Asymmetric Synthesis of *R* and *S* α-Alkylalkanoic Acids from Metalation and Alkylation of Chiral 2-Oxazolines

A. I. Meyers,* Gerald Knaus, Kazuyuki Kamata, and Michael E. Ford

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received May 22, 1975*

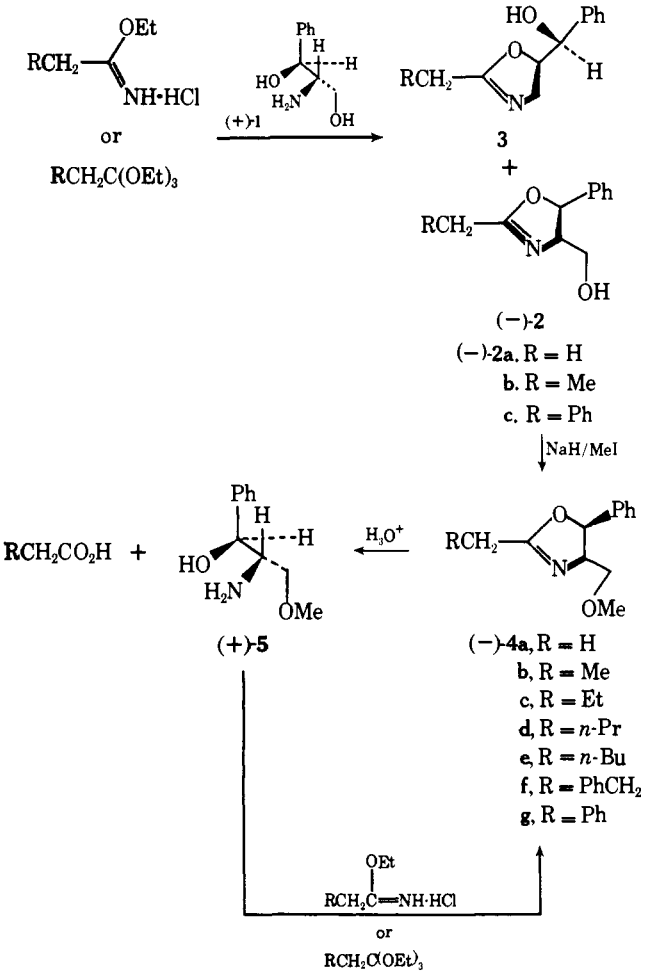
Abstract: The use of readily available chiral oxazolines **4** for the synthesis of enantiomerically enriched α-alkylalkanoic acids is described. A study of the reaction characteristics indicates that the critical step in the asymmetric synthesis is the alkylation of the rigid lithio oxazolines **6**. Stereoselectivity increases as the alkylation temperature is lowered. Hydrolysis of the elaborated oxazolines leads to α-alkylalkanoic acids in enantiomeric purity 45–85%. A mechanism for this process is proposed which involves underside entry of the electrophile to the lithio oxazoline by initial halide–lithio cation complexation.

Introduction

Over the years there has been a large number of reported efforts designed to generate optically active compounds via asymmetric induction.[1,2] Unfortunately, the ratio of efficient methods to the number of published methods is rather low, leaving this area of endeavor still in a relatively primitive state of development. Rarest among efficient asymmetric syntheses is carbon–carbon bond formation with the simultaneous creation of a new chiral center. Since it is generally agreed that C–C bond formation is a synthetic achievement of considerable significance, it follows that asymmetric C–C bond forming reactions must be of even greater significance.

We now report, in some detail, the results of a study[3] which leads to chiral α-substituted alkanoic acids of high enantiomeric purity possessing sufficient generality such that one may prepare, *in a predictable manner*, either the *R* or the *S* enantiomer in the series from a single chiral substrate. To date there are no methods available for alkylating carboxylic acids in comparable optical yields.[1] Of prime importance is the fact that a lithio salt of a 2-oxazoline **6** gains its chirality by virtue of a chelate with a suitably disposed methoxyl ligand. This lithio-methoxyl chelate is responsible for the high degree of asymmetric induction and appears to play a key role in such processes. Although several chiral lithium reagents have been alkylated[2] to give α-alkyl ketones, none has possessed the added feature of a rigid lithio intermediate (such as **6**), and thus the enantiomeric purity of the products has suffered. Furthermore, the present technique allows for efficient and complete recovery of the chiral reagents utilized to induce the asymmetric C–C bond formation. The following discussion will describe (a) the chiral reagents, (b) the stereoselective alkylation of chiral oxazolines and the parameters governing its successful implementation, and (c) the mechanistic aspects of the processes.

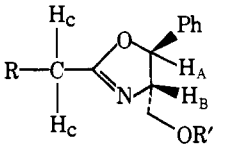
Scheme I



Chiral Reagents

The chiral reagents employed for this study are the oxazolines **2** readily prepared by condensing (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol (**1**)[4] with imino ethers or orthoesters (Scheme I). Accompanying the formation of **2** is a small quantity (10–12%) of the isomeric oxazoline **3** which is conveniently removed by crystallization. The hydroxyl group in **2** was transformed into its methoxyl derivative **4** using sodium hydride–methyl iodide. In order to determine whether **4** could be hydrolyzed to the carboxylic acids while recovering the methoxyamino alcohol **5** without racemization, **4b** was heated to reflux in aqueous hydrochloric (3–6 *N*) and sulfuric (3–6 *N*) acids. Recovered **5** was again treated with the imidate of propionitrile or ethyl orthopropionate to give **4b** whose optical purity was within ±2% of the material prior to hydrolysis. Thus, the chiral methoxyamino alcohol may be reused to prepare the oxazoline for additional asymmetric syntheses. A number of chiral oxazolines (**4a–4g**) were prepared using various nitriles in the form of their imino ethers and condensing them with the aminodiol **1** (method A, Table I), or orthoesters heated with **1** in DMF or dichloromethane (method A′, Table I). Alternatively, if the appropriate nitrile or orthoester was unavailable, metalation (−78°) of the 2-methyloxazoline **4a** with *n*-butyllithium or lithium diisopropylamide followed by addition of an alkyl iodide provided the 2-alkyloxazolines **4** (**c–f**) (method C, Table I). In the case of 2-benzyloxazoline **2c** formed from the imidate of phenylacetonitrile and **1**, the

Table I. Properties[a] and Yields of Chiral Oxazolines **2** and **4**



Oxazoline	R	R'	Method of preparation (%)[b]	Bp (Torr) or (mp), °C	$[\alpha]^{24}_{589}$ (c, solvent)	Ir (C=N)	NMR H_A	NMR H_B	NMR H_C[c]
2a	H	H	A(72), A'(71)	(64–65)	−174.6 (10.5, $CHCl_3$)	1670	5.62 (d)	4.45–3.78[d]	2.15 (d)
4a	H	Me	B (89)	85–87 (0.20)	−117.8 (10.5, $CHCl_3$)	1670	5.30 (d)	4.33–3.93	2.10 (m)
2b	Me	H	A(68), A'(81)	(68–69)	−135.1 (10.4, $CHCl_3$)	1660	5.37 (d)	4.23–3.50[d]	2.45 (m)
4b	Me	Me	B(87)	91–93 (0.25)	−84.2 (10.1, $CHCl_3$)	1665	5.32 (d)	4.37–3.90	2.40 (m)
4c	Et	Me	C(78)	94–96 (0.05)	−87.7 (13.8, $CHCl_3$)	1670	5.35 (d)	4.30–4.00	2.45 (m)
4d	*n*-Pr	Me	C(92)	103–104 (0.10)	−89.0 (8.8, EtOH)	1670	5.30 (d)	4.33–3.90	2.40 (m)
4e	*n*-Bu	Me	C(74)	162–164 (1.0)	−75.5 (11.3, $CHCl_3$)	1670	5.30 (d)	4.33–3.95	2.42 (m)
4f	$PhCH_2$	Me	C(57)	145–147 (0.03)	−59.1 (8.4, EtOH)	1670	5.26 (d)	4.30–3.90	2.9 (m)[e]
2c	Ph	H	A(58)	(131–132)	−44.6 (5.4, $CHCl_3$)	1670	5.34 (d)	4.30–3.96[e]	3.70 (s)[d]
4g	Ph	Me	D(69)	127–128 (0.02)	−38.2 (9.3, EtOH)	1670	5.30 (d)	4.30–3.90	3.73 (s)[d]

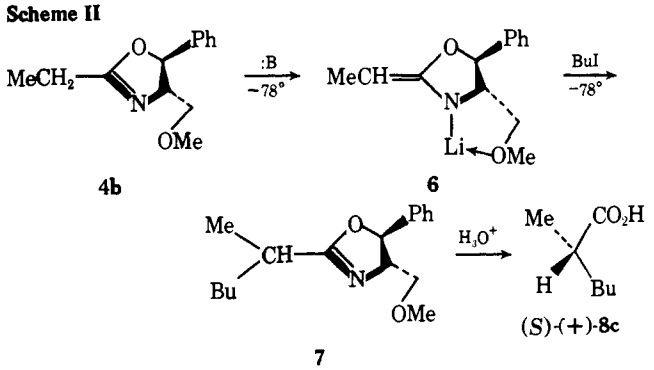
[a] Elemental analyses are within ±0.3% of calculated values (Experimental Section). [b] Method A, reaction of imidate hydrochloride with amino diol (+)-1; method A', reaction of ortho esters with amino diol (+)-1; method B, methylation of the hydroxymethyloxazolines **2** with sodium hydride–methyl iodide, method C, alkylation of **4a** with LDA–RX; method D, reaction of imidate hydrochloride with methoxyamino alcohol (+)-**5**. [c] All above compounds showed slight coupling of H_C to H_B (~1.5 Hz). [d] Overlaps with the $-CH_2OH$ protons. [e] Overlaps with $PhCH_2$ protons.

corresponding methyl ether **4g** was not cleanly prepared using sodium hydride–methyl iodide. Simultaneous proton removal from the C–H and O–H groups led to polymethylation which necessitated an alternative procedure. In this single instance, the 2-benzyloxazoline **4g** was prepared in good yield by condensing the methoxyamino alcohol **5** with the imidate of phenylacetonitrile (method D, Table I). The yields, physical properties, and methods of preparation for the chiral oxazolines are presented in Table I.

Results

Metalation and Alkylation of Chiral Oxazolines (−)-(4). Based on our previous observations that simple, achiral oxazolines containing a 2-alkyl group may be alkylated to give α-alkylalkanoic acids after hydrolytic removal of the oxazoline moiety,[5] we proceeded to apply this technique to the chiral oxazolines **4**. In our earliest experiments, the 2-ethyloxazoline (**4b**) was metalated with 1.05 equiv of *n*-butyllithium (THF, −78°) to give a yellow anion solution (**6**) which was treated with *n*-butyl iodide at −78° to produce the oxazoline **7** in 92% isolated yield. Hydrolysis (4 *N* HCl, 95°, 3 hr) gave (*S*)-(+)-2-methylhexanoic (**8c**) acid in 43% optical purity (Scheme II). Repeating this reaction using

Scheme II



tert-butyllithium gave the same acid, (+)-**8c**, in 49% optical purity. However, when lithium diisopropylamide was employed, (+)-**8c**, was formed in 66% optical purity. Although all three bases gave overall synthetic yields of 72–75%, the optical purity of the product using LDA was distinctly superior. An "aging" effect was observed when the lithiooxazoline **6** was prepared from *n*-butyl- or *tert*-butyllithium, but not from lithium diisopropylamide. When the anion was prepared (−78°, THF) and allowed to warm to −30° for 20 hr, recooled to −78°, and alkylated, the optical purity of (+)-**8c** decreased from 43 to 28%. If the aging at −30° was extended to 40 hr and recooled, a 10% optical yield of (+)-**8c** was obtained. When these aging conditions were employed for LDA, no change in the optical purity of the acid was observed. Since organolithium reagents are known to form aggregates in solution and to dissociatively coordinate with added nitrogenous bases,[6a] it appears that the isopropylamine stabilizes the monomeric forms of **6**, while in its absence the anion **6** tends to associate reducing stereoselectivity of the alkylation.[6b] Attempts to dissociate the lithio oxazolines **6** formed with *n*-butyl- or *tert*-butyllithium, by addition of various amines (diisopropylamine, triethylamine, TMEDA, Dabco), gave only slight increases in optical yields of the acids.

The nature of the electrophile used to alkylate **6** at low temperatures was found to be most efficient using alkyl iodides or "active halides" such as allylic or benzylic chlorides. The use of alkyl bromides gave lower synthetic yields (40–60%) under these conditions as well as poorer optical yields (20–30%). Alkyl chlorides gave little or no alkylation when added to the lithio oxazoline **6**.

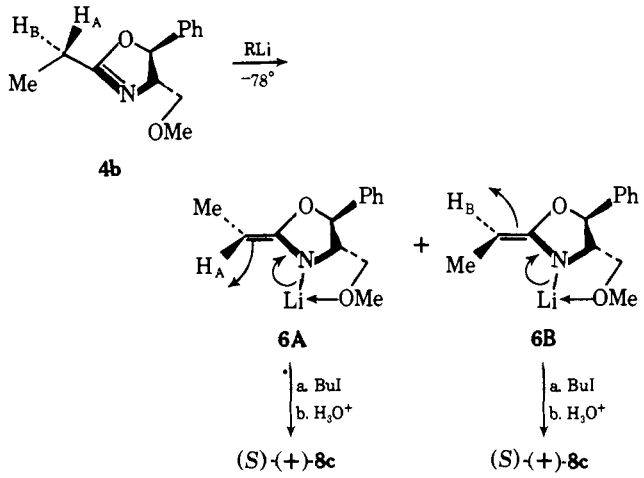
A study was made to assess which of the two steps (proton abstraction from **4b** or alkylation of **6**) was critical to the asymmetric induction leading to **7**. Since **4b** contains α-diastereotopic protons (H_A, H_B), it is possible that the proton abstraction could be kinetically stereoselective[7] furnishing the isomeric lithio salts **6A** and **6B** in highly disproportionate amounts (Scheme III). Selective alkylation of **6A** from the bottomside or selective alkylation of **6B** from the topside would lead to an enantiomeric excess of the observed (*S*)-(+)-methylhexanoic acid (**8c**). If the ratio of **6A** and **6B** varied with the temperature of metalation, this would result in a variance of the optical yields of **8c**. That the temperature of metalation was of no consequence is seen by the data in Table II. Regardless of the temperature at which the proton was removed, the optical yields for (*S*)-(+)-**8** were virtually unchanged after butylation and hydrolysis. Furthermore, the diastereotopic protons in **4b** showed complete magnetic equivalence by a clean quartet at 60 and 100 MHz at 25 to −70° indicating rapid rotation

Table II. Effect of Metalation Temperature of 4b on the Optical Purity of (*S*)-(+)-2-Methylhexanoic Acid (8c)[a]

Temp, °C	$[\alpha]^{24}_{589}$ (neat)	Optical purity, %[b]	Overall yield[c]
−22	+12.6	67	76
−45	+12.7	68	74
−64	+12.5	67	72
−78	+12.4	66	72
−98[d]	+12.5	67	75

[a] Oxazoline 4b was metalated in THF using LDA (1.05 equiv) at the indicated temperatures and allowed to stir for 30 min. The temperature for all cases was then adjusted to −78° and treated with *n*-butyl iodide immediately after the solution had reached this temperature. [b] Based upon the highest value reported for 2-methylhexanoic acid, $[\alpha]^{25}_{589}$ −18.7° (neat): P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 98, 1 (1932). [c] Based upon 4b. [d] Methanol–liquid N_2 bath.

Scheme III



at least for the NMR time scale. If proton removal was not involved in the asymmetric induction, then the alkylation must be the chiral bond-forming step. A study was performed to determine the optical purity of 2-methylhexanoic acid (**8c**) as a function of different alkylation temperatures. The results are given in Table III along with two additional examples **8a** and **8b**. From the data it is apparent that lowering the temperature of alkylation increases the degree of asymmetric induction, and this is in accord with widening the $\Delta\Delta G^{\ddagger}$ for the competing transition states which lead to the respective diastereomers in the dialkyloxazolines **7** (vide infra).

In order to gain some insight into the reasons for the highly biased approach of alkyl iodides to the chiral lithio oxazolines **6A** and/or **6B**, further experiments were performed in an effort to determine the nature of these species. The effect, if any, of the 4-(oxymethyl) substituent in **9** was investigated by varying the group on oxygen. If chelation of the lithium cation in **6** is critical to the approach of the alkyl halides, then changing the nucleophilicity of the oxygen should result in significant changes in the optical purity of the chiral acid (Scheme IV). The results of varying the oxygen substituent are given in Table IV. It is clear from the data that the OLi or ONa substituents give poor alkylation selectivity, whereas the OMe, OEt, and surprisingly $OSiMe_3$ substituents provide comparably selective alkylation. This may be interpreted by the fact that alkoxy is a more effective ligand for lithium ion than the lithio-oxy or sodio-oxy group. The effect of an alkoxy ligand on lithium cations to control stereochemical approaches in alkylations has been noted by others.[8] Furthermore, when **9** (X = Na

Table III. Effect of Alkylation Temperature on the Optical Purity of 2-Alkylalkanoic Acids 8[a]

RX	Temp, °C	$[\alpha]^{24}_{589}$ (neat)	Optical purity, %	Overall yield, %[b]
n-BuI	−30	8c +5.1	27	76
n-BuI	−45	+8.4	45	78
n-BuI	−64	+10.0	54	75
n-BuI	−78	+12.4	66	72
n-BuI	−95[c]	+14.5	78	79
n-BuI	−105[d]	+14.3	77	82
n-PrI	−78	8b +11.1	60[e]	68
n-PrI	−105	+13.1	72	79
EtI	−78	8c +12.0	68[f]	68
EtI	−105	+14.0	80	84

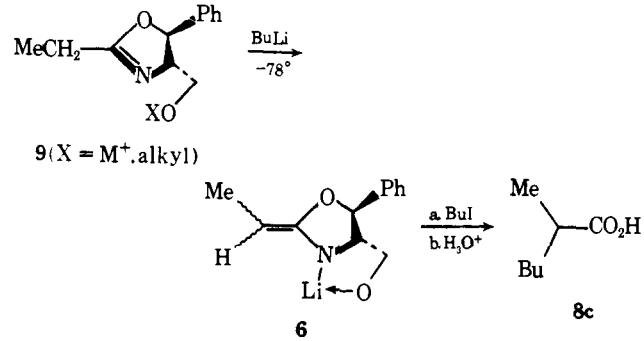
[a] Oxazoline 4b was treated with 1.05 equiv of LDA at −78° in THF, stirred for 30 min, and adjusted to the indicated temperature. After 30 min, the alkyl halide (1.05 equiv) was added (15–20 min) and the solution maintained at the indicated temperature for 4 hr, although the reactions were complete after 30 min. [b] Based on 4b. [c] Acetone–liquid N_2. [d] Ethanol–liquid N_2. [e] Based upon the highest rotation available for (*R*)-(−)-2-methylpentanoic acid, $[\alpha]^{25}_{589}$ −18.4° (neat), Levene and Marker, cf. ref *b* in Table II. [f] Based on $[\alpha]^{25}_{589}$ +17.6° (neat): Levene and Marker, cf. footnote *b* in Table II.

Table IV. Optical Purity of 2-Methylhexanoic Acid (8c) as a Function of the 4-(Oxymethyl) Substituent in 9 (Scheme IV)[a]

X	$[\alpha]^{24}_{589}$ (neat)	Optical purity, % 8c	Overall yield, % 8c
Li[b]	−1.4	7	72
Na[c]	+1.9	10	66
Et	+6.6	35	82
Me_3Si	+7.2	38	64
Me	+8.1	43	62

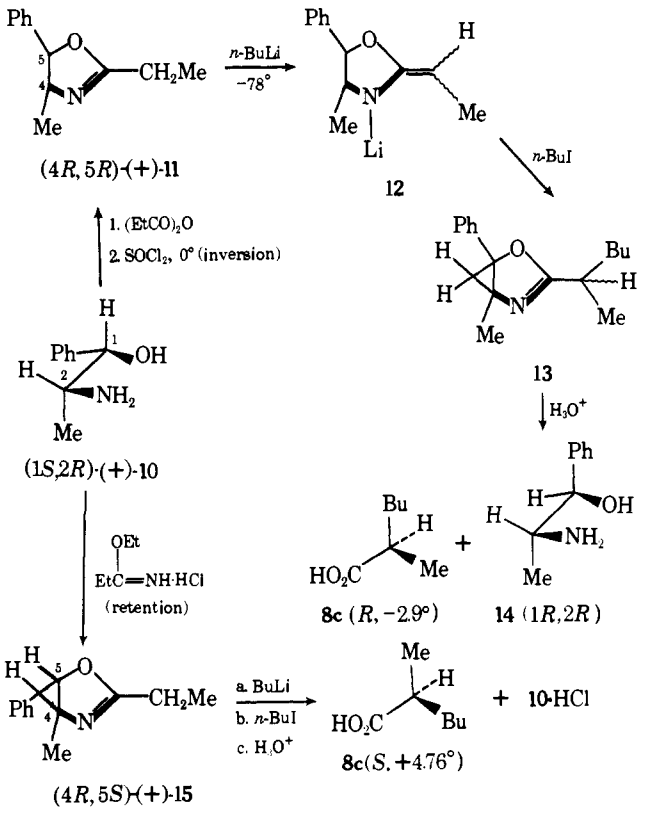
[a] Butyllithium was used as the base and metalations were carried out at −78° (THF). *n*-Butyl iodide was introduced and stirring was continued for 4 hr at −78°. Work-up was performed in the general manner (Experimental Section). [b] Prepared by treating **2b** with 2.0 equiv of *n*-butyllithium. [c] Prepared by treating **2b** with 1.0 equiv of NaH followed by addition of *n*-butyllithium.

Scheme IV



or Li) was alkylated with *n*-butyl iodide, only C-alkylation occurred. This was found to be rather general since we were unable to alkylate the oxyanion in **9** with any electrophile other than those shown in Table IV. It was concluded that the presence of the oxygen–lithium chelate in **6** (**A** or **B**) was extremely important to the asymmetric alkylation, and further proof of this hypothesis was deemed necessary. The most direct approach to gathering this evidence seemed to be low-temperature NMR studies. However, this was quite disappointing in that no firm conclusion could be reached without deuterating all of the protons in **4b** and using perdeuterated solvent (THF) and base (lithium diisopropylamide). The approach finally taken involved (1*S*,2*R*)-(+)-norephedrine (**10**) acquired by resolution[9] and transforming it into the *trans*-oxazoline **11** by successive treatment with

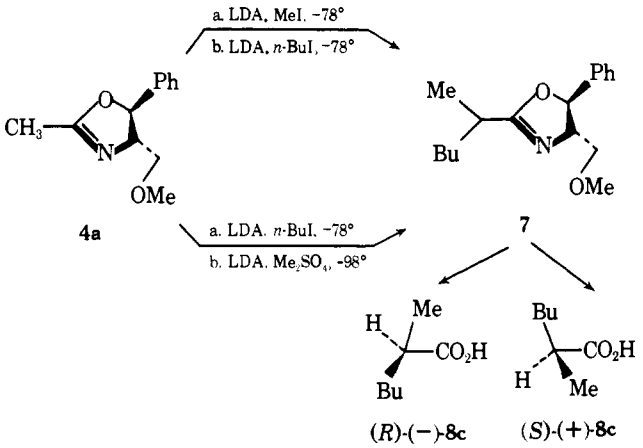
Scheme V



propionic anhydride and thionyl chloride (Scheme V). The absolute configuration of **11** was known to be related to diastereomeric (1*R*,2*R*)-**14** which in turn is configurationally related to (1*R*,2*R*)-(−)-1-phenyl-2-amino-1,3-propanediol, (−)-**1**.[4] The *trans*-oxazoline **11** arises during the thionyl chloride step which is also known to proceed with inversion at the carbinol carbon in **10**.[10] Metalation (BuLi) of **11** under the same conditions as **4b** gave a lithio oxazoline **12** which was treated with *n*-butyl iodide furnishing the oxazoline **13**. Hydrolysis of the latter gave (*R*)-(−)-2-methylhexanoic acid (**8c**) which had a rotation of only −2.9° and corresponded to an optical purity of 18%. Also isolated was the hydrochloride salt of nor-ψ-ephedrine (**14**) which has the 1*R*,2*R* configuration[10a] and is diastereomeric with the starting amino alcohol **10**, thus proving that inversion had indeed occurred during the preparation of **11**. Since **14** and (−)-**1** have the same absolute configuration,[4] this also confirms the fact that **11** and (+)-**4b** are configurationally identical except for the methoxy group[11] and may be directly compared in their relative efficiency toward asymmetric induction. The role of the methoxyl group in **4b** therefore appears to be consistent with the chelated lithium cation in **6A** and **6B** since in its absence (in **11**), the optical yield of acid is considerably lower. The relative stereochemistry of the methyl and phenyl groups was also investigated by treating **10** with the imidate of propionitrile furnishing the *cis*-4-methyl-5-phenyloxazoline (**15**) (with retention of configuration). The lithio salt was generated with *n*-butyllithium (−78°) and, after addition of *n*-butyl iodide and acid hydrolysis, gave (*S*)-(+)-2-methylhexanoic acid in 30% optical purity. Even though the asymmetric induction in the *cis*-oxazoline **15** was substantially higher than that obtained from the trans isomer **11**, it still fell considerably short of the results acquired with the methoxy-substituted oxazoline **4b**.

We next addressed ourselves to reversing the order of introduction of alkyl groups in anticipation of producing the enantiomeric acids, (−)-**8**. Alkylation of the 2-methyloxazoline **4a** with LDA–MeI, followed by LDA–*n*-BuI, gave as previously described, the (*S*)-(+)-acid **8c** in 70–75% optical purity (Scheme VI). Introduction of the *n*-butyl group onto

Scheme VI



4a followed by methyl iodide gave **7** in good yield. However, after hydrolysis, **8c** was obtained in only 20% optical purity. The use of methyl sulfate in place of methyl iodide also gave **7** in good yield and after acidic hydrolysis (*R*)-(−)-**8c** was obtained in 70% optical purity. The poorer asymmetric induction using methyl iodide as compared to using methyl sulfate indicates that the nature of the leaving group may also be important in this process. Of equal significance is the fact that it should be possible not only to prepare either enantiomer of an α-alkylalkanoic acid by merely reversing the order of substituent introduction, but *the absolute configuration may be predicted prior to the synthesis of the acids*. Thus, if the group of lower priority (Cahn-Ingold-Prelog rule) is introduced first, the acids will have the *S* configuration, while if the group of higher priority is introduced first, the acid will have the *R* configuration. This prediction has been borne out in a number of examples which are tabulated in Table V. In those cases where the rotations and/or the absolute configurations were not known, CD curves indicated that they had the same sign as related known acids, implying similar configurations (**8d, 8e, 8f, 8g**).

The overall synthetic yields of acids **8** as seen from Table V are all quite acceptable, although in certain instances (**8e, 8f, 8g, 8l**) they were only on the order of 22–40%. Nevertheless, the high optical purity of these compounds more than compensates for the poorer synthetic yields. The major difficulty in achieving high synthetic yields rests not with the alkylation step but with the hydrolytic cleavage of 2-alkyloxazolines possessing bulky side chains. Acidic cleavage of the oxazolines to the carboxylic acids required stronger acid (6 *N* H_2SO_4) and longer heating time (6–8 hr) when larger alkyl groups were present (**8d–8l**).

As mentioned earlier, the percent asymmetric induction (alkylation of the lithio oxazolines) increases in efficiency as the temperature of this step is lowered (Table III). It was also found that the asymmetric alkylation can be just as efficient at −78° as it was at −98° by a slower addition of the alkyl iodide to the chiral anion solution. Similarly, the use of more dilute solutions at −78° also gave higher asymmetric alkylation. These observations are also considered significant and will be discussed in our proposed mechanism for this process.

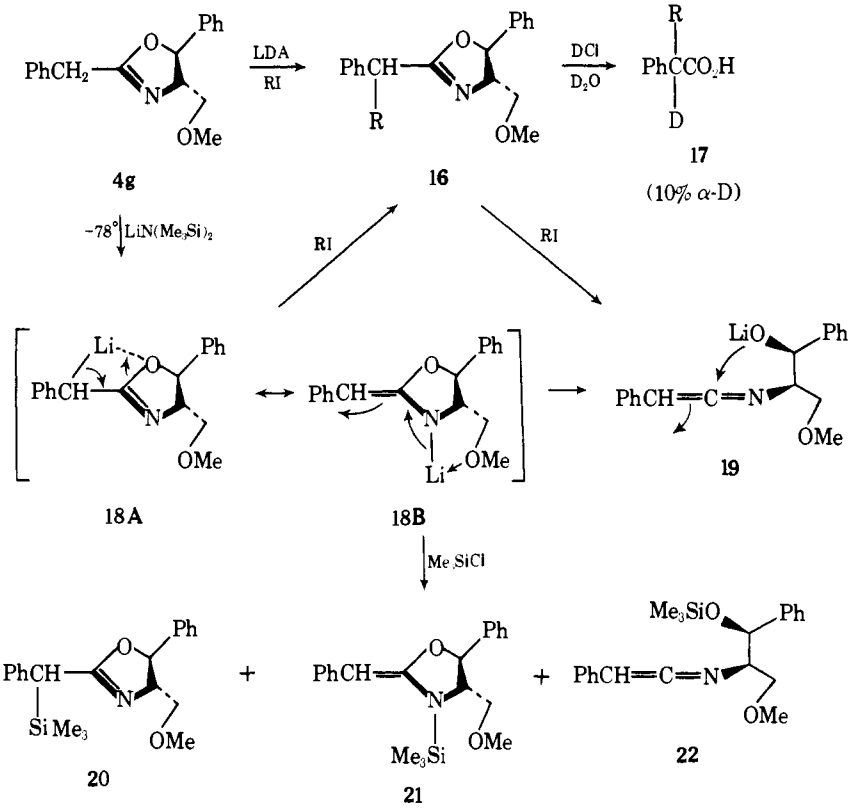
In Table V the optical yields of α-alkylphenylacetic acids **8i–8l** were generally found to be slightly lower (50–65%), and this was partly due to racemization during the hydroly-

Table V. Alkylation of Chiral Oxazolines 4 to α,α'-Dialkylacetic Acids (+)- or (−)-8

4 (R)	R'X	Alkn temp, °C	α-Alkylalkanoic acids (8) Overall[c] yield, %	$[\alpha]^{24}_{589}$[d]	$[\alpha]_{589}$	% OP[l]	Confign.[n]
Me	EtI	−98[a]	(+)-8a (84)	+14.0	+18.0[e]	78	*S*
Et	Me_2SO_4	−98	(−)-8a (83)	−14.2		79	*R*
Me	*n*-PrI	−98	(+)-8b (79)	+13.1	+18.4[e]	72	*S*
n-Pr	Me_2SO_4	−98	(−)-8b (74)	−13.2		72	*R*
Me	BuI	−78[b]	(+)-8c (65)	+14.1	+18.7[e]	75	*S*
n-Bu	Me_2SO_4	−98	(−)-8c (78)	−13.1		70	*R*
Me	$PhCH_2Cl$	−78	(+)-8d (62)	+17.3	+23.5[f]	74	*So,p*
$PhCH_2$	Me_2SO_4	−98	(−)-8d (75)	−18.2		78	*R*
Et	$PhCH_2Cl$	−78	(+)-8e (30)	+34.7[g] (*c* 8.5, C_6H_6)	+40.9[g]	85	*So,q*
$PhCH_2$	EtI	−98	(−)-8e (37)	−29.9[h] (*c* 4.5, C_6H_6)		73	*R*
n-Pr	$PhCH_2Cl$	−78	(+)-8f (30)	+26.8 (*c* 3.7, C_6H_6)		...[m]	*So,r*
$PhCH_2$	*n*-PrI	−78	(−)-8f (44)	−25.5 (*c* 4.8, C_6H_6)			*R*
n-Bu	$PhCH_2Cl$	−78	(+)-8g (41)	+18.7 (*c* 4.7, C_6H_6)	−22.8[h]	82	*So,s*
$PhCH_2$	*n*-BuI	−78	(−)-8g (39)	−19.6 (*c* 5, C_6H_6)		86	*R*
Ph	Me_2SO_4	−98	(+)-8h (59)	−45.5	−101.9[i]	45	*R*
Ph	EtI	−98	(−)-8i (42)	−48.7	−95.6[j]	51	*R*
Ph	*n*-PrI	−98	(−)-8j (57)	−42.3	−76.2[k]	56	*R*
Ph	*n*-BuI	−78	(−)-8k (38)	−37.9	−72.9[k]	52	*R*
Ph	*i*-PrI	−63	(−)-8l (22)	−40.5 (*c* 4.5, $CHCl_3$)	−62.4[t]	65	*R*

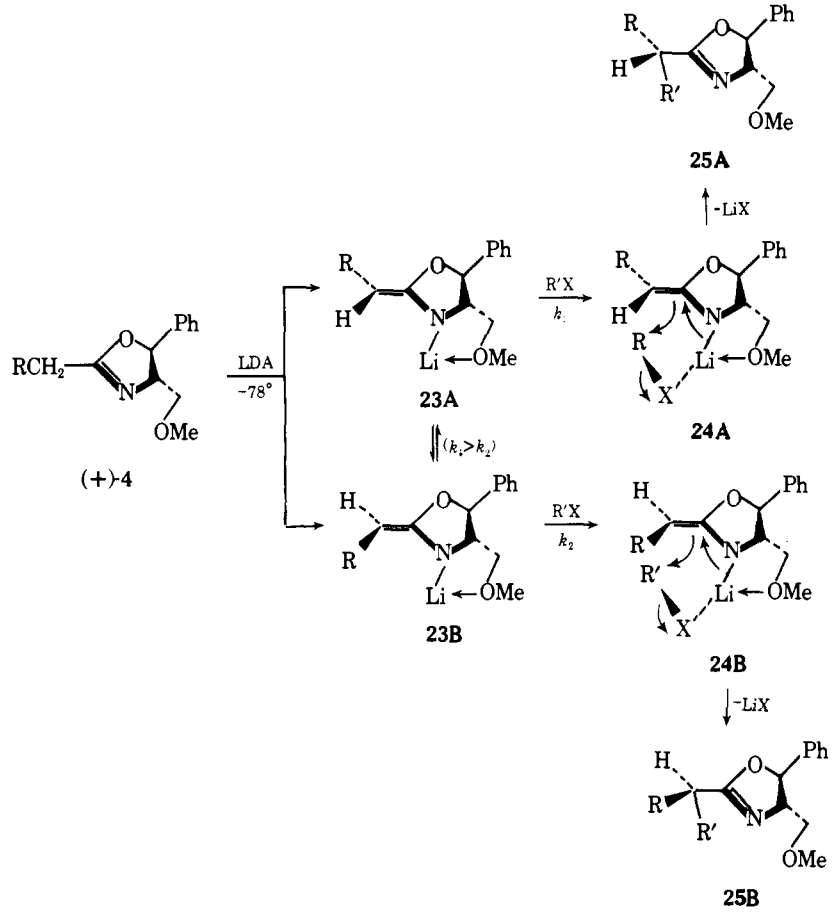
[a] Methanol–liquid nitrogen. [b] Dry ice–acetone. [c] Yields are based on 1 and have not been optimized. All acids were distilled and found to be 96+% pure as determined by VPC. [d] Optical rotations were taken neat (unless otherwise specified) so that direct comparisons with literature values could be made. [e] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 98, 1 (1932). [f] A. W. Schrecker, *J. Org. Chem.*, 22, 33 (1957). [g] R. H. Pickard and J. Yates, *J. Chem. Soc.*, 95, 1011 (1909). [h] M. B. Watson and G. W. Youngson, *J. Chem. Soc. C*, 258 (1968). [i] K. S. Y. Lau, R. W. Fries, and J. K. Stille, *J. Am. Chem. Soc.*, 96, 4983 (1974). [j] K. Petterson, *Ark. Kemi*, 10, 283 (1956). [k] K. Petterson and G. Willdeck, *ibid.*, 9, 333 (1956). [l] Optical purities are based upon the highest literature values available. [m] Rotation for optically pure material has not been reported. [n] Absolute configurations are based on the literature unless otherwise specified. [o] All gave positive CD curves at 217–219 nm (EtOH). [p] 219 nm, $[\theta] = +4200$. [q] 217 nm, $[\theta] = +4380$. [r] 217 nm, $[\theta] = +3680$. [s] 217 nm, $[\theta] = +3430$. [t] C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, 32, 2797 (1967).

Scheme VII



sis step. The increased acidity of the α-benzyl proton causes a higher degree of racemization than is found in the aliphatic chiral acid. When the hydrolysis of the oxazolines **16**, derived from the 2-benzyloxazolines **4g**, was performed in D_2O-DCl, the α-alkylphenylacetic acids **17** contained 8–10% deuterium at the α position (via NMR). When **4g** was metalated with lithium hexamethylsilazane and then quenched with trimethylchlorosilane, three alkylated products were observed: **20, 21, 22** (Scheme VII). The latter could not be isolated free from the former two products, but the ketenimine was clearly evident in the ir (2018 cm^{-1}). Oxazoline anions have been previously observed to rear-

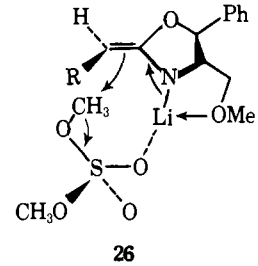
Scheme VIII



range to ketenimines under these conditions.[12] Because of the presence of the oxazoline anion **18** (**A** and **B**) and the ketenimine **19**, alkylation to **16** proceeds via both species and one of them (**19**) lacks chirality in the vicinity of the alkylation site. Although **19** forms only to the extent of 10–15%, it also contributes to the lower optical yields of the phenylacetic acids when compared to the aliphatic acids. A search to detect the ketenimine in the 2-alkyloxazolines (**4a–4f**) turned out negative. The isolation of **21** further supports the belief that the lithium cation is bound to nitrogen and chelated to the methoxy group.

Discussion

Based on the previous results presented, the following mechanism may be set forth which appears consistent with all the facts. Proton removal from (+)-**4** leads to a thermodynamic mixture of two isomeric lithio salts **23** (**A** and **B**) which are capable of interconversion (Scheme VIII). The approach of the alkyl halides takes place from the underside of **23** such that the nonbonded pairs of electrons on the halogen coordinate to the lithium cation (**24A** and **24B**). This is followed by rotation of the alkyl halide to achieve the proper alignment for an SN2 displacement. Nucleophilic displacement must occur faster in **24A** than in **24B** owing to lesser nonbonded interaction between the alkyl group attached to halide and the alkyl group present on the chiral oxazoline. If the latter process is faster ($k_1 > k_2$), this results in a shifting of the equilibrium (**23A–23B**) toward the major product of this process in a ratio of 8–9 to 1 (optical purity of **25A**, 75–85%). This mechanism is consistent with the following experimental facts: (1) the nondependence of metalation temperature on optical yield (Table II); (2) the increased optical yields with decreasing alkylation temperature (Table III) which increases k_1 over k_2; (3) the chelation of the lithium cation with the *O*-methyl group providing a chiral environment for the alkylation step; (4) the predictability of *R* vs. *S* acids by virtue of the fact that the alkyl group (*R'*) is approaching from the side opposite to the group (*R*) already present; (5) the underside approach of the incoming electrophile and methyl sulfate (or tosylate) leading to acids of higher optical purity than methyl iodide. [This fact may be rationalized by assuming that methyl iodide is too reactive (due to its size) to afford any stereoselectivity on approaching **24A** or **24B** and thus $k_1 \sim k_2$. On the other hand, the sulfate can complex with **24B** in a fashion depicted by **26** now creating a more serious interac-



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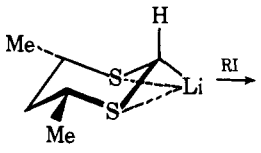
tion and causing k_1 to proceed without meaningful competition from k_2. It is also likely that methyl sulfate displaces more slowly and thus increases the selectivity of the less encumbered nucleophile **24A**.]; (6) the comparable optical yields of acids by slow (2–3 hr) or more dilute addition of alkyl halides at −78° as opposed to rapid addition (15–20 min) at 98°. This would allow the conversion of **23B** to **23A** to occur uninterrupted rather than allowing both lithio salts to react with alkyl halide at a more competitive rate.

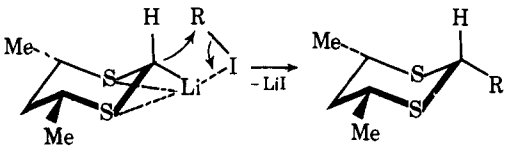
No mention has been made of the possibility of topside alkylation of **23**. In order to obtain **25A** with the observed

configurations, alkylation must occur on the topside of **23B** (since bottomside attack would lead to a predominance of **25B,** which is not observed). Examination of space-filling models indicates no topside steric preference for alkylation of **23A** or **23B** since the alkyl halide should align itself directly over the π orbitals of **23** (**A** or **B**). Furthermore, the equilibrium concentrations of **23A** and **23B** should provide an excess of **23A** due to the cisoid interactions found in **23B.** In this case, if alkylation should proceed from the topside, the product would be richer in **25B** (topside attack on **23A**), and this is not found to be the case.

An important aspect of these studies suggests that the displacement of halides from alkyl groups using organolithium reagents may originate from a halide–metal ion complex which precedes the nucleophilic substitution.[13] Eliel[14] has reported the alkylation of conformationally rigid 1,3-dithianes with very high selectivity to the equatorial isomer **29**. If the lithio dithiane is depicted as **27** with the lithium



27



28 **29**

cation coordinated to the sulfur atoms, as Eliel suggests, then the electrophile would first "complex" as shown in **28,** followed by realignment and displacement, with loss of lithium iodide to the observed equatorially substituted product **29.**

Further studies involving the chiral oxazolines are in progress and continue to be consistent with the mechanistic proposals set forth.[23]

Experimental Section[15]

General. Tetrahydrofuran was dried by reflux over the potassium ketyl of benzophenone. Lithium diisopropylamide was routinely prepared by adding, at 0°, 1.0 equiv of *n*-butyllithium (2.3 *M* in hexane) to 1.05 equiv of diisopropylamine (distilled from sodium hydride). The LDA solutions, stirred 15 min prior to use, were usually 0.5 *M*. Optical rotations were taken on a Perkin-Elmer 141 or JASCO DIP-180 polarimeter standardized daily with a known solution of (+)-menthol. Infrared spectra were taken on a Perkin-Elmer 457 instrument, NMR spectra taken on a Varian T-60 or JEOL MH-100 instrument. Butyllithium was obtained from Ventron, Inc., Beverly, Mass.

(1*S*,2*S*)-(+)-1-Phenyl-2-amino-1,3-propanediol (1) was purchased in 5-kg lots from Parke-Davis Co., Industrial Chemicals Division, Detroit, Mich., and purified prior to use by the following procedure. One hundred grams of (+)-**1** was dissolved in 100 ml of methanol and 200 ml of ethyl acetate added. Cooling in an ice bath or standing in the refrigerator overnight produced the recrystallized material which was collected by vacuum filtration. The crystalline product (80–85 g) was washed twice with cold ethyl acetate and air-dried, mp 112–113°. $[\alpha]^{22}_{589}$ +26.6° (*c* 10.0, MeOH).[4]

Ethyl iminoacetate hydrochloride, mp 107–108°, was prepared from acetonitrile as described:[16] NMR ($CDCl_3$) δ 4.93–4.47 (q, 2), 2.57 (s, 3), 1.70–1.37 (t, 3).

Ethyl iminopropionate hydrochloride was prepared from propionitrile according to the procedure[16] given for acetamido derivative: yield 86%; mp 97–98° (from methylene chloride–ether); NMR ($CDCl_3$) δ 5.00–4.50 (8, 2), 3.09–2.60 (q, 2), 1.77–1.33 (t, 3), 1.50–1.09 (t, 3).

Ethyl iminophenylacetate hydrochloride was prepared from phenylacetonitrile, ethanol, and hydrogen chloride according to the previous procedure:[16] yield 84%; mp 94° (methylene chloride–ether); NMR ($CDCl_3$) δ 7.70–7.23 (m, 5), 4.70 (q, J = 7.5 Hz, 2), 4.09 (s, 2), 1.46 (t, J = 7.5 Hz, 3).

***trans*-(4*S*,5*S*)-2-Substituted-4-hydroxymethyl-5-phenyl-2-oxazolines (2). Method A.** (1*S*,2*S*)-1-Phenyl-2-amino-1,3-propanediol [(+)-**1**, 52.2 g, 0.31 mol] was added in one portion to a solution of the imino ether hydrochloride (0.35 mol in 250 ml) in dry methylene chloride at 0°. After stirring for 6 hr at 0°, the white turbid mixture was poured into ice water (300 g). The methylene chloride layer was separated and the aqueous layer extracted twice with methylene chloride, dried ($MgSO_4$), and concentrated to give a colorless oil which solidified on standing. Crystallization from ether (ca. 300 ml) by cooling to −78° gave crystalline **2a, 2b,** or **2c** (physical data given in Table I). An additional crop of crystals (3–4 g) was obtained from the ethereal mother liquors by storing at −20° for 2–3 days.

Method A′ (DMF Solvent). A solution of 52.2 g (0.31 mol) of (+)-**1** and 0.37 mol of ethyl orthoacetate or ethyl orthopropionate, previously distilled, in 90 ml of dimethylformamide was heated to 110° for 9.5 hr and the solvent removed in vacuo. The resulting oil, which crystallized on standing, was treated with 30 ml of ether and cooled in a dry ice–acetone bath, and the crystalline material was collected. This material was dissolved in 300 ml of ether, treated with charcoal, filtered, and concentrated to 125 ml and cooled (−78°). The crystalline products (**2a** or **2b**) were washed with a small amount (~10 ml) of ether previously cooled to −78°.

Method A′ (Dichloroethane Solvent). In a second experiment, 126.5 g (0.76 mol) of (+)-**1** and 160 g (0.91 mol) of ethyl orthopropionate in 550 ml of 1,2-dichloroethane was heated under reflux for 7 hr. The solvent was removed leaving an oil (159 g) which crystallized on standing. Purification was accomplished as described for the reaction using DMF as solvent. This procedure gave 106.9 g (69%) of **2b** (physical data given in Table I).

Method B. The formation of **4b** is typical and was used also for **4a.** 2-Ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline (**2b,** 18.0 g, 88 mmol) in 150 ml of dry THF was added dropwise at room temperature to a stirred heterogeneous solution (N_2) of sodium hydride (105.3 mmol; oil removed by washing with 50 ml of dry benzene) at a rate to maintain a mild evolution of hydrogen. When addition was complete, the mixture was heated at 50–60° for 1.5 hr and cooled to ambient; a solution of methyl iodide (16.2 g, 114 mmol) in 10 ml of dry THF was added dropwise. The reaction mixture was stirred for 2 hr and slowly poured into 300 ml of ice-water, then extracted (2 × 200 ml) with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give an oil, which was distilled, in vacuo, furnishing the methoxyoxazolines **4a** and **4b** (Table I).

Method C. 2-Alkyloxazolines **4c–4f** were obtained by alkylation of **4a** using ethyl iodide, *n*-propyl iodide, *n*-butyl iodide, and benzyl chloride, respectively. The procedure for **4f** is typical. A solution of lithium diisopropylamide in THF [prepared from 7.84 g (77.5 mmol) of diisopropylamine and 33.7 ml (77.5 mmol) of *n*-butyllithium (2.3 *M* in hexane) in 70 ml dry THF] was added dropwise to a stirred solution (N_2) of 15.9 (77.5 mmol) of **4a** in 200 ml of THF at −78° over 30 min. The mixture was stirred for 45 min at −78° and a solution of benzyl chloride (11.77 g, 93.0 mmol) in 40 ml of THF was added slowly (2–3 hr). After complete addition, the mixture was stirred an additional 4 hr and then allowed to slowly warm to −50° (to avoid polyalkylation) and quenched by pouring into ice-water. The aqueous mixture was extracted (3 × 150 ml) with ether and the combined ether extracts were then washed with saturated brine, dried ($MgSO_4$ or Na_2SO_4), and concentrated. The pure oxazoline was obtained by distillation and verified by gas chromatography (99+% purity) (physical data in Table I).

Method D. A mixture of 42.4 g (0.212 mol) of ethyl iminophenylacetate hydrochloride (from phenylacetonitrile, ethanol, and HCl) and 35.0 g (0.193 mol) of (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol [(+)-**5**] in 350 ml of dichloromethane was stirred at room temperature for 11 hr. The reaction mixture was poured into ice-water and the organic layer separated. The aqueous layer was extracted (2 × 50 ml) with dichloromethane, and the combined extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated leaving 53.7 g of an oil, which con-

tained 89% **4g** (by VPC) and small amounts of ethyl phenylacetate and phenylacetamide. Distillation gave pure material (>99.5% VPC) (Table I, **4g**).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.80; H, 6.81. Found: C, 76.19; H, 6.77.

(1*S*,2*S*)-(+)-1-Phenyl-2-amino-3-methoxy-1-propanol (5). Hydrolysis of the oxazolines **4** using 3 *N* HCl, reflux 2–3 hr, or 6 *N* H_2SO_4, reflux 5–7 hr (depending upon the bulk of the 2-substituent), and rendering the acid solution alkaline to pH 10 with sodium or potassium hydroxide, gave an oil. Extraction with ether, drying ($MgSO_4$), and concentration gave **5** in 82–88% yield as an oil which crystallized on standing: mp 48.5–50.0° (from ether); $[\alpha]^{23}_{589}$ + 24.4° (*c* 10.6, $CHCl_3$); NMR ($CDCl_3$) δ 7.33 (s, 5), 4.60 (d, J = 6 Hz, 1), 3.50–3.23 (m, 2), 3.23–2.87 (quintet, 1), 2.67–2.33 (br s, 3, exchanges with D_2O).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 66.53; H, 8.48.

General Procedures. The following are typical procedures for the preparation of *S* and *R* acids **8**.

(*S*)-(+)-2-Methylhexanoic Acid [(+)-8c]. Alkylation of 4b at −98°. A solution of 15.4 g (70 mmol) of (4*S*,5*S*)-2-ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (**4b**) in 160 ml of dry THF under nitrogen was cooled to −78° with a dry ice–acetone bath. To this was added a solution of 70 mmol of lithium diisopropylamide (LDA) (from 9.8 ml of diisopropylamine and 33 ml of 2.2 *M* *n*-butyllithium in 75 ml of THF) over a 20-min period. The resulting yellow solution was stirred for 40 min at −78°, and then the cooling bath was changed to methanol–liquid nitrogen and the reaction mixture allowed to cool to −98° for 30 min. A solution of *n*-butyl iodide (14.7g, 80 mmol) in 20 ml of THF was added dropwise over 15–20 min at −98° and the resulting, almost colorless solution was stirred at this temperature for 2 hr, then slowly allowed to reach room temperature. The reaction mixture was poured into 300 ml of saturated brine and extracted (2 × 150 ml) with ether, dried ($MgSO_4$), and concentrated to give 17.7 g (92%) of **7**. Although the crude material could be used in the hydrolysis to the carboxylic acid **9c**, a small portion was distilled (bulb-to-bulb) to give analytically pure **7**: $[\alpha]^{24}_{589}$ −35.2° (*c* 10.1, $CHCl_3$); ir (film) 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5), 5.33 (d, J = 7 Hz, 1), 4.33–3.93 (q, 1), 3.80–3.33 (m, 2), 3.43 (s, 3), 2.87–2.33 (m, 1), 2.00–0.67 (m, 12).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.01; H, 9.18.

The crude oxazoline **7** (17.2 g) was dissolved in 250 ml of 4 *N* sulfuric acid and heated to reflux for 3.5 hr, at which time the solution became homogeneous. When the heating of the solution was initiated, a crystalline solid appeared which slowly dissolved as the reflux progressed. This solid material is the amino ester hydrochloride described earlier.[3] After the heating was discontinued, the solution was cooled to room temperature and extracted with ether (3 × 75 ml). The combined ether extracts were washed with 5% aqueous potassium carbonate (3 × 100 ml) and the aqueous extracts neutralized to pH 1 with 12 *M* hydrochloric acid. The resulting turbid mixture was extracted with ether (3 × 75 ml) and dried ($MgSO_4$). Concentration of the ethereal solution left an oil which was distilled (bulb-to-bulb) to give 5.80 g (66% based on **4b**) of pure (*S*)-(+)-2-methylhexanoic acid (**8c**, Table V). VPC analysis (10% UCW-98) indicated only a single component; $[\alpha]^{24}_{589}$ +14.5° (neat) 78% OP; ir (film) 3000, 1710 cm^{-1}.

Alkylation of 4b at −78°. A solution of 15.4 g of **4b** in 600 ml of dry THF was treated as above with LDA at −78°, and after 1 hr a solution of 14.7 g of *n*-butyl iodide in 100 ml of THF was added over a 4-hr period. The resulting mixture was stirred for 3 hr at −78° and worked up in the same manner as described above: yield, 5.56 g (61%) of (*S*)-(+)-2-methylhexanoic acid, $[\alpha]^{24}_{589}$ +14.1° (neat).

(*R*)-(−)-2-Methylhexanoic Acid [(−)-8c]. A solution of LDA (18 mmol) in THF (50 ml) was added dropwise to a stirred solution of 18 mmol of 2-methyloxazoline (**4a**) (Table I) in 75 ml of THF at −78°. After 30 min, the resulting yellow solution was treated with 18.5 mmol of *n*-butyl iodide added dropwise over 10 min. Stirring was continued for 4 hr and the solution allowed to warm to ambient. The reaction contents were poured into ice-water (150 ml) and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and concentrated leaving an amber oil which was distilled (bulb-to-bulb) to give **4e** (Table I).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.46; H, 8.89. Acidic hydrolysis as above gave (−)-**8c** (Table V).

(*R*)-(−)-2-Benzylhexanoic Acid [(−)-8g]. 2-Phenethyloxazoline (**4f**) (4.60 g, 15.6 mmol) in 65 ml of THF was treated with LDA (15.6 mmol) in 15 ml of THF at −78° and stirred for 30 min. The mixture was then cooled to −100° (ethanol–liquid nitrogen) and kept at this temperature for 20 min. A solution of 3.45 g (18.7 mmol) of *n*-butyl iodide in 15 ml of THF was added dropwise over a period of 25 min, and stirring was continued at −100° for 5.8 hr; then the mixture was allowed to warm to −78°, packed in dry ice–acetone, and stirred overnight (12 hr). The reaction was quenched in ice-water, extracted with ether, dried, and concentrated leaving 5.90 g of a light yellow oil. The crude oxazoline was heated under reflux with 100 ml of 6 *N* sulfuric acid for 8 hr. After cooling, the aqueous solution was extracted with ether, the latter washed with 5% potassium carbonate to remove the acid, and the aqueous solution acidified. Extraction of the acidic solution (3 × 50 ml) with ether, drying, and evaporation gave an oil, which on distillation at 114–116° (0.15 mm) furnished 1.26 g (39% based on **4f**) of (−)-**8g** (Table V).

One Pot Sequential Alkylations. (*S*)-(+)-2-Benzylbutanoic Acid [(+)-8e]. A solution of LDA in THF [prepared from 2.02 g (20 mmol) of diisopropylamine and 8.3 ml (20 mmol) of *n*-butyllithium (2.4 *M* in hexane) in 15 ml of THF] was added over 15 min to a stirred solution of 4.11 g (20 mmol) of 2-methyloxazoline (**4a**) in 50 ml of dry THF at −78°. After stirring for 30 min, 3.28 g (21 mmol) of ethyl iodide in 15 ml of THF was added during 20 min and stirred an additional 3 hr while maintaining the −78° bath throughout the procedure. A second portion of LDA (20 mmol) was then added over 15 min and after stirring for 30 min, 3.03 g (24 mmol) of benzyl chloride in 15 ml of THF was added dropwise. The reaction mixture was kept at −78° for 17 hr (packed in dry ice–acetone) and then poured into 300 ml of water. The aqueous mixture was extracted (3 × 100 ml) with ether. The ether extracts were washed successively with dilute sodium thiosulfate and saturated sodium chloride solutions, dried ($MgSO_4$), and evaporated. The unreacted benzyl chloride was readily removed from the crude product at 0.05 mm and 90°. The residue, 6.76 g, was heated under reflux with 100 ml of 6 *N* sulfuric acid, and the separated oil was removed by ether extraction. The latter was shaken with 5% potassium carbonate and the aqueous solution acidified with 6 *N* sulfuric acid. Ether extraction of the acidified solution and drying of the extracts gave 2.02 g of an oil which was distilled, bp 93–94° (0.05 mm), furnishing 1.05 g (29.3% overall based on **4a**) of (+)-**8e**. VPC indicated 98.3% purity, $[\alpha]^{24}_{589}$ +34.67° (*c* 8.45, benzene). This corresponds to an optical purity of 84.6% (Table V).

(*R*)-(−)-2-Phenylbutanoic Acid [(−)-8i]. A solution of 5.0 g (17.8 mmol) of **4g** in 80 ml of THF was treated with 17.8 mmol of LDA in 15 ml of THF at −78° and stirred for 15 min prior to cooling to −100° with an ethanol–liquid nitrogen bath. After 30 min, a solution of 3.05 g (19.6 mmol) of ethyl iodide in 25 ml of THF was added at −100° over a period of 1.25 hr. Stirring was continued for 4 hr, and the solution was allowed to warm to −76° and kept at this temperature overnight by a well-packed dry ice–acetone bath. The reaction was quenched in 300 ml of water and the oxazoline product (5.30 g) isolated in the usual manner. The crude oxazoline was heated to reflux in 100 ml of 6 *N* sulfuric acid for 4.5 hr, and the crude acid (−)-**8i** was isolated as previously described. The yield was 1.23 g (42% based on **4g**) of an oil (97.5% purity by VPC), bp 76–77° (0.04 mm), d^{24} 1.0580, $[\alpha]^{24}_{589}$ −48.68° (neat) (Table V).

Optical Stability of (−)-α-Phenylhexanoic Acid (8k). A solution containing 1.06 g of **8k** [$[\alpha]^{24}_{589}$ −36.90° (*c* 6.07, ethanol)] in 40 ml of 6 *N* sulfuric acid was heated to reflux for 7 hr. The solution was then extracted with ether, dried, and concentrated to give 1.05 g of a colorless oil which had $[\alpha]^{24}_{589}$ −36.07° (*c* 7.18, ethanol).

Deuterium Exchange of (−)-α-Phenylbutanoic Acid [8i; 17 (R = Et)]. A solution containing 8 ml of DCl [prepared from 12.8 ml of acetyl chloride and 17.2 ml of D_2O at room temperature (N_2)] and 351 mg of **8i** [$[\alpha]^{24}_{589}$ −10.83° (*c* 5.17, benzene)] was heated under reflux for 5 hr. The acid was recovered by ethereal extraction and gave 285 mg of an oil which was molecularly distilled, $[\alpha]^{24}_{589}$ −10.40° (*c* 5.29, benzene). NMR analysis indicated the deuterium incorporation at the α position was 5%.

Deuterium Exchange and Racemization of 16 (R = Et). A solution of **16** [$[\alpha]^{24}_{589}$ −17.59° (*c* 8.98, ethanol)], 850 mg, in 20 ml

of DCl solution prepared as above, was heated to reflux for 2 hr. Isolation of α-phenylbutyric acid, 299 mg, showed $[\alpha]^{24}_{589}$ −17.95° (*c* 5.46, benzene), which was 90–92% pure by VPC. NMR indicated an α-deuterium content to be 8–10%.

Reaction of 4g with Lithiohexamethyldisilazane and Trimethylchlorosilane. Formation of 20, 21, and 22. To a stirred solution of 3.39 g (21 mmol) of hexamethyldisilazane in 12 ml of dry ether was added a solution of 8.5 ml (19.5 mmol) of *n*-butyllithium. The resulting mixture was heated under reflux for 30 min, and then the solvent was distilled off under a stream of dry nitrogen.[17] The residual solid was dissolved in 20 ml of THF and added dropwise (15 min) to a cooled solution of 4.22 g (15 mmol) of 2-benzyloxazoline (**4g**) in 53 ml of dry THF in an ice-salt bath. The resulting mixture was allowed to warm to room temperature (ca. 2.5 hr) and then recooled to 0°.

After the addition of 2.28 g (21 mmol) of trimethylchlorosilane in 8 ml of THF was complete, the mixture was allowed to warm to ambient. The solvent was removed in vacuo, and the residue was treated with CCl_4. The precipitated solid was removed by suction, and the filtrate was evaporated to yield 7.09 g of a dark brown oil; ir (neat); 2018 cm^{-1} (C=C=N, sharp).

The crude oil, 2.73 g, was distilled (bulb-to-bulb) at a bath temperature of ~123° (0.01 mm), and the distillate was redistilled at a bath temperature of ~111° (0.01 mm) to give 0.50 g of a colorless oil, **20, 21,** and **22** as seen by ir and NMR. A second fraction, 0.72 g, also contained a mixture of **21** (ca. 90%), **22,** and **20** as analyzed by ir and NMR: ir (neat) 2018 (C=C=N), 1660 (s, sh), and 1640 cm^{-1} (s), C=N, C=C, respectively; NMR (CCl_4) δ 0.05 (s, C-$SiMe_3$) 0.18 (s, N-$SiMe_3$), 3.36 (s, OMe), 4.52 (s, PhC*H*=C), 5.20 (d, *J* = 6 Hz, O-C*H*-Ph), ~6.6–7.5 (m, overlapped, *Ph*C=C), 7.23 (s, overlapped, O-CH-*Ph*).

(1*S*,2*R*)-(+)-Norephedrine (10). Resolution of (±)-norephedrine was accomplished via its tartrate salt.[9,18] The (+)-enantiomer **10** [$[\alpha]^{24}_{589}$ +14.15° (*c* 9.82, ethanol) 95.9% optically pure] was isolated in 13.2% yield after four recrystallizations of the bitartrate salt [$[\alpha]^{24}_{589}$ +32.25° (*c* 10.17, H_2O)]. Release of the free base **10** was performed using 5% sodium hydroxide, mp 51–52° (lit.[9] 52°).

***cis*-(4*R*,5*S*)-(+)-2-Ethyl-4-methyl-5-phenyl-2-oxazoline (15).** To a mixture of 3.52 g (23.3 mmol) of (+)-**10** [$[\alpha]^{24}_{589}$ +14.15°] and 3.85 g (28 mmol) of ethyl iminopropionate hydrochloride in 20 ml of dry dichloromethane was slowly added 2.39 g of dry pyridine at 0°. The reaction mixture was stirred overnight at room temperature and poured into 50 ml of ice-water. The organic layer was separated and the aqueous layer extracted (3 × 30 ml) with dichloromethane. The combined organic extracts were dried (K_2CO_3) and evaporated leaving 6.1 g of a yellow oil. Distillation, bp 95–97° (2 mm), gave 3.52 g (79.9%) of **15,** 99.4% pure by VPC; $[\alpha]^{24}_{589}$ +220.90° (*c* 10.48, ethanol); ir (film) 1670 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (d, *J* = 7 Hz, 3), 1.30 (t, *J* = 8 Hz, 3), 2.45 (m, 2), 4.13–4.73 (m, 1), 5.56 (d, *J* = 10 Hz, 1), 7.3 (m, 5).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 75.88; H, 8.22.

Metalation and Butylation of (+)-15. Preparation of (*S*)-(+)-2-Methylhexanoic Acid [(+)-8c]. A solution (N_2) containing 3.28 g (17 mmol) of **15** in 30 ml of THF was treated at −78° with 12.1 ml (19 mmol) of 15% *n*-butyllithium in hexane.[19] After 1 hr, a solution of 3.52 g (19 mmol) of *n*-butyl iodide in 10 ml of THF was added during 10 min and the reaction slowly allowed to warm to room temperature (5 hr). Work-up, as described in the General Procedure, gave 4.8 g of 2-(2-hexyl)-4-methyl-5-phenyl-2-oxazoline, as a yellow oil. Distillation, bp 94–95° (0.2 mm), provided 3.60 g (84.7%) of the oxazoline, 98.3% pure by VPC; $[\alpha]^{24}_{589}$ +197.45° (*c* 10.19, ethanol); ir (film) 1668 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (d, *J* = 7 Hz, 3), 0.93 (t, *J* = 5 Hz, 3), 2.3–2.9 (m, 1), 4.1–4.7 (m, 1), 5.56 (d, *J* = 10 Hz, 1), 7.3 (m, 5).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.23; H, 9.45. Found: C, 78.16; H, 9.46.

Hydrolysis of the above oxazoline was accomplished by heating a mixture of 1.517 g (6.2 mmol) in 30 ml 3 *N* hydrochloric acid for 2.5 hr. The tan oil was removed by extraction with ether, dried ($MgSO_4$), and concentrated leaving 812 mg of an oil. Molecular distillation (0.15 mm, bath temperature 60–70°) gave 606 mg (75.3%) of (+)-**8c,** 97.6% pure by VPC, $[\alpha]^{24}_{589}$ +4.76° (*c* 10.72, $CHCl_3$). Based upon **15** having an optical purity of 95.9% and optically pure **8c** showing $[\alpha]^{24}_{589}$ 15.9° (*c* 11, $CHCl_3$),[20] the value of +4.76° corresponds to an optical purity for **8c** of 29.9%.[21]

The aqueous solution from above was concentrated under reduced pressure giving a white solid which was dissolved in ethanol and treated dropwise with ether. The precipitated salt, 773 mg (66.6%) of (+)-norephedrine (**10**), had mp 171–172° and $[\alpha]^{24}_{589}$ +32.89° (*c* 9.67, H_2O) indicating no change in the stereochemistry of (+)-norephedrine used to prepare the oxazoline **15.**

***trans*-(4*R*,5*R*)-(+)-2-Ethyl-4-methyl-5-phenyl-2-oxazoline (11).** To a cooled suspension (0°) of 3.07 g (20 mmol) of (+)-**10** [$[\alpha]^{24}_{589}$ +12.29° (*c* 10.0, ethanol), 83.3% optical purity] in 30 ml of ether was added 3.17 g (24 mmol) of propionic anhydride and 3.4 g of solid sodium bicarbonate in portions at a rate such that the pH of the two-phase system was between 7 and 8. The reaction mixture was stirred at 25° for 45 min and then extracted with ethyl acetate (3 × 50 ml). The combined extract was washed successively with dilute hydrochloric acid and saturated brine, dried ($MgSO_4$), and concentrated leaving 3.81 g (90.5%) of crystalline material. Recrystallization (benzene–petroleum ether) gave pure *n*-(propionyl)norephedrine: mp 107.5–108.5°; $[\alpha]^{24}_{589}$ +26.72° (*c* 2.62, ethanol); ir (Nujol) 3320, 1652 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (d, *J* = 7 Hz, 3), 1.1 (t, *J* = 7 Hz, 3), 2.16 (m, 2), 4.0–4.6 (m, 2), 4.83 (d, *J* = 3 Hz, 1), 6.16 (d, *J* = 7 Hz, 1), 7.3 (s, 5).

This amide (4.50 g, 21.7 mmol) was suspended in 70 ml of dry dichloromethane and treated (−10°) dropwise with a solution of 5.95 g (49.9 mmol) of thionyl chloride in 10 ml of dry dichloromethane. After stirring at 0 to −5° for 40 min, 90 ml of cold 20% aqueous potassium carbonate was added and the organic layer separated. The aqueous solution was extracted with dichloromethane and the combined dichloromethane solutions were dried ($MgSO_4$) and evaporated leaving 4.7 g of an oil. Distillation, bp 88–90° (1.6 mm) gave 3.18 g (77.4%; 99% purity by VPC) of **11:** $[\alpha]^{24}_{589}$ +80.59° (*c* 9.89, ethanol); ir (film) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.5 Hz, 3), 1.36 (d, *J* = 6 Hz, 3), 2.1–2.66 (m, 2), 3.7–4.3 (m, 1), 4.9 (d, *J* = 8 Hz, 1), 7.3 (s, 5).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 75.89; H, 8.22.

***trans*-(4*R*,5*R*)-(+)-2-(2-Hexyl)-4-methyl-5-phenyl-2-oxazoline (13).** The conditions were the same as described for the metalation and butylation of **15** using the following quantities: 30 ml of THF, 7.5 ml of *n*-butyllithium (2.25 *M*), 3.13 g of *n*-butyl iodide. Work-up furnished 2.97 g (78.8%) of **13,** 99% pure by VPC: bp 82–84° (0.1 mm); $[\alpha]^{24}_{589}$ +50.40° (*c* 3.73, ethanol); ir (film) 1668 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, *J* = 4.5 Hz, 3), 1.3 (d, *J* = 7 Hz, 3), 1.4 (d, *J* = 6 Hz, 3), 2.2–2.8 (m, 1), 3.7–4.3 (m, 1), 4.9 (d, *J* = 8 Hz, 1), 7.33 (s, 5).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.23; H, 9.45. Found: C, 78.05; H, 9.64.

Hydrolysis of 13 to (−)-8c. A mixture of (+)-**13** (1.506 g) in 50 ml of 3 *N* hydrochloric acid was heated to reflux for 3 hr, and the separated oil was removed by ether extraction. Drying ($MgSO_4$) and concentration left 753 mg of an oil which was molecularly distilled at 0.15 mm (bath temperature 60–70°) furnishing 599 mg (75%) of a 2-methylhexanoic acid (83% pure by VPC), $[\alpha]^{24}_{589}$ −2.01 (*c* 9.93 $CHCl_3$). This rotation corresponded to an [α] of −2.90° based upon the optical purity of 83.3% for (+)-**10** and a chemical purity for the acid **8c** of 82.9%. Correcting for these values, the optical purity of (−)-**8c** was 18%.[22]

The aqueous solution from the hydrolysis was evaporated to produce a colorless solid which was recrystallized from ethanol–ether to give 743 mg (64.6%) of the hydrochloride of **14:** mp 177–181°, $[\alpha]^{24}_{589}$ −40.66° (*c* 9.74, H_2O), lit.[9] mp 180–181°; $[\alpha]^{20}_{589}$ −42.68° (H_2O).

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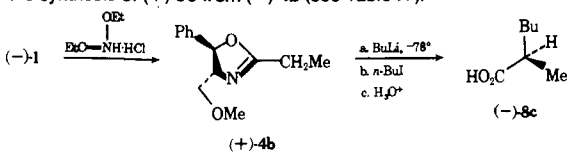

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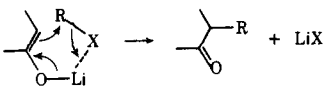

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(21) Shorter hydrolysis time (3 *N* HCl, 1 hr) gave (+)-**8c** in 36% optical yield, but the chemical yield was only 42%. Thus, racemization of the intermediate amino ester is enhanced with longer hydrolysis times (cf. ref 3).
(22) Hydrolysis was also performed in a stepwise acid–base–acid manner[3] with no significant increase in optical purity.
(23) Some recently published studies wherein the underside attack of the electrophile are consistent with the observed steric course of the reaction are: A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975); A. I. Meyers and K. Kamata, *ibid.*, **39**, 1603 (1974); A. I. Meyers, E. D. Mihelich, and K. Kamata, *Chem. Commun.*, 768 (1974).

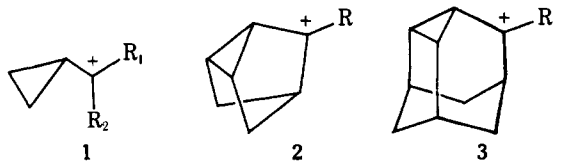
Stable Carbocations. 184.[1a] 2,4-Dehydro-5-homoadamantyl Cations

George A. Olah,* [1b] Gao Liang,[1b] Kevin A. Babiak,[1c] Thomas K. Morgan, Jr.,[1c] and Roger K. Murray, Jr.* [1c]

Contribution from the Departments of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, and University of Delaware, Newark, Delaware 19711. *Received April 14, 1975*

Abstract: The parent secondary 2,4-dehydro-5-homoadamantyl cation (**4**) has been prepared under stable ion conditions from both 5-*endo*-hydroxy-2,4-dehydrohomoadamantane and 2-*endo*-hydroxyhomoadamant-4-ene. Examination of cation **4** by ^{1}H and ^{13}C NMR spectroscopy shows that, although **4** is static at −120°C, upon warming to −60°C it undergoes a degenerate cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement. The static tertiary 5-methyl-2,4-dehydro-5-homoadamantyl and 5-phenyl-2,4-dehydro-5-homoadamantyl cations (**7** and **10**) have been prepared under stable ion conditions at low temperature from both the corresponding tertiary alcohols and, unexpectedly, from 2-*endo*-hydroxy-2-*exo*-methylhomoadamant-4-ene and 2-*endo*-hydroxy-2-*exo*-phenylhomoadamant-4-ene, respectively. Ions **7** and **10** have been characterized by ^{1}H and ^{13}C NMR spectroscopy. Ions **4**, **7**, and **10** are all classical carbenium ions with varying degrees of charge delocalization into the cyclopropane ring. Mechanisms are proposed to account for the degenerate rearrangement of ion **4** and for the formation of 2,4-dehydro-5-homoadamantyl cations from 2-homoadamant-4-enyl precursors.

The rapid interconversion of cyclopropylcarbinyl, cyclobutyl, and homoallyl derivatives in solvolytic systems has attracted considerable attention.[2] We have previously reported the direct observation of a series of cyclopropylcarbinyl cations **1** under stable ion conditions.[3] This work has been extended to the study of cyclopropylcarbinyl cations with rigid carbon skeletons, such as the 3-nortricyclyl cations **2**.[4] More recently, we have shown that both secondary and tertiary 8,9-dehydro-2-adamantyl cations **3** are of a carbenium ion nature with charge delocalization into the cyclopropane ring.[5] We now report the continuation of our studies with secondary and tertiary 2,4-dehydro-5-homoadamantyl cations which are homologous with **3**.



1 2 3

Results and Discussion

The parent 2,4-dehydro-5-homoadamantyl cation (**4**) was prepared from alcohol **5**[6] in FSO_3H-SO_2ClF (SO_2) so-