carries the bromo substituent at the 6 position[16] reflecting presumably some biosynthetic pathway still to be elucidated.

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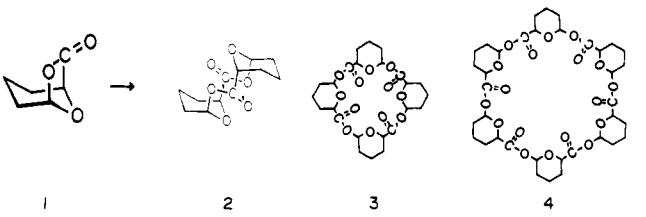
A Novel 30-Membered Synthetic Macrolide from (+)-(1*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-7-one

Sir:

Recent advances in the chemistry of crown ethers and cryptands have stimulated many groups of investigators to design macrocyclic ligands for molecular recognition and synthetic ionophores with biological functionality. In the course of the studies on the ring-opening polymerization of bicyclic compounds containing a tetrahydropyran ring, we found that racemic 6,8-dioxabicyclo[3.2.1]octan-7-one (**1**) underwent cationic polymerization at low temperature to provide 10-, 20-, and 30-membered cyclic oligoesters (**2–4**) consisting of alternating tetrahydropyran and ester moieties,[1,2] which bear structural resemblance to naturally occurring antibiotics, nonactin and its analogues. Furthermore, each of these cyclic oligomers was formed selectively, even nearly quantitatively for the cyclic dimer and tetramer, by proper choice of reaction conditions.[2,3]



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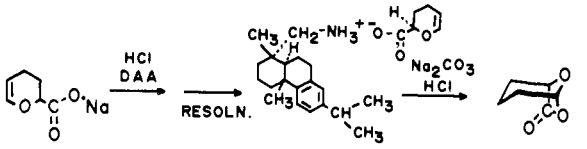
These intriguing findings prompted us to investigate the oligomerization of an optically active monomer, in expectation of obtaining macrocyclic oligoesters with well-defined configuration. The present communication describes convenient synthetic procedures for (+)-(1*R*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-7-one and its cyclic hexamer, a 30-membered synthetic macrolide.

(+)-(1*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-7-one (**7**) was successfully prepared through the optical resolution of racemic 3,4-dihydro-2*H*-pyran-2-carboxylic acid by using dehydroabietylamine, a base which has lately been used with success in optical resolution of several carboxylic acids.[4,5] An aqueous solution of sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (**5**) was slightly acidified with 6 N hydrochloric acid, and the liberated carboxylic acid was extracted several times with ethyl ether. The ethyl ether extract was then added to an ice-cooled



5 6 7

ethyl ether solution of dehydroabietylamine with occasional shaking. Immediately, a white mass was formed, which was separated and recrystallized repeatedly from methanol solution to yield pure (+)-dehydroabietylammonium 3,4-dihydro-2*H*-pyran-2-carboxylate (**6**) as white needles: $[\alpha]^{24}_D$ +11.7° (*c* 1 g/dL, ethanol); mp 168–171 °C. Anal. ($C_{26}H_{39}NO_3$) C, H, N. The diastereomeric ammonium salt was converted to the sodium salt on treatment with aqueous sodium carbonate, and the liberated dehydroabietylamine was removed by extraction with ethyl ether. The sodium salt was subsequently transformed to the free acid followed by immediate distillation under reduced pressure to afford an optically active monomer **7** with $[\alpha]^{24}_D$ +128° (*c* 1.0 g/dL, ethanol); bp 61 °C (5 mm).

The ammonium carboxylate **6** was converted to the sodium carboxylate, which was then esterified with ethyl iodide in dimethylformamide. Subsequent reduction of the ethyl ester with lithium aluminum hydride in ethyl ether gave 2-hy-

Table I. Oligomerization of (+)-(1*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-7-one[a]

monomer, g	solvent,[b] mL	initiator, mol %	time, h	conversion, %[c] dimer	tetramer	hexamer	other	total
0.5	MC, 0.5	1	48	0	5	63	7	75
1.0	AN, 1.0	1	24	0	25	59	0	84
1.0	CF, 1.0	5	24	0	0	46	0	46
1.0	NP, 1.0	1	24	0	0	81	0	81

[a] Initiator, BF_3OEt_2; temperature, −40 °C. [b] MC, methylene chloride; AN, acetonitrile; CF, chloroform; NP, 1-nitropropane. [c] Determined by gel permeation chromatography.

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droxymethyl-3,4-dihydro-2*H*-pyran, which was cyclized on heating in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene to provide 6,8-dioxabicyclo[3.2.1]-octane. It showed a specific rotation of $[\alpha]^{26}_D$ +111.4° (*c* 0.86 g/dL, *n*-hexane), compared with the reported value,[6] $[\alpha]_D$ −115° (*n*-hexane), of (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octane derived from D-glucose. Therefore, the 6,8-dioxabicyclo[3.2.1]octane synthesized here possesses the opposite configuration (1*R*,5*S*), and, hence, the absolute configuration of the two asymmetric carbon atoms of **7** prepared from the same diastereomeric salt **6** is determined to be (1*R*,5*R*). The details of the preparation of (+)-(1*R*,5*S*)-6,8-dioxabicyclo[3.2.1]octane and its cationic polymerization will be published elsewhere.[7]

The oligomerization of **7** was carried out at −40 °C in four different solvents with boron trifluoride etherate as the initiator. The reaction products were analyzed by gel permeation chromatography. The results are summarized in Table I. Very interestingly, cyclic hexamer was preferentially formed in each run. In particular, the extremely high selectivity, as well as high conversion to the cyclic hexamer, observed in 1-nitropropane is surprising, in view of the fact that the cyclic hexamer is a 30-membered macrocyclic compound. Such an unusually high selectivity for the formation of the cyclic hexamer may suggest that a growing chain consisting of the configurationally identical monomeric units tends to take a conformation especially favorable for the ring closure to the cyclic hexamer. Probably the main factor contributing to the selective formation of the cyclic hexamer is its precipitation out of the solution during the reaction owing to the low solubility (1.4 g/dL of 1-nitropropane at −40 °C).

It is of interest to note here that the racemic monomer produces exclusively cyclic tetramer **3** in chloroform under the specified conditions given in Table I. Therefore, the complete absence of cyclic tetramer in chloroform in the oligomerization of the optically active monomer indicates that the cyclic tetramer **3** from the racemic monomer is not an equimolar mixture of optically active, enantiomeric cyclic tetramers, but an optically inactive compound consisting of alternating enantiomeric monomeric units.[2]

It is worthy of remark that no cyclic dimer was formed from the optically active monomer irrespective of the reaction conditions, in remarkable contrast to the oligomerization of the racemic monomer.[1,2] This is compatible with the fact that the cyclic dimer **2** from the racemic monomer consisted of a pair of different enantiomeric units as revealed by X-ray analysis.[2]

The optically active cyclic hexamer thus prepared was isolated by means of a preparative gel permeation chromatography and characterized: IR 1763 cm^{-1} ($\nu_{C=O}$); UV (CH_3CN) λ_{max} 215 nm (ϵ 720); $[\alpha]^{24}_D$ −112° (*c* 1.0 g/dL, CH_3CN); CD (CH_3CN) λ_{min} 215 nm, $[\theta]$ −2200°; ^1H NMR (CD_3CN, Me_4Si), δ 6.20 (s, 1, OC*H*O), 4.42 (d, 1, C*H*CO), and 1.76 (br, 6, $CH_2CH_2CH_2$); ^{13}C NMR (CD_3CN, Me_4Si) δ 169.97 (*C*=O), 92.59 (OCHO), 70.22 (*C*HCO), 28.70 ($OCHCH_2$), 28.56 (CH_2CHCO), and 18.13 ($CH_2CH_2CH_2$); DSC (heating rate 1.25 °C/min), began to decompose at 125 °C; molecular weight, calcd 768, found (vapor pressure osmometry, $CHCl_3$) 778; crystallized from acetonitrile solution in the form of hexagonal flat plates. Anal. $(C_6H_8O_3)_6$ C, H.

Complexation of the optically active cyclic hexamer with a variety of thiocyanates has been studied qualitatively in acetonitrile-d_3 by means of ^1H and ^{13}C NMR spectroscopy. Preliminary experiments have shown that the cyclic hexamer shows a specific affinity toward barium thiocyanate. Quantitative evaluation of the complexing ability of the newly prepared, optically active macrolide toward metallic ions, together with the X-ray analysis of its crystalline structure, is currently in progress.

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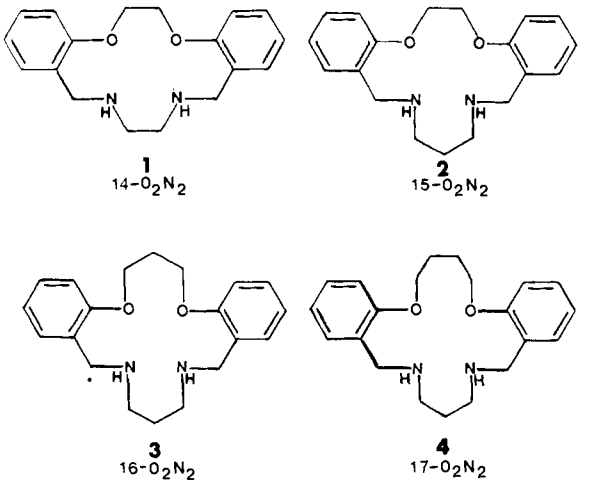
Macrocyclic Ring-Size Control of Kinetic Lability. Kinetics of Dissociation of a Range of Nickel(II) Complexes of O_2N_2-Donor Macrocycles in Acid

Sir:

The use of macrocyclic ligands of the polyether crown or cryptand class to selectively complex alkali and alkaline earth metal ions has been well documented[1,2] and kinetic aspects of such complexation are also receiving considerable attention[1,3] since such data are of fundamental significance to aspects of metal-ion transportation in biological systems.[4]

The interaction of macrocycles containing four nitrogen donors with transition metal ions has also been studied in considerable detail.[5,6] Such studies have been largely directed toward elucidation of the nature of the macrocyclic effect—the enhanced kinetic and thermodynamic stabilities of macrocyclic ligand complexes when compared with their open-chain ligand analogues.[7] However, because of extreme kinetic inertness and associated high formation constants, comparative studies of kinetic and thermodynamic stabilities of the complexes of an extended series of N_4-donor ligands varying only in macrocyclic ring size have proved difficult.[8] In addition, the study of the effects of alteration of macrocyclic ring size on the kinetics of dissociation of nickel complexes of saturated N_4-donor macrocycles are complicated by stereochemical and spin-state changes along the series.[6]

We now report an investigation of the relative labilities of nickel complexes of the ligands **1**–**4** which are structurally



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