Table I. Reaction Times (min) for (Methoxymethyl)indole Formation

substituent	temperature (°C) 20–25	5 to −5	−10 to −15
5-nitro	15	30	30
5-methoxy	15	90	165

alkylate via an elimination–addition mechanism (Scheme II). Methylation of the dimethylamino function of **4**, with subsequent elimination of trimethyl amine, first yields a 3*H*-pseudoindole intermediate **5** which then undergoes a Michael addition by a sufficiently nucleophilic species to yield the final product **6**. Albright and Snyder[6] used gramines with a chiral 3-substituent to investigate this mechanism, basing their kinetic results upon both the rate of amine evolution and the rate of racemization. They proposed two even more detailed mechanisms but could draw no specific conclusion about which of these was operating.

The major difference between these two variants was the point in the elimination sequence at which base abstracted the proton on the indole nitrogen. In one mechanism ("A") the rate-determining step was the formation of the pseudoindole **5** after the base abstracted the proton on the indole nitrogen in a fast step. In the alternative mechanism ("B"), the base abstraction of the indole nitrogen proton was the rate-determining step. The pseudoindole **5** then resulted from elimination of trimethylamine in a series of fast steps.

Our reasoning was that if mechanism B represents both the role of the base and the correct rate determining step, then the presence of the methoxy group "para" to the indole nitrogen should reduce the acidity of this proton. Thus, base abstraction of this proton would proceed slowly, especially at reduced temperatures. With a "para" nitro group the reaction should proceed faster. If mechanism A was the correct one, then the rate of reaction of the nitro compound would be decreased by resonance stabilization of the newly formed anion.

A very elementary rate study to compare the rate of reaction of 5-nitrogramine to that of 5-methoxygramine was undertaken. Standard reaction conditions were developed and followed with each compound. The appropriate gramine was dissolved in anhydrous methanol containing potassium cyanide. This mixture was treated with methyl iodide, and the reaction was followed by TLC. Samples were taken at 15-min intervals, and the times at which the methoxymethyl impurity first appeared were observed at room temperature, 5 to −5 °C, and −10 to −15 °C.

The results in Table I show that the methoxy group in position 5 of the indole ring slows the reaction rate considerably while the reaction proceeds with no significant rate change when the nitro group is in the same position. This strongly suggests that the overall mechanism of alkylation by 1*H*-gramines proceeds by the base abstraction, rate-determining-step sequence, mechanism B. This is detailed for gramine in Scheme III showing the incorporation of methanol to yield the methoxymethyl type byproduct.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 710B spectrophotometer and the NMR spectra on a Hitachi/Perkin-Elmer R-21B instrument using tetramethylsilane as internal reference with chemical shifts expressed in ppm. Chromatography was on Kodak Chromagram silica gel strips using a 1:1 ether/hexane–10% ethanol solvent system. Analyses were performed by Atlantic Microlab, Inc.

5-Methoxygramine was purchased from Aldrich Chemical Co.

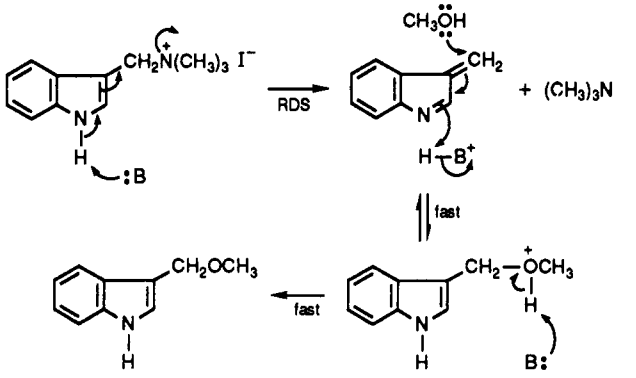
5-Nitrogramine (1) was prepared following the basic procedure of Cavallini and Ravenna.[7]

5-Nitro-3-(methoxymethyl)indole (3). 5-Nitrogramine (11.0 g, 0.05 mol) and methanol (250 mL) were introduced to a 500-mL Erlenmeyer flask and stirred. Excess methyl iodide was added, and after about 15–20 min a solid appeared. This mixture was allowed to stir at room temperature for another 48 h. TLC showed nothing above the origin. Sodium methoxide (3.25 g, 0.06 mol) was then added, and the mixture was stirred for 15 min when TLC showed product forming. The mixture was stirred for 4 h and filtered. The filtrate was evaporated, and the resulting solid was stirred with water and refiltered to give 10 g (96%) of dull yellow solid. Recrystallization from methanol gave bright yellow crystals: mp 133–134 °C; IR (KBr) ν 3200 (N–H), 1520 and 1330 (NO_2), 1055 cm^{-1} (C–O); ^1H NMR (Unisol) δ 3.35 (3 H, s, CH_3), 4.65 (2 H, s, CH_2), 7.35–7.5 (s and d overlapping, 2 H, $J_{6,7}$ = 5 Hz, C-2 and C-7), 8.0 (1 H, dd, $J_{6,7}$ = 5 Hz, C-6), 8.55 (1 H, s, $J_{4,6}$ = 3 Hz, C-4), 11.3 (br s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.22; H, 4.89; N, 13.58. Found: C, 58.13; H, 4.91; N, 13.50.

Standard Reaction Conditions for Rate Study Using 5-Nitrogramine and 5-Methoxygramine. A stock solution of the gramine (0.005 mol) in methanol was prepared in a 50-mL volumetric flask. To potassium cyanide (0.002 mol) was added 10 mL (0.001 mol of gramine) of this stock solution. The mixture was stirred, and to it was added (0.002 mol) of methyl iodide. The reaction was followed by TLC, and the times at which the methoxymethyl impurity first appeared were observed at room temperature, 5 to −5 °C, and −10 to −15 °C.

Scheme III



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Asymmetric Alkylation of Oxindoles: An Approach to the Total Synthesis of (−)-Physostigmine

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(−)-Physostigmine (1) is a clinically useful anticholinesterase agent that has been used in the treatment of glaucoma and myasthenia gravis.[1] More recently, selected

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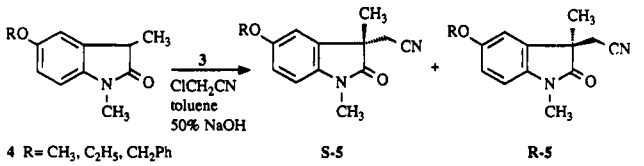
Scheme I

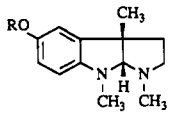


4 R= CH_3, C_2H_5, CH_2Ph S-5 R-5

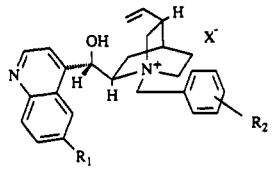
Table I. Asymmetric Alkylation of Oxindole 4 (R = CH_3)[10]

3	R_1	R_2	X	(S)-5, % ee
a	H	H	Br	10
b	H	2-CF_2	Br	4
c	H	3-CF_3	Br	69
d	H	4-CF_3	Br	72
e	H	3-Br	Br	48
f	H	4-Br	Br	68
g	H	4-Cl	Br	69
h	H	3,4-Cl_2	Br	77
i	H	3,4-Cl_2	Cl	78
j	H	2,6-Cl2	Br	0
k	OCH_3	H	Br	39
l	OCH_3	3,4-Cl_2	Br	77

(−)-physostigmine analogues have shown promise as Alzheimer's disease therapeutic agents.[2] While there have been numerous approaches to the total synthesis of (±)-physostigmine,[3] relatively few stereoselective syntheses have been reported.[4-6] We describe herein a practical, multigram, enantioselective synthesis of (−)-esermethole (**2**), a penultimate intermediate to (−)-physostigmine.



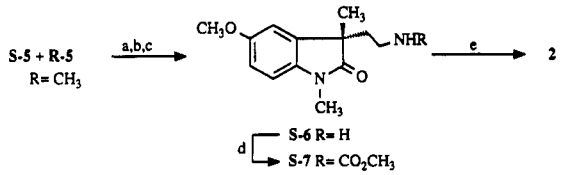
1 R= CH_3NHCO
2 R= CH_3



3

Our approach was based on the pioneering work of U.-H. Dolling on chiral phase-transfer catalysis[7] and subsequent application of this methodology to other substrates.[8] Thus, asymmetric alkylation of oxindoles **4** by phase-transfer catalysis using chiral catalyst **3** seemed to be a particularly attractive approach to the total synthesis of (−)-physostigmine (Scheme I).[9] Initial exploratory experiments were carried out by the slow addition of chloroacetonitrile to oxindole **4** (R = CH_3) in the presence of commerically available chiral catalyst **3d** (R_1 = H, R_2 = 4-CF_3, X = Br) under phase-transfer conditions. A 73% enantiomeric excess (ee) of the *S* enantiomer was realized.[10] Increasing the catalyst concentration up to 50 mol % or extending the addition time of chloroacetonitrile up to 2 h did not further increase the enantiomeric excess of the reaction. On the other hand, changing the NaOH concentration from 50% to 25% lowered the enantiomeric excess of the reaction to 61%. Similarly, rapid addition of chloroacetonitrile in one portion decreased the enantiomeric excess to 66%.

Scheme II[a]



[a] (a) $H_2/PtO_2/H^+$/MeOH; (b) dibenzoyl-D-tartaric acid/CH_3CN; (c) aqueous NaOH/CH_2Cl_2; (d) $ClCO_2CH_3/Et_3N/CH_2Cl_2$; (e) $LiAlH_4$/THF.

The effect of the structure of the chiral catalyst **3** on asymmetric induction was then explored (Table I). In general, the selectivity increases when the benzyl group is substituted by a progressively more electron-withdrawing group in the 3 and/or 4 positions. Best results (77% ee) were obtained with catalyst **3h** (R_1 = H, R_2 = 3,4-Cl_2, X = Br). Similar results (77% ee) were obtained with catalyst **3i** (R_1 = H, R_2 = 3,4-Cl_2, X = Cl), suggesting little counterion effect of the catalyst on the amount of induction. In addition to electronic factors, the enantiomeric excess of the reaction also appeared to be sensitive to the steric bulk of the substituent on the benzyl moiety of the catalyst. Little or no stereoselectivity was observed with substitution in the 2 and/or 6 positions. These results are consistent with formation of a tight ion pair during the alkylation. Interestingly, unsubstituted benzylquinidinium bromide **3k**, unlike the cinchoninium catalyst, promotes some selectivity. However, no further improvement in enantiomeric excess can be realized when 3,4-dichlorobenzyl-substituted quinidinium salt **3l** is used as the chiral phase-transfer catalyst.

In a preparative experiment, alkylation of oxindole **4** (R = CH_3) with chloroacetonitrile in the presence of catalyst **3i** (15 mol %) gave 83% of the nitrile with a 73% ee of the *S* enantiomer. HPLC assays of the reaction mixture

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(10) Enantiomeric excesses were determined directly by means of HPLC on a Chiralcel OD or Chiralcel OJ chiral column (Daicel Chemical Industries Ltd.). Details on the conditions for the chromatographic separation will be published elsewhere.

at 50% and 100% conversion showed that the enantiomeric excess of the reaction remained constant throughout at 73%. Separation of the undesired *R* enantiomer of nitrile **5** (R = CH_3) by means of fractional recrystallization proved difficult. The crude nitrile was therefore catalytically reduced ($H_2/PtO_2/H^+$/MeOH) to the corresponding primary amine **6** as an optically enriched mixture. Treatment of the amine with 0.85 equiv of dibenzoyl-D-tartaric acid in acetonitrile followed by a single recrystallization of the diastereomeric salt gave 48% unoptimized yield (based on oxindole **4**) of the optically pure tartrate salt, mp 135–137 °C, $[\alpha]^{21.5}_D$ +57.1° (*c* 1.05, MeOH). Finally, conversion of amine (*S*)-**6** to carbamate (*S*)-**7** followed by reductive cyclization gave (−)-esermethole (**2**), mp 52.5–54 °C, $[\alpha]^{22}_D$ −136.7° (*c* 0.33, benzene) [lit.[4c] $[\alpha]^{34}_D$ −134° (*c* 0.35, benzene)] in 65% overall yield (Scheme II).[11] The optical purity of the synthetic material was further established by HPCL analysis.

Other variables on the asymmetric alkylation were also studied: the amount of induction appears to be insensitive to the rate of agitation as well as the temperature (15–25 °C). Additionally, changing the steric bulk of the 5-alkoxy substituent on oxindole **4** apparently has little effect on the enantiomeric excess of the reaction (R = Et, 73% ee; R = CH_2Ph, 75% ee). The asymmetric alkylation is general and can also be extended to other electrophiles. The optical yields[10] for the electrophiles studied were benzyl bromide (36% ee); benzyl chloride (58% ee); allyl chloride (78% ee); 4-chloro-2-methyl-2-butene (73% ee). Thus, it appears that more reactive and bulky electrophiles result in lower induction. It should be noted that both allyl-substituted adducts can be converted to (−)-physostigmine via ozonolysis and reductive amination. In addition, the allyl-substituted oxindole is a critical intermediate leading to geneserine, a (−)-physostigmine-related alkaloid.[12]

In summary, we have demonstrated that catalytic chiral phase-transfer asymmetric alkylation of oxindoles followed by chemical resolution represents a practical method of preparing natural (−)-esermethole (**2**) in 32% overall unoptimized yield from oxindole **4** (R = CH_3). Since **2** has already been converted into (−)-physostigmine (**1**) in two steps, this constitutes a formal total synthesis of the natural product. Additionally, the availability of optically pure amine (*S*)-**6** allows the syntheses of (−)-physostigmine analogues wherein the substituent on the N-1 nitrogen is modified. Research effort is being continued to further understand and improve the overall stereoselectivity of the reaction.

Experimental Section

Melting points are uncorrected. *N*-[4-(Trifluoromethyl)-benzyl]cinchoninium bromide and *N*-benzylcinchoninium chloride were purchased from Chemical Dynamics Corporation and Fluka Chemical Corporation, respectively. The other catalysts were prepared according to the literature.[7b]

General Procedure for the Asymmetric Alkylation. (A) Oxindole 4 (R = CH_3) with Chloroacetonitrile Using Different Chiral Phase-Transfer Catalysts. To a solution containing 2.51 mmol of 5-methoxy-1,3-dimethyloxindole in 20 mL of toluene was added, under N_2, the chiral phase-transfer catalyst (10 mol %) followed by 8 mL of 50% NaOH. After this mixture was stirred for 10 min, a solution containing 2.78 mmol of chloroacetonitrile in 20 mL of toluene was added dropwise over 1 h. After the reaction was complete, 25 mL of ice-cold H_2O was added. The mixture was filtered through a small Celite pad and rinsed with 10 mL of toluene. The toluene layer was concentrated under reduced pressure, and the residue was analyzed on a Chiralcel OD column (Daicel Chemical Industries, Ltd.), eluting with a 10% 2-propanol–hexanes mixture.

(B) Oxindole 4 (R = Et, CH_2Ph) with Chloroacetonitrile and Oxindole 4 (R = CH_3) with Other Electrophiles. To a solution containing 10.5 mmol of oxindole **4** in 80 mL of toluene was added, under N_2, the chiral phase-transfer catalyst (15 mol %) followed by 8 mL of 50% NaOH. After this mixture was stirred for 10 min, a solution containing 11.6 mmol of the electrophile in 8 mL of toluene was added dropwise over 1 h. After complete reaction, the reaction mixture was worked up and analyzed by chiral HPLC as described in (A).

(3*S*)-1,3-Dimethyl-3-(β-aminoethyl)-5-methoxyoxindole [(*S*)-6]. To a mixture containing 5.0 g (26.1 mmol) of oxindole **4** (R = CH_3) and 1.92 g of 3,4-Cl_2-BCNC (*N*-[3,4-dichlorobenzyl]cinchoninium bromide) (3.92 mmol, 15 mol %) in 200 mL of toluene was added, under an efficient N_2 purge, 40 mL of 50% NaOH. After this mixture was stirred for 10 min, a solution containing 2.17 g (28.7 mmol) of chloroacetonitrile in 20 mL of toluene was added over 1 h. After complete reaction, the mixture was cooled to 10–15 °C, and 160 mL of ice-cold H_2O was added. The reaction mixture was filtered through a Celite pad and rinsed with 40 mL of toluene. The toluene layer was extracted with 100 mL of cold 3 N HCl and 100 mL of cold H_2O. After evaporation of the solvent, 5.02 g (83%) of **5** was isolated as a slightly brownish oil. The enantiomeric excess of isomer (*S*)-**5** was determined to be 73% by chiral HPLC analysis on a Chiralcel OD column.

The above oil was taken up in 50 mL of MeOH and 7.25 mL of concentrated HCl, and 0.5 g of PtO_2 was added. The mixture was hydrogenated for 3 h at 45 psi. The catalyst was filtered and rinsed with 15 mL of MeOH. The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in 100 mL of ice-cold H_2O. The acidic aqueous solution was first extracted with 50 mL of CH_2Cl_2 and then basified with 5 mL of 50% NaOH. The basic aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure, giving 4.70 g (92%) of the corresponding amine **6**.

The above amine was dissolved in 25 mL of CH_3CN, and a solution containing 6.42 g of dibenzoyl-D-tartaric acid in 25 mL of CH_3CN was added rapidly under N_2. After stirring the mixture for another 30 min, the precipitate that formed was collected to give 10.38 g of a white solid. This solid was recrystallized from 60 mL of a 10% H_2O–CH_3CN mixture to give 7.86 g (47.4%) of the optically pure tartrate salt of amine (*S*)-**6**: mp 136–137 °C $[\alpha]_D$ +57.1° (*c* 1.05, MeOH); NMR (DMSO-d_6) δ 1.24 (s, 3 H), 1.94–2.06 (m, 2 H), 2.08 (s, 3 H, CH_3CN), 3.11 (s, 3 H), 5.64 (s, 2 H), 6.84–8.04 (m, 13 H); IR (KBr) 3240, 2960, 2260, 1720, 1685, 1600, 1500, 1280, 1260, and 1125 cm^{-1}; MS, *m/s* (M − $C_{18}H_{14}O_8$) 234, 191, 122, 105, and 77. Anal. Calcd for $C_{31}H_{32}N_2O_{10}\cdot CH_3CN$: C, 62.55; H, 5.57; N, 6.63. Found: C, 62.61; H, 5.52, N, 6.63.

A 1.0-g sample of the above tartrate was dissolved in 15 mL of 5% NaOH solution and extracted with CH_2Cl_2 (2 × 15 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure to give 0.37 g (100%) of amine (*S*)-**6**. This material was used in the next step without further purification.

(3*S*)-1,3-Dimethyl-3-[β-[(methoxycarbonyl)amino]-ethyl]-5-methoxyoxindole [(*S*)-7]. To a solution containing 0.37 g (1.58 mmol) of amine (*S*)-**6** and 0.25 mL (1.78 mmol) of Et_3N in 50 mL of CH_2Cl_2 at 0 °C under N_2 was added 0.13 mL (1.68 mmol) of $ClCO_2CH_3$. The reaction mixture was allowed to warm to room temperature over 1 h. Standard workup gave 0.40 g (85.6%) of (*S*)-**7** as an oil: NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.88–2.2 (m, 2 H), 2.83–3.0 (m, 2 H), 3.16 (s, 3 H), 3.57 (s, 3 H), 3.80 (s, 3 H), 4.73 (br s, 1 H), 6.72–6.82 (m, 3 H). This material was used in the next step without purification.

(−)-Esermethole (2). To a solution containing 0.27 g (0.9 mmol) of carbamate (*S*)-**7** in 15 mL of anhydrous THF under N_2 was added 1.85 mL (1.8 mmol) of a 1.0 M solution of $LiAlH_4$ in THF. The reaction mixture was heated under reflux for 50 min and then concentrated under reduced pressure. The residue was dissolved in 15 mL of 0.5 N HCl and extracted with 20 mL of Et_2O. The aqueous solution was basified with Na_2CO_3 and extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude reaction mixture was passed through a small pad of SiO_2 and eluted with a 20% 2-propanol–hexanes

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mixture. The eluant was concentrated under reduced pressure to give 0.16 g (74.5%) of **2** as an oil, which crystallized on standing: mp 52.5–54 °C; $[\alpha]_D$ −136.7° (*c* 0.33, benzene) [lit.[4c] $[\alpha_D]$ −134° (*c* 0.35, benzene)]. This material was determined to be optically pure by chiral HPLC analysis on a Chiralcel OJ column. The spectroscopic properties of **2** were identical with those reported in the literature.[4a]

Chiral Recognition of Asymmetric Amine Salts by Chemically Modified Polyether Antibiotics

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The most striking feature of polyether antibiotics is their ability to form stable complexes with alkali and alkaline earth metal cations. They are known to accommodate guest metal cations in their pseudo-cyclic cavities and to transport them selectively across the biomembrane.[2] Since they are composed of a number of optically active segments, they may provide chiral and ordered pseudo-cavities that specifically accommodate certain enantiomerically pure ammonium cations as well as some metal cations. Westley et al. first applied naturally occurring lasalocid to the preferential crystallization of salts with racemic amines.[3] More recently, Maruyama et al. demonstrated that some monensin amide derivatives exhibit enantiomer selectivity for several chiral ammonium cations comparable to those with chiral crown ethers.[4] Although only a limited number of successful examples have been reported, these findings clearly offer the interesting possibility that a new series of chiral host molecules may be derivable from natural polyether antibiotics.

We prepared a new series of chiral host molecules **1c–e**, **2b**, **3b**, and **4b** from natural monensin (**1a**), lasalocid (**2a**), salinomycin (**3a**), and nigericin (**4a**) (Chart I). Although the polyether antibiotics employed are themselves incapable of discriminating between optical isomers of chiral amine salts, some modified materials formed diastereomeric complexes with chiral amine salts and exhibited potential enantiomer selectivity in the electrochemical sensory system.

Results and Discussion

We obtained various ester derivatives of polyether antibiotics in 80–98% yields by cryptand[2.2.2]-promoted reaction with the corresponding bromides.[5] Their guest-binding properties were characterized by ion-selective electrode techniques.[6] The enantiomer selectivity coefficient $K_{S,R}$ is defined as $10^{(E_S-E_R)/0.059}$ (at 25 °C), where E_S and E_R represent the potentials to the *S*- and *R*-guest

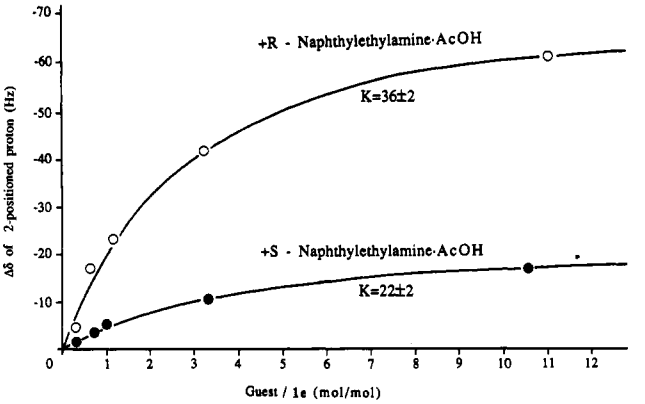

Figure 1. ^{1}H NMR (500 MHz) titration curves of monensin pentafluorobenzyl ester (**1e**) with (*S*)- and (*R*)-naphthylethylamine·AcOH. Concentration of **1e**: 0.0146 M in $CDCl_3$.

containing solutions. This selectivity coefficient should correlate with the stability constants of the complexes between the employed ionophore and optically active ammonium cations in the membrane.[7] Typical results are summarized in Table I.

The sensor electrodes incorporating the parent and modified polyether antibiotics generally exhibited near Nernstian responses for chiral ammonium salts in the range of 1×10^{-1} to 1×10^{-4} mol/L. Although some of them had been employed as specific ionophores of certain metal cations,[8] they also formed stable complexes with primary ammonium cations. Interestingly, chemically modified polyether antibiotics **1b–e**, **2b**, **3b**, and **4b** showed chiral recognition behavior toward some chiral ammonium cations, while natural antibiotics **1a**, **2a**, **3a**, and **4a** having carboxylic acid moieties exhibited little discrimination between these enantiomers. The enantiomer selectivity coefficients $K_{S,R}$ are largely dependent on the structures of the parent polyether antibiotics. In particular, monensin derivatives **1b–e** showed excellent chiral recognition ability; the potential differences for phenylglycine ester salt (Ph-GlyOMe·HCl), $E_S - E_R$, reached the relatively high values of 33–38 mV, and enantiomer selectivity coefficients $K_{S,R}$ were calculated as 3.7–4.4. Monensin lactone (**1f**)[9] and nonactin (**5a**) with similar chiral polyether linkages and ester groups in the macrocyclic skeletons were also examined for comparison. Since they show low enantiomer selectivity coefficients, monensin ester derivatives **1b–e** are believed to have neutral, acyclic (but pseudo-cyclic) polyether skeletons suitable for chiral recognition of asymmetric ammonium cations.

The enantiomer-selective complexation behavior of monensin ester derivatives was investigated by 500-MHz ^{1}H NMR spectroscopy. Table II summarizes guest-induced ^{1}H NMR spectral changes of several monensin derivatives. For example, the addition of (*R*)-naphthylethylamine salt to a $CDCl_3$ solution of monensin ester **1e** caused shifts of the signals for several protons attached to the carbons surrounding the pseudo-cavity, such as those positioned at 2, 5, 20, 21, and 31. These observations strongly suggest that the guest ammonium cation is located at the center of the pseudo-cavity of monensin ester and effectively interacts with several oxygen atoms. Its *S* isomer showed definite but different spectral changes.

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