Optical Enrichment of Diols via Their Organotin Complexes

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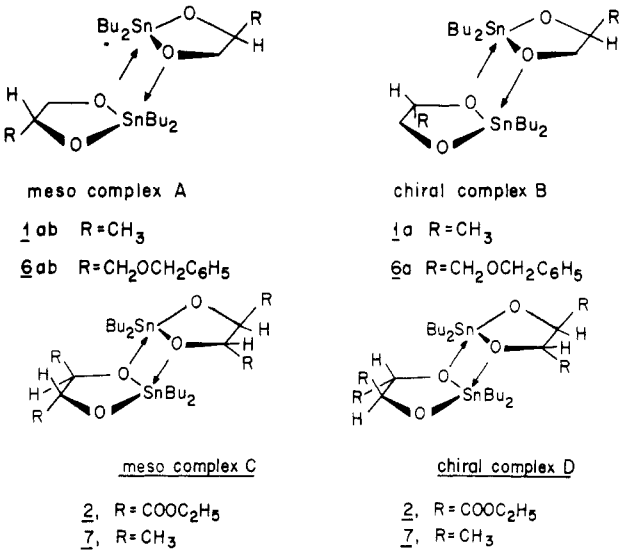
Received January 18, 1983

Tin–oxygen compounds derived from asymmetric diols are shown to form molecular complexes which are composed of either two molecules of opposite configuration (meso complexes A and C) or of identical configuration (chiral complexes B and D). The diastereomeric relationship of these complexes is used for the optical enrichment of diols (1,3-propanediol, diethyl tartrate, 1-benzylglycerol, and 2,3-butanediol). The method involves conversion of diols to cyclic tin derivatives (**1**, **2**, **6**, and **7**) and fractionating crystallization. Regeneration of the parent diols under mild, anhydrous conditions provides optically pure compounds in a single crystallization step. Extensive NMR data on the molecular complexes are given, and their high degree of orientation is demonstrated by their conversion to macrocyclic products (**3aa**, **3ab**, **5aa**, and **5ab**) in high regio- and stereospecificity.

Many organic molecules, and particularly molecules with pronounced electron-accepting or electron-donating properties, are known to associate to molecular complexes.[1,2] These complexes are often characterized by charge-transfer interactions: n, σ interactions through two bonds (point-to-point) as exemplified in the complex of pyridine with iodine,[3] or π,π interactions through aromatic ring systems (face-to-face), as exemplified in the complex of tetracyanobenzene with tetramethyl-*p*-phenylenediamine.[4] A different type of molecular complex is formed between tin–oxygen compounds.[5-9] These complexes are characterized by "edge-to-edge" interactions and derive from the expansion of the coordination number of tin from four to five and the concurrent formation of noncovalent, intermolecular bonds between tin and oxygen. An outstanding feature of these complexes is the pronounced dependence of their thermodynamic stability on stereochemical factors.[5-7] This observation led us to think that such molecular associates could be employed for the optical enrichment of enantiomeric mixtures of diols, provided diastereomeric complexes could be obtained from asymmetric tin–oxygen compounds that can be separated. Optical enrichment is a problem which is often encountered in the development of asymmetric syntheses where products of varying optical purity are being obtained.[10] In this publication we describe cyclic tin–oxygen compounds derived from asymmetric diols, provide evidence for their association to diastereomeric complexes, and demonstrate their applicability for the optical enrichment of enantiomeric mixtures of diols. We have chosen as model compounds vicinal diols with one or two chiral centers, since this type of functionality is often encountered in natural products such as sugars, nucleotides, and membrane-active glycerol derivatives. The method put forward here provides optically pure compounds in a single crystallization step and under extremely mild, anhydrous conditions.

Results and Discussion

Asymmetric stannoxanes may, a priori, form two types of molecular complexes: those composed of two molecules of opposite configuration ("meso"-type complexes A or C)



or those composed of two molecules of identical configuration (chiral complexes B or D). Since these two types of complexes are of diastereomeric relationship, they should differ in their properties and should be readily distinguishable by physicochemical tools.

We selected high-resolution proton NMR spectrometry in combination with structural analysis of chemical products derived from these complexes in order to differentiate between the two types. NMR spectrometry of both optically active and racemic stannoxanes at varying concentrations was chosen to confirm the formation of complexes and to provide an estimate for their relative stability. Comparison of the NMR data for the optically active compounds and for the racemic mixtures was anticipated to indicate if, and to what extent, different molecular complexes may be formed from racemic and optically active precursors. Since molecular associates have earlier been shown to react with retention of configuration with diacyl dihalides to give macrocyclic products of defined geometry, condensation of both the optically pure and the racemic stannoxanes to such chemical products and structural analysis of these products was expected to

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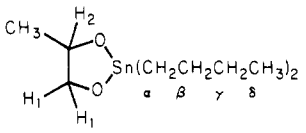
Table I. Proton NMR Data for Stannoxanes 1



(a) Spectra for 0.20 M Solutions in $CDCl_3$

proton	multiplicity (J, Hz)	chemical shift,[a] δ: stannoxane 1ab "associate"	stannoxane 1ab "monomer"	stannoxane 1a "associate"	stannoxane 1a "monomer"
$CH^1 + CH^2$	m	3.706[b]		3.719[b]	
CH^1	t (9.5)	3.000		3.014	
$CHCH_3$	d (6)	1.118	1.134	1.138	1.154
α-CH_2	m	1.637		1.628	
β-CH_2	m	1.297		1.300	
γ-CH_2	m	1.386		1.387	
δ-CH_3	t (7)	0.918	0.946	0.919	0.948

(b) Effect of Dilution

proton	chemical shift,[a,c] δ: stannoxane 1ab 0.200 M	0.050 M	0.010 M	stannoxane 1a 0.200 M	0.050 M	0.010 M
$CHCH_3$						
"associate"	1.118	1.123	1.127	1.138	1.123	1.127
"monomer"	1.134	1.159	1.172	1.154	1.158	1.171
CH_3						
"associate"	0.918	0.921	0.921	0.919	0.920	0.921
"monomer"	0.946	0.948	0.947	0.948	0.947	0.948
ratio[d]	8.1	2.2	0.44	5.6	3.0	0.60

[a] The spectra were recorded on a WH-270 (Bruker, 270 MHz) instrument at ambient temperatures, and the chemical shifts given are relative to internal Me_4Si. Only the chemical shifts of those signals are given that appeared clearly resolved. [b] The line shapes of the two multiplets are different, indicating that the spectral parameters involved (chemical shift or/and coupling constant) are different. [c] The identical shifts obtained for the monomeric species of 1ab and of 1a at a 0.010 M concentration indicates that these values may be regarded as limiting values. [d] Associate/monomer from $CHCH_3$ signals.

provide information on the composition and geometry of the intermediate complexes.

Solutions of both racemic stannoxane **1ab**[8] and optically active stannoxane **1a** (derived from 1,2(*R*)-propanediol) were prepared and subjected to proton NMR analysis at ambient temperatures and varying concentrations. The observed chemical shifts of each of the samples are summarized in Table I as are the relative intensities of the most pronounced signals.

Inspection of the data given for stannoxanes **1** in Table I shows the following points. (i) The chemical shifts and NMR patterns are different for the racemic (**1ab**) and the optically active (**1a**) samples. The most pronounced chemical shift differences between the racemic (**1ab**) and the optically pure (**1a**) samples are observed for the protons that are nearest to the chiral center [$CH_2CH(CH_3)O$, Table Ia). (ii) The methyl protons of the propanediol and the methyl protons of the butyl residues give rise to two clearly distinguishable signals in both the racemic (**1ab**) and the optically active (**1a**) samples (Table I); the relative intensities of these signals change gradually upon dilution in favor of the lower field signals in both samples (Table Ib). The slope of the change is higher for the racemic (**1ab**) than for the optically active (**1a**) sample. (iii) The chemical shifts for both species, the monomer and the associates, are dependent on the concentration (table Ib). At high concentration (0.20 M), the chemical shifts for the racemic (**1ab**) and the optically active (**1a**) samples are different, while at low concentration (0.01 M) they become identical.

The occurrence of two distinct sets of signals in both the racemic (**1ab**) and the optically active samples (**1a**) and the change of their intensity upon dilution demonstrate that both the racemic and optically active derivatives form molecular complexes which dissociate into their components upon dilution and that their exchange rate is slow (life time $>10^{-1}$ s). The higher field signals observed for the associated species than for the monomeric ones are compatible with mutual shielding. Moreover, the pronounced chemical shift differences observed for the protons near the chiral center indicate that these are most affected by association. Since the NMR patterns of the two samples at high concentration are different, and since in the optically pure samples only chiral complexes can be formed, it may be concluded that in the racemic mixture meso complexes composed of molecules of opposite configuration are present. Since the chemical shifts of both the associates and the monomeric species change upon dilution, it may be concluded that an additional fast equilibrium is superimposed on the first, slow equilibrium between dimer and monomer. The latter may be attributed to the presence of oligomeric species.[5-9]

The overall scheme for the behavior of stannoxanes may accordingly be envisioned as shown in Scheme I. This scheme is in compliance with the occurrence of two equilibria, a slow and a fast equilibrium, and is compatible with the different NMR pattern for the racemic and optically active stannoxanes at high concentrations and with the identical NMR pattern at low concentrations. Meso complexes such as A and C are derived from oligomeric complexes and are thus formed preferentially at high concentrations.

Cyclic stannoxanes derived from diethyl tartrate **2ab** and **2a**[12] gave rise to an NMR pattern analogous to those

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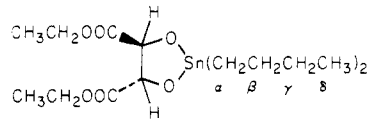
Table II. Proton NMR Data for Stannoxanes 2



(a) Spectra for 0.20 M Solutions in $CDCl_3$

		chemical shift,[a] δ			
		stannoxane 2ab		stannoxane 2a	
proton	mult (J, Hz)	"associate"	"monomer"	"associate"	"monomer"
*CH*COOEt	s	4.552		4.562	
$COOCH_2$	q (7)	4.207[b]	4.296	4.209[b]	4.297
				4.201[b]	
$COOCH_2CH_3$	t (7)	1.306		1.307	
CH_2 (α-γ)	m	0.9-1.6		0.9-1.6	
CH_3 (δ)	t (7)	0.900		0.902	

(b) Approximate "Associate"/"Monomer" Ratio[c]

	concn, M		
sample	0.200	0.050	0.010
2ab	10.0	5.3	1.8
2a	11.3	4.8	2.4

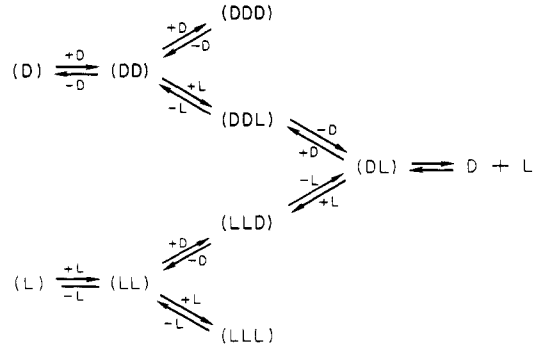
[a] The spectra were recorded on a WH-270 (Bruker, 270 MHz) instrument at ambient temperatures, and the chemical shifts given are relative to internal Me_4Si. Only data for those signals are given that appeared clearly resolved. [b] Two quartets are observed for the optically pure sample **2a**, one broad quartet in the racemic sample (**2ab**). [c] Calculated from the integrals of the OCH_2CH_3 signals.

Table III. Spectroscopic Data of Macrocyclic Tetralactones 3 and 5

					¹H NMR,[c] δ					
compd	mp, °C	yield, %	IR,[a] cm^{-1}	MS,[b] *m/e* (rel intens)	CHO	CH_2O	CH_3	CH-CO	CH	$COOCH_2CH_3$
3aa	58-59	37	1730	400 (6.5),[d] 201 (65.8)[e]	5.13 (t)	4.21 (dd), 3.91 (dd)	1.17 (d)	2.24 (m)	1.3-1.8 (m)	
3ab	92-94	24	1730	400 (29.6),[d] 201 (100)[e]	5.19 (dq)	4.32 (dd), 3.96 (dd)	1.24 (d)	2.3 (m)	1.3-1.8 (m)	
5aa	oil	39	1740	600 (3.3),[d] 587 (47.2),[f] 331 (72.2)[e]	5.69 (s)			2.4 (m)	1.6 (m)	4.24 (q), 1.27 (t)
5ab	83-85	71	1735	587 (2.02),[f] 331 (12.7)[e]	5.68 (s)			2.35 (m)	1.63 (m)	4.23 (q), 1.27 (t)

[a] The IR spectra were recorded in Nujol mulls. [b] The mass spectra were recorded on a Varian MAT-731 (double focusing) instrument. [c] The NMR spectra were recorded in $CDCl_3$ solutions on a FT-80A (Varian, 80 MHz) instrument. The chemical shifts given are relative to internal Me_4Si. Coupling constants are given in ref 12. [d] Molecular ion peak M. [e] Fragment M/2 + 1. [f] Fragment derived from molecular ion peak by loss of $COOCH_2CH_3$.

Scheme I[a]

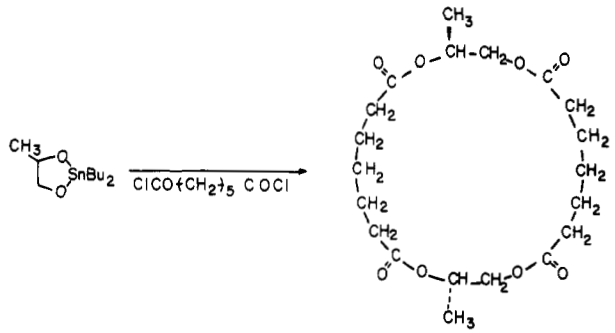


[a] D = stannoxane of D configuration, and L = stannoxane of L configuration.

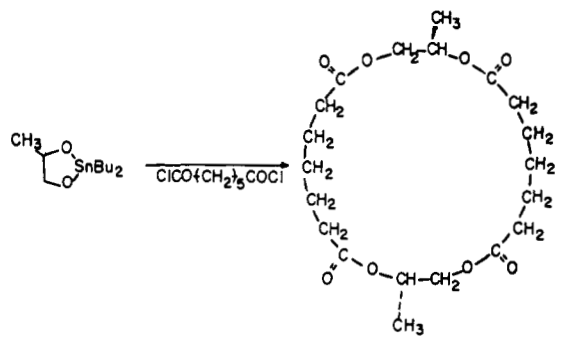
derived from 1,2-propanediol (**1ab** and **1a**, Table II). Two signals were observed for the ethyl ester protons in both the racemic and the optically active samples (**2ab** and **2a**, Table IIa). The relative intensity of these signals changed in favor of the lower field signals upon dilution (Table IIb), indicating a slow equilibrium between the associate and monomer. Here there was also a preference for the chiral complex D as compared to the meso complex C, and the presence of a second equilibrium was indicated by line broadening.

In order to further elucidate the nature of these associates and paraticularly their geometry (the mutual orientation of their components), we applied a chemical reaction previously developed in our laboratory[12] as an analytical tool. The stannoxanes **1a,ab** and **2a,ab** were reacted with diacyl dihalides to give macrocyclic products, and their stereochemistry was determined.

Reaction of optically active stannoxane **1a** with pimeloyl dichloride in chloroform provided a sole macrocyclic product, **3aa**. On the basis of its spectroscopic properties (Tables III and IV), this product proved to be diastereomeric to the macrocyclic product **3ab** obtained previously from racemic stannoxane **1ab**.[12] Its detailed stereochemistry was determined by carbon-13 NMR analysis (Table IV). A priori, two different macrocyclic tetralactones could have been formed when reacting stannoxane **1a** with pimeloyl dichloride: a product in which the two 1,2-propanediol residues assume a parallel orientation

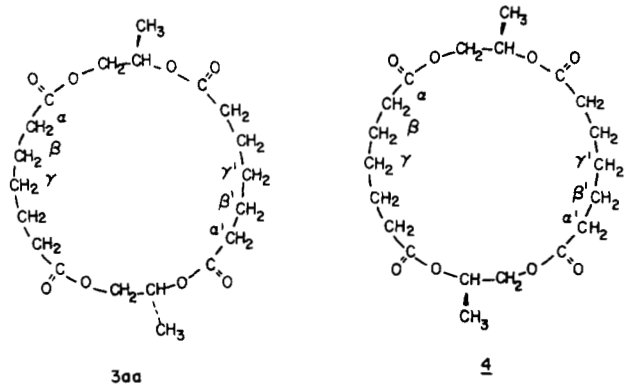


1a (optically active) 3aa



1ab (racemic) 3ab (meso)

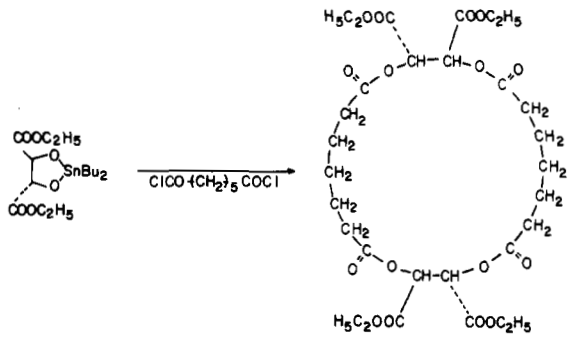
(structure **3aa**) or a product in which they assume an



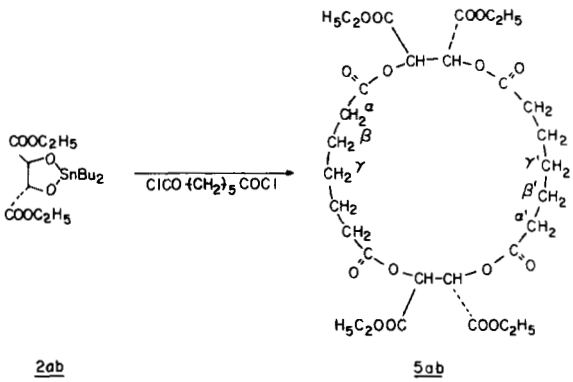
3aa 4

antiparallel orientation, **4**. In the former (structure **3aa**) the two acyl residues are in a different environment, and in the latter (structure **4**) the two acyl residues are in an identical environment. Carbon atoms at positions γ and γ' should therefore be different in compound **3aa** but identical in compound **4**. The data given in Table IV show that the isolated product gave rise to different signals for the carbon atoms at positions γ (28.4 ppm) and γ' (28.6 ppm), indicative of structure **3aa**, as opposed to the reported **3ab**, which gave only one signal for this carbon at 28.5 ppm.[12]

Stannoxanes **2a** and **2ab** derived from diethyl tartrate followed a similar pattern when reacted with pimeloyl dichloride. Optically active stannoxane **2a** had earlier been shown to provide tetralactone **5aa** upon condensation with pimeloyl dichloride.[12] We have now found, that racemic stannoxane **2ab** when condensed under analogous conditions with pimeloyl chloride provided in 71% yield a macrocyclic tetralactone which is diastereomeric to the compound obtained from the optically active stannoxane **2aa** (see Tables III and IV). The product is therefore assigned to have structure **5ab**.[13]



2a 5aa



2ab 5ab

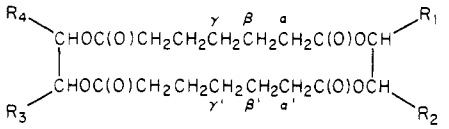
The formation of different products from the chiral and the racemic stannoxanes implies the intermediacy of molecular complexes of different composition. The formations of **3aa** from stannoxane **1a** and of **5aa** from stannoxane **2a** suggest the intermediacy of chiral complexes of type B and D. As to their geometry, in complex B the methyl groups of the 1,2-propanediol residue are located at the rear side. Reaction of this structure with two diacyl dihalide molecules (from the back and from the front, respectively) may then be visualized to provide the isolated compound **3aa**. The formation of **3ab** and **5ab** from the racemic precursors **1ab** and **2ab** is, on the other hand, indicative of the meso complexes A and C as intermediates. In complex A the methyl groups are located at the most distant positions from each other to provide the meso product **3ab**. The configuration of these complexes seems to be determined by stereochemical factors: steric repulsion between the methyl groups and the butyl groups is minimized by their choosing a location as far as possible from each other.

The nature of the macrocyclic products **3** and **5** obtained by condensation of stannoxanes **1** and **2** with diacyl dihalides may be regarded as direct evidence for the existence of dimeric complexes A–D. The formation of the meso macrocyclic products **3ab** and **5ab** from the racemic stannoxanes **1ab** and **2ab** is likely to derive from the higher chemical reactivity of the meso associates A and C, rather than from their preponderance, since the NMR data discussed above demonstrate that the meso complexes are thermodynamically less favored, implying less stabilized and therefore more susceptible to electrophilic attack.

These results show that asymmetric cyclic stannoxanes can form molecular associates which differ in their relative stability and chemical reactivity. These associates are characterized by an edge-type arrangement of well-defined

(13) Although both compounds, **5aa** and **5ab**, were identical in their spectroscopic properties, they are believed to be diastereomeric on grounds of their different physical properties. Compound **5aa** was obtained as oil and compound **5ab** as crystalline material, and addition of a crystal of **5ab** to oily **5aa** did not induce crystallization.

Table IV. ^{13}C NMR Data for Tetralactones 3 and 5

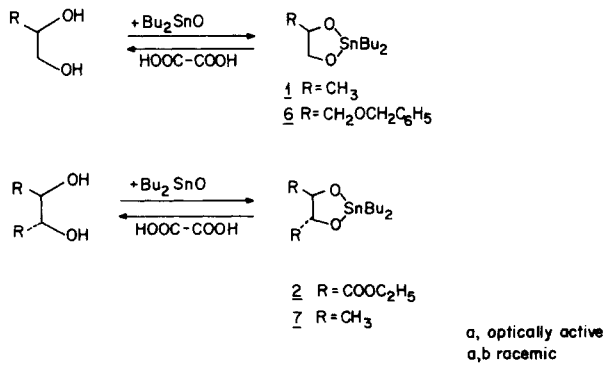


carbon	chemical shift,[a] δ parent, $R_1 = R_2 = R_3 = R_4 = H$	3aa, $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$	5ab, $R_1 = R_2 = R_3 = R_4 =$ $COOCH_2CH_3$	5aa,[b] $R_1 = R_2 = R_3 = R_4 =$ $COOCH_2CH_3$	3ab,[b] $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$
CHR_1	61.9	66.0	70.8	70.8	66.0
CO	173.2	173.1	172.0	172.0	173.1
C^{α}	34.2	34.3	33.8	33.8	34.3
C^{β}	24.7	24.7	24.5	24.5	24.8
C^{γ}	28.3	28.4	28.0	28.0	28.5
CHR_2		68.1			68.0
C'O		173.0			172.8
$C^{\alpha'}$		34.5			34.5
$C^{\beta'}$		24.7			24.9
$C^{\gamma'}$		28.6			28.5
$CHCH_3$		16.4			16.3
$COOCH_2CH_3$			166.0	166.0	
$COOCH_2CH_3$			62.3	62.3	
$COOCH_2CH_3$			14.1	14.1	

[a] The NMR spectra were measured in $CDCl_3$ solutions on a WH-90 (Bruker, C-13, 22.6 MHz) instrument. The chemical shifts given are relative to internal Me_4Si. [b] See ref 12.

geometry and are therefore highly susceptible to stereochemical factors. The high orientation observed in these complexes and the proximity of their components was anticipated to allow their use for the optical enrichment of enantiomeric mixtures. In an enantiomeric mixture of stannoxanes, one enantiomer may associate either with a molecule of identical configuration or of opposite configuration to give diastereomeric associates which may be separated by common separation techniques. In order to test this possibility, the optical enrichment of enantiomeric mixtures of diols via their stannoxanes was examined. The enrichment of diols appears to be a challenging problem, as the methods currently available often cause difficulties, due to the drastic regeneration processes which may cause racemization.[14,15]

Enantiomeric mixtures rich in 1,2(*R*)-propanediol, diethyl 2(*S*),3(*S*)-dihydroxysuccinate (diethyl tartrate), 1-benzyl-2(*R*)-glycerol or 2(*R*),3(*R*)-butanediol were converted to their cyclic stannoxanes **1**,[8] **2**,[12] **6**, and **7**,[8] respectively. The crude products were crystallized and the



crystalline precipitates separated from the mother liquors. The optical purity of each fraction was established by regenerating the free diol via treatment with oxalic acid[16] and by subsequently determining their optical rotation. The results of these experiments are summarized in Table V. Inspection of these data shows that all of the samples could be significantly enriched by a single crystallization step. However, in the case of 1,2-propanediol and 1-benzylglycerol the crystalline precipitates were rich in racemic material, and the filtrate was rich in optically pure material. In the case of diethyl tartrate and 2,3-butanediol, the crystalline precipiates contained the optically pure material and the filtrate the major enantiomeric impurity. Although the different solubility pattern for these two types of complexes can at present not be accounted for, the parallel behavior of the systems with one chiral center (**1** and **6**) and of those with two chiral centers (**2** and **7**) suggests pronounced regularities of their properties.

The effectiveness of using cyclic stannoxanes for the optical enrichment of enantiomeric mixtures deserves particular attention. It has been pointed out that for separating enantiomers via diastereomeric derivatives two factors are to be considered: the proximity of the two chiral residues within each diastereomeric derivative[17] and the number of their interacting points.[18] In the diastereomeric complexes of types A–D the two chiral units are close to each other in an "edge"-like arrangement, and they are interlinked via a two-atom interaction. They therefore meet both requirements for effective separation.

Conclusions

We have demonstrated in this work that cyclic tin–oxygen compounds derived from asymmetric diols may form diastereomeric molecular associates of defined orientation and that this phenomenon may be applied for the optical enrichment of enantiomeric mixtures. Many

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Table V. Optical Enrichment of Vicinal Diols via Stannoxanes 1, 2, 6, and 7

diol	initial optical purity, %	precipitate		filtrate	
		yield, %	optical purity, %	yield, %	optical purity, %
1,2-propanediol	80	63	75	34	100
diethyl tartrate	75	62	83	13	42
1-benzylglycerol	75	33	19.3	68	100
2,3-butanediol	75	48.5	98	38	37

questions are still to be answered. It is not clear what determines the relative stability of the meso and chiral complexes and why stannoxanes with one chiral center show a different solubility pattern from those with two chiral centers. It has also still to be established if molecular association between tin–oxygen compounds may also be applied for the resolution of racemic mixtures. Experiments aimed at clarifying these points are in progress as are investigations on the scope and limitations of the method.[19]

Experimental Section

Preparation of Cyclic Stannoxanes 1[8] and 2.[12] Solutions of 0.02 mol of diol [1,2(*R*)-propanediol, racemic 1,2-propanediol, diethyl 2(*S*),3(*S*)-dihydroxysuccinate, or racemic diethyl tartrate] in 150 mL of benzene were heated with 0.02 mol of dibutyltin oxide in a Dean–Stark apparatus under reflux for several hours. After 1 equiv of water had separated, the reaction mixtures were concentrated to a volume of 100 mL. When the mixture cooled, stannoxanes **1a** (mp 195–200 °C), **1ab** (mp 195–200 °C), **2a** (mp 140–145 °C), and **2ab** (mp 140–145 °C), respectively, precipitated as colorless solids in 75–85% yields.

Preparation of Macrocyclic Tetralactones 3aa and 5ab. Reaction of optically active stannoxanes **1a** (0.050 M, derived from 1,2(*R*)-propanediol) with 1 equiv pimeloyl chloride in chloroform as described earlier[11] provided after chromatography on silica gel 37.5% of crystalline **3aa**. Similarly, racemic stannoxanes **2ab** (0.050 M) reacted with 1 equiv pimeloyl chloride[11] to give the tetralactone **5ab** in 71% yield. The physical, analytical, and spectroscopic properties of these compounds are summarized in Tables III and IV.

(19) Preliminary experiments performed after submission of this manuscript demonstrated the feasibility of this approach, when stannoxane **2ab** derived from racemic diethyl tartrate could be partially resolved by fractionating crystallization in the presence of chiral stannoxane **1a**.

Optical Enrichment of Enantiomeric Mixtures Rich in 1,2(*R*)-Propanediol, Diethyl 2(*S*),3(*S*)-Dihydroxysuccinate, 1-Benzyl-2(*R*)-glycerol, and 2(*R*),3(*R*)-Butanediol. Solutions of 0.020 mol diol (75–80% optically pure) in 150 mL of benzene were treated with 0.020 mol of dibutyltin oxide under reflux in a Dean–Stark apparatus. After 1 equiv of water separated, the reaction mixtures were concentrated to dryness and the residues crystallized as follows. Stannoxane 1[8] was crystallized from 750 mL of dry benzene to give 3.8 g (0.013 mol, 62.5%) of precipitate (mp 195–200 °C), stannoxane 2[12] was crystallized from 100 mL of benzene to give 5.5 g (0.013 mol, 62.5%) of precipitate (mp 140–145 °C), stannoxane 6[20] was crystallized from methylene chloride–hexane (200 mL) to give 3.316 g (0.008 mol, 40%) of precipitate (mp 125–128 °C), and stannoxane 7[8] was crystallized from 200 mL of benzene to give 3.4 g (0.01 mol, 50%) of precipitate (mp 142–145 °C). Each of the precipitates and concentrated mother liquids were subsequently suspended in 150 mL of acetonitrile and treated at room temperature for 2 days with 1 equiv of oxalic acid. Subsequent removal of the solid tin oxalate by filtration and concentration of the filtrates in vacuo provided the parent diols in quantitative yields. Their chemical purity was confirmed by TLC and NMR analyses and their optical purity by their optical rotation. The yields of each of the fractions and their optical purities are given in Table V.

Acknowledgment. We thank the U.S.–Israel Binational Science Foundation for their support of this work.

Registry No. **1a**, 87279-46-7; **1ab**, 82112-71-8; **2a**, 87279-47-8; **2ab**, 87333-58-2; **3aa**, 87279-51-4; **3ab**, 82093-89-8; **5aa**, 87333-60-6; **5ab**, 87333-61-7; **6a**, 87279-49-0; **6ab**, 87279-48-9; **7a**, 87333-59-3; **7ab**, 87279-50-3; (*R*)-1,2-propanediol, 4254-14-2; *rac*-1,2-propanediol, 4254-16-4; 1-benzyl-2(*R*)-glycerol, 56552-80-8; 2-(*R*),3(*R*)-butanediol, 24347-58-8; diethyl 2(*S*),3(*S*)-dihydroxysuccinate, 13811-71-7; *rac*-diethyl tartrate, 57968-71-5; dibutyltin oxide, 818-08-6; pimeloyl chloride, 142-79-0; parent tetralactone, 74783-05-4.

(20) Anal. Found: C, 51.5; H, 6.9. Calcd for $C_{19}H_{30}O_4Sn$: C, 51.7; H, 6.7.