Synthesis and Antagonistic Activities of Enantiomers of Cyclic Platelet-Activating Factor Analogues

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Enantiomers of platelet-activating factor (PAF) antagonists, 3-{6-[*O*-(*trans*-3-heptadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}hexylthiazolium (inner salt) (3), 3-[5-(*trans*-3-heptadecylcarbamoyloxytetrahydropyran-2-yl)methoxycarbonylamino]pentylthiazolium bromide (4) and 3-{5-[*O*-(*cis*-3-heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}pentylthiazolium (inner salt) (5), were synthesized, starting from (2*R*,2*R*)- and (2*S*,2*S*)-tartaric acid.

Antagonistic activities of these compounds against C_{16}-PAF were measured *in vitro* (rabbit platelet aggregation, IC_{50}) and *in vivo* (hypotension in rats, ID_{50}). In these three enantiomeric pairs, the (3*S*)-(tetrahydropyran numbering) enantiomers were one order more potent than the (3*R*)-isomers: (2*R*,3*S*)-3a (R-74,654), IC_{50} 0.59 μM and ID_{50} 0.054 mg/kg, i.v.; (2*S*,3*R*)-3b, IC_{50} 4.7 μM and ID_{50} 0.30 mg/kg, i.v.; (2*R*,3*S*)-4a, IC_{50} 0.20 μM and ID_{50} 0.032 mg/kg, i.v.; (2*S*,3*R*)-4b, IC_{50} 2.2 μM and IC_{40} 0.21 mg/kg, i.v.; (2*R*,3*R*)-5a, IC_{50} 1.1 μM and ID_{50} 0.92 mg/kg, i.v.; (2*S*,3*S*)-5b (R-74,717), IC_{50} 0.27 μM and ID_{50} 0.064 mg/kg, i.v.

Keywords platelet-activating factor (PAF); platelet aggregation; hypotension; PAF antagonist; enantiomeric cyclic ether PAF analogue; R-74,654; R-74,717

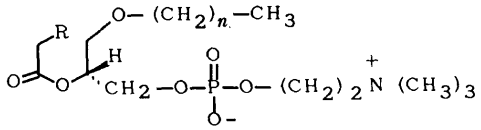
During the decade after the characterization of platelet-activating factor (PAF),[1] a vast amount of information on the biological role of this phospholipid mediator has been accumulated.[2] As the involvement of PAF in certain pathological conditions, *e.g.* septic shock, asthma, nephritis or gastrointestinal ulcer, has been suggested,[2c,e,h-k] great efforts have been made to find PAF antagonists among PAF analogues,[3] synthetic heterocycles,[4] plant products and related compounds,[5] or microbial metabolites and their derivatives.[6] The first specific PAF antagonist (CV-3988[3a]), and the most potent compound so far discovered (CV-6209[3b]) belong to the category of PAF analogues.

As the inhibition of the binding of PAF to the specific receptors by these antagonistic PAF analogues has been reported,[7] similarity is expected in the conformations of the antagonists and PAF that bind to the receptor. On the other hand, the enantiomers of CV 3988, CV-6209 and another antagonistic PAF analogue ONO-6240[3d] have shown no difference in their PAF antagonistic activities[3b-d] despite the strict enantiomeric specificity of PAF itself. This suggests that stereospecific binding of the C(2) substituent of the antagonists is not necessary for the antagonistic activities. The possibility still remains, however, that the two side chains at C(1) and C(3) may be arranged asymmetrically in the three dimensional space during the receptor binding.

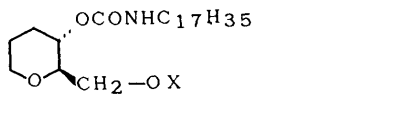
In the preceding paper,[8] we have reported the potent antagonistic activities of the cyclic PAF analogues **3** and **5**, which represent the conformationally restricted glycerol backbone of propionyl PAF.[9] To examine the conformational binding mode of the two side chains at C(1) and C(3) of PAF and its analogues, it is of interest to investigate whether the enantiomers of **3** or **5** differ in their antagonistic activities or not.

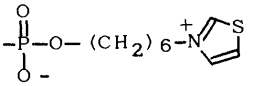
We report here the synthesis of both enantiomers of **3**, **5** and a related non-phosphate antagonist **4**, and the marked difference in the biological activities of the three enantiomeric pairs.

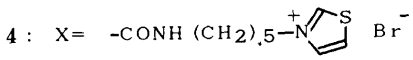
Synthesis The common intermediate for the (2*R*)-(tetrahydropyran numbering) series, (2*R*, 3*S*)-3-hydroxy-2-triphenylmethyltetrahydropyran (**14a**), was prepared from dimethyl (2*R*,3*R*)-tartrate (**6a**) as illustrated in Chart 1. According to Ohno *et al*'s method,[10a] **6a** was converted into the threitol derivative **7a**.[10] The methanesulfonate of **7a** was treated with sodium iodide and the resulting iodide was condensed with diethyl malonate in the presence of sodium hydride to afford **8a**. The diester **8a** was deethoxycarbonylated with sodium chloride in wet dimethyl sulfoxide[11] to yield the monoester **9a**, which was in turn reduced with lithium aluminum hydride to the alcohol **10a**. Protection of **10a** with the *tert*-butyldiphenylsilyl group followed by deacetalization gave the 1,2-diol **11a**. By successive tritylation, mesylation and desilylation, **11a** was converted into the (2*S*,3*S*)-hexane-1,2,3,6-tetraol derivative **12a**. On treatment with potassium *tert*-butoxide in *tert*-butanol, **12a** cyclized with inversion of configuration at C(2) to yield the



1: R=H, R=CH$_3$ (n=15 or 17)



3: X= 

4: X= 

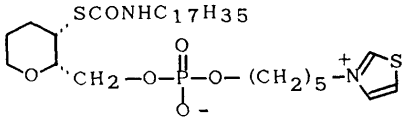


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Fig. 1

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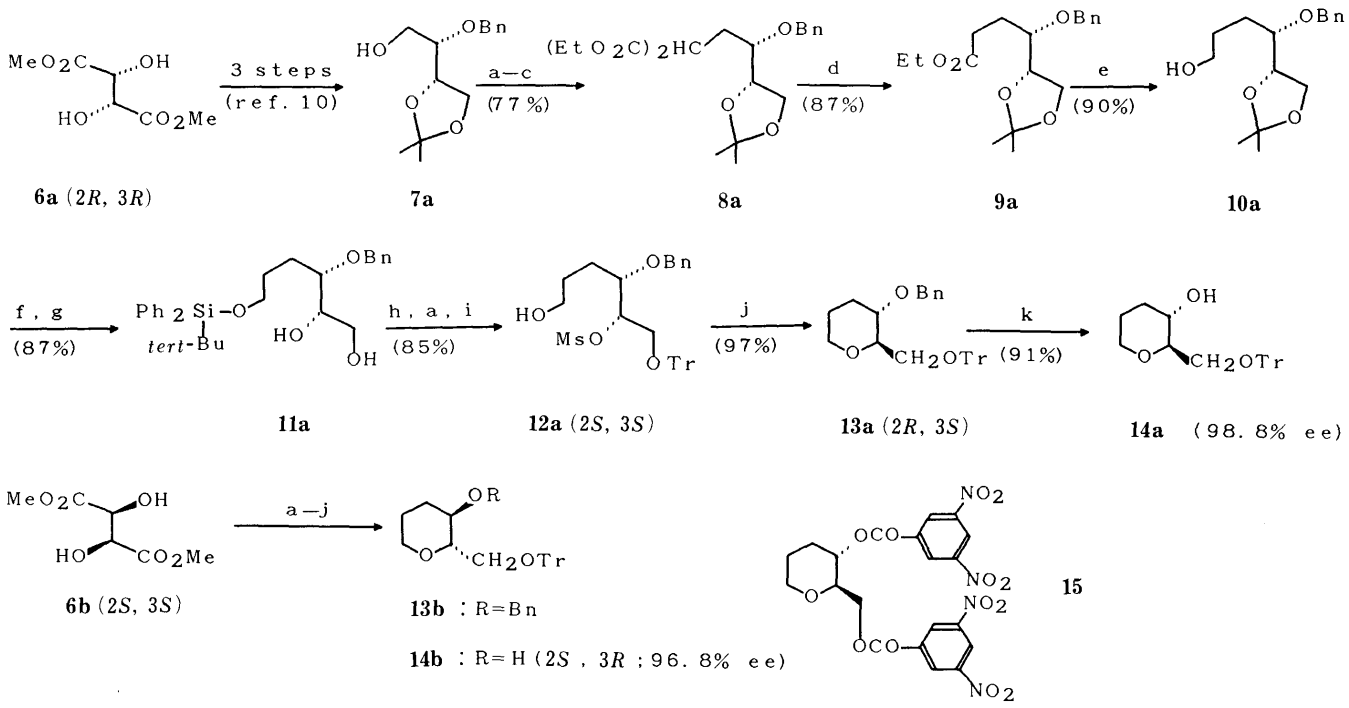


Bn=benzyl, Tr=triphenylmethyl, Ms=methanesulfonyl

a) MsCl, Et_3N; b) NaI, $NaHCO_3$, Me_2CO; c) NaH, $CH_2(CO_2Et)_2$, DMF; d) DMSO–H_2O, NaCl, 190°C; e) $LiAlH_4$, THF; f) *tert*-$BuPh_2SiCl$, imidazole, DMF; g) aq. AcOH; h) TrCl, Et_3N; i) Bu_4NF, THF j) *tert*-BuOK, *tert*-BuOH; k) H_2, Pd–C, EtOH

Chart 1

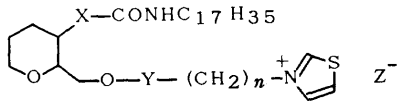
(2*R*,3*S*)-tetrahydropyran derivative **13a**. Catalytic hydrogenation of **13a** with 10% palladium on carbon in ethanol selectively removed the benzyl group, affording the secondary alcohol **14a**. The optical purity of **14a** was determined by preparation of its (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) ester, which showed 98.8% ee on high-pressure liquid chromatography (HPLC). To confirm the absolute configuration, **14a** was transformed into the bis-(3,5-dinitro)benzoate **15** {mp 168—169 °C, $[\alpha]_D^{24}$ +59.3° (c=0.30, $CHCl_3$); lit.,[12] mp 168 °C, $[\alpha]_D^{20}$ +50° (c=0.3, $CHCl_3$)} by detritylation and acylation with 3,5-dinitrobenzoyl chloride.

Starting from dimethyl (2*S*,3*S*)-tartrate (**6b**), the (2*S*,3*R*)-intermediate **14b** was similarly synthesized. The (*S*)-MTPA ester of **14b** exhibited 96.8% ee on HPLC.

The enantiomers of the PAF antagonists **3**—**5** were prepared from **14a** and **14b** as illustrated in Chart 2. Heating of **14a** with heptadecyl isocyanate, prepared from octadecanoic acid and diphenylphosphoryl azide (DPPA)[13] in the presence of triethylamine, and subsequent acidic deprotection gave the primary alcohol **16a**. As described in the synthesis of racemic **3**,[8] the 6-thiazoliohexylphosphoryl side chain was attached to the hydroxy group of **16a** to yield (2*R*,3*S*)-**3a** (R-74, 654). Similarly, the enantiomeric (2*S*,3*R*)-isomer **3b** was prepared from **14b**.

The synthesis of the non-phosphate type antagonist (2*R*,3*S*)-**4a** was achieved through the urethane formation from **16a** and 5-bromopentyl isocyanate (generated *in situ* from 6-bromohexanoic acid and DPPA), and the sub-

Table I. Antagonistic Activities of Enamtiomeric and Racemic Cyclic PAF Analogues



3: X=O, Y=$-P(=O)(O^-)-O-$, n=6,

4: X=O, Y=–CONH–, n=5, Z=Br

5: X=S, Y=$-P(=O)(O^-)-O-$, n=5

Compd.	Configuration	Platelet aggregation (Rabbit, IC_{50} μM)	Hypotension (Rat, ID_{50} mg/kg, i.v.)
3a (R-74,654)	2*R*,3*S* (*trans*)	0.59	0.054
3b	2*S*,3*R* (*trans*)	4.7	0.30
3	rac- (*trans*)	0.55	0.046
4a	2*R*,3*S* (*trans*)	0.20	0.032
4b	2*S*,3*R* (*trans*)	2.2	0.21
4	rac- (*trans*)	0.24	0.034
5a	2*R*,3*R* (*cis*)	1.1	0.92
5b (R-74,717)	2*S*,3*S* (*cis*)	0.27	0.064
5	rac- (*cis*)	0.57	0.076

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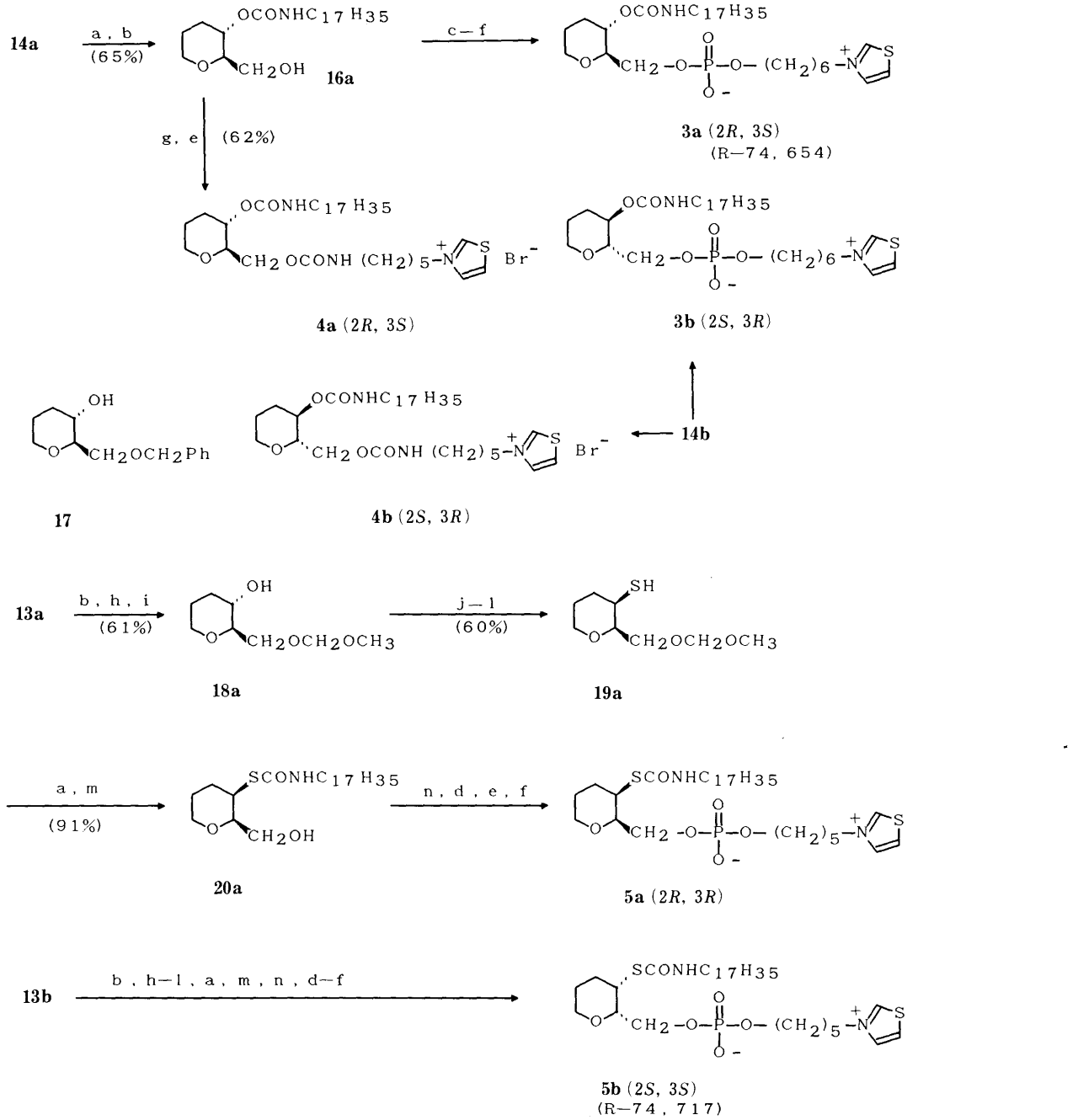
sequent quaternization of thiazole[3a] with the resulting bromourethane. The corresponding (2*S*,3*R*)-isomer **4b** was obtained in a similar manner, starting from **14b**. Racemic **4** was also synthesized, utilizing racemic **16**.[8]

In order to synthesize the *cis*-antagonist **5a**, inversion of the *trans* alcohol **14a** to the corresponding *cis* thiol was attempted. Under the conditions described for the similar inversion of (2*R**,3*S**)-2-benzyloxymethyltetrahydropyran-3-ol (**17**),[8] however, **14a** did not afford the desired thiol. The bulky trityl group of **13a** was replaced with the methoxymethyl group in two steps (steps b and h in Chart 2) and the benzyl group was catalytically removed. The methoxymethyl *trans* alcohol **18a**, thus obtained, was smoothly converted into the *cis* thiol **19a** under the conditions reported for the inversion of **17**.[8] Formation of thiourethane from **19a** and heptadecyl isocyanate and subsequent deprotection gave the *cis* alcohol **20a**. Introduction of the 5-thiazoliopentylphosphate side chain into **20a** was carried out in a similar manner to the synthesis of **3a**,[8] yielding the (2*R*,3*R*)-antagonist **5a**. Starting from **14b**, the (2*S*,3*S*)-enantiomer **5b** (R-74, 717) was similarly prepared.



a) $C_{17}H_{35}COOH$, DPPA, Et_3N; b) *p*–TsOH, MeOH; c) Br $(CH_2)_6OPOCl_2$, Et_3N; d) H_2O; e) thiazole; f) Amberlite MB–3; g) Br $(CH_2)_5COOH$, DPPA, Et_3N; h) NaH, $MeOCH_2Cl$; i) H_2, 10% Pd–C, THF; j) MsCl, Et_3N; k) AcSNa; l) MeONa, MeOH; m) conc. HCl; n) Br $(CH_2)_5OPOCl_2$, Et_3N

Chart 2

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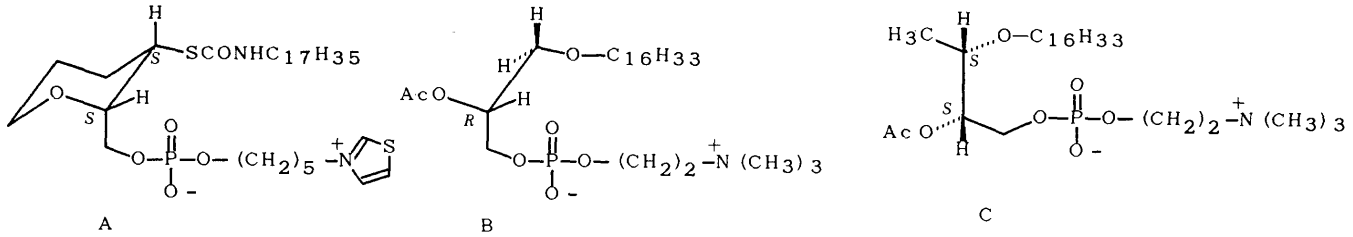

Fig. 2

Biological Results and Discussion The antagonistic activities of newly synthesized enantiomers **3a,b**—**5a,b** against *in vitro* (platelet aggregation in rabbits) and *in vivo* (hypotension in rats) effects of PAF were determined as described in the preceding paper.[8] The results are summarized in Table I, together with the data reported elsewhere for the racemic compounds.[8]

In each pair of enantiomers, the (3*S*)-(tetrahydropyran numbering, corresponding to the *sn*-1 position of the PAF molecule) enantiomer was one order more potent as an antagonist, both *in vitro* and *in vivo*, than the (3*R*)-isomer. On the other hand, the racemic compounds showed activities similar to those of the (3*S*)-enantiomers, except racemic **5** *in vitro*. The reason for this phenomenon is not clear at present.

It is noteworthy that the (3*S*)-*trans* isomers **3a** and **4a**, despite their (2*R*)-configuration,[14] opposite to that of natural PAF, showed more poten activities than **3b** and **4b** with PAF like (2*S*)-configuration,[14] respectively. In addition, the (2*S*,3*S*)-*cis* compound (**5b**) was a more potent antagonist than the (2*R*,3*R*)-enantiomer. Clearly, the (3*S*)-configuration is favorable for these cyclic PAF analogues to exert their antagonistic activities. As CV-3988, with octadecylcarbamoyl and thiazolioethyl phosphate side chains, has been shown to bind to the specific PAF receptor,[7] the stable conformations of **3a** and **5b** (*e.g.* A in Fig. 2 for **5b**) seem to be related to the binding configuration of the open chain antagonist.

If the conformations of PAF and CV-3988 binding to the receptor are similar, the stable conformation of **5b** (*e.g.* A) might reflect the binding conformation of PAF, such as B. In agreement with this argument, Ohno *et al.* reported that (1*S*)-methyl PAF (C) exhibited more potent agonistic activities than the (1*R*)-methyl isomer.[15]

Experimental

All melting points and boiling points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a Varian EM-390 (90 MHz), a JEOL JNM-GX270 (270 MHz), or a JEOL JNM-GX400 (400 MHz) instrument. The solvent was $CDCl_3$ and the frequency was 90 MHz unless otherwise noted. Infrared (IR) spectra were taken in $CHCl_3$ solutions on a JEOL IR-A2 spectrometer unless otherwise specified. Mass spectra (MS) were obtained with a JEOL JMS-01SG spectrometer. Fast atom bombardment (FAB)-MS were taken with a JEOL JMS-HX100 spectrometer. Specific rotations ($[\alpha]_D$) were measured with a Perkin-Elmer 241 polarimeter.

Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Dimethylformamide (DMF) was refluxed over CaH_2 and distilled. Other aprotic solvents for reactions were passed through a short column of neutral alumina (ICN Alumina N-Super I) just before use. All reactions in aprotic solvents were carried out under a nitrogen atmosphere. For silica gel column chromatography, Kieselgel 60 (Merck, 60—230 mesh) was used.

Compounds **3a**—**14a** and **3b**—**14b** were synthesized similarly, starting from (2*R*,3*R*)- and (2*S*,3*S*)-tartrate, respectively. Only the preparation of **3a**—**14a** is described in detail.

Ethyl (4*S*,5*S*)-4-Benzyloxy-2-ethoxycarbonyl-5,6-isopropylidenedioxyhexanoate (8a) According to the method of Ohno *et al.*,[10a] (2*S*,3*S*)-2-*O*-benzyl-3,4-*O*-isopropylidenethreitol (**7a**)[10] {$[\alpha]_D^{26}$ −21.2° (*c*=1.31, $CHCl_3$); lit.[10] $[\alpha]_D^{22}$ −16.8° (*c*=1.31, $CHCl_3$)} was prepared from dimethyl (2*R*,3*R*)-tartrate (**6a**). Three-step conversion of **7a** into **8a** was carried out as described for racemic **8**,[8] *via* the methanesulfonate of **7a** and (2*S*,3*R*)-3-*O*-benzyl-4-iodo-1,2-*O*-isopropylidenebutane-1,2,3-triol {bp 130—150 °C (bath temperature)/1 mmHg, $[\alpha]_D^{26}$ −8.40° (*c*=1.00, $CHCl_3$)}, yielding **8a** (77% from **7a**) as a colorless oil, bp 170—180 °C (bath temperature)/1 mmHg. Spectral data were identical with those of racemic **8**.[8] $[\alpha]_D^{26}$ −39.5° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 64.12; H, 7.66.

Ethyl (4*R*,5*R*)-4-Benzyloxy-2-ethoxycarbonyl-5,6-isopropylidenedioxyhexanoate (8b) A colorless oil. $[\alpha]_D^{26}$ +39.1° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 63.66; H, 7.49.

Ethyl (4*S*,5*S*)-4-Benzyloxy-5,6-isopropylidenedioxyhexanoate (9a) The deethoxycarbonylation of **8a** was carried out as described for the synthesis of racemic **9**,[8] to give **9a** as a colorless oil, bp 150—160 °C (bath temperature)/1 mmHg, $[\alpha]_D^{26}$ −47.4° (*c*=1.30, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.01; H, 8.08.

Ethyl (4*R*,5*R*)-4-Benzyloxy-5,6-isopropylidenedioxyhexanoate (9b) A colorless oil. $[\alpha]_D^{26}$ +47.6° (*c*=1.32, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.06; H, 8.13.

(4*S*,5*S*)-4-Benzyloxy-5,6-isopropylidenedioxyhexan-1-ol (10a) A solution of **9a** (41.00 g, 127 mmol) in THF (200 ml) was added to a stirred suspension of $LiAlH_4$ (5.78 g, 152 mmol) in THF (620 ml) at 5—8 °C under ice-water cooling. The mixture was stirred at room temperature for 2 h, and then 4% aqueous NaOH solution (23 ml) was added dropwise at 4—7 °C. The mixture was filtered through a layer of Celite, which was washed with EtOAc. The filtrate and the washing were combined, and evaporated to dryness. The residue was chromatographed on silica gel (700 g). Elution with hexane–EtOAc (2:1) gave **10a** (32.15 g, 90%) as a colorless oil, bp 150—160 °C (bath temperature)/1 mmHg. $[\alpha]_D^{26}$ −42.5° (*c*=1.10, $CHCl_3$). ^{1}H-NMR δ: 1.36 (3H, s), 1.44 (3H, s), 1.5—1.8 (4H, m), 1.71 (1H, s), 3.4—3.8 (4H, m), 4.02 (1H, dt, *J*=7.5, 6 Hz), 4.25 (1H, dt, *J*=7.5, 6 Hz), 4.62 (1H, d, *J*=11 Hz), 4.80 (1H, d, *J*=11 Hz), 7.38 (5H, m). IR cm^{-1}: 3450. MS *m/z*: 280 (M^+), 265 (M^+ − Me). *Anal.* Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.78; H, 8.90.

(4*R*,5*R*)-4-Benzyloxy-5,6-isopropylidenedioxyhexan-1-ol (10b) A colorless oil. $[\alpha]_D^{26}$ +41.8° (*c*=1.06, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.23; H, 8.58.

(2*S*,3*S*)-3-Benzyloxy-6-(*tert*-butyldiphenylsiloxy)hexane-1,2-diol (11a) A solution of *tert*-butyldiphenylsilyl chloride (19.41 g, 70.6 mmol) in DMF (90 ml) was added to a stirred solution of **10a** (18.00 g, 64.2 mmol) and imidazole (9.62 g, 141 mmol) in DMF (270 ml) at 5—7 °C under ice-water cooling. After being stirred at room temperature for 3 h, the reaction mixture was poured into water and extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (700 g). Elution with hexane–EtOAc (98:2—95:5) afforded (2*S*,3*S*)-3-benzyloxy-6-(*tert*-butyldiphenylsiloxy)-1,2-isopropylidenedioxyhexane (30.97 g, 93%) as a colorless oil. $[\alpha]_D^{26}$ −20.8° (*c*=1.25, $CHCl_3$). ^{1}H-NMR δ: 1.04 (9H, s), 1.37 (3H, s), 1.43 (3H, s), 1.4—1.8 (4H, m), 3.3—3.8 (4H, m), 4.00 (1H, dt, *J*=7.5, 6 Hz), 4.20 (1H, dt, *J*=7.5, 6 Hz), 4.58 (1H, d, *J*=12 Hz), 4.74 (1H, d, *J*=12 Hz), 7.2—7.8 (15H, m). MS *m/z*: 503 (M^+ − Me). *Anal.* Calcd for $C_{32}H_{42}O_4$ Si: C, 74.09; H, 8.16. Found: C, 74.05; H, 8.10.

A mixture of the above compound (30.48 g, 58.8 mmol), H_2O (30 ml) and AcOH (300 ml) was stirred at room temperature for 17 h, and heated at 50 °C for 2 h. The mixture was evaporated to dryness *in vacuo*, and the residue was chromatographed on silica gel (400 g). Elution with hexane–EtOAc (2:1) gave **11a** (26.15 g, 93%) as a colorless oil. $[\alpha]_D^{26}$ +20.6° (*c*=1.15, $CHCl_3$). ^{1}H-NMR δ: 1.05 (9H, s), 1.5—1.9 (4H, m), 1.9—2.3 (1H, m), 2.3—2.7 (1H, m), 3.4—3.9 (6H, m), 4.44 (1H, d, *J*=12 Hz), 4.62 (1H,

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d, J=12 Hz), 7.2—7.8 (15H, m). IR cm^{-1}: 3590, 3460. MS m/z: 479 (M^++1).

(2*R*,3*R*)-3-Benzyloxy-6-(*tert*-butyldiphenylsiloxy)hexane-1,2-diol (11b) A colorless oil. $[\alpha]_D^{26}$ −20.4° (c=1.12, $CHCl_3$).

(2*S*,3*S*)-3-Benzyloxy-6-hydroxy-1-triphenylmethoxy-2-hexyl Methanesulfonate (12a) A mixture of **11a** (25.96 g, 54.2 mmol), Et_3N (18.20 ml, 131 mmol), triphenylmethyl chloride (18.11 g, 65.1 mmol) and toluene (520 ml) was heated under reflux for 3 h. After cooling, the mixture was poured into water and extracted three times with EtOAc. The combined extracts were washed successively with water, aqueous $NaHCO_3$ and aqueous NaCl solutions, dried over Na_2SO_4 and evaporated *in vacuo*. The oily residue was dissolved in THF (260 ml), mixed with saturated aqueous $NaHCO_3$ solution (90 ml) and stirred at room temperature for 1 h. (Without this operation the triphenylmethoxy group of the product was cleaved on subsequent silica gel chromatography.) The mixture was poured into water and extracted twice with EtOAc. The combined extracts were dried, evaporated to dryness, and the residue was chromatographed on silica gel (500 g). Elution with hexane–EtOAc (95:5—9:1) gave (2*S*,3*S*)-3-benzyloxy-6-(*tert*-butyldiphenylsiloxy)-1-triphenylmethoxyhexan-2-ol (36.50 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ +3.56° (c=1.01, $CHCl_3$). ^{1}H-NMR δ: 1.05 (9H, s), 1.4—1.8 (4H, m), 2.30 (1H, d, J=6 Hz), 3.22 (2H, d, J=6 Hz), 3.5—3.9 (4H, m), 4.38 (1H, d, J=12 Hz), 4.51 (1H, d, J=12 Hz), 7.1—7.8 (30 H, m). MS m/z: 477 ($M^+ - C_{19}H_{16}$). *Anal.* Calcd for $C_{48}H_{52}O_4Si$: C, 79.96; H, 7.27. Found: C, 79.68; H, 7.00.

Methanesulfonyl chloride (4.59 ml, 59.3 mmol) was added to a solution of the above compound (35.60 g, 49.4 mmol) and Et_3N (8.26 ml, 59.3 mmol) in CH_2Cl_2 (500 ml) under ice-water cooling. After being stirred at room temperature for 1 h, the mixture was poured into water, and the organic layer was separated, washed with aqueous NaCl solution, dried over Na_2SO_4 and evaporated to dryness. The oily residue (39.42 g) was dissolved in THF (500 ml), and to this solution was added a solution of Bu_4NF in THF (1 M, 59.3 ml, 59.3 mmol) under ice-water cooling. After being stirred at room temperature for 14 h, the mixture was diluted with EtOAc and poured into water, and the aqueous layer was extracted twice with EtOAc. The combined organic solutions were washed with aqueous NaCl solution, dried, and evaporated to dryness, and the residue was chromatographed on silica gel (700 g). Elution with hexane–EtOAc (4:1—2:1) gave **12a** (25.18 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ −21.7° (c=1.23, $CHCl_3$). ^{1}H-NMR δ: 1.37 (1H, s), 1.4—1.8 (4H, m), 3.00 (3H, s), 3.30 (1H, dd, J=11, 6 Hz), 3.4—3.6 (2H, m), 3.60 (1H, dd, J=11, 3 Hz), 3.6—3.9 (1H, m), 4.56 (2H, s), 4.82 (1H, ddd, J=6, 6, 3 Hz), 7.2—7.6 (20H, m). IR cm^{-1}: 3500, 1360. MS m/z: 483 ($M^+ - C_6H_5$).

(2*R*,3*R*)-3-Benzyloxy-6-hydroxy-1-triphenylmethoxy-2-hexyl Methanesulfonate (12b) A colorless oil. $[\alpha]_D^{25}$ +21.7° (c=1.22, $CHCl_3$).

(2*R*,3*S*)-3-Benzyloxy-2-triphenylmethoxymethyltetrahydropyran (13a) A solution of **12a** (24.98 g, 44.6 mmol) in *tert*-BuOH (250 ml) was added to a solution of *tert*-BuOK (6.06 g, 54.0 mmol) in *tert*-BuOH (250 ml) at 25 °C. After being stirred at 40 °C for 4 h, the reaction mixture was neutralized with AcOH (0.54 ml) and the solvent was evaporated off. The residue was mixed with ice water and extracted three times with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$ and aqueous NaCl solutions, dried over Na_2SO_4, and evaporated to dryness, and the residue was chromatographed on silica gel (425 g). Elution with hexane–EtOAc (95:5) gave crystalline **13a** (20.12 g, 97%), mp 86.5—88.5 °C (MeOH). $[\alpha]_D^{25}$ +33.0° (c=1.00, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 1.41 (1H, dddd, J=12.3, 10.9, 9.3, 6.7 Hz), 1.70 (2H, m), 2.26 (1H, ddddd, J=12.3, 4.2, 3.9, 3.9, *ca.* 1 Hz), 3.20 (1H, dd, J=9.8, 5.0 Hz), 3.37 (1H, ddd, J=9.3, 5.0, 2.0 Hz), 3.39 (1H, ddd, J=11.4, 9.3, 5.3 Hz), 3.48 (1H, dd, J=9.8, 2.0 Hz), 3.49 (1H, ddd, J=10.9, 9.3, 4.2 Hz), 4.00 (1H, dddd, J=11.4, 2.9, 2.9, *ca.* 1 Hz), 4.27 (1H, d, J=11.5 Hz), 4.48 (1H, d, J=11.5 Hz), 7.0—7.5 (20H, m). MS m/z: 387 ($M^+ - C_6H_5$), 373 ($M^+ - C_7H_7$). *Anal.* Calcd for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.78; H, 6.81.

(2*S*,3*R*)-3-Benzyloxy-2-triphenylmethoxymethyltetrahydropyran (13b) White crystals, mp 86.0—88.0 °C (MeOH). $[\alpha]_D^{25}$ −32.8° (c=1.01, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.56; H, 6.83.

(2*R*,3*S*)-2-Triphenylmethoxymethyltetrahydropyran-3-ol (14a) A mixture of **13a** (2.835 g, 6.10 mmol), 10% Pd–C (1.499 g) and EtOH (100 ml) was hydrogenated in a Paar apparatus at 4 atm for 30 h. After the removal of the catalyst by passing the mixture through a layer of Celite, the solvent was evaporated off, and the residue was chromatographed on silica gel (75 g). Elution with hexane–EtOAc (7:1) gave **14a** (2.075 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ −38.0° (c=1.12, $CHCl_3$). ^{1}H-NMR δ: 1.2—1.8 (3H, m), 1.9—2.3 (1H, m), 3.00 (1H, s), 3.1—3.7 (5H, m), 3.75—4.05 (1H, m), 7.2—7.7 (15H, m). IR cm^{-1}: 3500. MS m/z: 374 (M^+), 297 ($M^+ - C_6H_5$).

(*S*)-(−)-MTPA chloride (45.7 mg, 0.181 mmol) was added to a solution of **14a** (45.4 mg, 0.121 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1.5 mg) in benzene–pyridine (1:1, 0.46 ml) under ice-water cooling. After being stirred at room temperature for 28 h, the mixture was poured into water, and extracted twice with EtOAc. The combined extracts were washed successively with water, 10% aqueous HCl solution, water and aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness to afford the MTPA ester of **14a** (70.0 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ +4.65° (c=1.01, $CHCl_3$). ^{1}H-NMR δ: 0.7—2.5 (4H, m), 2.9—3.7 (4H, m), 3.08 (3H, s), 3.8—4.2 (1H, m), 4.8—5.2 (1H, m), 7.0—7.7 (20H, m). IR cm^{-1}: 1745. MS m/z: 590 (M^+), 513 ($M^+ - C_6H_5$). HPLC (ERC-Silica 1161 column, 100×6 mm; pressure, 20 kg/cm^2; flow rate, 1.0 ml/min; solvent system, hexane–EtOAc, 95:5) showed two peaks at the t_R values of 8.81 (99.4%) and 9.71 min (0.6%), indicating an optical purity of 98.8% ee (The MTPA ester of racemic **14** showed these two peaks in 1:1 ratio under the same conditions.)

(2*S*,3*R*)-2-Triphenylmethoxymethyltetrahydropyran-3-ol (14b) A colorless oil. $[\alpha]_D^{25}$ +38.2° (c=1.07, $CHCl_3$). The (*S*)-(−)-MTPA ester of **14b** was prepared in the same way as described above: $[\alpha]_D^{25}$ −38.4° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.7—2.6 (4H, m), 2.9—3.6 (4H, m), 3.22 (3H, s), 3.8—4.2 (1H, m), 4.8—5.2 (1H, m), 6.9—7.7 (20H, m). IR cm^{-1}: 1745. MS m/z: 590 (M^+), 513 ($M^+ - C_6H_5$). HPLC (under the same conditions as described above) showed two peaks at t_R values of 8.76 min (1.6%) and 9.63 min (98.4%), indicating an optical purity of 96.8% ee.

(2*R*,3*S*)-2-(3,5-dinitrobenzoyloxy)methyltetrahydropyran-3-yl 3,5-Dinitrobenzoate (15) A mixture of **14a** (120.3 mg, 0.321 mmol), *p*-TsOH (H_2O) (18 mg) and MeOH (2.4 ml) was heated under reflux for 1 h. After cooling, the mixture was treated with $NaHCO_3$ (28 mg) and the solvent was evaporated off. The residue was mixed with ice water and extracted ten times with EtOAc. The combined extracts were dried over Na_2SO_4, and then evaporated to dryness, and the residue was chromatographed on silica gel (1 g). Elution with CH_2Cl_2–MeOH (9:1—4:1) afforded (2*R*,3*S*)-2-hydroxymethyltetrahydropyran-3-ol (36 mg, 85%) as a colorless oil.

3,5-Dinitrobenzoyl chloride (120.3 mg, 0.522 mmol) was added to a solution of the above diol (29.4 mg, 0.222 mmol) in pyridine (1 ml) under ice-water cooling. After being stirred at room temperature for 2 h, the mixture was poured into ice water and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, evaporated to dryness, and the residue was flash-chromatographed on silica gel (3 g). Elution with hexane–EtOAc (3:1—2:1) gave crystalline **15** (109.3 mg, 95%), mp 168.0—169.0 °C (acetone–petroleum ether). $[\alpha]_D^{24}$ +59.3° (c=0.30, $CHCl_3$) {lit.[12] mp 168 °C, $[\alpha]_D^{20}$ +50° (c=0.3, $CHCl_3$)}. ^{1}H-NMR δ: 1.5—2.6 (4H, m), 3.3—4.3 (3H, m), 4.62 (2H, d, J=4 Hz), 4.9—5.4 (1H, m), 9.0—9.4 (6H, m). IR cm^{-1}: 1735. MS m/z: 308 ($M^+ - C_7H_4N_2O_6$), 295 ($M^+ - C_8H_5N_2O_6$). *Anal.* Calcd for $C_{20}H_{16}N_4O_{13}$: C, 46.16; H, 3.10; N, 10.77. Found: C, 46.11; H, 3.28; N, 10.70.

(2*R*,3*S*)-2-Hydroxymethyltetrahydropyran-3-yl *N*-Heptadecylcarbamate (16a) A mixture of stearic acid (3.553 g, 12.5 mmol), DPPA (2.69 ml, 12.5 mmol), Et_3N (1.74 ml, 12.5 mmol) and benzene (80 ml) was heated under reflux for 3 h. After cooling, the mixture was washed with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted twice with EtOAc. The combined organic solutions were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in toluene (20 ml) containing Et_3N (1.74 ml, 12.5 mmol), and to this solution was added a solution of **14a** (1.871 g, 5.0 mmol) in toluene (20 ml). The mixture was heated on an oil bath at 100 °C for 90 h, cooled, and poured into saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic solutions were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness, and the residue was chromatographed on silica gel (90 g). Elution with hexane–EtOAc (7:1) gave (2*R*,3S)-2-triphenylmethoxymethyltetrahydropyran-3-yl *N*-heptadecylcarbamate (2.491 g, 76%) as a syrup. $[\alpha]_D^{25}$ +28.8° (c=1.13, $CHCl_3$). ^{1}H-NMR δ: 0.7—2.4 (37H, m), 2.8—3.6 (6H, m) 3.8—4.1 (1H, m), 4.2—4.8 (2H, m), 7.1—7.6 (15H, m). IR cm^{-1}: 3460, 1720. MS m/z: 412 ($M^+ - C_{19}H_{15}$), 396 ($M^+ - C_{19}H_{15}O$), 382 ($M^+ - C_{20}H_{17}O$).

A mixture of the above compound (2.400 g, 3.66 mmol), *p*-TsOH (H_2O) (0.209 g) and MeOH (48 ml) was heated under reflux for 1 h, and then allowed to cool. $NaHCO_3$ (0.307 g, 3.66 mmol) was added, and the mixture was concentrated. The residue was dissolved in EtOAc and filtered through a layer of Celite. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (50 g). Elution with hexane–EtOAc (2:1—1:1) gave crystalline **16a** (1.305 g, 86%), mp 92.5—93.5 °C

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(Et_2O). $[\alpha]_D^{25}$ +7.25° (c=1.02, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{47}NO_4$: C, 69.69; H, 11.45; N, 3.39. Found: C, 69.99; H, 11.29; N, 3.38. The spectral data of this compound were identical with those of racemic **16**.[8]

(2*S*,3*R*)-2-Hydroxymethyltetrahydropyran-3-yl *N*-Heptadecylcarbamate (16b) White crystals, mp 92.0—93.5 °C (Et_2O). $[\alpha]_D^{25}$ −7.20° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{47}NO_4$: C, 69.69; H, 11.45; N, 3.39. Found: C, 69.33; H, 11.40; N, 3.53.

3-{6-[*O*-(2*R*,3*S*)-(3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)-methyl]phosphonoxy}hexylthiazolium (Inner Salt) (3a) (R-74,654) In the same way as described for the synthesis of racemic **3**,[8] **3a** (43% overall) was prepared from **16a** as an amorphous powder, mp 125—128 °C. $[\alpha]_D^{25}$ +26.2° (c=1.02, MeOH). *Anal.* Calcd for $C_{33}H_{61}N_2O_7PS \cdot H_2O$: C, 58.38; H, 9.35; N, 4.13; P, 4.56; S, 4.72. Found: C, 58.47; H, 9.26; N, 3.86; P, 4.77; S, 4.92. The spectral data of this compound were identical with those of racemic **3**.[8]

3-{6-[*O*-(2*S*,3*R*)-(3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)-methyl]phosphonoxy}hexylthiazolium (Inner Salt) (3b) An amorphous powder, mp 125—128 °C. $[\alpha]_D^{25}$ −26.3° (c=1.02, MeOH). *Anal.* Calcd for $C_{33}H_{61}N_2O_7PS \cdot H_2O$: C, 58.38; H, 9.35; N, 4.13; P, 4.56; S, 4.72. Found: C, 58.24; H, 9.28; N, 3.96; P, 4.47; S, 4.62.

3-{5-[(2*R*,3*S*)-(3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)methoxycarbonylamino]}pentylthiazolium Bromide (4a) A solution of 6-bromohexanoic acid (1.698 g, 8.71 mmol), DPPA (1.88 ml, 8.73 mmol) and Et_3N (2.03 ml, 14.6 mmol) in benzene (50 ml) was refluxed for 3 h. After cooling, the mixture was shaken with aqueous $NaHCO_3$ solution, and the aqueous layer was extracted twice with EtOAc. The combined organic solutions were washed with aqueous NaCl solution, dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in toluene (5 ml), and mixed with a solution of **16a** (1.200 g, 2.90 mmol) in toluene (15 ml). The mixture was heated on an oil bath at 85 °C for 20 h, and then allowed to cool. The solvent was evaporated off, and the residue was chromatographed on silica gel (100 g). Elution with hexane–EtOAc (4:1) gave [(2*R*,3*S*)-3-(*N*-heptadecylcarbamoyloxy)tetrahydropyran-2-yl]methyl *N*-(5-bromopentyl)carbamate (1.283 g, 73%) as a white waxy substance, mp 71.5—72.0 °C. $[\alpha]_D^{25}$ +26.5° (c=1.00, $CHCl_3$).

A mixture of the above compound (0.540 g, 0.892 mmol), thiazole (0.63 ml, 8.88 mmol) and toluene (1.4 ml) was heated at 80 °C for 70 h, and then allowed to cool. The solvent was evaporated off, and the residue was chromatographed on silica gel (15 g). Elution with CH_2Cl_2–MeOH (19:1—4:1) yielded **4a** (0.524 g, 85%) as an amorphous powder, mp 97—99 °C. $[\alpha]_D^{25}$ +27.2° (c=1.05, MeOH). FAB-MS: 610 $(M-Br)^+$. *Anal.* Calcd for $C_{33}H_{60}BrN_3O_5S \cdot 1.5H_2O$: C, 55.22; H, 8.85; N, 5.85; S, 4.47. Found: C, 55.18; H, 8.40; N, 5.86; S, 4.32.

3-{5-[2*S*,3*R*)-(3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)methoxycarbonylamino]}pentylthiazolium Bromide (4b) An amorphous powder, mp 97—99 °C. $[\alpha]_D^{25}$ −27.3° (c=1.05, MeOH). FAB-MS: 610 $(M-Br)^+$. *Anal.* Calcd for $C_{33}H_{60}BrN_3O_5S \cdot 1.2H_2O$: C, 55.63; H, 8.83; N, 5.90; S, 4.50. Found: C, 55.58; H, 8.62; N, 5.78; S, 4.36.

(2*R*,3*S*)-2-Methoxymethoxymethyltetrahydropyran-3-ol (18a) A mixture of **13a** (2.800 g, 6.03 mmol), *p*-TsOH(H_2O) (0.344 g, 1.81 mmol) and MeOH (56 ml) was heated under reflux for 1 h, and then allowed to cool. $NaHCO_3$ (0.506 g, 6.03 mmol) was added, and the mixture was concentrated. The residue was mixed with water and extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated to dryness, and the residue was chromatographed on silica gel (50 g). Elution with hexane–EtOAc (3:1—2:1) gave [(2*R*,3*S*)-3-benzyloxytetrahydropyran-2-yl]methanol (1.224 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ +85.9° (c=1.13, $CHCl_3$). ^{1}H-NMR δ: 1.2—1.9 (3H, m), 1.9—2.5 (2H, m), 3.0—4.1 (6H, m), 4.48 (1H, d, J=12 Hz), 4.64 (1H, d, J=12 Hz), 7.36 (5H, m). IR cm^{-1}: 3470. MS m/z: 223 $(M^+ +1)$, 222 (M^+), 191 $(M^+ - CH_3O)$. *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.00; H, 8.01.

A solution of the above compound (1.198 g, 5.39 mmol) in DMF (6 ml) was added to a stirred suspension of NaH (55% in mineral oil, 0.306 g, 7.01 mmol) in DMF (18 ml) under ice-water cooling. After the mixture had been stirred at room temperature for 1 h, methoxymethyl chloride (0.49 ml, 6.45 mmol) was added under ice-water cooling. After being stirred at room temperature for 17 h, the mixture was poured into water and extracted three times with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated to dryness, and the residue was subjected to medium-pressure liquid chromatography (MPLC) (Lobar B column). Elution with hexane–EtOAc (4:1) gave (2*R*,3*S*)-3-benzyloxy-2-methoxymethoxymethyltetrahydropyran (1.071 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ +65.9° (c=1.48, $CHCl_3$). ^{1}H-NMR δ: 1.1—1.9 (3H, m), 2.1—2.5 (1H, m), 3.2—4.1 (6H, m), 3.39 (3H, s), 4.50 (1H, d, J=12 Hz), 4.65 (1H, d, J=12 Hz), 4.70 (2H, s), 7.37 (5H, m). MS m/z: 221 $(M^+ - C_2H_5O)$. *Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.58; H, 8.43.

A mixture of the above compound (0.950 g, 3.57 mmol), 10% Pd–C (0.655 g) and THF (20 ml) was hydrogenated in a Paar apparatus at 4 atm for 40 h. The catalyst was filtered off through a layer of Celite, the filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (20 g). Elution with hexane–EtOAc (1:1—1:2) gave **18a** (0.568 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ +21.8° (c=1.19, $CHCl_3$). ^{1}H-NMR δ: 1.2—1.9 (3H, m), 1.9—2.3 (1H, m), 2.50 (1H, m), 3.1—4.1 (6H, m), 3.40 (3H, s), 4.70 (2H, s). IR cm^{-1}: 3500. MS m/z: 175 $(M^+ - 1)$, 145 $(M^+ - CH_3O)$. *Anal.* Calcd for $C_8H_{16}O_4$: C, 54.53: H, 9.15. Found: C, 54.23; H, 9.22.

(2*S*,3*R*)-2-Methoxymethoxymethyltetrahydropyran-3-ol (18b) A colorless oil. $[\alpha]_D^{25}$ −21.8° (c=1.19, $CHCl_3$). *Anal.* Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.34; H, 9.15.

(2*R*,3*R*)-2-Methoxymethoxymethyltetrahydropyran-3-thiol (19a) A solution of **18a** (0.519 g, 2.95 mmol) and Et_3N (0.62 ml, 4.45 mmol) in benzene (10 ml) was treated with MsCl (0.30 ml, 3.88 mmol) under ice-water cooling. After being stirred at room temperature for 1 h, the mixture was washed with water, dried over Na_2SO_4 and evaporated to dryness to yield the methanesulfonate of **18a** (0.749 g) as a colorless oil. ^{1}H-NMR δ: 1.5—2.1 (3H, m), 2.1—2.6 (1H, m), 3.04 (3H, s), 3.1—4.2 (5H, m), 3.38 (3H, s), 4.4—4.6 (1H, m), 4.67 (2H, s).

Thioacetic acid (0.66 ml, 9.23 mmol) was added to a stirred suspension of NaH (55% in mineral oil, 0.437 g, 10.0 mmol) in DMF (7 ml) under ice-water cooling. The mixture was stirred at room temperature for 1 h, and then a solution of the above methanesulfonate (0.749 g) in DMF (3 ml) was added. The reaction mixture was heated at 100 °C for 7.5 h, cooled, poured into ice water, and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4 and evaporated to dryness, and the residue was chromatographed on silica gel (15 g). Elution with hexane–Et_2O (1:0—2:1) gave *S*-(2*R*,3*R*)-2-methoxymethoxymethyltetrahydropyran-3-yl thioacetate (0.438 g, 63%) as a colorless oil. $[\alpha]_D^{25}$ −10.0° (c=1.15, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 1.47—1.54 (1H, m), 1.83 (1H, ddddd, J=13.5, 13.2, 12.7, 4.4, 4.4 Hz), 1.90—1.97 (1H, m), 2.04 (1H, dddd, J=13.8, 13.2, 3.9, 3.9 Hz), 2.35 (3H, s), 3.35 (3H, s), 3.48 (1H, dd, J=11.6, 4.1 Hz), 3.53 (1H, ddd, J=12.7, 11.9, 2.6 Hz), 3.57 (1H, dd, J=11.6, 7.6 Hz), 3.82 (1H, ddd, J=7.6, 4.1, 2.0 Hz), 3.88 (1H, m), 4.01—4.08 (1H, m), 4.64 (2H, s). IR cm^{-1}: 1690. MS m/z: 234 (M^+), 203 $(M^+ - OMe)$, 191 $(M^+ - COMe)$. *Anal.* Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; S, 13.69. Found: C, 51.14; H, 7.76; S, 13.45.

A solution of MeONa in MeOH (1 M, 1.90 ml, 1.90 mmol) was added to a solution of the above thioacetate (0.402 g, 1.72 mmol) in MeOH (8 ml) at −20 °C. The mixture was stirred at −20—20 °C for 2 h, and then acidified by adding AcOH (0.11 ml, 1.90 mmol), and the whole was poured into ice water and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness, and the residue was chromatographed on silica gel (9 g). Elution with hexane–Et_2O (3:1—2:1) yielded **19a** (0.312 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ +4.73° (c=1.12, $CHCl_3$). ^{1}H-NMR δ: 1.2—2.3 (4H, m), 1.72 (1H, d, J=10 Hz), 2.9—4.2 (6H, m), 3.39 (3H, s), 4.66 (2H, s). MS m/z: 192 (M^+), 160 $(M^+ - CH_4O)$. *Anal.* Calcd for $C_8H_{16}O_3S$: C, 49.98; H, 8.39; S, 16.67. Found: C, 49.95; H, 8.35; S, 16.66.

(2*S*,3*S*)-2-Methoxymethoxymethyltetrahydropyran-3-thiol (19b) A colorless oil. $[\alpha]_D^{25}$ −4.73° (c=1.12, $CHCl_3$). *Anal.* Calcd for $C_8H_{16}O_3S$: C, 49.98; H, 8.39; S, 16.67. Found: C, 49.79; H, 8.37; S, 16.39.

***S*-(2*R*,3*R*)-2-Hydroxymethyltetrahydropyran-3-yl *N*-Heptadecylthiocarbamate (20a)** The reaction of **19a** with heptadecyl isocyanate was carried out as described for the synthesis of **16a** to afford crystalline *S*-(2*R*,3*R*)-2-methoxymethoxymethyltetrahydropyran-3-yl *N*-heptadecylthiocarbamate (96%), mp 59.5—60.5 °C (Et_2O–hexane). $[\alpha]_D^{25}$ −8.20° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.8—2.2 (37H, m), 3.1—4.2 (8H, m), 3.35 (3H, s), 4.64 (2H, s), 5.31 (1H, m). IR cm^{-1}: 3450, 1675. MS m/z: 474 $(M^+ +1)$, 442 $(M^+ - OMe)$, 398 $(M^+ - C_3H_7O_2)$. *Anal.* Calcd for $C_{26}H_{51}NO_4S$: C, 65.92; H, 10.85; N, 2.96; S, 6.77. Found: C, 65.63; H, 11.08; N, 2.74; S, 6.65.

A solution of the above thiocarbamate (0.623 g, 1.32 mmol) in CH_2Cl_2–MeOH (1:1, 12 ml) containing concentrated HCl (1.50 ml) was stirred at room temperature for 14 h. The mixture was poured into water and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4 and evaporated to dryness, and the residue was chromatographed on silica gel (15 g). Elution with hexane–EtOAc (3:1—2:1) gave crystalline **20a** (0.537 g, 95%), mp 92.0—93.0 °C (CH_2Cl_2–hexane). $[\alpha]_D^{25}$ +19.8° (c=1.03, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{47}NO_3S$: C, 67.08: H, 11.02; N, 3.26; S, 7.46. Found: C, 66.98; H,

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11.11; N, 3.26; S, 7.26. Spectral data of **20a** were identical with those of racemic **20**.[8]

***S*-(2*S*,3*S*)-2-Hydroxymethyltetrahydropyran-3-yl *N*-Heptadecylthiocarbamate (20b)** White crystals, mp 92.0—93.0 °C (CH_2Cl_2–hexane). $[\alpha]_D^{25}$ −19.9° (c=1.02, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{47}NO_3S$: C, 67.08; H, 11.02; N, 3.26; S, 7.46. Found: C, 66.89; H, 11.08; N, 3.39; S, 7.37.

3-{5-[*O*-(2*R*,3*R*)-(3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)-methyl]phosphonoxy}pentylthiazolium (Inner Salt) (5a) The reaction of **20a** as described for the synthesis of racemic **5**[8] afforded **5a** as an amorphous powder, mp 150—153 °C. $[\alpha]_D^{25}$ +3.40° (c=1.00, MeOH). FAB-MS: 663 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{59}N_2O_6S_2 \cdot 0.5H_2O$: C, 57.20; H, 9.00; N, 4.17; P, 4.61; S, 9.54. Found: C, 57.45; H, 8.96; N, 4.08; P, 4.55; S, 9.45. Spectral data of **5a** were identical with those of racemic **5**.[8]

3-{5-[*O*-(2*S*,3*S*)-(3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}pentylthiazolium (Inner Salt) (5b) (R-74,717) An amorphous powder, mp 150—153 °C. $[\alpha]_D^{25}$ −3.40° (c=1.00, MeOH). FAB-MS: 663 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{59}N_2O_6PS_2 \cdot H_2O$: C, 56.44; H, 9.03; N, 4.11; P, 4.55; S, 9.42. Found: C, 56.74; H, 9.13; N, 3.82; P, 4.59; S, 9.63.

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