34}_D$ -134° (*c* 0.41, benzene) [lit.[3a] $[\alpha]_D$ -129° (*c* 0.33, benzene)], directly in 34% yield, presumably via the carbinolamines **19** and **20**. Since **21** has previously been transformed into natural (-)-physostigmine (**2**) in two steps[3a] via (-)-eseroline (**22**),[1,2] this sequence constitutes a formal synthesis of the natural product.

Acknowledgment. We are grateful to Professors Keiichiro Fukumoto and Kozo Shishido for a sample of physovenine.

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(9) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.
(10) Enantiomeric excess was determined to be ≥98% by HPLC [CHIRACEL OJ, ^{i}PrOH-hexane (1:9)]. Spectral data (IR, ^{1}H NMR, and MS) and TLC were identical with those of an authentic material.[3a,b]

Supplementary Material Available: Experimental details and spectroscopic data (IR and ^{1}H NMR) for compounds **1**, **4**, **7-10**, **15**, **17**, **18**, and **21** (6 pages). Ordering information is given on any current masthead page.

Articles

β-Lactams from Ester Enolates and Silylimines: Enantioselective Synthesis of the *trans*-Carbapenem Antibiotics (+)-PS-5 and (+)-PS-6

Patrizia Andreoli,[†] Gianfranco Cainelli,*[,†] Mauro Panunzio,*[,†] Elisa Bandini,[‡] Giorgio Martelli,*[,‡] and Giuseppe Spunta[‡]

Dipartimento di Chimica, "G. Ciamician" Università and C.S.F.M.-C.N.R., Via Selmi, 2, 40126 Bologna, Italy, and I.Co.C.E.A.-C.N.R., Via della Chimica, 8, 40064 Ozzano Emilia, Italy

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A new synthetic route to the antibiotics (+)-PS-5 and (+)-PS-6 is described. The preparation involves a fully stereocontrolled reaction between the enantiomerically pure *N*-trimethylsilylimine of lactic or mandelic aldehyde and the lithium enolate of the *tert*-butyl butanoate or *tert*-butyl isovalerate, respectively. Conversion of the azetidinones obtained to 4-acetoxy derivatives via oxidative cleavage of the hydroxyethyl or hydroxybenzyl side chain and introduction of the necessary appendage in the position 4 of the azetidinone ring, followed by assemblage of the bicyclic ring system, afforded the natural *trans*-carbapenems (+)-PS-5 and (+)-PS-6.

Introduction

The control of absolute stereochemistry is a central problem in the synthesis of biologically significant enantiomers of natural products. Of the large volume of literature on the synthesis of enantiomerically pure 3- and 4-disubstituted azetidin-2-ones as well as their corresponding bicyclic derivatives, the approach that leads to products of high enantiomeric purity either involves the use of an enantiomerically pure auxiliary, which is subsequently cleaved, or of an enantiomerically pure building block, which is retained in the target compound.[1]

The cycloaddition reaction of ester enolates with aldimines has proved to be an effective method for preparing β-lactams.[2] Recently, in fact, we and others[3] have demonstrated the synthetic usefulness of this reaction in the synthesis of thienamycin, using (*S*)-ethyl 3-hydroxybutanoate as the chiral nucleophilic component in the cycloaddition[4] (Chart I). However, there are some β-lactam antibiotics bearing no stereogenic centres in the C-3 side chain of the azetidinone ring. For instance, the carbapenems (+)-PS-5 and (+)-PS-6 have an ethyl and isopropyl group, respectively, in this position. In these case,[5] in order to prepare enantiomerically pure compounds, the asymmetry can be incorporated in the electrophilic partner

[†] "G. Ciamician" Università.
[‡] I.Co.C.E.A.-C.N.R.

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