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# Synthesis and Chemistry of Agrochemicals

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## Asymmetric Synthesis of Selected Insect Pheromones

This is a review of synthetic efforts made at these laboratories in recent years. Stereoisomers of sex pheromones of various insect species were synthesized in order to facilitate identification and permit more thorough evaluation of their potential in insect control programs. Syntheses are described for pheromones of the stable fly, tsetse fly, southern and western corn rootworms, and the Mediterranean fruit fly attractant, trimedlure. In each instance centers of asymmetry were generated that made use of diastereomer formation using readily available (R)- and (S)- $\alpha$ -methylbenzylamine. Resolutions were achieved either by preparative HPLC, or fractional crystallization of amides. The latter technique was rendered synthetically useful for the preparation of configurationally pure acids by virtue of transformations wrought upon the amides that made them subject to cleavage under very mild conditions.

The Agricultural Research Service of the USDA has supported investigations of chemical cues that have led to useful alternative measures in pest control. Some of these are designed as early detection systems; others are being used to reduce infestations directly (1). Because insect behavioral responses are generally keyed to stereochemistry, the investigation of chemical structure must be concluded with syntheses and studies performed on stereoisomers of the identified natural products. We describe here some of our work in this area emphasizing syntheses of rootworm pheromone stereoisomers -- compounds that we expect will have application both in detection and control. We also describe our synthesis of the stereoisomers of a purely "synthetic" attractant, namely trimedlure, a mixture of materials that has been employed as a bait in monitoring for Mediterranean fruit fly for a long time.

#### Biological Activity vs. Stereostructure

Usually when a male insect is presented with a racemic candidate pheromone, it does respond sexually (2) (Figure 1). Examination of the responses toward stereoisomers generally results in the following: strong response toward one enantiomer; little or no response toward the other enantiomer or other stereoisomers. Occasionally an insect may respond to both enantiomers of a structure; and occasionally one enantiomer actually inhibits the male's response to the "active" isomer. In such cases, the original isolation/identification adventure could unearth the situation as a problem that hinders identification. Since the initial research generally culminates in a synthesis of the assigned structure that is not stereodifferentiated, the inactivity of the candidate synthetic may cause the champagne to be set aside while collaborators eye each other with grave suspicion.

The point has often been made, but seems worth repeating, that there is as yet no substitute for asymmetric synthesis in assigning stereostructure to most insect semiochemicals. The amount of natural product available is usually far less than 1 mg. More important, the centers of asymmetry are often far removed from the chemical functionality that one traditionally employs as leverage for spectral evaluation of configuration. As a rule, stereocontrolled syntheses of a set of stereoisomers follows initial assignment of structure, and a methodical investigation of the activity of these isomers individually and as mixtures is then conducted.

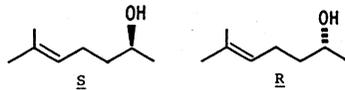
#### Resolution of Carboxylic Acids

Among simple structures that are suitable as key synthetic intermediates,  $\alpha$ -branched carboxylic acids are easily prepared and versatile (Figure 2). One would like to obtain such a material from an available chiral pool and proceed, but few  $\alpha$ -branched alkanic acids are available as natural products. (S)-2-Methylbutyric acid, uniquely, can be obtained in 99% enantiomeric excess (ee) by Jones oxidation of the commercially available alcohol (3).

1. Response to one enantiomer, not the other

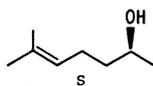
Very common

2. Response optimal to a ratio of enantiomers

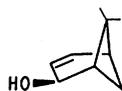


Gnathotricus sulcatus  
=65:35 ratio S:R

3. Response to one enantiomer, other is inhibitory

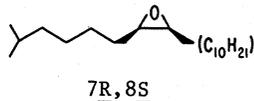


Gnathotricus retusus. Does not respond  
to the pheromone of G. sulcatus

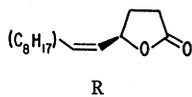


S,cis-verbenol

Ips calligraphus and typographus



Gypsy moth



Japanese beetle

Figure 1. Relationship of Biological Activity to Enantiomeric Composition

A number of methods for generating such acids in high configurational purity by asymmetric induction are known in which the use of chiral amide enolates may be cited (4, 5). The degree of configurational bias in these reactions is often excellent although they show dependency on the alkylating agent. They are, in fact, least effective for the less hindered halides, e.g., methyl iodide. Nevertheless, faced with the task of developing a useful route to an agricultural chemical, one could indeed opt for such an approach, particularly if a few percent of the unwanted enantiomer can be removed easily, or offers no problem in the product's application.

Resolution of diastereomeric amides by preparative HPLC has been developed for  $\alpha$ -branched alkanolic acids, and has been employed to prepare dimethyl branched alkanes implicated in tsetse fly sexual communication (6). In much of our own work we have made use of fractional crystallization whereby racemic acids are converted to amides of either (R)- or (S)- $\alpha$ -methylbenzylamine. These amines are available from Hexcel Corp., Zeeland, MI, and the diastereomeric amides can be analyzed for purity chromatographically.

One such method employs cholesteric liquid crystals, such as cholesterol p-chloro cinnamate, as stationary phases for capillary gas chromatography (7) (Figure 3). The basis of the chromatographic resolutions of these amides is related to the rigidity of a central backbone containing the amide link (8). For the purposes of this comparison, the greater the size difference between the two alkyl groups on the acid residue, the better the separation. As a corollary, the more highly organized the liquid phase, the greater the differentiation between diastereomers also. In the liquid crystal phase, it appears that the high degree of organization optimizes the nonpolar phase's capacity to distinguish the solute's length to breadth ratio (9) and retains the more linear diastereomer.

In order to reap the reward of purification, we had to develop methods to cleave the amides without racemizing the acid (Figure 4). The usual hydrolytic procedures were too severe; and recently developed milder methods generally required base that caused some loss of configurational purity. Deprotonation of the pure amide with a strong, but nonnucleophilic base followed by reaction of the anion with, e.g., methyl chloroformate produces an acyl urethan. For simple  $\alpha$ -alkylacyl groups reaction of the acyl urethan with nucleophiles occurs preferentially on the acyl group, so cleavage to the acid can be affected with, e.g., cold aqueous base. An alternative sequence involves reaction of the amide anion with ethylene oxide to give a hydroxyethylated analog. The acyl group migrates from nitrogen to oxygen under acid catalysis. We have found that the crude aminoester intermediate can be conveniently reduced by lithium aluminum hydride to the corresponding carbinol. Since the recovered amides from the fractionations can be converted to free amines and racemic acids, the process can be repeated. It quickly provides quantities of  $\alpha$ -substituted acids and carbinols in  $\geq 99.6\%$  enantiomeric excess (ee).

1. Available natural products
2. Asymmetric induction
3. Resolution

fractional crystallization of amides  
(R- and S-  $\alpha$ -methylbenzylamine)

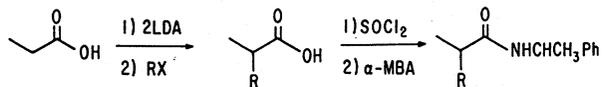


Figure 2. Synthesis of Enantiomers of  $\alpha$ -Branched Carboxylic Acids

$R_1R_2CH(CO)NHCH_2CH_2Ph$				
$R_1$	$R_2$	SE-54 $\alpha$	C-20M $\alpha$	CpCC $\alpha$
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	1.021	1.018	1.036
CH <sub>3</sub>	i-C <sub>3</sub> H <sub>7</sub>	1.040	1.046	1.064
CH <sub>3</sub>	n-C <sub>3</sub> H <sub>7</sub>	1.060	1.056	1.071
CH <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	1.058	1.068	1.100
n-C <sub>5</sub> H <sub>11</sub>	n-C <sub>6</sub> H <sub>13</sub>	1.000	1.000	1.011

CHOLESTEROL para-Chlorocinnamate

$\alpha$  = Ratio of Corrected Retention Volumes

Figure 3. Comparison of GLC separations of diastereomeric amides on several liquid phases

### Methyl Branched Alkanes (Stable Fly, Tsetse Fly-Type Hydrocarbons)

An example of the application of this sequence is the synthesis of the stereoisomers of 15,19-dimethyltritriacontane (Figure 5) (10). Propionic acid was alkylated with 1-bromotetradecane and the sequence just described followed to obtain (R)- and (S)-2-methylhexadecanols. Using known methods, the alcohols were converted to aldehydes of one greater carbon number and also to phosphonium salts. The aldehydes and salts were condensed in Wittig condensations, and the resulting alkenes reduced to give the three stereoisomers of the target alkane. These structures have been implicated as a sex excitant for the stable fly (11), and one of the tsetse fly species (12).

### Southern Corn Rootworm

The southern corn rootworm is a member of the genus *Diabrotica*, family Chrysomelidae. This genus contains a large number of pest species that feed upon include corn, cucumber, squash and melon. Mint and mesquite grass have also been attacked by an occasional species (13).

The sex pheromone structure, 10-methyl-2-tridecanone, was synthesized using the carboxyl group as the source of the methyl branch (14) (Figure 6). Undecylenic acid was  $\alpha$ -propylated and resolved via amides. The procedure followed allowed us to obtain the alcohols, (R)- and (S)-2-propyl-10-undecenol (>99.6% ee). The corresponding bromide was reduced with lithium triethylborohydride (15); then the double bond was converted to a methyl ketone by a) oxymercuration, b) reduction of the C-Hg bond with sodium borohydride, and c) oxidation with dichromate. The male southern corn rootworm responds only to the (R)-configuration; no biological activity was noted for the (S)-enantiomer. Therefore, in this instance the racemic compound would be predicted to monitor this species adequately.

### Western Corn Rootworm

Another important member of this family is the western corn rootworm, *Diabrotica virgifera virgifera* LeConte. Our research with this insect's sex pheromone gave ample indication that much can be learned both by biologists and chemists if a project to identify chemical cues is not focused solely on a designated pest species, but is instead broadened to encompass closely related species.

The structure of the western corn rootworm sex pheromone is 8-methyl-2-decanol propanoate (16) and four stereoisomers are possible (Figure 7). In our synthesis (3), we coupled a chiral 5-carbon unit to a 6-carbon fragment that had the requisite substitution to allow resolution at the oxygenated carbon. As mentioned earlier, (S)-2-methylbutyric acid was available to us from the alcohol. D-Isoleucine served as a source for the (R)-acid. Nitrosation, followed by decarboxylative oxidation of the intermediate hydroxyacid led to the (R)-2-methylbutyric acid in 96% ee. The process of fractional crystallization was

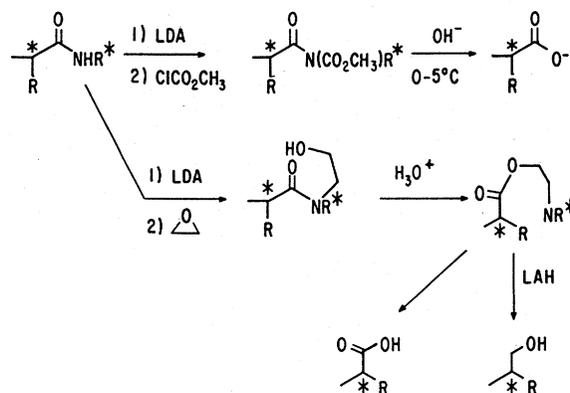


Figure 4. Cleavage of diastereomerically pure amides

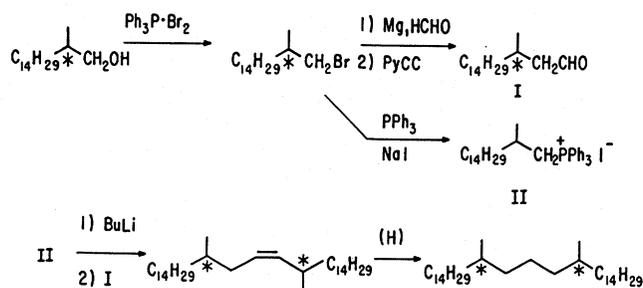


Figure 5. Synthesis of the stereoisomers of 15,19-dimethyl-tritriacontane

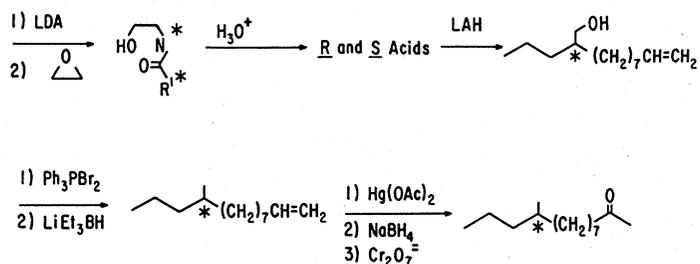
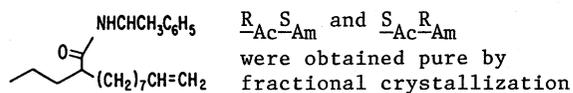


Figure 6. Synthesis of the southern corn rootworm sex pheromone stereoisomers

unsuccessful for this particular amide, and it was resolved by preparative HPLC (silica gel: THF, EtOAc, hexane; 1:2:7). The purified diastereomers were hydroxyethylated and then hydrolyzed with 1N HCl under reflux. The acids obtained were each 94% ee.

The (R)- and (S)-acids were then reduced to the alcohols and converted to derivatives suitable for organometallic coupling to the ethylene ketal of 6-bromo-2-hexanone (Figure 8). Hydrolytic cleavage of the ketal, and reduction gave 8-methyl-2-decanol that has strong configurational bias at the 8-carbon. The alcohols were converted to carbamates with (R)- $\alpha$ -naphthylethylisocyanate (synthesized from (R)- $\alpha$ -naphthylethylamine) and resolved by preparative HPLC (silica gel: EtOAc, hexane; 7:93). Separation is also possible though less efficient with the more available  $\alpha$ -methylbenzylisocyanate. The pure alcohols are then obtained from the carbamates (LAH) and these were then propionylated.

Examination of the responses of other *Diabrotica* species yielded very interesting results. The western corn rootworm responded most strongly to the 2R,8R-isomer, and less so to 2S,8R. Another species, the Mexican corn rootworm, *D. v. zeae* Krysan & Smith, was found to respond identically. Their ranges differ, though, and reproductive isolation might have occurred by that geographical partitioning. The northern corn rootworm, *D. l. barberi* Smith & Lawrence, was known to be attracted to the western species (northern male to western female), but mating was mechanically deterred. The male was only responsive to the 2R,8R-isomer, however. Although it was attracted to the racemate, high concentrations show lessened response and, in fact, the 2S,8R-isomer was inhibitory.

*Diabrotica longicornis* (no common name) was only recently accorded species status to separate it from the northern corn rootworm. Its stereobias (2S,8R) offered convincing evidence that this insect indeed possessed its individual communications system (17). Two other nonpests, *D. porracea* and *D. lemniscata*, also responded to the 2S,8R-isomer. Finally, we have discovered that traps containing the acetate ester (2R,8R) caught *D. cristata* (18). So far it appears that the hydrocarbon center must be (R) for rootworm perception. Even that isomer most effective for inhibition had the 8R configuration. The obligatory nature of that asymmetric center allows preparations that are racemic at that site (the [S] is not perceived). The ester site is, however, species differentiating and syntheses must be geared to the biological result desired.

#### Mediterranean Fruit Fly

As a closing example of the value of asymmetric synthesis in the area of insect chemistry, we describe the synthesis of the stereoisomers of trimedlure, a material discovered by empirical screening and used to monitor for "Medfly" (Figure 9). The commercial preparation of this attractant mixture involves a non-selective addition of HCl to a substituted cyclohexene. The several products are shown in abbreviated form (Figure 9); the t-butyl esters of this mixture of acids has been employed for many years as a bait for the medfly (19). Each component,

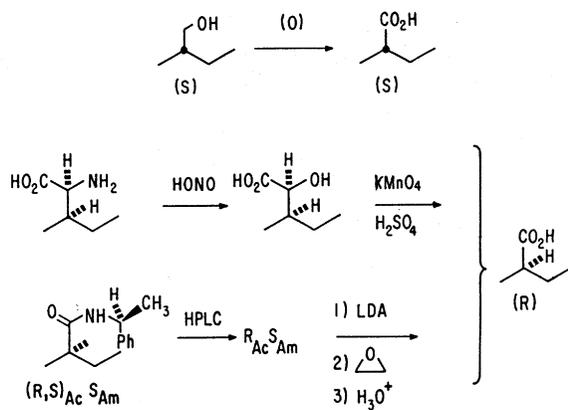
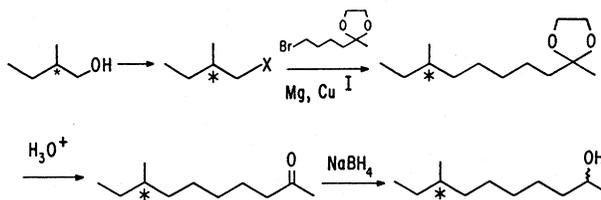


Figure 7. Syntheses of (R)- and (S)-2-methylbutyric acid



- a) X is halogen/tosylate  
 b) Alcohol site resolved (HPLC) as  $\alpha$ -Naphthylethyl carbamates

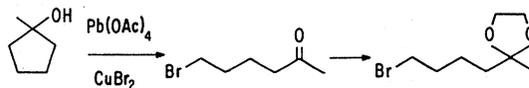


Figure 8. Synthesis of the western corn rootworm sex pheromone stereoisomers

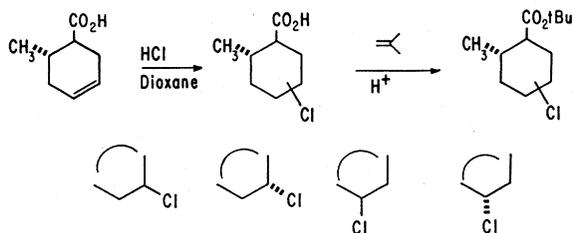


Figure 9. Commercial synthesis of "trimedlure", a synthetic attractant for Mediterranean fruit fly. (Reproduced from Reference 21. Copyright 1966, American Chemical Society.)

however, is a racemate, and the racemate labeled "C" (20) has been shown previously to be most active.

The unsaturated acid, a compound that could not be prepared readily by asymmetric induction, seemed a good candidate for resolution. In fact, this acid was resolved by fractional crystallization of diastereomeric amides (Figure 10), and then the pure diastereomers were cleaved by means described above. Other plays suggested themselves (recrystallization of salts rather than amides, recrystallization of amides of purified HCl adducts, etc.), but these alternative approaches were unsuccessful (21). Additionally, hydrolysis of intermediate aminoesters gave poor yields of the desired unsaturated acids, and the hydrolysis was instead interrupted to reduce the crude aminoester-acid product with LAH. The rotations of the carbinols and acids were the basis for initial assignment of absolute configuration.

Further evidence was obtained from spectral data. Because of the rigidity of the amide link and the consequent solution conformation preferences as mentioned earlier, the ring-methyl group is opposed by either the methyl or phenyl substituents on the amine based asymmetric center (Figure 11 illustrates the likely major solution conformations). The phenyl ring's anisotropy shifts the ring-methyl protons significantly upfield. This observation was made repeatedly with various synthetic intermediates and the subject was described in our original publication (21).

We also felt that the relative solubilities of the diastereomeric amides (or their crystal lattice energies) might be related to the sense of steric bulk disymmetry about that central backbone. If one could perform a chemical reaction, such as addition to the double bond, that could alter the distribution of steric bulk, one could hope to invert diastereomer solubility. Addition of a symmetrical reagent, such as bromine, avoids positional isomerism and the stability of the bromonium ion ensures stereoselectivity. Thus each diastereomeric amide gave only one bromine adduct. The solubilities were indeed dramatically altered and, since bromine is easily removed (Zn, acetic acid) it became possible to use the amide mixture that had been recovered from purification to claim the more soluble diastereomer as its bromine adduct. A process was established to obtain both enantiomeric cyclohexene acids using only one chiral amine.

A derivative based on chiral oxazolidones has been described by Pirkle (22) that can be used to gain information about configuration (Figure 12). Again a strong conformational bias is afforded such compounds in solution both by the nature of the bonding involved and the tendency for the carbonyls to be aligned in opposition. The effects of alignment result in differential shielding of substituents thus permitting NMR to be used as a probe for absolute configuration. The oxazolidone shown (Figure 12) was synthesized from (R)-phenylglycine via the corresponding alcohol. The phenyl substituent of this chiral auxiliary shields the ring methyl protons of the 1S,6S unit by

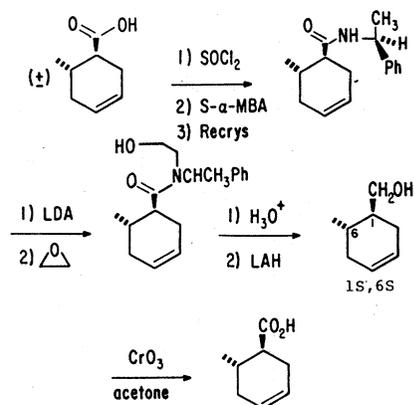


Figure 10. Synthesis of the stereoisomers of trans-6-methyl-3-cyclohexene carboxylic acid

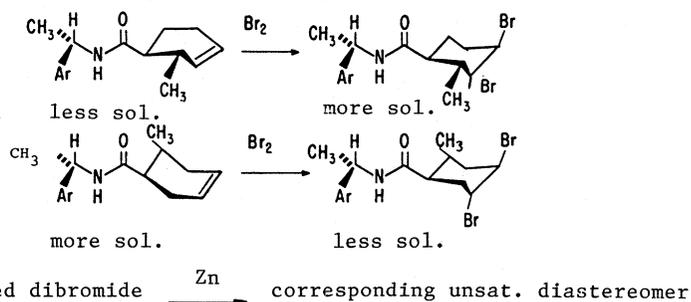


Figure 11. Relationship of stereostructure to solubility of key synthetic intermediates in the synthesis of trimedlure stereoisomers

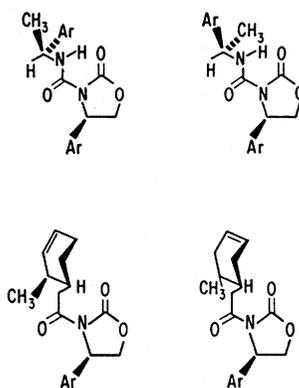


Figure 12. (R)-4-phenyl-1,2,3-oxazolidone derivatives

0.2 ppm, offering additional confirmation of configurational assignments.

The syntheses were completed by following essentially the commercial procedure and adding HCl to enantiomerically pure cyclohexene acids. The esterified mixtures were then subjected to preparative HPLC. Each isolated component would, of course, be configurationally pure. Commercial trimedlure was tested in field traps with wicks that had been baited with 50 mg each (Figure 13). The 1S,2S,4R-enantiomer of "C" was more effective even at 5 mg/wick. Since this enantiomer makes up more than 10% of the commercial lure, and another component (as a racemate) has also shown some activity, there is a hint that isomeric purity may provide a better lure.

Since, the original presentation of this paper, the pheromone of the Mediterranean fruit fly has been identified (23). The compounds, 3,4-dihydro-2H-pyrrole, ethyl-E-3-octenoate, E,E,- $\alpha$ -farnesene, and geranyl acetate, bear no obvious resemblance to the active components of trimedlure. The origin of the biological activity of the synthetic, therefore, remains enigmatic.

	<u>Compound</u>	<u>Configuration</u>	<u>Total Caught (15 reps)</u>
	Commercial Trimedlure (50 mg/wick)	-	963
	"C"	1S,2S,4R	1584
	"C"	1R,2R,4S	273
	"A"	1S,2S,5R	529
	"A"	1R,2R,5S	402

Figure 13. Stereoisomers tested at 5 mg/wick.

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