H. *Tetrahedron Lett.* **1979,** 853. (i) Shea, K. J.; Wise, S. *J. Am. Chem. Soc.* **1978,** *100,* 6519. (j) Shea, K. J.; Wise, S. *Tetrahedron Lett.* **1979,** 1011. (k) Yamamoto, H.; Sham, H. L. *J. Am. Chem. Soc.* **1979,** *101,* 1609. (l) Taber, D. F.; Gunn, B. P. *Ibid.* **1979,** *101,* 3992. (m) Roush, W. R. *Ibid.* **1978,** *100,* 3599. (n) Bazan, A. C.; Edwards, J. M.; Weiss, U. *Tetrahedron* **1978,** *34,* 3005. (o) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978,** *100,* 8034. (p) Wilson, S. R.; Mao, D. T. *J. Org. Chem.* **1979,** *44,* 3093. (q) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979,** *62,* 114. (r) W. R. Roush, *J. Org. Chem.,* **1979,** *44,* 4008.

(3) For notable exceptions, see ref 2a and 2r.

(4) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979,** *101,* 5073.

(5) (a) Lora-Tomayo, M. In "1,4-Cycloaddition Reactions", Hamer, J., Ed.; Academic Press: New York, 1967; pp 127–142. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979,** *12,* 949.

(6) For stereochemical studies on the *intermolecular* imino Diels–Alder reaction, see: (a) Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978,** 1971. (b) Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* **1973,** *95,* 5273.

(7) Except for the examples in ref 4, only one other intramolecular imino Diels–Alder reaction has been described: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1971,** *11,* 1031.

(8) (a) Wälchli, P. C.; Eugster, C. H. *Helv. Chim. Acta* **1978,** *61,* 885. (b) Rüedi, P.; Eugster, C. H. *Ibid.* **1978,** *61,* 899. (c) Mayer, C.; Green, C. L.; Trueb, W.; Wälchli, P. C.; Eugster, C. H. *Ibid.* **1978,** *61,* 905. (d) Wälchli, P. C.; Mukherjee-Müller, G.; Eugster, C. H. *Ibid.* **1978,** *61,* 921. (e) Wälchli-Schaer, E.; Eugster, C. H. *Ibid.* **1978,** *61,* 928.

(9) Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1963** *28,* 3421.

(10) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis,* **1972,** 544.

(11) We have been unable to separate isomers **12** and **13.** The isomeric *p*-nitrobenzyl esters prepared from acid **15** could be separated by analytical LC on a 1-ft μ-Bondapak C_{18} reverse-phase column (70:30 H_2O–CH_3CN, five recycles). Exact isomer ratios were determined at this stage.

(12) A detailed description of pyrolysis experiments with various leaving groups will be given in the full paper.

(13) We are extremely grateful to Professor Eugster for supplying us with these valuable samples.

(14) Cf. Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975,** *5,* 47.

(15) Reesterification of this acid with ethereal diazomethane established that no epimerization had occurred in the hydrolysis step.

(16) Single crystals of acid **22** (5:1 from benzene–ethyl acetate) belonged to space group $Pna2_1$, with a = 10.421 (2), b = 13.220 (4), and c = 6.270 (5) Å. A total of 2175 independent reflections were collected out to 2θ = 70° using a fully automated four-circle diffractometer (Enraf-Nonius) and monochromated Mo Kα (0.70930 Å) X-rays. After Lorentz, polarization, and background corrections, 571 reflections were judged observed [$I \geq 3\sigma(I)$]. Full-matrix, least-squares refinement with anisotropic temperature factors for C, N, and O and isotropic temperature factors for H converged to R = 0.039.[17] Complete data will be published in the full paper.[18]

(17) All programs used for this study were part of the "Structure Determination Package", Enraf-Nonius, Delft, Holland, 1975, revised 1977, and were implemented on a PDP 11/34 computer.

(18) We are grateful to Marguerite Bernheim (PSU) for carrying out this determination.

(19) If a (*Z*)-acylimine were an intermediate, these cyclizations would have to go through a transition state having *both* carbonyl groups exo. Although secondary orbital effects would not be significant in this transition state, such a possibility cannot be ruled out, based upon work by Roush[2r] and by White.[2a] It is conceivable that a *Z*-exo transition state might be favored over **24** based upon conformational and steric factors.[21] However, we have no way of proving whether the actual reacting acyl imine has the *E* or *Z* configuration.

(20) Cf.: (a) Gschwend, H. W. *Helv. Chim. Acta* **1973,** *56,* 1763, and references cited. (b) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975,** 903.

(21) Kikuchi, O. *Tetrahedron* **1971,** *27,* 2791.

(22) Fellow of the A. P. Sloan Foundation, 1975–1979; Recipient of a Research Career Development Award from NIH (HL-00176 and HL-00541). To whom correspondence should be addressed at The Pennsylvania State University.

Bassam Nader, Richard W. Franck, Steven M. Weinreb*[22]

Departments of Chemistry
Fordham University, Bronx, New York 10458
and The Pennsylvania State University
University Park, Pennsylvania 16802

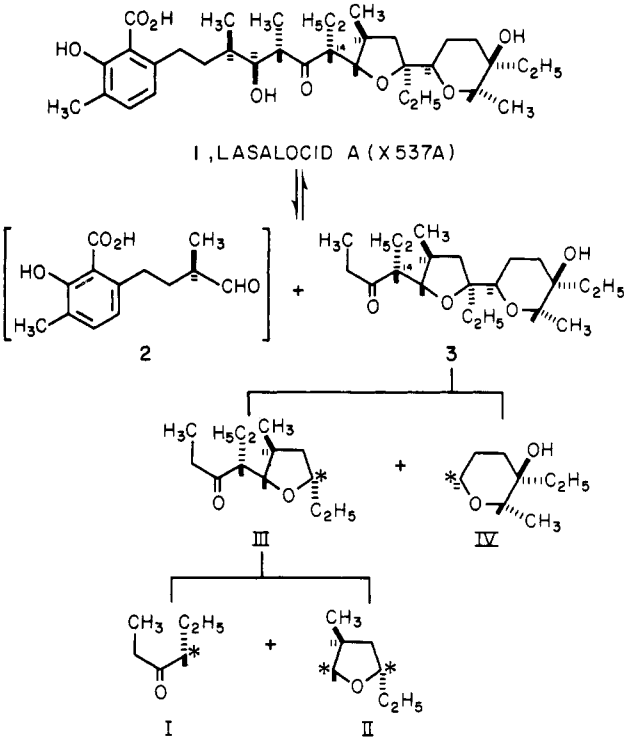
Received September 21, 1979

Total Synthesis of Lasalocid A (X537A)

Sir:

The polyether antibiotics[1] represent a class of structurally fascinating, complex organic molecules that possess potent physiological activity by virtue of their ionophoric character. While several members of this class have yielded to chemical total synthesis,[2] the biological importance of these molecules justifies continued excursions into their synthesis. In that vein, we report here a highly convergent, "building block" approach from carbohydrate precursors that has led to a total synthesis of lasalocid A (X537A)[3] and has broad potential as a strategy for the synthesis of other natural polyether ionophores, as well as many structural analogues.

Scheme I



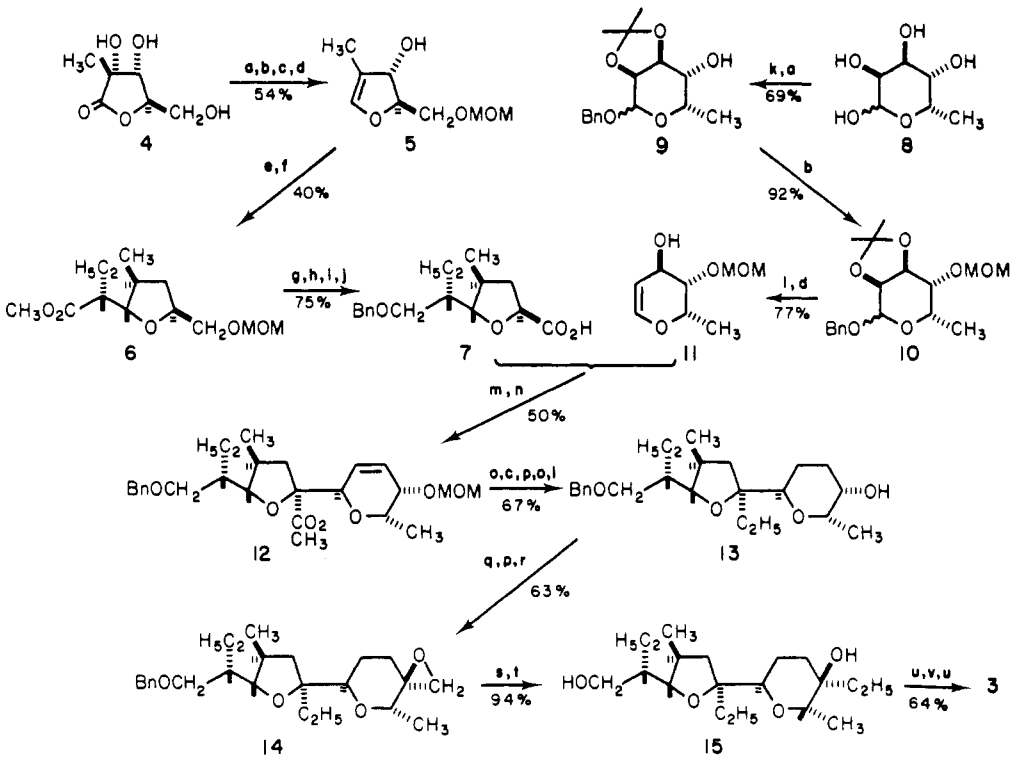
Degradative work by Westley[4] showed that lasalocid A (**1**) underwent reverse aldol-type cleavage on either heat or base treatment, and, while the aldehyde **2** was unstable and underwent further degradation, the polyether ketone **3** was readily available. A key feature of both the present synthesis and that described by Kishi[2a] is the ability to affect an aldol-type condensation between these two degradation products. This point, as well as a synthesis of the benzyl ester of the acid aldehyde **2,** has been demonstrated by Kishi,[2a,5] and a synthesis of the stereochemically more demanding polyether ketone **3** then constitutes the requirements for a total synthesis. In addition, the similarity between this ketone **3** and the components of the other polyether antibiotics[1] meant knowledge gained in this effort might be applied to the other even more complex systems.

For this work, the ketone **3** was schematically envisaged as arising from the three subunits I, II, and IV (Scheme I). The plan called for the initial union of parts I and II, and then subsequent joining of that product III with the remaining subunit IV. This approach has the advantage of not only being highly convergent, but also amenable to extensive variation of the subunits used.

The starting point for the synthesis of the furanoid equivalent III was "α"-D-glucosaccharino-1,4-lactone (**4**)[6] (Scheme II). After appropriate blocking, this lactone was converted into the furanoid glycal **5**[7] (subunit equivalent II) by the procedure[8] developed in these laboratories. The ketone equivalent I was then added in the form of the α-butyryl side chain by enolate Claisen rearrangement of the glycalyl butyrate. Stereocontrol of the α-ethyl group in the ester **6** was made possible by control of the *E*/*Z* ratio of enolates formed[9] prior to Claisen rearrangement, and the diastereomer **6**[7] is the principal product (ratio 75:25) under the conditions shown. After purification

0002-7863/80/1502-1155$01.00/0

Scheme II. Synthesis of Polyether Ketone 3[a]



[a] (a) CH_3COCH_3, H^+; (b) KH, $ClCH_2OCH_3$; (c) Dibal, Et_2O; (d) $P(NMe_2)_3$, CCl_4, Li, NH_3; (e) *n*-BuLi, n-C_3H_7COCl, LDA, 23% HMPA–THF, TMSCl, RT, H_2O, OH^-, CH_2N_2; (f) H_2, Pt/C, EtOAc; (g) $LiAlH_4$, Et_2O; (h) KH, $C_6H_5CH_2Br$; (i) H_3O^+; (j) Pt, O_2, aqueous $NaHCO_3$; (k) BnOH, HCl; (l) H_2, Pd/C, EtOAc; (m) $(COCl)_2$, C_6H_6; (n) *n*-BuLi, THF, LDA, THF, TMSCl, RT, H_2O, OH^-, CH_2N_2; (o) H_2, Ni(R), EtOAc; (p) $(C_6H_5)_3PCH_2$, THF; (q) Me_2SO, $(COCl)_2$, Et_3N; (r) MCPBA, CH_2Cl_2; (s) $Li(CH_3)_2Cu$, pentane; (t) Li, NH_3; (u) PCC, CH_2Cl_2; (v) C_2H_5MgBr, THF.

by silica gel chromatography, conversion of the ester **6**[7] into the furanoid equivalent III in the form of the acid **7**[7] then required only manipulation of the oxidation states of the terminal carbons.

The pyranoid equivalent IV in the form of the glycal **11**[7] was prepared from 6-deoxy-L-gulose **8**[10] in a manner[8] similar to that used for the construction of the glycal **5**. Conversion of 6-deoxy-L-gulose **8** first into the benzyl glycoside and then to the acetonide **9**[7] not only sets the stage for glycal formation, but also provides an opportunity to operate selectively on the 4-hydroxyl group.[11] For the present work, this hydroxyl group was merely blocked, and the incorporation of the C-4 ethyl group was postponed to a later stage. Further transformation of the acetonide **10**[7] into the required gulal derivative **11**[7] follows the previously described procedures.[8]

The union of the furanoid and pyranoid equivalents III and IV was again accomplished through use of the enolate Claisen rearrangement[8,9] which gave a 67% yield of a mixture of the syn isomer **12**[7] and its anti epimer[7] in a 76:24 ratio. These isomers were readily separated on silica gel chromatography, and the syn isomer **12** was converted into the alcohol **13**.[7] To incorporate the C-4 ethyl group, the epoxide **14**,[7] obtained after chromatographic separation of a 78:22 isomer mixture from oxidation, was formed from the alcohol **13**, as shown. Subsequent dimethyl cuprate cleavage of this epoxide **14** and then removal of the benzyl blocking group produced the diol **15**.[7] Conversion of the diol **15** into the polyether ketone **3**,[7] identical with naturally derived material[12] (IR, NMR, TLC, $[\alpha]_D$), followed standard procedures. At the present stage of development the furanoid equivalent III is available in 16% and the pyranoid equivalent IV in 25% overall yield from easily accessible precursors, and their union results in the formation of the polyether ketone **3** in 12% overall yield. Further refinement of this process, as well as its adaptation to lasalocid A analogues and other polyether antibiotics, is under active investigation.

Acknowledgment. Grateful acknowledgement is made for support of this investigation through Public Health Service Research Grant No. HL 21367 from the National Heart and Lung Institute and the Hoffmann-La Roche Foundation.

Supplementary Material Available: Infrared and proton magnetic resonance spectra, optical rotations, physical constants, thin layer chromatographic mobility, and elemental combustion analyses of compounds **5–7**, **9–15**, and **3** and isolated intermediates (10 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Westley, J. W., *Adv. Appl. Microbiol.* **1977,** *22,* 172–223. Pressman, B. C. *Annu. Rev. Biochem.* **1976,** *45,* 501–530. Westley, J. W. *Annul. Rep. Med. Chem.* **1975,** *10,* 246.

(2) (a) Lasolocid A: Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978,** *100,* 2933. (b) Monensin: Fukuyama, T.; Akasaka, K.; Karanewsy, S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979,** *101,* 262. (c) A23187: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. A. *Ibid.*, in press.

(3) Westley, J. W.; Blount, J. F.; Evans, R. H., Jr.; Stempel, A.; Berger, J. *J. Antibiot.* **1974,** *27,* 597.

(4) Westley, J. W., Evans, R. H., Jr.; Williams, T.; Stempel, A. *J. Org. Chem.* **1973,** *38,* 3431. Later Westley (Westley, J. W.; Pitcher, R. G.; Seto, H. *J. Antibiot.* **1979,** *31,* 289) reported that, when the reverse aldol-type reaction was effected by *either* base or heat treatment of lasalocid A, the polyether ketone **3** was obtained as a mixture of epimers about the 14 position, as judged by ^{13}C NMR spectroscopy. We have confirmed this result when the reaction is effected *by base treatment* of lasalocid A, but only a *single epimer,* corresponding to the original lasalocid A structure, was formed as a result of *the pyrolytic procedure,* as judged by ^{13}C NMR spectroscopy.

(5) An alternate synthesis[2a] of the racemic methyl ester of the aldehyde **2** and its aldol-type condensation with polyether ketone **3** have been accomplished in these laboratories (McGarvey, G., unpublished results), but isomer separation and ester cleavage are not sufficiently reliable to warrant publication; further work in progress will be reported later.

(6) Whistler, R. L.; BeMiller, J. N. *Methods Carbohydr. Chem.* **1963,** *II,* 484.

(7) Satisfactory infrared and proton magnetic resonance spectra, optical rotations, and elemental combustion analyses were obtained on all new compounds, and these data are recorded in the microfilm edition.

(8) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.*, in press.

(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976,** *98,* 2868.

(10) Ireland, R. E.; Wilcox, C. S. *J. Org. Chem.*, in press.

(11) Work currently in progress in these laboratories has led to the synthesis of the 4-α-ethyl derivative of this glycoside **9** and thence to the 4-α-ethyl derivative of the 6-deoxygulal **11** (MEM blocking group in place of MOM) (W. Noall, unpublished results). The use of this gulal derivative for further synthesis of polyether ketone **3** is under investigation.

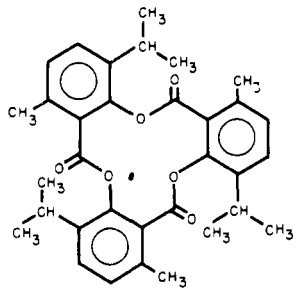
(12) The authors are grateful to Dr. W. Leimgruber of Hoffmann-La Roche for supplying a generous sample of lasalocid A which was degraded to the polyether ketone **3** by the procedure of Dr. Westley.[4]

Robert E. Ireland,* Suvit Thaisrivongs, Craig S. Wilcox
Contribution No. 6119, The Chemical Laboratories
California Institute of Technology
Pasadena, California 91125
Received October 18, 1979

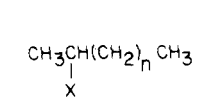
Enantiomer Recognition and Guest–Host Configurational Correlation in Crystals of Tri-*o*-thymotide Clathrate Inclusion Compounds

Sir:

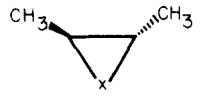
Chiral recognition by host molecules or molecular assemblies has attracted considerable attention in recent years.[1] We describe chiral recognition aspects in single crystals of tri-*o*-thymotide (TOT) clathrate inclusion complexes.[2] In the latter, a large variety of guest molecules may be accommodated in cavities (channels or cages) which are built up by TOT molecules during crystallization from media containing the guest.



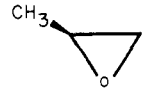
TOT



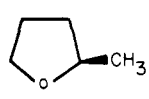
	1a	b	c	d	e	f
X)	Cl	Br	Cl	Br	Br	Br
n)	1	1	5	5	6	9



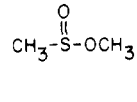
2a X = S
b X = O



3



4



5

TOT generally undergoes "spontaneous resolution" on crystallization in clathrate structures (cage clathrate, trigonal crystals, space group $P3_121$ or $P3_221$; channel clathrate, hexagonal crystals, space group $P6_1$ or $P6_5$).[3,4] Any such single crystal thus contains only *P* or only *M* configurated TOT species and provides a chiral environment about included guest molecules. When such clathrates are formed from solutions containing a racemic mixture of guest species, the two guest enantiomers should be included to a different extent by a growing crystal of given handedness and, indeed, such qualitative results have been described in the past.[6] To better understand the nature of chiral molecular recognition, we have undertaken a chemical and crystallographic study of the TOT clathrates and herein evaluate the degree of chiral recognition that is possible with some of these complexes, the scope of guest structure that may be included and resolved, and the possibility of correlating guest configuration with TOT chirality.

Single crystals of clathrate were grown from solutions of TOT in a large excess of the desired guest by slow cooling or slow evaporation. When larger crystals were desired, individual clathrate crystals were suspended in saturated guest solutions of TOT which were then slowly cooled; this procedure could be repeated more than once and crystals weighing up to 0.5 g were routinely prepared. The crystals were characterized by measurement of their unit cell constants and space groups; the TOT:guest ratios were established by NMR spectra and VPC analyses of solutions prepared from dissolved crystals and by density measurements.

The enantiomeric excess of the included guest, i.e., the degree of optical resolution, and the configuration of the predominant enantiomer were determined by direct polarimetric observations of solutions of the guests, by NMR analysis with chiral shift reagents, or by VPC analysis of the guest on a chiral phase (using recently developed, efficient analytical resolution techniques for *N*-trifluoroacetyl-2-aminoalkanes,[7] cyclic ethers,[1e,8] and episulfides[9]). For each guest, crystals containing excess *R* enantiomer and crystals containing excess *S* enantiomer were generally examined, and for each crystal the sign of rotation of the TOT was established; such "enantiomeric" experiments provided an estimate of reproducibility as well as a check that errors due to impurities were not introduced. This study is particularly feasible with TOT because it has a sufficiently high barrier to enantiomerization, M $\rightleftharpoons$ P (~21 kcal/mol),[10] and specific rotation ($[\alpha]_D > 70°$) in solution to enable measurement of its sign of rotation after dissolving only a small crystal chip in cold solvent.[3a]

Table I displays our results. The higher enantiomer selectivity generally observed in the cage clathrates compared with that in the channel complexes is intuitively understandable in terms of the more complete envelopment of the guest in the cages; however, a deeper insight awaits crystal structure analyses of representative complexes which will indicate guest geometry and guest–host contacts. It might have been thought[11] that sharp differences in chiral discrimination would occur in channel complexes when the length of the included guest matched the unit cell length, c = 29 Å, of the channel or a multiple of the asymmetric unit along the channel, $c/6$. However, on the basis of the results with **1e** (estimated length, 14.1 Å, ~$c/2$) compared with those of **1d** (12.8 Å) and **1f** (17.8 Å), there appears to be little if any such dependence.

Chiral guests having C_2 symmetry were expected to be differentiated to a high degree in cage clathrate cavities because the latter contain a twofold axis. Indeed, guests **2a** and **2b** afforded the expected cage clathrate crystals and the extracted guests had relatively high optical purities. This principle, the matching of guest molecular symmetry with the symmetry of the cavity, may be useful in the choice of appropriate host and guest species in other molecular recognition problems (cf. ref 5).

From the results presented, it appears that TOT enclathration may be used, at least within a related series of compounds, to establish *absolute* configurations by noting the sign of the TOT upon dissolution. Thus, all of the guests **1** having configuration *S* are preferentially enclathrated by (+)-TOT molecules. Similarly, (+)-TOT preferentially includes the *S,S* enantiomers of **2.** Such correlations may have application in configurational assignments where other approaches are problematic, e.g., when the formation of derivatives is difficult or the substance affords inherently weak chirality observations. Since the resolutions described here depend on the guest molecular geometry and not on specific functional groups, application to chiral hydrocarbons may also be envisaged.

With regard to preparative resolutions using TOT enclathration, it should be noted that, once single crystals of clath-

0002-7863/80/1502-1157$01.00/0