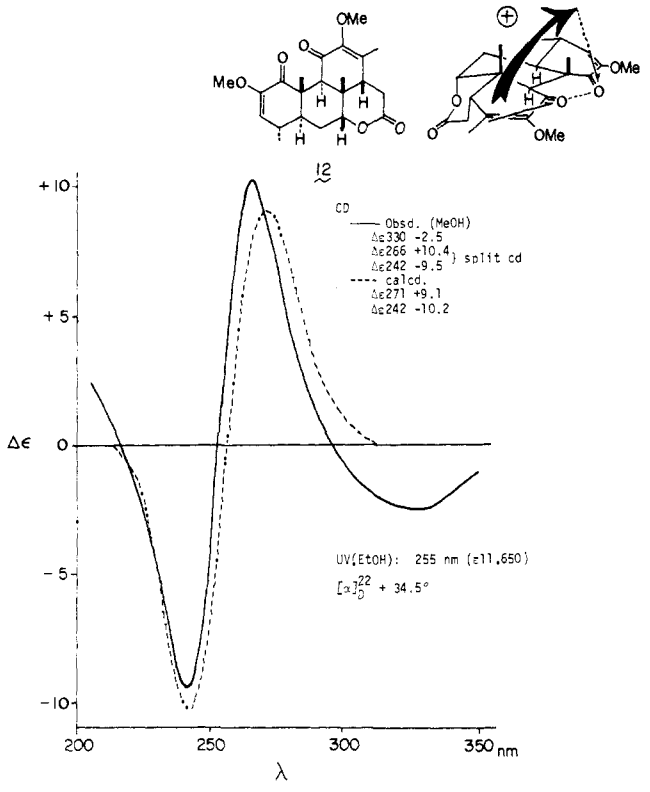


Figure 2. Circular dichroism spectra of quassin **12**: (—) observed in methanol, (-----) calculated.

The absolute configuration of plant bitter principles, the decanortriterpenoids exemplified by quassin, **12**,[7] is based on biosynthetic considerations and X-ray analysis of biogenetically related compounds.[8]

The excellent agreement seen between the observed and calculated cd curves of quassin (Figure 2) not only establishes the absolute configuration of quassin itself but also proves that the observed cd of quassin around 250 nm is due to exciton splitting.[9]

Values of transition dipole $r$ and $1/e$-width $\Delta\sigma$ of the $\alpha$-methoxy-$\alpha,\beta$-enone were obtained from the uv of 3-methoxycholest-3-en-2-one in ethanol ($r$ = 0.628 Å, $\Delta\sigma$ = 3043.0 cm$^{-1}$), and the wave number of the transition $\sigma_{max}$ was approximated with that of quassin itself ($\sigma_{max}$ = 39,215.6 cm$^{-1}$). The coordinate of each atom was determined by assuming that the B ring adopts an ideal chair conformation and the enone system is planar. The point dipole was assumed to be located at the mid point of the central single bond in the enone. The $\pi$–$\pi^*$ transition dipole direction was estimated by the Pariser–Parr–Pople molecular orbital method ($\theta$ = 44.83°, Figure 3).

The examples given clearly indicate the wide applicability of the exciton chirality method to conjugated enones, esters, and lactones and obviously to numerous other chromophores. The chromophores can be present in the molecule or can be introduced by derivatization. Finally, when employing the benzoate rule[10] (based on single measurements at sodium D line) to deduce the absolute configuration of secondary hydroxyl groups, great caution should be taken to ascertain that the benzoate group is not interacting with nearby chromophores.

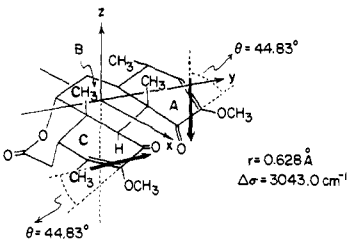


Figure 3. The positions of two transition dipoles in quassin **12**.

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(11) On leave of absence from Chemical Research Institute of Nonaqueous Solutions, Tohoku University, Sendai, Japan.

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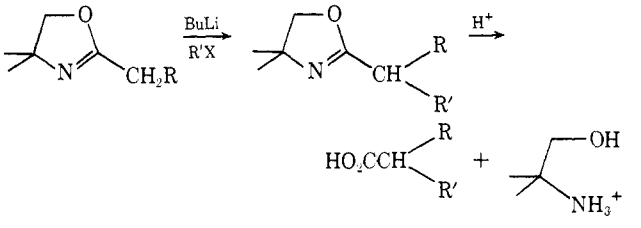
## Synthesis *via* 2-Oxazolines. IV. An Asymmetric Synthesis of 2-Methylalkanoic Acids from a Chiral Oxazoline

*Sir:*

We wish to report an asymmetric synthesis of 2-methylalkanoic acids, **6**, which leads to either the *S*-(+) or *R*-(−) enantiomers in *optical yields of 73–84%* and, furthermore, allows recovery of the chiral reagent for recycling purposes. The method relies on our earlier observation[1] that 2-oxazolines may be elaborated to higher homologs which are hydrolyzed to $\alpha$-alkylated carboxylic acids (Scheme I). If the latter scheme could

**Scheme I**




be implemented with a chiral heterocycle of high optical purity, the potential exists for transferring its chirality to the alkylated side chain and, hence, upon hydrolysis would provide optically active $\alpha$-substituted alkanoic acids. The sequence which follows bears out this prediction.

Condensation of the readily available[2,3] (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol (**1**) ([$\alpha$]$^{22}$°D

(7) J. D. Connolly, K. H. Overton, and J. Polonsky, *Progr. Phytochem.*, **2**, 385 (1970).

(8) W. A. C. Brown and G. A. Sim, *Proc. Chem. Soc., London*, 293 (1964).

(9) The *negative* cd at 320 nm is due to the n–$\pi^*$ transition. However, the D line rotation is *positive* because of the strongly positive extremum at 266 nm.

(10) J. H. Brewster, *Tetrahedron*, **13**, 106 (1961).

(1) A. I. Meyers and D. L. Temple, *J. Amer. Chem. Soc.*, **92**, 6644, 6646 (1970).

(2) The authors are grateful to Drs. George Moersch and Harry Crooks of Parke-Davis, Ann Arbor, Mich. for generous samples of (+)- and (−)-**1**. The (+) enantiomer is available commercially from Strem Chemicals, Inc., Danvers, Mass.

(3) The absolute configuration of (−)-**1** has been determined: J. D. Dunitz, *J. Amer. Chem. Soc.*, **74**, 995 (1952).

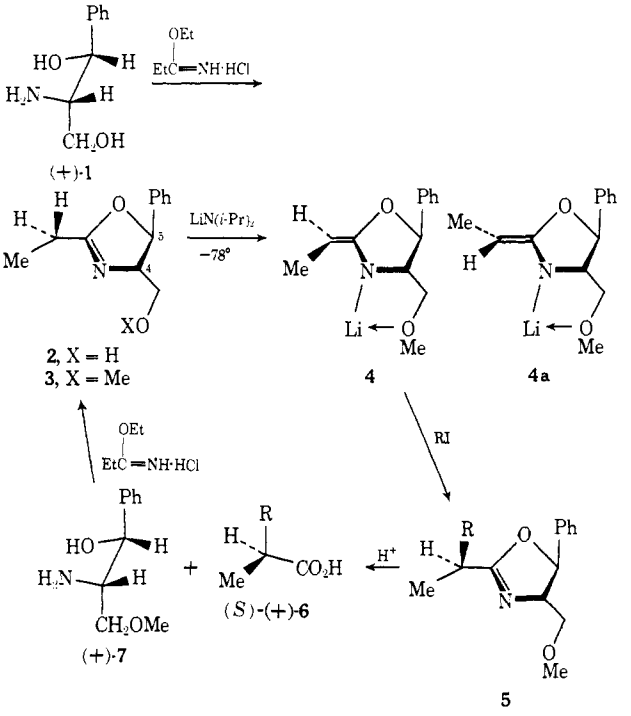
**Table I.** Synthetic and Optical Yields of (*S*)-(+)- and (*R*)-(−)-2-Methylalkanoic Acids (**6**)

| | | | Direct acid hydrolysis of **5** | | | | Acid-base-acid Hydrolysis of **5** | | |
|---|---|---|---|---|---|---|---|---|---|
| RI | % **5**[a] | $[\alpha]^{22}$°D **5**[b] | % yield[c] | $[\alpha]^{22}$°D (neat) | $[\alpha]$D (lit.[6]) (neat) | % Opt purity[d] | % yield[c] | $[\alpha]^{22}$°D (neat) | % Opt purity |
| | | | | *S*(+)-**6** | | | | | |
| Et | 95 | −50.2 | 68 | +12.0 | +18.0[e] | 67 | 59 | +13.7 | 76 |
| *n*-Pr | 94 | −42.5 | 68 | +11.1 | +18.4 | 60 | 54 | +14.3 | 78 |
| *n*-Bu | 92 | −42.4 | 72 | +12.4 | +18.7 | 66 | 57 | +14.1 | 75 |
| | | | | *R*(−)-**6** | | | | | |
| Et | 92 | | 76 | −11.5 | | 64 | 56 | −14.3 | 79 |
| *n*-Pr | 94 | | 79 | −11.4 | | 62 | 51 | −15.5 | 84 |
| *n*-Bu | 95 | | 77 | −11.6 | | 62 | 58 | −13.7 | 73 |

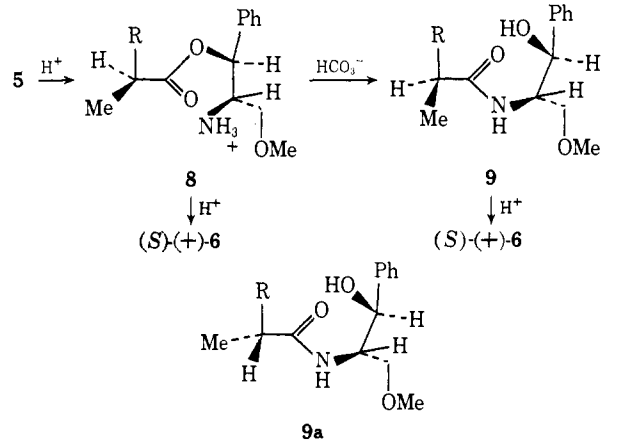
[a] Distilled yields. [b] 10% solutions in chloroform. [c] Distilled yields based on **3**. [d] Rotations taken in a 1-cm³ cell (10 cm) on a Perkin-Elmer 141 polarimeter. [e] W. E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.*, **75**, 393 (1953), report $[\alpha]$D +17.75° (neat), 98% optically pure.

+25.7° (*c* 11, MeOH)) with the ethyl imidate of propionitrile[4a] (mp 97–98°, 86%) in dichloromethane (0°, 4 hr) furnished the required chiral (4*S*,5*S*)-oxazoline (**2**)[4b] (75% mp 67–68°, $[\alpha]^{22}$°D −124.8° (*c* 9.7, $CHCl_3$))[5] which was transformed into its methyl ether **3** (NaH, $CH_3I$, 25°) in 90% yield (bp 94° (0.02 Torr), $[\alpha]^{22}$°D −84.2° (*c* 11, $CHCl_3$)). The diastereotopic protons in **3** were subjected to abstraction by lithium diisopropylamide (−78°, THF) affording the lithio salts (*i.e.*, **4** or **4a**) which were treated at low temperature with several alkyl iodides generating the alkylated oxazolines **5** in 92–95% yield (Table I). Hydrolysis in aqueous hydrochloric acid (4.5 *N*, reflux, 3 hr) produced the 2-methylalkanoic acids, **6**, possessing the *S* configuration with optical purities of 60–67%[6] and in synthetic overall yields (from **3**) of 68–72%. The methoxyamino alcohol **7** was also recovered after the hydrolysis in 80–90% yield ($[\alpha]^{22}$°D +24.1° (*c* 9.93, $CHCl_3$)) and treated with the imidate of propionitrile returning the oxazoline **3** in 92% yield ($[\alpha]^{22}$°D −88.6°). Thus, no racemization of the amino alcohol occurred during the hydrolysis and, furthermore, the recycled chiral oxazoline **3** may now be used directly for further synthesis. In a similar fashion the enantiomeric phenylamino-1,3-propanediol (−)-**1** ($[\alpha]$D −27.1° (*c* 10.5, MeOH)) gave the enantiomers of **2** and **3** and after hydrolysis produced the *R*(−)-2-methylalkanoic acids, **6**, in 62–64% optical purity (Table I). The recovered methoxyamino alcohol **7** ($[\alpha]^{22}$°D −24.4° (*c* 9.97, $CHCl_3$)) was also used to regenerate the corresponding oxazoline **3** ($[\alpha]^{22}$°D +88.2° (*c* 10, $CHCl_3$)). We have, therefore, demonstrated a viable approach to either optical antipode of the 2-methylalkanoic acids.

Hydrolysis of the oxazolines **5** was found to proceed *via* the initially formed[4b] amino ester hydrochloride **8** which precipitates from solution by warming (40–50°) the oxazolines in aqueous acid for a few minutes. Further heating in the acidic medium provided the chiral carboxylic acids, **6**. However, if the amino ester salt




was collected and neutralized with aqueous sodium bicarbonate, it dissolved and a new crystalline material appeared after several hours which was shown to be the hydroxyamide **9**. Acidic hydrolysis (4 *N* HCl, 3 hr) produced a slightly lower synthetic yield of the chiral acids, **6**, yet the optical purity had risen to 73–84% (Table I). Undoubtedly, partial resolution of the diastereomeric amides **9** and **9a** by crystallization accounted for the lower synthetic and higher optical



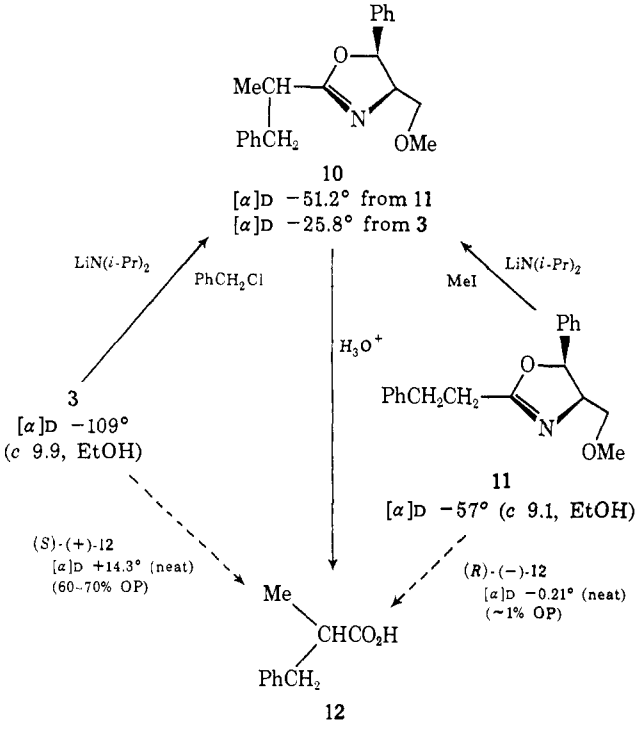

(4) (a) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 5. (b) Oxazolines are known to form with retention when imidates are condensed with amino alcohols: W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, 72, 2187 (1950).

(5) A small quantity of an isomeric oxazoline (~10%) was also formed but was readily removed by crystallization of crude **2** from ether (−78°). All new compounds reported herein gave satisfactory elemental and spectral analyses.

(6) Optical purities are based upon the highest values available in the literature: P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **98**, 1 (1932). Use of various chiral shift reagents was unsuccessful in determining the precise enantiomeric excess due to unsatisfactory peak separations, although agreement of ±8% was achieved.

yield. The sequential acid–base–acid cleavage of oxazolines currently appears to be the choice method for preparing the acids, **6**, since direct acid hydrolysis of **5** results in 5–10% racemization of the ester **8**.[7]

The order in which the alkyl groups are introduced into the chiral oxazoline was found to be critical to the success of the asymmetric synthesis. For example, when **3** was treated with base to form the lithio salt, **4** or **4a**, and then alkylated with benzyl chloride, the oxazoline **10** was smoothly formed which gave, after direct acidic cleavage, 2-methyl-3-phenylpropionic acid (**12**) in 60–70% optical purity.[8] However, when the 2-phenethyloxazoline (**11**) (*via* alkylation of the 2-methyloxazoline with benzyl chloride; BuLi, −78°, THF) was treated with base and methyl iodide (−78°, THF), the oxazoline **10** was formed which gave essentially racemic 2-methyl-3-phenylpropionic acid (**12**). These results




imply that the nature of the 2-alkyl groups originally present in the oxazoline (**3** or **11**) has a considerable effect upon the reactivity of the lithio anions.[9] Other data in hand also confirm the fact that 2-substituents on the oxazoline *larger than ethyl* also lead to nearly racemic products. The structures drawn for the lithio-oxazolines (**4** and **4a**) should, therefore, not be considered firm at this time, although they do represent a reasonable working hypothesis.[10] Further studies are in progress to evaluate the effect of a wide variety of substituents and scope of this method.

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**Supplementary Material Available.** Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-268.

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## Electron-Transfer Catalyzed Cis–Trans Isomerization of Stilbene. The Stability of Sodium *cis*-Stilbenide and the Existence of Sodium Salts of *cis*- and of *trans*-Stilbene Dianions

*Sir:*

Electron transfer from a radical anion, $A\cdot^-$, to an aromatic acceptor, B, *viz.*

$$A\cdot^- + B \longrightarrow A + B\cdot^- \qquad (1)$$

is extremely fast when the electron affinity of B, *EA*(B), is greater than that of A. Nevertheless, techniques for studying its kinetics are available.[1-3] The reverse reaction is inaccessible to a direct kinetic investigation when *EA*(B) ≪ *EA*(A), because the equilibrium concentration of $B\cdot^-$ is then exceedingly low. However, if some reaction different than the reverse of 1 rapidly removes $B\cdot^-$, reaction 1 might become rate determining and its progress could be measured then, *e.g.*, by the disappearance of B.

Having this strategem in mind, we decided to investigate the kinetics of electron transfer from sodium anthracenide, $A\cdot^-,Na^+$, to *cis*-stilbene, C, leading to the isomerization of the latter. This reaction was followed spectrophotometrically by monitoring the absorbance at 285 nm. At this wavelength the decimal extinction coefficients of *cis*- and *trans*-stilbenes are $1.02 \times 10^4$ and $2.45 \times 10^4$ $M^{-1}$ cm$^{-1}$, respectively, and the absorbance of the anthracenide is at minimum, $\epsilon$ $0.35 \times 10^4$ $M^{-1}$ cm$^{-1}$. The starting cis isomer was purified by vpc and contained about 6% of the trans isomer (determined spectrophotometrically at λ 320 nm).

It is known[4] that *cis*-stilbene isomerizes into *trans*-stilbene, T, when in contact with radical anions, and

(7) Evidence for racemization in the ester intermediate **8** was gathered by hydrolysis under different time intervals. The longer the ester was heated in 4.5 *N* HCl, the lower the optical purity of the acid, although the acids themselves were found to be completely stable to racemization under these conditions.

(8) M. B. Watson and G. W. Youngson, *J. Chem. Soc. C*, 258 (1968), report +20.4° (neat) for this acid.

(9) The nearly racemic acid obtained from **11** could also be due to the small electrophile being introduced (*i.e.*, methyl) which may enter the molecule from one of several approaches. However, alkylation of **4** with the slightly larger ethyl iodide gave 2-methylbutanoic acid (**6**) (R = Et) in high optical yield (Table I).

(10) The corresponding *trans*-4-methyl-5-phenyloxazoline [[α]D +81°] obtained by resolution of norephedrine was evaluated as a source of chiral carboxylic acids and found to give only 10–12% optically pure material. The absence of the methoxyl function in this oxazoline coupled with the poorer optical yields lends some credence to the structures depicted for the lithio salts **4** and **4a**.

(1) S. Arai and L. M. Dorfman, *J. Chem. Phys.*, **41**, 2190 (1964).

(2) S. Arai, D. A. Grev, and L. M. Dorfman, *J. Chem. Phys.*, **46**, 2572 (1967).

(3) G. Rämme, M. Fisher, S. Claesson, and M. Szwarc, *Proc. Roy. Soc., Ser. A*, **327**, 467 (1972).

(4) M. A. Doran and R. Waack, *J. Organometal. Chem.*, **3**, 94 (1965).