Synthesis of 20- and 25-Membered Optically Pure Macrolides by Cationic Ring-Opening Oligomerization of 6,8-Dioxabicyclo[3.2.1]octan-7-one of Lower Optical Purities

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Abstract: Two optically active macrolides consisting of alternating tetrahydropyran ring and ester moieties were synthesized by the cationic ring-opening oligomerization of 6,8-dioxabicyclo[3.2.1]octan-7-one enriched in the (1*S*,5*S*) enantiomer (**1S**). The present synthesis is based on the specific oligomerization behaviors of the bicyclic oxalactone, that is, under appropriate reaction conditions, the racemic monomer (**1**) affords exclusively optically inactive 10-membered macrolide (**2**) consisting of a pair of the different enantiomeric units, while the optically pure (1*R*,5*R*) enantiomer (**1R**) gives rise to the optically active 20-membered macrotetrolide (**4R**) and/or 25-membered macropentalide (**5R**) highly selectively. From a monomer mixture of 36% optical purity, optically pure macrotetrolide (**4S**) and macropentalide (**5S**) both of which were exclusively composed of the **1S** units were obtained in the oligomerization carried out in acetonitrile at −40 °C with boron trifluoride etherate as the initiator. The yields, however, were considerably low (4–11%). In the oligomerization in 1-nitropropane, **5S** of 98% optical purity was prepared from the same monomer mixture in higher yield (27%). In both cases, **2** was concomitantly produced in larger amounts. Chiroptical measurements along with ^1H and ^{13}C NMR spectroscopy revealed that the macrolides **4S** and **5S** thus obtained were the enantiomers of **4R** and **5R**, respectively, whose structures had been established by X-ray crystallographic analysis.

Since Pedersen's[1] discovery of crown ethers capable of capturing cations, a variety of multidentate macrocyclic ligands have been designed and their properties as artificial receptors and carriers have been evaluated in relation to their molecular structures.[2-7] Among them, there are some synthetic macrocycles containing not only ether groups but also ester linkages as often found in naturally occurring macrocyclic ionophores.[8-13] Most of these macrocyclic esters so far synthesized were obtained by using appropriate ring-closure reactions such as condensations between acid halides and alcohols, and there have been reported very few instances utilizing ring-opening polymerization methods. Ring-opening polymerizations of heterocyclic monomers such as cyclic ethers, cyclic acetals, lactones, and cyclic imines are often accompanied by the formation of cyclic oligomers of various ring sizes.[14] In some cases, however, cyclic oligomers of specific ring sizes are predominantly or selectively formed, for example, cyclic tetramer from (*R*)-*tert*-butyloxirane,[15] and cyclic tetramer from 1-benzyl-2-ethylaziridine.[16] Furthermore, attempts have been made to synthesize macrocyclic oligomers of specific ring sizes by proper control of the polymerization: Dale et al.[17,18] prepared crown ethers by the cationic ring-opening polymerization of oxirane using metal salts as templates. As for the ring-opening polymerization of lactones, Shanzer et al.[19,20] prepared a series of macrocyclic oligoesters with β-propiolactone as monomer and cyclic distanoxane as template and catalyst in an overall yield approaching 80%. In this case, the macrocyclic compounds are formed by the reaction involving multiple insertion of β-propiolactone into the tin-oxygen bond and subsequent expulsion of the macrocyclic products.

Recently, we found specific formation of macrocyclic oligoesters (macrolides) containing tetrahydropyran rings in the cationic ring-opening polymerization of a bicyclic oxalactone, 6,8-dioxabicyclo[3.2.1]octan-7-one (**1**):[21-27] thus, under properly selected reaction conditions, 10-, 20-, and 25-membered macrolides (macrodilide (**2**), macrotetrolide (**4**), macropentalide (**5**)) were highly selectively produced from the racemic monomer, and optically active macrotetrolide (**4R**) and macropentalide (**5R**) were obtained from one of the antipodes of **1**, (+)-(1*R*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-7-one (**1R**). (Hereafter, **1R** denotes the enantiomer having the *R* configuration of the asymmetric carbon bearing a carbonyl group and therefore **1S** denotes the enantiomer having the *S* configuration of the corresponding carbon.)

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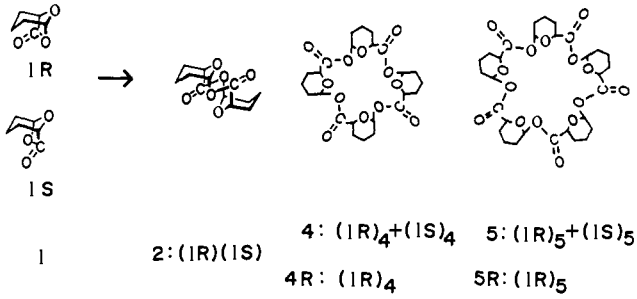

These synthetic macrolides consist of alternating tetrahydropyran ring and ester moieties, and they bear structural resemblance to a naturally occurring antibiotic nonactin which is a 32-membered macrotetrolide containing tetrahydrofuran rings. The synthetic macrolides except the macrodilide **2** were capable not only of transporting alkali and alkaline earth metal ions through organic liquid membranes[28] but also of forming stable complexes with neutral polar organic molecules such as acetonitrile and acetone.[29-31]

One of the intriguing features of the oligomerization of **1** is that the macrotetrolide **4** and macropentalide **5** obtained from the racemic monomer **1** are structurally identical with the optically active macrolides **4R** and **5R** derived from the optically active monomer **1R**. In other words, **4** and **5** are racemic mixtures of **4R** and its enantiomer **4S** and of **5R** and its enantiomer **5S**, respectively. In contrast, the macrodilide **2** obtainable only from the racemic monomer **1** is composed of a pair of **1R** and **1S** monomeric units. These findings stimulated us to attempt the oligomerization of enantiomerically unbalanced monomer mixtures of lower optical purities, in expectation that optically pure macrolides of the enantiomer being in excess in the initial monomer mixture can be obtained, along with the optically inactive macrodilide **2**, under appropriate reaction conditions where the racemic monomer **1** gives exclusively the macrodilide **2** and the optically pure monomer **1R** produces the optically active **4R** and **5R**.

The present paper deals with the synthesis of the optically pure, 20-membered macrotetrolide (**4S**) and 25-membered macropentalide (**5S**) by the cationic ring-opening oligomerization of enantiomerically enriched mixtures (**1S** > **1R**) of 6,8-dioxabicyclo[3.2.1]octan-7-one. Monomer mixtures enriched in **1S** were chosen here, because the optically pure **1S** could not be obtained from racemic sodium 3,4-dihydro-2*H*-pyran-2-carboxylate through the optical resolution of its dehydroabietylammonium salt which was successfully used for the preparation of **1R**, and as a consequence, the optically active macrolides **4S** and **5S** consisting of the **1S** enantiomeric units have not been synthesized.

Experimental Section

Preparation of 6,8-Dioxabicyclo[3.2.1]octan-7-one Enriched in the (1*S*,5*S*) Enantiomer (1S). An aqueous solution (120 mL) of sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (50 g) was slightly acidified with 6 N hydrochloric acid (64 mL), and the liberated carboxylic acid was extracted with ethyl ether (100 mL × 5). The extract was then added to an ice-cooled ethyl ether solution (200 mL) of dehydroabietylamine (92 g) with occasional shaking. Immediately, a white mass was formed, which was separated and crystallized from methanol solution. The crystal was filtered off, and removal of the solvent from the filtrate gave a yellowish solid. The solid was again dissolved in methanol and crystallized. The resulting crystal was separated, and the evaporation of the solvent from the filtrate afforded a yellow solid. This procedure was repeated once again. The dehydroabietylammonium salt thus obtained was converted to the sodium salt on treatment with aqueous sodium hydroxide, and the liberated dehydroabietylamine was extracted with ethyl ether (100 mL × 5). The aqueous solution was acidified with 6 N hydrochloric acid, saturated with sodium chloride, and extracted with ethyl ether (100 mL × 5). The ethyl ether extract was washed with saturated aqueous sodium chloride solution (30 mL × 3) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled under reduced pressure to give the bicyclic lactone: bp 60 °C (3 mmHg); yield, 12 g; $[\alpha]^{25}_D$ −50.0° (ethanol). The enantiomer composition of the monomer thus prepared was determined to be 1*R*:1*S* = 32:68 on the basis of the specific rotation of pure (1*R*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-7-one (**1R**), $[\alpha]^{25}_D$ +142° (ethanol). The monomer was dried over calcium hydride and redistilled before use.

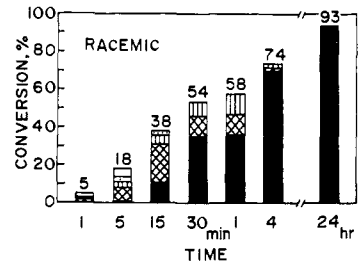

Figure 1. Time-conversion diagram for the oligomerization of racemic 6,8-dioxabicyclo[3.2.1]octan-7-one (**1**) in acetonitrile: monomer, 1 g; acetonitrile, 1 mL; BF_3OEt_2, 1 mol % to monomer; temperature, −40 °C; unshaded, polymer; dots, other oligomers; vertical bars, macropentalide (**5**); cross-hatched, macrotetrolide (**4**); shaded, macrodilide (**2**).

Polymerization. Freshly distilled monomer and solvent (acetonitrile (Table I) or 1-nitropropane (Table II)) were charged into a glass ampule. The mixture was frozen in liquid nitrogen, followed by the addition of a solution of boron trifluoride etherate dissolved in the same solvent. All these manipulations were carried out under a nitrogen atmosphere. The ampule was evacuated, sealed off, and allowed to stand in a bath kept at −40 °C. After the addition of a small amount of pyridine to terminate the reaction, the whole mixture was dissolved in chloroform and analyzed by gel permeation chromatography (column, JASCO JSP-101, 50 cm; eluent, chloroform). The composition of the reaction products was determined from the relative peak areas corrected for the differences in the refractive indices of the different compounds. The peak area per unit weight, relative to that of the dimer, was as follows: a_1/a_2 = 0.48, a_4/a_2 = 1.19, a_5/a_2 = 1.14, and a_p/a_2 = 1.22, where a_i is the peak area per unit weight of the cyclic *i* mer and a_p is that of the oligomers and polymers. Here the "polymers" in this paper refer to those with molecular weights higher than about 2 × 10^3 on the basis of the GPC calibration with standard polystyrene. The products were isolated by a preparative gel permeation chromatograph. When necessary, the reaction mixture was fractionated roughly by column chromatography (column, silica gel; eluent, dichloromethane–acetone (8:2) (v/v)) prior to gel permeation chromatographic separation.

Characterization. IR spectra were measured on a JASCO A-3 spectrophotometer. ^1H and ^{13}C NMR spectra were taken with JEOL JNM MH-100 and JEOL JNM FX-100 instruments in deuterioacetonitrile with tetramethylsilane as internal reference. Optical rotation was measured in chloroform by using a JASCO DIP-181 automatic polarimeter. CD spectra were recorded on a JASCO J-40A spectrometer in acetonitrile. The spectroscopic data for the optically active molecules **4S** and **5S** were as follows. **4S**: IR (CH_3CN) 1770 cm^{-1} ($\nu_{C=O}$); ^1H NMR (CD_3CN, Me_4Si) δ 6.16 (s, 1, OC**H**O 4.50 (d, 1, C**H**CO), and 1.78 (br, 6, (CH_2)$_3$); ^{13}C NMR (CD_3CN, Me_4Si) δ 169.82 (C=O), 91.08 (OCHO), 69.93 (CHCO), 27.73 ($OCHCH_2$, CH_2CHCO), and 18.42 ($CH_2CH_2CH_2$); $[\alpha]^{25}_D$ +188° (chloroform) (cf. **4R**: $[\alpha]^{25}_D$ −189° (chloroform); $[\theta]_{215}$ +2.6 × 10^4 deg cm^2 $dmol^{-1}$ (acetonitrile) (cf. **4R**: $[\theta]_{215}$ −2.6 × 10^4 deg cm^2 $dmol^{-1}$ (acetonitrile)). **5S**: IR (CH_3CN) 1768 cm^{-1} ($\nu_{C=O}$); ^1H NMR (CD_3CN, Me_4Si) δ 6.16 (s, 1, OC**H**O), 4.43 (d, 1, C**H**CO), and 1.78 (br, 6, (CH_2)$_3$); ^{13}C NMR (CD_3CN, Me_4Si) δ 169.80 (C=O), 92.51 (OCHO), 70.14 (CHCO), 28.65 ($OCHCH_2$), 28.50 (CH_2CHCO), and 18.09 ($CH_2CH_2CH_2$); $[\alpha]^{25}_D$ +136° (chloroform) (cf. **5R**: $[\alpha]^{25}_D$ −136° (chloroform)); $[\theta]_{215}$ +2.3 × 10^4 deg cm^2 $dmol^{-1}$ (acetonitrile) (cf. **5R**: $[\theta]_{215}$ −2.3 × 10^4 deg cm^2 $dmol^{-1}$ (acetonitrile)).

Results and Discussion

Figure 1 represents the time-conversion diagram for the oligomerization of the racemic monomer **1** in acetonitrile at −40 °C with boron trifluoride etherate as the initiator. Except in the early stage where a complicated mixture of oligomers and polymer was formed, the macrodilide **2** was predominantly produced, and it eventually became the sole product.

Under similar reaction conditions, the optically active monomer **1R** behaved in a completely different way as illustrated in Figure

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Table I. Preparation of Optically Active Macrotetrolide (4S) and Macropentalide (5S) by the Oligomerization of 6,8-Dioxabicyclo[3.2.1]octan-7-one of Lower Optical Purity in Acetonitrile[a]

g of monomer (1R:1S)[c]	mL of solvent	time, day	conversion,[b] % dilide	tetrolide (4R:4S)[c]	pentalide (5R:5S)[c]	others	% of residual monomer (1R:1S)[c]
2.5 (32:68)	5	1	54	8 (1:99)	11 (0:100)	3	24 (18:82)
3 (32:68)	6	3	60	4 (0:100)	11 (0:100)	2	23 (12:88)

[a] Initiator, BF_3OEt_2, 1 mol % to monomer; temperature, −40 °C. [b] By gel permeation chromatography. [c] By polarimetry.

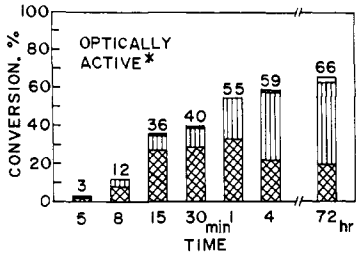

Figure 2. Time–conversion diagram for the oligomerization of (+)-(1*R*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-7-one (**1R**) in acetonitrile: monomer, 1 g; acetonitrile, 1 mL; BF_3OEt_2, 1 mol % to monomer; temperature, −40 °C; dots, other oligomers; vertical bars, macropentalide (**5R**); cross-hatched, macrotetrolide (**4R**).

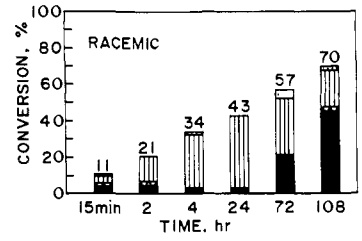

Figure 3. Time–conversion diagram for the oligomerization of racemic 6,8-dioxabicyclo[3.2.1]octan-7-one (**1**) in 1-nitropropane: monomer, 1 g; 1-nitropropane, 2 mL; BF_3OEt_2, 1 mol % to monomer; temperature, −40 °C; dots, other oligomers; vertical bars, macropentalide (**5**); cross-hatched, macrotetrolide (**4**); shaded, macrodilide (**2**).

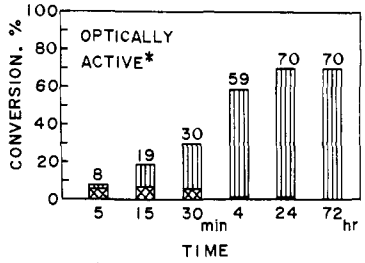

Figure 4. Time–conversion diagram for the oligomerization of (+)-(1*R*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-7-one (**1R**) in 1-nitropropane: monomer, 1 g; 1-nitropropane, 2 mL; BF_3OEt_2, 1 mol % to monomer; temperature, −40 °C; vertical bars, macropentalide (**5R**); cross-hatched, macrotetrolide (**4R**).

2: **1R** afforded the optically active macrotetrolide **4R** in preference to the macropentalide **5R** up to the middle stage of the reaction. With further increase in reaction time, the yield of **5R** increased steadily at the expense of **4R**. No macrodilide was formed from **1R** throughout the reaction.

Taking account of these specific behaviors in the oligomerization of the racemic monomer **1** and the optically active monomer **1R** in acetonitrile, it is anticipated that an enantiomerically unbalanced monomer mixture would give rise to the optically active macrotetrolide and macropentalide, together with the optically inactive macrodilide **2**, when the oligomerization is carried out for a sufficiently long period to complete the conversion of the initially formed oligomers and polymer to **2**. It should be pointed, however, that prolonged reaction increases the yield of the optically active macropentalide but conversely decreases the yield of the optically active macrotetrolide as shown in Figure 2. Therefore, in order to obtain the optically active macrotetrolide as much as possible, the reaction must be terminated in a relatively short period so as to minimize the conversion of the optically active macrotetrolide once formed to the optically active macropentalide.

Table I presents the results of the preparation of the optically active macrotetrolide (**4S**) and macropentalide (**5S**) by the cationic oligomerization of a monomer mixture enriched in the **1S** enantiomer in acetonitrile at −40 °C. As expected, **4S** and **5S** of optical purities of nearly 100% were successfully obtained from a monomer mixture of an optical purity of as low as 36%. The yields of the optically active macrolides, especially that of **4S**, were considerably low. This is unavoidable, because the moles of the **1R** enantiomer in the monomer feed amount to slighly lower than half of those of the **1S** enantiomer and therefore a large fraction of the **1S** enantiomer must be consumed for the formation of the optically inactive macrodilide **2** composed of a pair of the **1R** and **1S** monomeric units. As shown in the last column of Table I, the recovered monomer was found to be more enriched in the **1S** enantiomer.

Figure 3 illustrates the time–conversion diagram for the oligomerization of the racemic monomer **1** in 1-nitropropane at −40 °C with boron trifluoride etherate as the initiator. Up to the middle stage of the reaction, the racemic macropentalide **5** was preferentially formed, but it was converted, although gradually, to the macrodilide **2**. Oligomerization with a higher initial monomer concentration (monomer, 1 g; solvent, 1 mL) accelerated the conversion of **5** to **2**, thus giving almost exclusively the macrodilide **2** even after a reaction period of 24 h.

In contrast, the optically active monomer **1R** provided under similar conditions a mixture of the optically active macrotetrolide **4R** and macropentalide **5R** in the initial stage of the reaction, but **4R** once formed was almost completely transformed to **5R** in the later stage of the reaction, as clearly demonstrated in Figure 4. On the basis of such specific oligomerization behaviors in 1-nitropropane, the oligomerization of enantiomerically unbalanced monomer mixture (**1S > 1R**) was undertaken in order to obtain **5S** in a higher yield than that by the oligomerization in acetonitrile described above. The results are summarized in Table II.

Table II. Preparation of Optically Active Macropentalide (5S) by the Oligomerization of 6,8-Dioxabicyclo[3.2.1]octan-7-one of Lower Optical Purities in 1-Nitropropane[a]

g of monomer (1R:1S)[c]	mL of solvent	temp, °C	time, day	conversion,[b] % dilide	tetrolide	pentalide (5R:5S)[c]	other
9 (36:64)	9	−40	1	50	0	29 (6:94)	1
2 (32:68)	2	−40	3	57	1	27 (3:97)	1
2 (32:68)	2	−40	4	55	1	27 (1:99)	0
2 (32:68)	2	−40	5	57	1	27 (1:99)	0
1 (32:68)	1	−60	7	27	1	55 (19:81)	0
1 (32:68)	1	−60	21	30	2	52 (15:85)	0

[a] Initiator, BF_3OEt_2, 1 mol % to monomer. [b] By gel permeation chromatography. [c] By polarimetry.

Expectedly, the optically active macrolide **5S** of 98% optical purity was prepared from a monomer mixture of 36% optical purity in the prolonged reaction at −40 °C. Since the formation of the macrotetrolide **4S** was negligibly small under the reaction conditions, the yield of **5S** became higher than twice that in the oligomerization in acetonitrile. Also in this case, a large amount of the optically inactive macrodilide **2** was inevitably produced for the aforementioned reason. The optical purities of the ma-

cropentalide prepared in a shorter reaction time or at lower reaction temperature were not sufficiently high owing to the contamination of **5R**. In view of the facts that the macropentalide derived from the racemic monomer **1** is a racemic mixture of **5R** and **5S**, and that they are eventually converted to the macrodilide **2**, the lower optical purities of the macropentalide produced in a shorter reaction time or at lower reaction temperature indicate that the transformation of the macropentalide **5** to the macrodilide **2** is a considerably slow process, particularly at lower temperature.

The newly prepared macrolides **4S** and **5S** were characterized spectroscopically. Their chiroptical data along with the ^1H and ^{13}C NMR data given in the experimental section definitely prove that these macrolides are the enantiomers of the optically active macrolides **4R** and **5R** whose structures have been established by X-ray crystallographic analysis.[29,31]

The foregoing results clearly indicate that by the proper selection of the reaction conditions, the oligomerization of enantiomerically unbalanced 6,8-dioxabicyclo[3.2.1]octan-7-one gives rise to the optically pure macrolides of specific ring sizes which exclusively consist of the enantiomeric units being in excess in the initial monomer mixture (**1S** in the present case), with concomitant formation of the optically inactive macrodilide **2**. This is another way of saying that a kind of stereoclection takes place during the oligomerization of an enantiomerically enriched monomer mixture.

As described in the introductory section, the macrolides **4** and **5** derived from **1** are racemic mixtures of **4R** and **4S** and of **5R** and **5S**, respectively. In view of the fact that no other macrotetrolide and macropentalide with different structures were produced, it is highly probable that when the sequences of four or five consecutive **1R** (or **1S**) units are formed at a growing chain end, they tend to cyclize more rapidly than they propagate further. This is substantiated by the finding that no polymer was obtained from the optically active monomer **1R** under similar conditions where the racemic monomer **1** gave preferentially a polymer with a number average molecular weight of about 1×10^4.[27] In the polymerization of the racemic monomer **1**, there is a relatively small probability for a linear growing chain to consist of four or five consecutive **1R** (or **1S**) units, unless the monomer of the same chirality as that of the terminal unit of a growing chain is preferentially incorporated into the polymer chain. Actually, however, such enantiomer selection at a growing chain end occurs to some extent in the oligomerization of **1**, as proved by the preferential consumption of the enantiomer being in excess in a monomer mixture of 52% optical purity in oligomerization in chloroform at −40 °C.[26] Since **1** is a rigid bicyclic monomer with two asymmetric carbon atoms, steric and electronic repulsions in the propagation reaction between the growing chain end and monomer must depend on the chirality of the incoming monomer. Namely, there must be a difference in free energy between the addition reaction of the growing chain end with the monomer of the same chirality and that of the growing chain end with the monomer of the opposite chirality, thus causing enantiomer selection at the growing chain end. Similar enantiomer selection was observed in the cationic polymerization of 6,8-dioxabicyclo[3.2.1]octane[32] and its 4(e)-bromo derivative[33] having a skeleton similar to that of **1**.

In the later stage of the reaction, polymerization–depolymerization equilibrium must play an important role in producing the macrolides **4** and **5**; sequences of four or five consecutive **1R** (or **1S**) units would be formed at an active chain end by polymerization–depolymerization equilibrium, giving **4** and **5** by a backbiting reaction instead of propagating further.

The macrodilide **2**, which was predominantly produced in the later stages of the oligomerization of **1** (Figures 1 and 3), consists of a pair of the **1R** and **1S** units, and all four substituents attached to the tetrahydropyran rings are axially oriented.[29] This is in marked contrast to the structures of the macrotetrolide **4** and macropentalide **5** which consist of four and five identical enantiomeric monomeric units, respectively, and possess all their carbonyl carbons in the equatorial positions and all their ester oxygens in the axial positions of the tetrahydropyran rings. Therefore, the macrodilide **2** should be produced by a mechanism completely different from the mechanism of the formation of the macrolides **4** and **5**. In a previous paper,[26] we proposed a possible mechanism for the formation of **2**, involving the reaction of the oxonium ion of the chiral macrolides (for instance $\mathbf{4R}^+$) and the monomer of the opposite chirality (**1S**), followed by intramolecular reaction of the resulting unsymmetrical oligomer ion (Figure 7 in ref 26).

The macrodilide **2** is a symmetric molecule having a center of symmetry[29] and it is readily crystallized. In fact, among the three macrolides (**2**, **4**, and **5**), **2** has the lowest solubility in acetonitrile and 1-nitropropane,[26] and it precipitated out of the solution in the oligmerization of **1** in these solvents. Therefore, it would be reasonable to presume that the crystallization of **2** is an important driving force for the aforementioned, gradual transformation of macrolides **4** and **5** into **2**, even though other factors may be operative.

In the oligomerization of the racemic monomer **1**, the macrodilide **2** is exclusively formed after a prolonged reaction time as is clearly demonstrated in Figure 1. On the analogy of this oligomerization behavior of **1**, it would appear that in the oligomerization of the enantiomerically unbalanced monomer mixtures being rich in the **1S** enantiomer, practically all the macrotetrolide **4R** or macropentalide **5R** consisting of the **1R** units are eventually transformed into **2** by the reaction with the **1S** monomer existing in excess in the reaction mixture. On the contrary, some of the macrotetrolide **4S** or macropentalide **5S** consisting of the **1S** units remain without being transformed into **2** because of the shortage of the **1R** monomer. Thus the optically pure macrolides **4S** or **5S** are produced by the oligomerization of the enantiomerically enriched monomer mixtures. Needless to say, their yields depend on the extent of the unbalance in the enatiomer composition of the initial monomer mixture.

In summary, the 20- and 25-membered optically pure macrolides **4S** and **5S** were synthesized by the cationic ring-opening oligomerization of enantiomerically unbalanced 6,8-dioxabicyclo[3.2.1]octan-7-one (**1S** > **1R**) in acetonitrile and 1-nitropropane at −40 °C. The synthesis is based on the specific oligomerization behaviors of the bicyclic oxalactone, that is, under appropriate reaction conditions, the racemic monomer affords exclusively the macrodilide **2** consisting of a pair of the **1R** and **1S** enantiomeric units, while the optically pure monomer produces the optically active macrotetrolide and/or macropentalide. The present method is unique in that it does not require tedious work of complete optical resolution of a precursor of the monomer, in other words, it utilizes a special type of enantiomer selection during the oligomerization. The optically active macrolides synthesized in this work have a chiral cavity and they, particularly the macropentalide, seem to have potential utility for selective recognition and separation of chiral substances.

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Registry No. (−)-(1*S*,5*S*)-**1**, 88853-67-2; (+)-(1*R*,5*R*)-**1**, 71357-98-7; (±)-**1**, 78392-85-5; **2**, 78392-88-8; **4*S***, 88853-68-3; **4*R***, 78392-86-6; **5*S***, 88853-69-4; **5*R***, 78419-08-6; sodium 3,4-dihydro-2*H*-pyran-2-carboxylate, 78609-62-8.