



International Isotope Society

Central US Chapter Meeting, May 22-23, 1997 in Indianapolis

....ORAL PRESENTATIONS....POSTER PRESENTATIONS....MINI-SYMPOSIUM....

ORAL PRESENTATIONS

- [Synthesis of 2,6-Dialkylanilines \(Ring-UL-14C\)](#)
- [SPA & CYTOSTAR-T, Two Powerful Homogeneous Formats For HighThroughput Screening](#)
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POSTER PRESENTATIONS

- [Synthesis of Chiral Methyl Substrates For Use As Stereochemical Probes For Methyl-Methylene Eliminations In Terpene Biosynthesis](#)
- [Synthesis of LY333068-\[14C\] Succinate Based On Chiral Glycerol-\[14C\] Derivatives](#)
- [Synthesis of N-\(2,6-dichloro-3-methylphenyl\)-5-amino-1,2,4-triazole-3-sulfonamide-3-14C \(DE-511-ATSA-3-14C\)](#)
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- [Synthesis of \[14C\], \[125I\], and \[3H\] Labeled trans,trans-2-\(4-methoxyphenyl\)-4-\(1,3-benzodioxol-5-yl\)-1-\(dibutylamino-carbonylmethyl\)-pyrrolidine-3-carboxylic acid, ABT-627, A Potent Endothelin Antagonist](#)
- [Investigation of the CH₃ to CH₂ Elimination in the Biosynthesis of Limonene Through the Use of \(R\)-9-Chiral Methyl Geranyl Diphosphate](#)

Utilization of Carbon-14 Isotopes In The Registration Of Diclosulam, A New DowElanco Broad Spectrum Herbicide

A Mini-Symposium,

By L.H. McKendry, F.R. Batzer, and L.E. Stafford

- ★ [Fate of Carbon-14 Labeled Diclosulam Under Environmental Conditions](#)
- ★ [Synthesis of Aniline and Triazolopyrimidine Carbon-14 Labeled Samples of Diclosulam \(1\), A New DowElanco Broad Spectrum Broadleaf Herbicide](#)
- ★ [The Utility of Carbon-14 Labeling in Determining the Metabolic Fate of Diclosulam in Plants, Chickens and Goats](#)

SYNTHESIS OF 2,6-DIALKYLANILINES (RING-UL-¹⁴C)

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2-Ethylacetanilide (ring-UL-¹⁴C) was synthesized in 88% yield from acetanilide (ring-UL-¹⁴C) (which was prepared from Ba*CO₃ in 77% yield), by reaction with ethyl iodide and palladium (II) acetate. In a similar manner, 2-ethyl-6-methylaniline (ring-UL-¹⁴C) was prepared from 2-ethylacetanilide (ring-UL-¹⁴C) in 87% yield by reaction with methyl iodide in the presence of palladium (II) acetate followed by hydrolysis; 2,6-diethylaniline (ring-UL-¹⁴C) was produced by reacting with ethyl iodide and subsequent hydrolysis in 77% yield. The purity of these substituted anilines were greater than 98%; their structures were confirmed by 1H-NMR and radio-TLC.

SPA AND CYTOSTAR-T, TWO POWERFUL HOMOGENEOUS ASSAY FORMATS FOR HIGH THROUGHPUT SCREENING

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Based on the scintillation proximity effect, two homogeneous formats are now available for high throughput users. SPA has been developed for use in in vitro applications, such as receptor, enzyme, and protein/protein studies. Cytostar-T is now available for in vivo applications. The utility of the Cytostar-T technology has been demonstrated in applications such as cell proliferation and cell cycle studies, measurement of ion flux, metabolite, and drug transport, signal transduction and quantification of specific transcripts. SPA and Cytostar-T offer a powerful combination of high throughput screening technologies for a diverse range of biological applications.

APPLICATION OF ISOTOPES IN PHARMACOKINETIC AND DRUG METABOLISM STUDIES

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Pharmacokinetic and drug metabolism studies form an integral part of the drug development process. In addition to a new chemical entity's efficacy and safety, assessment of the duration of pharmacological effect and design of the most appropriate dosage regimen play a pivotal role in the success of the drug. Isotopically labeled analogs of the drug entity or its metabolites play a crucial role in defining the absorption, distribution, metabolism, and excretion profile of a candidate compound. Since the detection of radiolabeled compound in any sample matrix is

independent of the chemical nature of the compound, radiolabeled compounds have found extensive utility in the design of studies to follow the distribution and fate of the compound. These include metabolic profiling, comparison of species differences in metabolism, whole body distribution of drug and metabolites, mass balance, metabolite identification, and other specialized studies. Stable labeled analogs of a compound or its metabolites have also found extensive use in pharmacokinetics and drug metabolism due to significant advances in mass spectrometry. Several important uses include quantitative analytical applications, metabolite identification, determination of steady state pharmacokinetics, analysis of differences in the pharmacokinetics of enantiomers, determination of absolute bioavailability, and other specialized applications. Although both radiolabeled and stable labeled compounds have unique constraints associated with their applications in pharmacokinetic and drug metabolism studies, taken together they compliment each other ideally and are an indispensable tool to both pharmacokineticists and medicinal chemists. The seminar will outline several routine as well as imaginative uses of isotopically labeled compounds as they pertain to pharmacokinetic and drug metabolism.

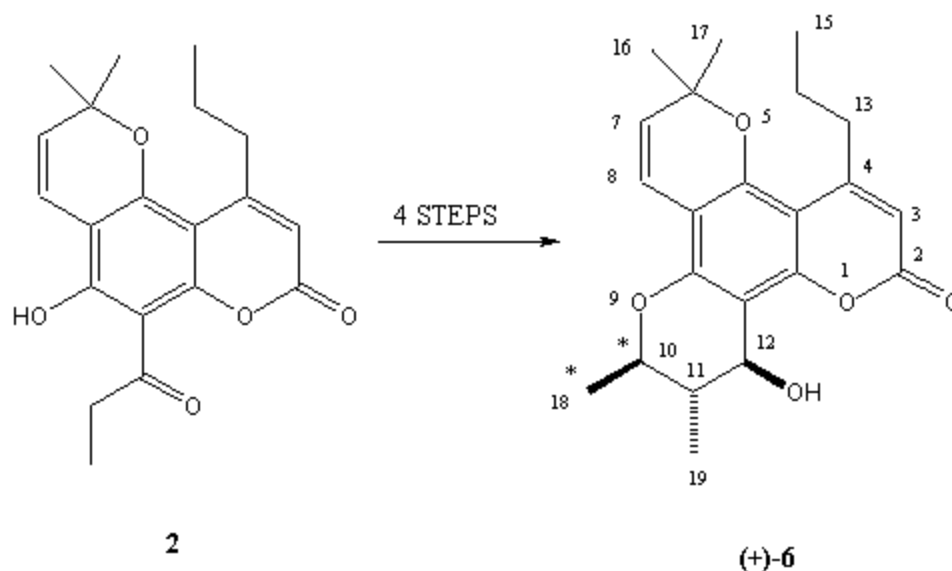
STEREOSELECTIVE SYNTHESIS OF (+)-[10, 18-¹⁴C]CALANOLIDE A, A NATURALLY OCCURRING ANTI-HIV AGENT

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and

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(+)-[10,18-¹⁴C]Calanolide A [(+)-6] was synthesized in four steps from chromeno-coumarin 2. Aldol reaction of 2 with anhydrous [1,2-¹⁴C]acetaldehyde in the presence of TiCl₄ stereoselectively produced the (±)-syn diastereomer of the hydroxyketone. Enzymatic resolution of the hydroxyketone afforded the required (+)-syn diastereomer, which was reacted under Mitsunobu reaction conditions to get the (+)-trans-10,11-dimethyl-12-oxo derivative. Stereoselective reduction of the oxo compound with sodium borohydride in the presence of cerium (III) chloride gave the (+)-[10,18-¹⁴C]calanolide A.



* indicates ^{14}C labelled carbon atom

CHROMATOGRAPHIC SEPARATION OF ENANTIOMERS USING CHIRAL STATIONARY PHASES

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An overview of the chromatographic separation of enantiomers using chiral stationary phases will be presented, including an introduction to the fundamentals of chromatographic enantiomer separations, discussion of available columns, column selection criteria, and preparative enantiomer separations. Recent advances in the chromatographic separation of the enantiomers of pharmaceutical and agrochemical products will be highlighted, and some recent examples of the chromatographic separation of the enantiomers of compounds which are chiral by virtue of isotopic substitution will be presented.

THE SYNTHESIS OF ^{14}C -LY303870 AND ITS METABOLIC PROFILE IN RATS, DOGS, AND HUMANS

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LY303870 is an antagonist of the endogenous peptide Substance P at the neurokinin-1 (NK-1) receptor subtype. ^{14}C -LY303870 was synthesized to evaluate the disposition of this candidate compound in both animals and humans. Ethyl bromoacetate-[carbonyl- ^{14}C] was utilized to alkylate 4-piperidinopiperidine and resulting ethyl [1,4'-bipiperidine]-1'-acetate-[carbonyl- ^{14}C] was used to acylate R-N-[2-amino-3-(1H-indol-3-yl)propyl]-N-(2-methoxyphenyl)methyl]acetamide, dihydrochloride and yield the final product of R-N-[2-[acetyl[2-methoxyphenyl)methyl]amino-1-(1H-indol-3-ylmethyl)ethyl]-[1,4'-bipiperididine]-1'-acetamide-[carbonyl- ^{14}C]. ^{14}C -LY303870 was used to evaluate the metabolism and elimination profiles in rats, dogs, and humans. The primary route of elimination of LY303870 and its biotransformation products was biliary elimination in both rats and dogs. This route of elimination was independent of route of administration. Metabolic profiling was done in plasma, bile, urine and feces of rats and in plasma, urine and feces of dogs and humans. The primary routes of metabolism of LY303870 were oxidative products. Similar metabolic profiles were observed in rats, dogs, and humans. These included multiple hydroxylation products and oxidative dealkylations of LY303870 and subsequent biotransformation products.

LC/NMR IDENTIFICATION OF NOVEL BILE AND MICROSOMAL METABOLITES OF LY335979

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Compound LY335979 is a P-glycoprotein inhibitor currently being developed by Eli Lilly and Co. for potential reversal of multi-drug resistance to cancer chemotherapy. In exploratory studies, LY335979 was found to be rapidly transformed in rat, dog, monkey and human liver microsomal suspensions. While the parent was completely metabolized, no prominent metabolite peaks were observed. One peak did appear early in the time course, but did not grow over time. In another preliminary experiment, rats were treated intravenously with [^3H] LY335979 and urine and bile fractions were collected. Analysis of the urine by reverse-phase LC/UV/Radioactivity revealed that almost all of the material eluted with the solvent front. In bile, less than half of the radioactivity eluted at the solvent front, but the remainder was observed as two peaks eluting just before parent. In both bile and microsomes, initial attempts to isolate these metabolites were futile. There was also evidence in both systems of products derived from cleavage of LY335979 (both by metabolism and degradation). LC/NMR was thus used to analyze materials directly in the matrices, which allowed us to identify an N-oxide metabolite in microsomes and three glucuronide metabolites in bile (structures below). Overall, the LC techniques used for LC/UV and LC/MS analysis of LY335979 metabolites proved readily adaptable for LC/NMR. Using a 500 MHz instrument, basic ^1H NMR spectra could be obtained in 2-3 hr with around 150 ng material in the NMR flow cell. In this case, up to 1 mg of material could be injected on-column, which also allowed 1H-1H TOCSY data to be obtained over times ranging from 4-12 hr. It is impossible to estimate how much time and effort it would have taken to identify these metabolites using traditional isolation techniques, but it is certain that obtaining this metabolism information at this stage of the project was only possible because of the LC/NMR technology.

APPLICATIONS OF STABLE ISOTOPES IN DRUG DISCOVERY AND DEVELOPMENT

P.G. Pearson, R.C. Steenwyk, W.T. Stolle, R.S.P. Hsi, L.C. Wienkers, J.A.Easter, J.P. McGrath, P.E. Sanders and M.J. Hauer.
Drug Metabolism Research, Pharmacia and Upjohn Inc, MI 49001

The incorporation of stable isotopes into novel chemical entities, when used in combination with contemporary mass spectrometry techniques, serves as a powerful tool to rapidly characterize the metabolic fate of novel drug candidates in a variety of in vivo and in vitro biological systems. This approach has profound qualitative and quantitative utility when the chemical entities of interest are subject to extensive metabolic biotransformation. The application of this approach in preclinical and clinical studies will be illustrated in a case study with tirilazad mesylate (FREEDOX™), a potent inhibitor of membrane lipid peroxidation in vitro, which is under clinical development for the treatment of subarachnoid

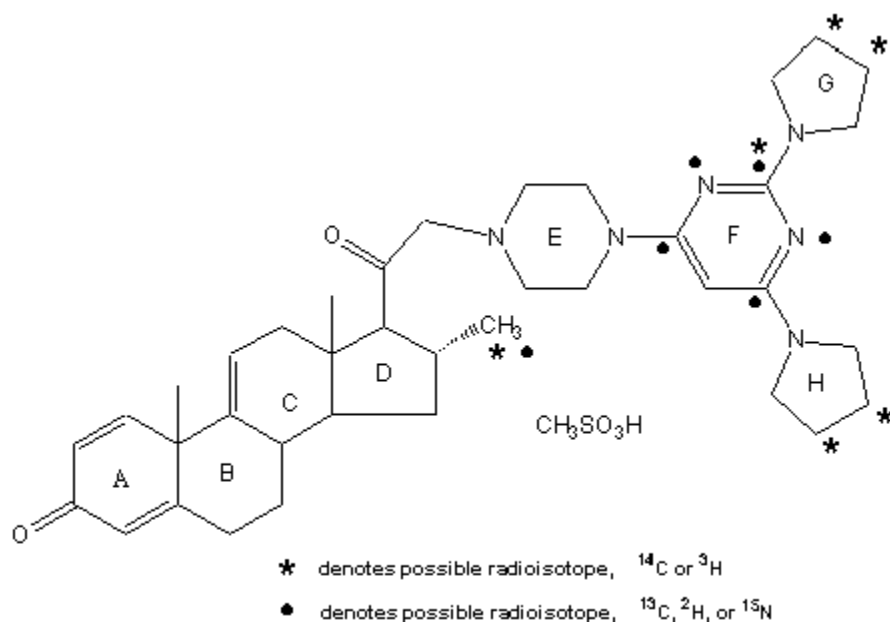


Figure 1. Structure of tirilazad mesylate and isotopically labeled analogs

hemorrhage. In human and preclinical models, tirilazad is cleared almost exclusively via hepatic elimination. To characterize the metabolic fate of tirilazad, a series of radio- and stable-isotopically labeled analogs of tirilazad have been prepared (see Figure 1). In preclinical models, tirilazad and stable-labeled analogs were co-administered in an equimolar ratio. In this manner, over 100 metabolites excreted in bile were characterized by mass spectrometry. In human, in vitro studies conducted with stable labels indicated that tirilazad was cleared via hepatic elimination catalyzed primarily by cytochrome P450 (CYP3A) and to a minor extent by D4-5a-reductase. Collectively, these data demonstrate the application of stable isotopes in drug discovery and development.

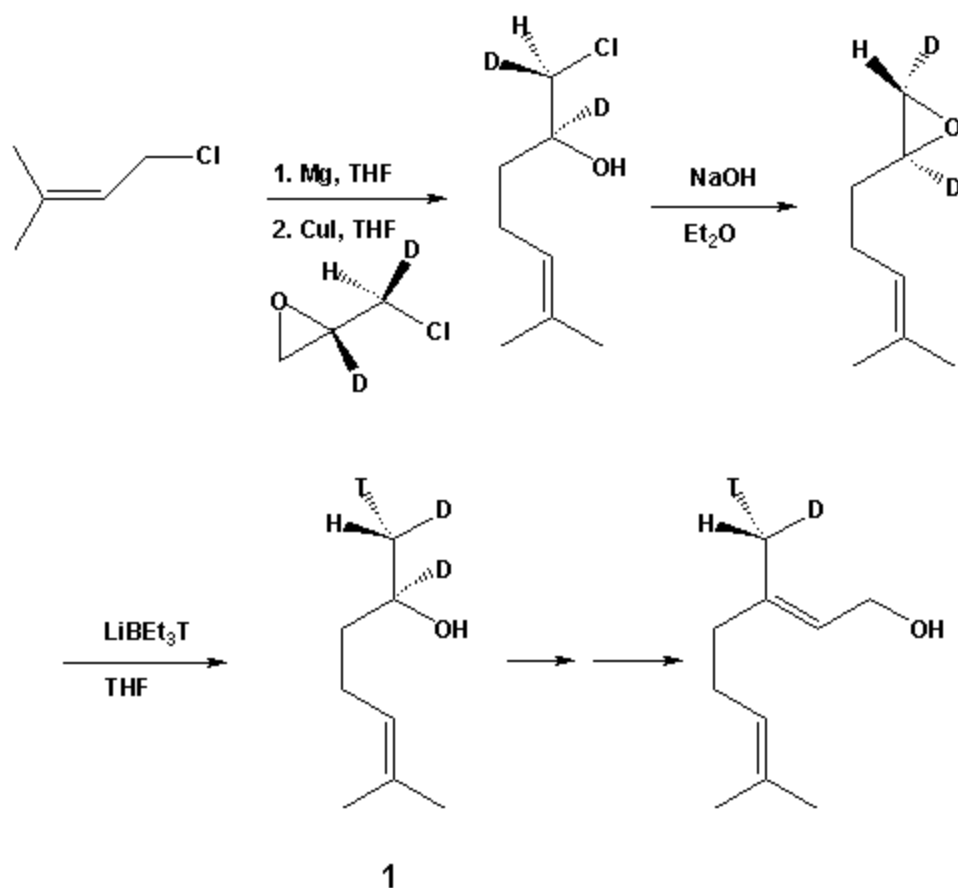
SYNTHESIS OF CHIRAL METHYL SUBSTRATES FOR USE AS STEREOCHEMICAL PROBES FOR METHYL-METHYLENE ELIMINATIONS IN TERPENE BIOSYNTHESIS

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** National Tritium Labeling Facility, Lawrence Berkeley Laboratory, University of California, Berkeley, CA 94720.

The olefinic methylene group commonly found in naturally occurring terpenes is thought to arise by regiospecific methyl to methylene eliminations. The stereochemical options associated with these eliminations can be elucidated by use of chiral methylene substrates. In connection with our interest in mechanisms of several terpene syntheses, in particular b-pinene, we have developed the synthesis of chiral alcohol 1, which can be a precursor to a variety of substrates bearing chiral methyl groups. The synthesis of other chiral methyl substrates will be discussed.

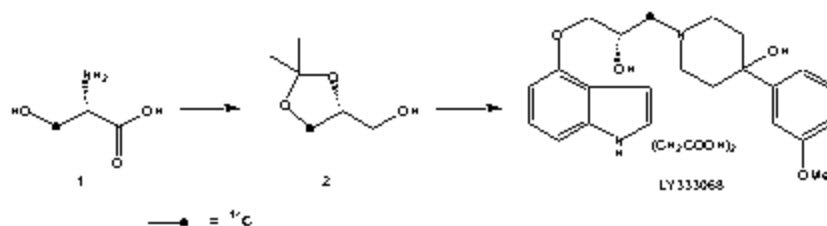


SYNTHESIS OF LY333068-^{[14}C] SUCCINATE BASED ON CHIRAL GLYCEROL-^{[14}C] DERIVATIVES

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Extensive research into receptors influenced by the neurotransmitter 5-hydroxytryptamine (serotonin, 5-HT) led to the discovery of several 5-HT receptor subtypes. Even within certain subtypes some receptors show preferential binding for various agonists and antagonists. LY333068 succinate has been identified as a potent antagonist of 5-HT which acts specifically at the 5-HT_{1A} receptor. For the preclinical drug metabolism studies in laboratory animals, radiolabeled material was needed. The established synthetic route for the preparation of LY333068 offered no convenient steps for the introduction of the C-14 label, so an alternate method has been developed. The method includes the transformation of (L)-serine-^[3-¹⁴C] (1) into protected chiral glycerol 2 which was used as a key intermediate in the 10 step synthesis of ¹⁴C-labeled LY333068.



SYNTHESIS OF N-(2,6-DICHLORO-3-METHYLPHENYL)-5-AMINO-1,2,4-TRIAZOLE-3-SULFONAMIDE-3-¹⁴C (DE-511-ATSA-3-¹⁴C)

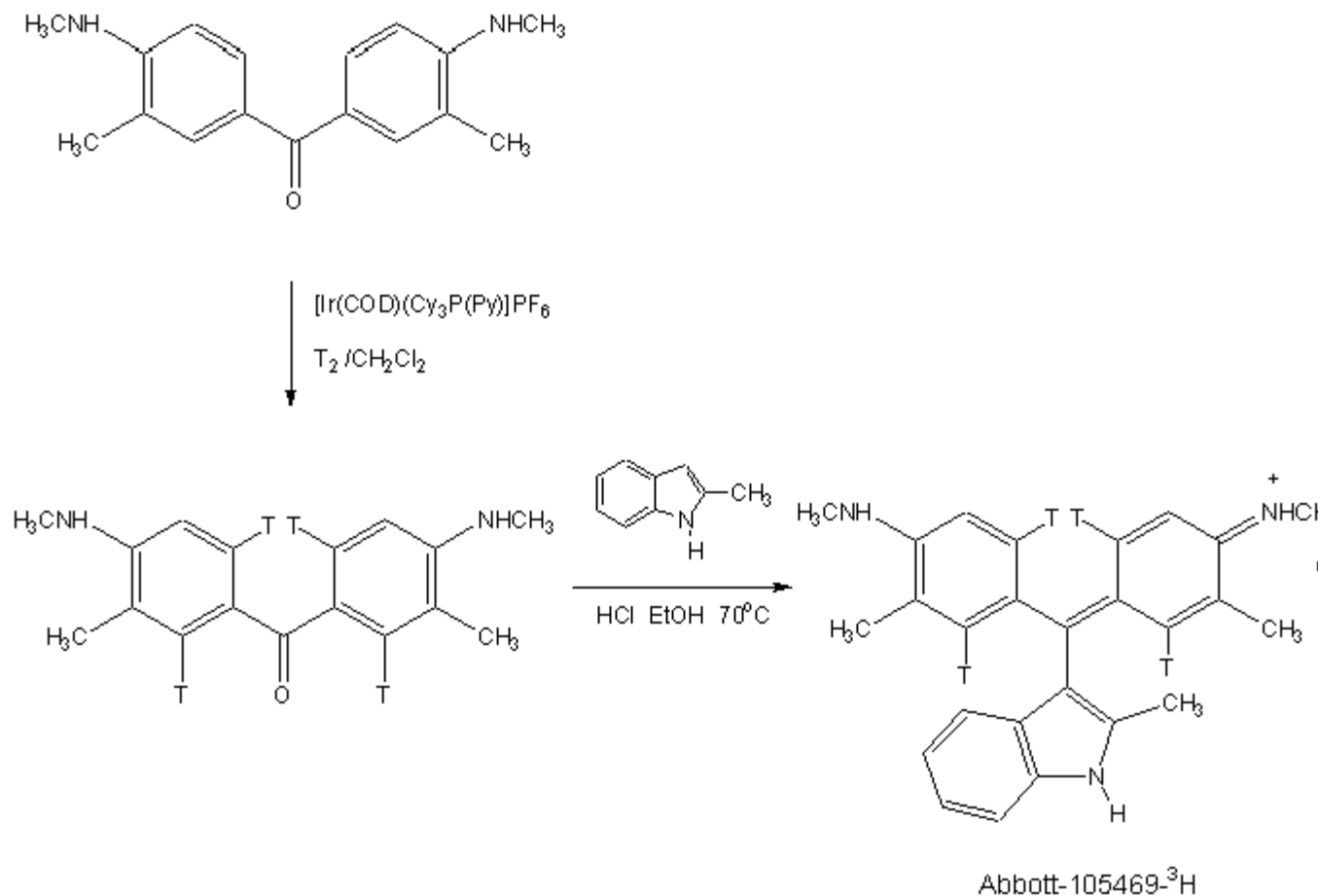
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A 0.921 mCi sample of N-(2,6-dichloro-3-methylphenyl)-5-amino-1,2,4-triazole-3-sulfonamide-3-¹⁴C (DE-511-ATSA-3-¹⁴C) with a specific activity of 17.9 mCi/mmol and a radiochemical purity of 95.9% was isolated in a 6.1% radiochemical yield via a six step process. The tracer was required for metabolism studies.

Isotope Exchange Tritiation of 4,4'-Diamino-N,N',3,3'- tetramethylbenzophenone Using Crabtree's Catalyst. Preparation of Abbott-105469-³H.

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Using 1.9 Curies of tritium gas, 2.8 mg of ketone, and 2.3 mg of catalyst, 0.45 Curies of product was obtained. The tritiated ketone was condensed with 2-methylindole to provide the final product which was purified by HPLC. The tritium was found by tritium NMR to be ortho to the carbonyl group in agreement with literature predictions.¹ The specific activity was determined by HPLC, mass spectrometry, and NMR. The two specific activities estimated spectrally were in good agreement (56 ± 2 Ci/mmol) but were about twice that of the HPLC value (22Ci/mmol). The discrepancy was attributed to impurities in the nonlabeled reference material used to make the standard curve in the HPLC method.



SYNTHESIS OF [¹⁴C], [¹²⁵I], AND [³H] LABELED TRANS,TRANS-2-(4-METHOXYPHENYL)-4-(1,3-BENZODIOXOL-5-YL)-1-(DIBUTYLAMINO-CARBONYLMETHYL)-PYRROLIDINE-3-CARBOXYLIC ACID, ABT-627, A POTENT ENDOTHELIN ANTAGONIST

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ABT-627, a potent endothelin antagonist was required in three separate isotopically labeled forms in order to carry out biotransformation investigations as part of its development as a therapeutic agent.

[¹⁴C]-ABT-627 was prepared from [¹⁴C]-chloroacetic acid in a four step reaction sequence.

[¹⁴C]-Chloroacetic acid was cleanly converted by the action of benzoyl chloride and heat into

[¹⁴C]-chloroacetyl chloride. Treatment with di-n-butylamine gave the di-n-butylamide which was coupled with 2-(4-methoxyphenyl)-4-(1,3-benzodioxo-5-yl)-pyrrolidine-3-ethylcarboxylate to give the ethyl ester derivative of ABT-627. Ethyl ester saponification with aqueous sodium hydroxide in ethanol at room temperature gave [¹⁴C]-ABT-627 at a specific activity of 58.8 mCi/mmol and a radiochemical purity of 98%.

The preparation of [¹²⁵I] and [³H]-ABT-627 required the synthesis of iodo-ABT-627 bearing an iodo substituent at C-4 of the n-butyl group of the di-N-butylamide. The iodo derivative was prepared from its corresponding mesylate by the action of sodium iodide in refluxing acetone. Ethyl ester saponification furnished iodo-ABT-627. Iodo-ABT-627 was converted to [³H]-ABT-627 by treating an ethyl acetate solution containing an equivalent weight amount of Pd/C (10%) with 2.43 Ci of carrier-free tritium gas. Removal of the catalyst by filtration and evaporation of the volatile tritium gave 33 mCi of product. Ethyl ester saponification at room temperature with sodium hydroxide in ethanol and purification of the crude reaction mixture by preparative HPLC gave 0.8 mCi of [³H]-ABT-627 at a specific activity of 6.43 Ci/mmol.

[¹²⁵I]-ABT-627 was prepared from iodo-ABT-627 via isotope exchange with [¹²⁵I]-sodium iodide. The precursor was exposed to a total [¹²⁵I] activity of 10 mCi and the crude reaction mixture purified by preparative HPLC. This gave 540 microcuries of [¹²⁵I]-ABT-627 at a specific activity of 2200 Ci/mmol.

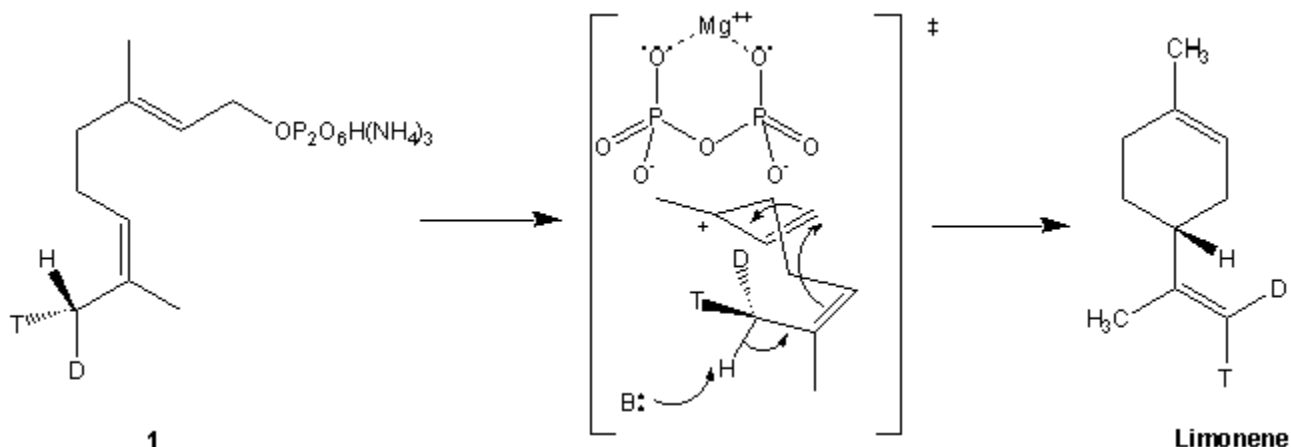
INVESTIGATION OF THE CH₃ to CH₂ ELIMINATION IN THE BIOSYNTHESIS OF LIMONENE THROUGH THE USE OF (R)-9-CHIRAL METHYL GERANYL DIPHOSPHATE

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D. Williams~, and R. Croteau~

*Department of Chemistry, University of Illinois, Urbana-Champaign, Urbana, IL 61801.

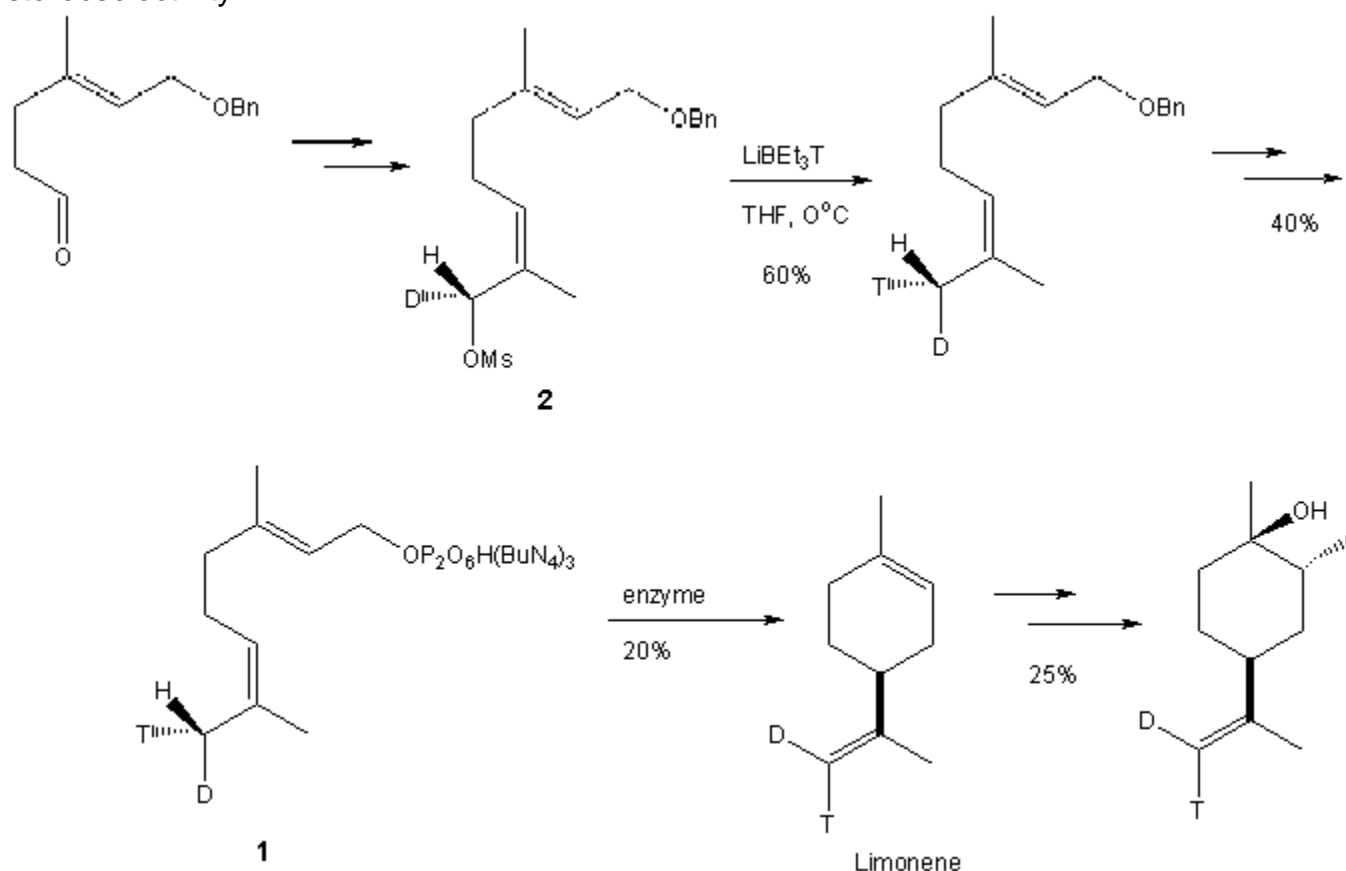
#National Tritium Labeling Facility, Lawrence Berkeley Laboratory, University of California, Berkeley, CA 94720.

~Institute of Biological Chemistry, Washington State University, Pullman, WA 99164



Scheme 1: Depiction of the deprotonation of the terpinyl cation in the active site of limonene synthetase

The synthesis of (R)-9-chiral methyl geranyl diphosphate (GPP), 1, was conducted to elucidate the stereochemistry of deprotonation of the enzyme bound carbocation intermediate leading to limonene (Scheme 1). (S)-Mesylate 2 was synthesized in greater than 94% ee in several steps from geranyl benzyl ether utilizing ozonolysis, Horner-Emmons olefination, AID3 reduction, TRAP oxidation, and Midland reduction. LiBEt₃T reduction yielded (R)-9-chiral methyl geranyl benzyl ether in moderate yield. This compound was converted into chiral methyl GPP, 1, by deprotection of the benzyl ether, chlorination, and diphosphorylation; it was then incubated with limonene synthetase to give limonene in a 20% radiochemical yield. ³H-NMR analysis of limonene-1,2-diol revealed that the elimination occurred with predominant si/si stereoselectivity.



Scheme 2. The synthesis of 9-Chiral Methyl Geranyl Diphosphate

FATE OF CARBON-14 LABELED DICLOSULAM UNDER ENVIRONMENTAL CONDITIONS

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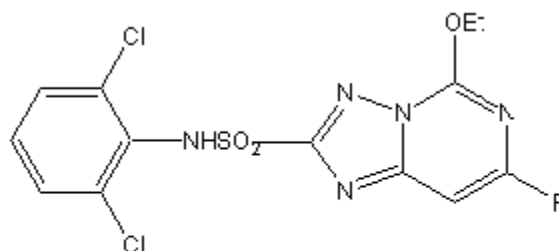
Diclosulam with carbon-14 incorporated into two different, stable ring positions was used to investigate the fate of diclosulam in soil, water, and sediment/water test systems. These studies were conducted to support its development as a broadleaf weed herbicide in the

soybean and peanut markets. The use of two carbon-14 labeled diclosulam tracers facilitated tracking of the degradation of diclosulam and of common and unique degradates resulting from the two ring moieties of diclosulam. The detection of the carbon-14 labeled degradates when coupled to liquid chromatography mass spectrometry enhanced the ability to identify major degradates. In addition, carbon-14 field dissipation studies were conducted to more fully understand the potential environmental impact of diclosulam. The use of carbon-14 labeled diclosulam in the field dissipation study permitted tracking of diclosulam, its degradates, and bound residues through the soil profile. Under field conditions, diclosulam and its degradates did not persist or leach to significant depth.

SYNTHESIS OF ANILINE AND TRIAZOLOPYRIMIDINE CARBON-14 LABELED SAMPLES OF DICLOSULAM (1), A NEW DOWELANCO BROAD SPECTRUM BROADLEAF HERBICIDE

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Diclosulam (1) is a new broad spectrum broadleaf herbicide being commercialized by DowElanco for use on soybeans and peanuts. As part of a symposium involving the use of carbon-14 labeling in the registration of diclosulam, the synthesis of the radiolabeled samples will be discussed. Initially, the label had been placed in the 5-position of the triazole ring but probe studies indicated that this represented a labile position. Therefore, diclosulam was subsequently labeled in the 7,9-positions of the triazolopyrimidine ring as well as uniformly labeled in the phenyl ring. The processes used for preparing the radiolabeled samples will be discussed.



1

THE UTILITY OF CARBON-14 LABELING IN DETERMINING THE METABOLIC FATE OF DICLOSULAM IN PLANTS, CHICKENS, AND GOATS

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Diclosulam, the proposed common name for N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide, is the active ingredient in Strongarm* herbicide. It is being developed for the control of many broadleaf weeds in soybeans and peanuts. To register diclosulam for these uses, it was necessary to conduct a battery of experiments to study the nature of the residue in soybeans and peanuts, in rotational crops (wheat and potatoes), in ruminant animals (goats), and poultry (chickens). The results of these studies and the utility of carbon-14 in conducting the studies will be presented.

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