for α-ammonium groups in model compounds, the value for the standard enthalpy of ionization of 1 kcal/mol is not, 10 kcal/mol being a frequently reported value.[23] There are several plausible explanations for our results. (1) The ionization process may be improperly assigned to ILE-16 as has been suggested by several groups of investigators.[21,24] This alternative would contradict considerable apparently sound sets of data and we consider it improbable. (2) The electrostatic environment of the ammonium group in form E_1 may be very abnormal. This alternative receives some support from the salt-dependence studies,[25] but as yet such a severe perturbation appears unlikely and needs more extensive support. (3) The process may be linked to an undetected conformational rearrangement with near-zero free-energy change but a large negative enthalpy change. In this interpretation the environment of ILE-16 would be quite different in HE_I and E_I.

References and Notes

(1) Contribution No. 103 from the Laboratory for Biophysical Chemistry.
(2) G. P. Hess, *Enzymes*, 3rd ed, **3**, 239 (1971).
(3) M. L. Bender and J. V. Killheffer, *Crit. Rev. Biochem.*, **1**, 149 (1973).
(4) G. P. Hess, J. McConn, E. Ku, and G. McConkey, *Phil. Trans. R. Soc. B*, **257**, 89 (1970).
(5) J. McConn, G. D. Fasman, and G. P. Hess, *J. Mol. Biol.*, **39**, 551 (1969).
(6) A. R. Fersht and Y. Requena, *J. Mol. Biol.*, **69**, 279 (1971).
(7) A. R. Fersht, *J. Mol. Biol.*, **64**, 497 (1972).
(8) P. B. Valenzuela and M. L. Bender, *Biochemistry*, **9**, 2440 (1970).
(9) N. C. Robinson, H. Neurath, and K. A. Walsh, *Biochemistry*, **12**, 420 (1973).
(10) D. Karibian, C. Jones, A. Gerther, K. J. Dorrington, and T. Hofmann, *Biochemistry*, **13**, 2891 (1974).
(11) H. Kaplan, K. J. Stevenson, and B. S. Hartley, *Biochem. J.*, **13**, 289 (1971).
(12) D. M. Shotton and H. C. Watson, *Nature*, **225**, 811 (1970).
(13) M. Krieger, L. M. Kay, and R. M. Stroud, *J. Mol. Biol.*, **83**, 209 (1974).
(14) P. B. Sigler, D. M. Blow, B. W. Matthews, and R. Henderson, *J. Mol. Biol.*, **35**, 143 (1968).
(15) R. Lumry and R. Biltonen in "Structure and Stability of Biological Macromolecules", Vol. 2, S. Timasheff and G. Fasman, Ed., Marcel Dekker, New York, N.Y., 1969, p 65.
(16) Reduced χ square values ($\bar{\chi}^2$) were used as criteria for goodness of the fits. All $\bar{\chi}^2$ values were <1.5, most below 1.0.
(17) R. Biltonen and R. Lumry, *J. Am. Chem. Soc.*, **91**, 4256 (1969).
(18) J. F. Brandts, in ref 15, p 213.
(19) J. M. Sturtevant, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2236 (1977). The well-known basis for large heat capacity effects in protein systems are the several water–polypeptide interactions, but recently Sturtevant argues that vibrational changes of the folded polypeptide may also be important. Since internal degrees of freedom are not lost, large changes in many force constants are required to explain the magnitude of the heat-capacity changes. Abrupt changes in protein internal modes as opposed to "iceberg" formation or loss and changes in hydrogen bonds between peptide hydrogen atoms and water during conformational rearrangements appear to be attributable to changes in secondary bond arrangements ("mobile defects") which control the breadth of the energy distribution manifested in the distribution of force-constant values. Insofar as heat-capacity effects not due to changes in protein–water interactions are concerned, we agree with Sturtevant, but believe the abrupt changes can only be explained by such mobile-defect rearrangements. (Cf. R. Lumry and A. Rosenberg. *Colloq. Int. CNRS*, **246**, 53 (1976).)
(20) Y. Nakagawa and M. L. Bender, *Biochemistry*, **9**, 259 (1970).
(21) S. K. Sharma, Ph.D. Dissertation, University of Otago, Dunedin, New Zealand, 1977.
(22) H. Kaplan, *J. Mol. Biol.*, **72**, 153 (1972).
(23) D. D. F. Shiao and J. M. Sturtevant, *Biopolymers*, **15**, 1201 (1976).
(24) T. T. Blair. M. A. Marini. S. P. Aggarwal, and C. J. Martin. *FEBS Lett.*, **14**, 86 (1971).
(25) J. Stoesz. Ph.D. Dissertation, University of Minnesota, Minneapolis, Minn., 1977.

James D. Stoesz

Department of Biochemistry. Brandeis University
Waltham, Massachusetts 02154

Rufus W. Lumry*

Laboratory for Biophysical Chemistry
Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455
Received September 12, 1977

# A Virtually Completely Asymmetric Synthesis

Sir:

We wish to report an asymmetric synthesis of (S)-$(+)$-atrolactic acid methyl ether which proceeds in extremely high ($\sim$100%) optical yield, effects the separation of the chiral product from the original inducing chiral center, and allows, in principle, for the recovery of the chiral auxiliary reagent.

The reaction sequence includes two highly stereoselective steps. The first makes use of the observation[1] that electrophilic attack on 2-lithio salts of conformationally locked 1,3-oxathianes—like that on 2-lithio-1,3-dithianes[2]—leads exclusively to equatorially substituted products. The second step is an extremely diastereoselective reaction of a Grignard reagent with a ketone (Cram's rule). Scheme I outlines the reactions involved.

Metalation of **1a** ($[\alpha]^{25}_D$ $-30.4°$ ($CHCl_3$), 44% e.e. (enantiomer excess)) was effected in THF by addition of BuLi at -78 °C, followed by stirring of the reaction mixture for 15 min at ambient temperature. Addition of 1 equiv of C_6H_5CHO after recooling to -78 °C gave, after workup, **2a** (yield 95%, $[\alpha]^{25}_D$ $-42.3°$ ($CHCl_3$)) as a mixture of diastereomers which were exclusively equatorially substituted at C-2. Oxidation of **2a** with Me_2SO in the presence of trifluoroacetic anhydride and triethylamine[4] gave, in 75% yield, **3a** ($[\alpha]^{25}_D$ $-27.4°$ ($CHCl_3$)), 44% e.e. as determined by ^1H NMR using the optically active shift reagent $Eu(hfc)_3$. Ketone **3a** in ether/THF[5] was added to an excess[6] of methylmagnesium iodide in ether which afforded diastereomer **4a** ($[\alpha]^{25}_D$ $-40.9°$ ($CHCl_3$)) in 95% yield (no **5a** could be detected[7] by either ^1H NMR or ^{13}C NMR[8]). Methylation of **4a** with sodium hydride/methyl iodide produced **6a** (96%, $[\alpha]^{25}_D$ $-23.1°$ ($CHCl_3$)) which was cleaved[9] in a refluxing mixture of excess methyl iodide and 80% aqueous acetonitrile in the presence of $CaCO_3$ to give the aldehyde **7** (90%, $[\alpha]^{25}_D$ $-44.5°$ ($CHCl_3$)). Compound **7** was oxidized with Jones reagent to atrolactic acid methyl ether (**8**) (68%, $[\alpha]^{25}_D$ $+13.9°$ (MeOH)) which was (by CH_2N_2), converted to its methyl ester **9** (96%, $[\alpha]^{25}_D$ $+6.4°$ (MeOH)). The e.e. in this product was again 44%[10] as determined by ^1H NMR using $Eu(hfc)_3$ and its physical and spectral properties

Scheme I
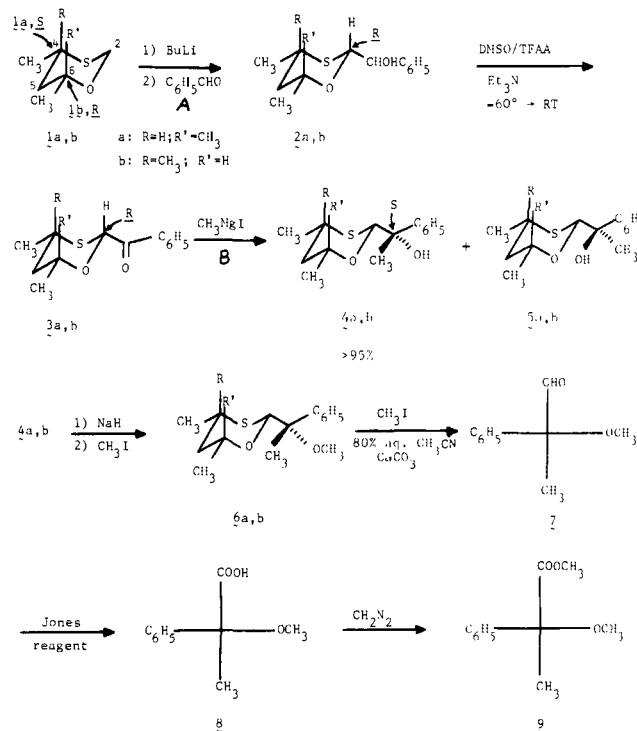
in achiral environment were identical with those of a sample made from authentic (±)-atrolactic acid by esterification with MeOH and subsequent methylation with NaH/CH$_3$I. Based on its sign of rotation the major enantiomer in **8** and **9** has the *S* configuration.[11]

The sequence shown was also followed starting with **1b** ([α]^{25}D +14.7° (petroleum ether), 51% e.e.) under virtually the same reaction conditions. Thus, **1b** gave **2b** (86%, [α]^{25}D −18.1° (CHCl$_3$)) which was converted into **3b** (79%, [a]^{25}D +6.4° (CHCl$_3$), 51% e.e. by LSR experiment). Grignard reaction with **3b**, using exclusively ether as solvent, afforded **4b** and **5b** in a ratio of 97.5:2.5[12] (94%, [α]^{25}D −16.0° (CHCl$_3$)). Methylation of the Grignard product gave **6b** ([α]^{25}D + 4.6° (CHCl$_3$)) which was cleaved to give **7** ([α]^{25}D −47.4° (CHCl$_3$)). Oxidation of aldehyde **7** produced **8** ([α]^{25}D +15.3° (MeOH)), the overall yield in the last three steps being 53%. Acid **8** was converted into the methyl ester **9**, again purified by distillation (96%, [α]^{25}D +6.9° (MeOH)), whose enantiomeric excess was determined by LSR experiment to be 47%, corresponding to an optical yield in this series of ~92%. Again, the *S* enantiomer was produced.

To prepare the optically active oxathiane **1a**, (−)-3-benzylthiobutyric acid, CH$_3$CH(SCH$_2$C$_6$H$_5$)CH$_2$COOH[13] was resolved with cinchonidine[14] and the resulting acid ([α]^{25}D −8.31° (ethanol))[15] converted to its methyl ester by treatment with methanol, 2,2-dimethoxypropane, and acetyl chloride. Reaction with excess methylmagnesium iodide gave 2-methyl-4-thiobenzyl-2-pentanol, CH$_3$CH(SCH$_2$C$_6$H$_5$)-CH$_2$C(OH)(CH$_3$)$_2$. Cleavage of the benzyl group in liquid ammonia[16] afforded, after distillation, chemically pure partially resolved (*S*)-(+)-4-mercapto-2-methyl-2-pentanol (**10**, 77% from the acid, [α]^{25}D +16.6° (ethanol)) which was heated with paraformaldehyde in the presence of sulfuric acid and water[17] to give (−)-4,6,6-trimethyl-1,3-oxathiane **1a** in 81% yield.

To obtain the optically active starting material for the **b** series, 4,4,6-trimethyl-1,3-oxathiane, benzyl mercaptan was added to mesityl oxide in the presence of sodium ethoxide[18] to give 4-methyl-4-thiobenzyl-2-pentanone. This ketone was reduced with LiAlH$_4$ to the racemic thiobenzyl alcohol which was resolved as the monophthalate ester with brucine. Alternatively, the ketone was reduced with a Darvon alcohol-lithium aluminum hydride[19] complex to (−)-(CH$_3$)$_2$-C(SCH$_2$C$_6$H$_5$)CH$_2$CH(OH)CH$_3$ which was obtained in up to 52.5% e.e.[20] (98%, [α]^{25}D −23.5° (CHCl$_3$)). The combined product of several small runs (overall 51% e.e.) with sodium in ammonia yielded (−)-4-mercapto-4-methyl-2-pentanol (90%, [α]^{25}D −5.2°) which was condensed with paraformaldehyde[17] to give **1b** in 78% yield.

The absolute configuration of the starting material **1a** at C-4 was established on the basis of an independent asymmetric synthesis (Scheme II).[2] In this transformation (+)-**10**, the precursor of (−)-**1a** (vide supra), yielded, via **11, 12, 13** and **14**, ethyl (−)-mandelate known to have the *R* configuration,[21] though only in 17% chemical and 18% optical yield. It follows (see Scheme II) that **11** and therefore also **1a** is *S* at C-4.

Scheme II
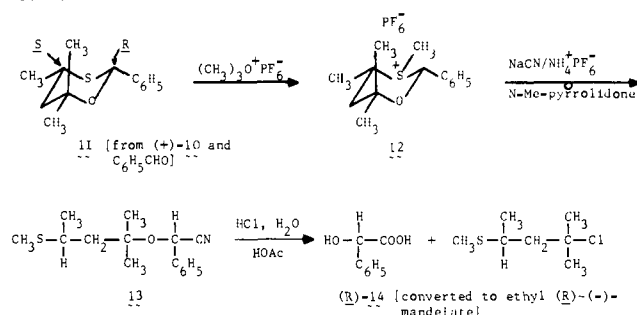
Scheme III
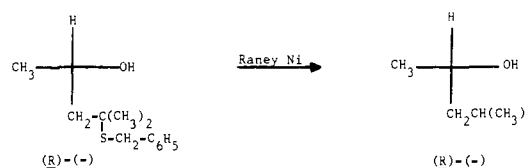
The absolute configuration at C-6 in the **b** series was determined in one step (Scheme III) by desulfurization of (−)-4-methyl-4-thiobenzyl-2-pentanol (**15**) with Raney nickel[22] which gave (−)-4-methyl-2-pentanol[23] known to have the *R* configuration at C-2.[24]

The absolute configurations of starting materials and products in the synthesis described are thus correlated as shown in Scheme I. Since substitution at C-2 is exclusively equatorial, *S* configuration at C-4 in the **a** series or *R* configuration at C-6 in the **b** series both induce *R* configuration at C-2 which, in turn, leads to *S* configuration at the exocyclic carbon. The latter induction step (Grignard reaction) exemplifies a striking case of Cram's rule where the rigid (cyclic) model applies (cf. Scheme IV).

Scheme IV
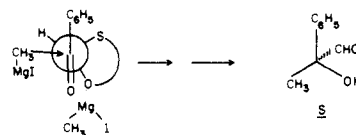
The magnesium of the Grignard reagent (hard acid) complexes simultaneously with the ketone oxygen and the ring oxygen (hard base) in preference to the ring sulfur (soft base). This leads to a rigid structure (with the two oxygens nearly eclipsed) which is then attacked by the Grignard reagent virtually exclusively from the side of the (small) hydrogen. Presumably formation of the rigid magnesium complex combined with the big difference in size of hydrogen vs. sulfur are the key to the extraordinary stereoselectivity in this reaction leading to the unusually high overall optical yield of ~100% in the **a** series and 92% in the **b** series. The latter value can no doubt be increased to at least 99%[25] by carefully controlling conditions in the Grignard step.

Highly stereoselective Grignard reactions of open-chain ketones involving Cram's cyclic model have been reported earlier.[26,27] In these syntheses, however, the newly created chiral center is vicinal to the chiral center of the (potential) auxiliary reagent and it is therefore virtually impossible to recover both chiral centers intact at the same time. The present synthesis involves a case of *two sequential asymmetric inductions* where the original chirality at C-6 (or C-4) in the oxathiane ring is first transferred to C-2 (Scheme I, step A) and from there to the exocyclic carbon (Scheme I, step B). This procedure permits subsequent sacrifice of the chirality at C-2 with recovery of the new chiral center and, in principle, also the chiral auxiliary reagent. The latter point is presently under investigation as are the broader applications to potential asymmetric syntheses of optically active tertiary alcohols, secondary hydroxy acids, amino acids, etc.

References and Notes

(1) Jorma K. Koskimies, Ph.D. Dissertation, University of North Carolina, Chapel Hill, N.C. 1976.
(2) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Am. Chem. Soc.*, **96**, 1807 (1974).
(3) The scheme shows the absolute configurations of the enantiomers in excess (**a**, *S* configuration at C-4; **b**, *R* configuration at C-6) used in the synthesis.
(4) K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976), procedure A.
(5) THF had to be added in order to effect dissolution of **3a**.
(6) Four equivalents were used.
(7) A previous run with racemic **3a** had given a ratio of 94:6 (**4a/5a**), probably due to some moisture contained in the THF used.
(8) A diastereomeric mixture of **4a** and **5a** obtained by addition of racemic **1a**–Li to acetophenone served as reference.
(9) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 68 (1977), and references there cited.
(10) Based on the rotation reported by L. Angiolini, P. Costa Bizzarri, and M. Tramontini, *Tetrahedron*, **25**, 4211 (1969), in MeOH for 82.1% optically pure ester (cf. ref 11), the optical purity of our material would be 43.8%.
(11) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
(12) A previous experiment with racemic material had afforded **4b** in >99% diastereomeric purity; traces of moisture, again, may have caused the drop in diastereomeric purity; cf. note 7.
(13) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3098 (1949).
(14) C. E. Hagberg and S. Allenmark, *Chem. Scr.*, **5**, 13 (1974).
(15) This value corresponds to 48% e.e., if the reported rotation[14] of $[\alpha]^{25}_{D}$ −17.1° (ethanol), is the true value for the optically pure compound. If so, some racemization must have occurred in the preparation of **1a** from the precursor acid.
(16) H. Schulz and V. du Vigneaud, *J. Am. Chem. Soc.*, **88**, 5015 (1966).
(17) Modification of a procedure by F. Aftallon, D. Lumbroso, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1958 (1965).
(18) H. J. Backer and G. J. DeJong, *Recl. Trav. Chim. Pays-Bas*, **70**, 377 (1951).
(19) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973).
(20) Determined by an LSR experiment using Eu(hfc)₃.
(21) R. Roger, *J. Chem. Soc.*, 2168 (1932): $[\alpha]^{25}_{D}$ −126.2° (CHCl₃) for ethyl (*R*)-mandelate.
(22) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 729: ½-h reflux in 2-propanol with Raney nickel, prepared according to the procedure therein described, led to complete desulfurization.
(23) $[\alpha]^{25}_{D}$ −0.349°, neat (i.e., the sample had been dissolved in 20.76 times its weight of racemic 4-methyl-2-pentanol). The rotation value indicates that some racemization (~45%) took place during desulfurization; cf. E. L. Eliel and S. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965).
(24) P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931).
(25) Cf. note 12.
(26) E.g., B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957): 99% stereoselectivity. Reference 11: 90–92%. Reference 10: 100%.
(27) R. Méric and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, **327** (1973). These investigators have described a synthesis of **9** in 97% optical yield using manitol (which is consumed) as the chiral auxiliary reagent. They have also suggested (but not reduced to practice) a synthesis of the general type described here.

**Ernest L. Eliel,* Jorma K. Koskimies, Bruno Lohri**

Department of Chemistry, University of North Carolina
Chapel Hill, North Carolina 27514

Total Synthesis of (±)-Eriolanin

Sir:

Eriolanin (**1**) and eriolangin (**2**) are novel antileukemic 1,10-*seco*-eudesmanolides which were isolated from *Eriophyllum lanatum* Forbes (Compositae) by Kupchan and co-workers during a search for tumor-inhibitory natural products from plant sources.[1] The structural elucidation of **1** and **2** involved a combination of NMR and mass spectral techniques along with x-ray analysis of a mixed crystal of dehydroeriolanin (**3**) and dehydroeriolangin (**4**).[2] Both eriolanin and eriolangin possess significant activity in vivo against P-388 leukemia in mice and in vitro against cell cultures derived from human carcinoma of the nasopharynx (KB). In this communication we wish to report a stereocontrolled total synthesis of (±)-eriolanin (**1**). In addition we report the stereospecific total synthesis of (±)-6-epieriolanin (**5**) which is more active than
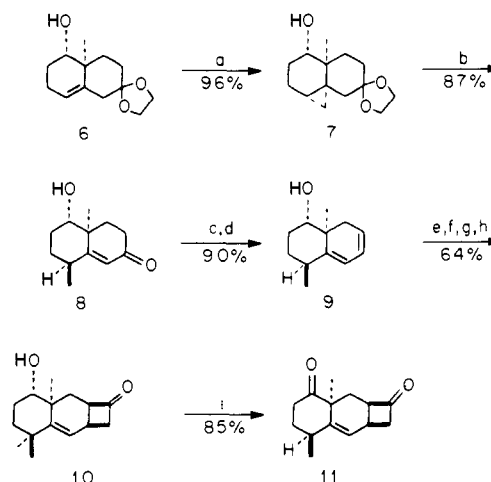
1, R = CO— / 2, R = CO— / 3, R = CO— / 4, R = CO— / 5
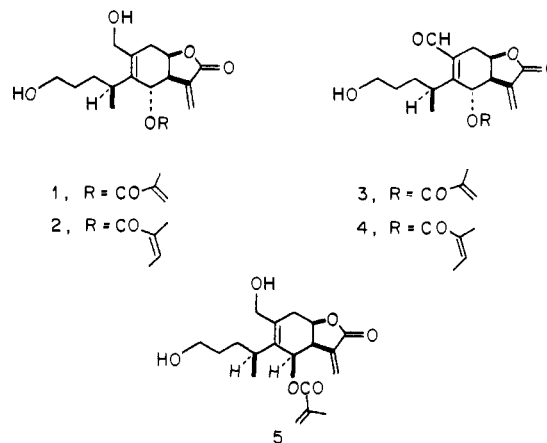
either **1** or **2** in vivo against the P-388 leukemia in mice.[3,4] (±)-6-Epieriolanin also exhibited significant activity (ED_{50} = 1.8 μg/mL)[5] in vitro against KB cells in tissue culture.

The key intermediate **11**, mp 111–112 °C, which can be converted into either racemic eriolanin or racemic 6-epieriolanin, was prepared in 41% overall yield by a nine-step sequence from the known octalol **6**[6] (Chart I). Cyclopropanation of octalol **6** employing the LeGoff modification[7] of the Simmons–Smith reaction gave the 4α,5α-methanodecalol **7** in 96% yield. Exposure of ketal **7** to 70% perchloric acid in methylene chloride resulted in cleavage of the cyclopropane ring and equilibration of the methyl group to the more stable equatorial position.[8] Tosyl hydrazone formation followed by treatment with excess lithium diisopropylamide in tetrahydrofuran gave in 90% yield the conjugated diene **9**[10] which was silylated in near-quantitative yield with *tert*-butyldimethylsilyl chloride in dimethylformamide containing imidazole.[11] As anticipated addition of dichloroketene[12] took place from the β face of the diene system providing, after dechlorination and cleavage of the silyl ether, cyclobutanone **10** (65%): IR (CCl₄) 3640, 3460, 1780 cm⁻¹. Oxidation of **10** with pyridinium chlorochromate[13] gave in 85% yield crystalline diketone **11**: IR (CCl₄) 1783, 1714 cm⁻¹.

With the olefinic diketone **11** in hand we focused our attention on its direct oxidation to the dilactone epoxide **12** which having all chiral centers established would allow for its con-

Chart I[a]