S_N2-type substitution product and 50% 9-*i*-Pr_2NFlH (from an elimination reaction): ^1H NMR ($CDCl_3$) δ 1.0-2.0 (m, 18.2 H), 2.9 (br, 2 H), 4.95 (s, 0.5 H), 7.2-7.8 (m, 8 H); MS, *m/e* 348 (1.3), 347 (substitution molecular ion, 3.1), 265 (19.2), 265 (elimination molecular ion, 61.7), 247 (30.6), 222 (36.0), 165 (100).

UV/Vis Spectra of 9-*i*-Pr_2NFl^- + Ph_2CHCl Reaction. The anion of 9-(diisopropylamino)fluorene has been shown to have three peaks (λ_{max} = 479, 510, 556 nm) in Me_2SO while the corresponding radical has a peak at 450 nm.[21] UV/vis spectra taken at various points during the reaction of *i*-Pr_2NFl^- ion with benzhydryl chloride showed the appearance of a small peak at 450 nm in addition to the three anion peaks. However, unlike reactions of this anion with electron acceptors ($PhSO_2CH_2Cl$, c-$C_6H_{10}(NO_2)Ts$, and F_3CCH_2I), the radical peak is not persistent and a colorless solution results when all of the anion absorbance has dissipated, presumably because of coupling of the *i*-Pr_2NFl^- radical with the Ph_2CH^- radical.

Acknowledgment. This work was supported by the National Science Foundation. We are indebted to C. A. Wilson for some of the rate and product studies with benzyl chloride and cyclohexyl bromide and to T.-Y. Lynch for the rate data for F_3CCH_2I and for checking for the appearance of 9-*i*-$Pr_2NFl^\bullet$ in the product study of 9-*i*-Pr_2NFl^- with Ph_2CHCl.

Registry No. 9-MeFl$^-$, 31468-21-0; 9-$PhCH_2Fl^-$, 53629-11-1; 9-MeOFl$^-$, 71805-70-4; 9-(4-MeC_6H_4)Fl$^-$, 42730-14-3; 9-PhFl$^-$, 31468-22-1; 9-(3-ClC_6H_4)Fl$^-$, 73872-45-4; 9-(4-$MeSO_2C_6H_4$)Fl$^-$, 73872-44-3; 9-c-$C_6H_{11}Fl^-$, 117959-61-2; 9-*t*-BuFl$^-$, 73838-69-4; 9-c-$C_3H_6NFl^-$, 111933-70-1; 9-c-$C_4H_8NFl^-$, 111933-71-2; 9-Me_2NFl^-, 83936-70-3; 9-c-$C_5H_{10}NFl^-$, 111933-72-3; 9-(2-Me-c-C_5H_9N)Fl$^-$, 111933-73-4; 9-(2,2,6,6-Me_4-c-C_5H_6N)Fl$^-$, 111933-74-5; 9-*i*-Pr_2NFl^-, 109495-02-5; Ph_2CHCl_2, 90-99-3; $PhCH_2Cl$, 100-44-7; F_3CCH_2I, 353-83-3; (*p*-$ClC_6H_4)_2CHCl$, 782-08-1; *n*-BuBr, 109-65-9; c-$C_6H_{11}Br$, 108-85-0; 9-Me_2NFl, 53156-46-0; 9-Ph_2CH-9-Me_2NFl, 117959-62-3; 9-c-C_4H_8NFl, 7596-59-0; 9-Ph_2CH-9-c-C_4H_8NFl, 117959-63-4; 9-*i*-Pr_2NFl, 109495-00-3; 9-Ph_2CH-9-*i*-Pr_2NFl, 117959-64-5; 9-(4-MeC_6H_4)Fl, 18153-43-0; 9-Ph_2CH-9-(4-MeC_6H_4)Fl, 117959-65-6; 9-PhFl, 789-24-2; 9-(*p*-$ClC_6H_4)_2CH$-9-PhFl, 117959-66-7; 9-Bu-9-*i*-Pr_2NFl, 117959-67-8; 9-c-C_6H_{11}-9-*i*-Pr_2NFl, 117959-69-0; 9-*i*-Pr_2NFl^-, 117959-70-3; 4,4'-dichlorobenzhydrol, 90-97-1.

Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-[2,3-$^2H_2$]Oxirane and Application of It to the Synthesis of Chirally Labeled Homoserine†

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Abstract: (2*R*,3*R*)- and (2*S*,3*S*)-[2,3-$^2H_2$]oxirane have been synthesized from 2-propynol, the key step being the asymmetric epoxidation of (*E*)-3-(triphenylsilyl)-2-propenol. To determine the enantiomeric purities of the oxiranes, they were reacted with phenyllithium, and the resulting 2-phenylethanol samples were converted to esters of (1*S*)-(-)-camphanic acid. ^2H NMR analysis (in the presence of Eu(dpm)$_3$) showed that (*R*)- and (*S*)-oxirane had ee values of 92% and 94%, respectively. The utility of (2*R*,3*R*)- and (2*S*,3*S*)-[2,3-$^2H_2$]oxirane as chiral labeling synthons was demonstrated by a two-step synthesis of chirally labeled homoserine lactone, which was resolved chromatographically as its *N*-(3,5-dinitrobenzoyl) derivative. The diastereomeric purity of the latter was assessed by ^1H NMR. Acid hydrolysis of (2*R*,3*S*,4*S*)-*N*-benzoyl[3,4-$^2H_2$]homoserine lactone resulted in extensive epimerization at C-4 of the lactone. An ^{18}O-labeling experiment failed to support a mechanism involving amide participation. It is concluded that the lactone was hydrolyzed by an unprecedented $A_{AL}2$ mechanism.

In many cases, syntheses of chirally labeled compounds are quite long, owing to the limited number of reagents and stereoselective reactions by which isotopic labels can be introduced.[1-3] While this has been true in our own work, in one recent instance it was clear that the necessary labeled substrates could be made economically by using a divergent route in which chirally labeled oxirane would serve as a common synthetic intermediate.

In this paper, we report the details of our synthesis and analysis of (2*R*,3*R*)- and (2*S*,3*S*)-[2,3-$^2H_2$]oxirane, including improvements over the methods that we have described in a preliminary communication.[4] The *general* utility of chirally labeled oxirane is also demonstrated by the synthesis of homoserine that is chirally labeled at carbons 3 and 4.[5] In addition, in the course of the homoserine synthesis, a mechanistically unprecedented acid-catalyzed epimerization at homoserine C-4 was observed.

Results

Synthesis and Analysis of Chirally Labeled Oxirane. The synthesis of chirally labeled oxirane (Scheme I) begins with 3-(triphenylsilyl)-2-propynol,[6,7] which is readily available from propargyl alcohol.[6] Reduction of the triple bond with lithium aluminum deuteride,[8] using deuterium oxide to quench the reaction, leads to (*E*)-3-(triphenylsilyl)-2-[2,3-$^2H_2$]propenol.[6,9] This labeled allylic alcohol is epoxidized by using a modified Sharpless procedure,[10,11] with (+)- and (-)-diisopropyl tartrate (DIPT) giving

† C.-K.H.'s portion of these studies was performed in partial fulfillment of the requirements for the Ph.D. degree from the Department of Chemistry, The Catholic University of America, Washington, DC 20064.

(1) Parry, R. J. In *Bioorganic Chemistry*; Van Tamelen, E. E., Ed.; Academic: New York, 1978; Vol. 2, pp 247-272.
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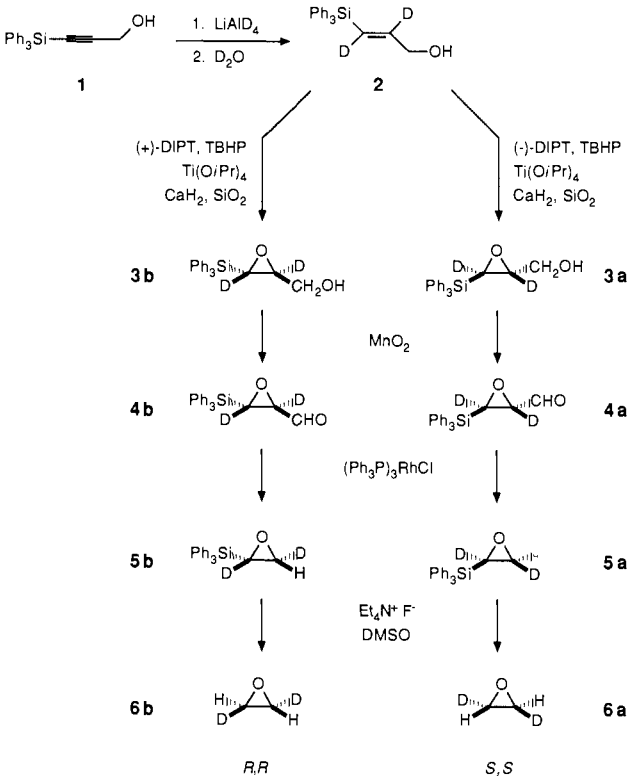
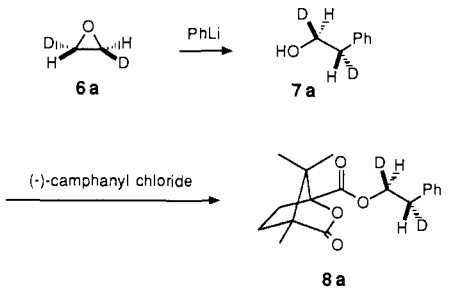
0002-7863/89/1511-1057$01.50/0

Scheme I



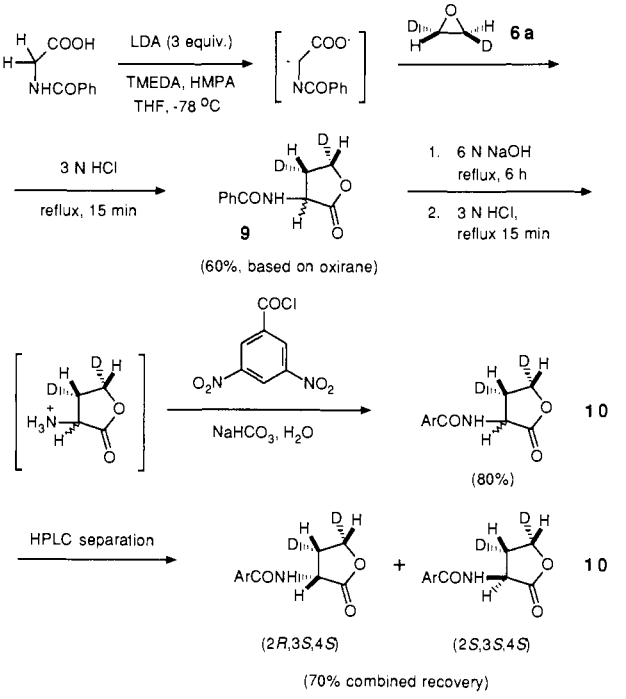
Scheme II



S,S and R,R forms, respectively, of 3-(triphenylsilyl)glycidol.[12] Removal of carbon 1 is effected by a two-step sequence: oxidation of the carbinol carbon with freshly prepared, activated manganese dioxide[13] and decarbonylation[14] with tris(triphenylphosphine)-rhodium(I) chloride. Finally, deuterated oxirane is generated by fluoride-mediated desilylation[15] of the last synthetic intermediate. With a stream of nitrogen, oxirane is entrained into a receiver for subsequent purification or reaction. Significantly, all of the triphenylsilyl-bearing intermediates are stable, crystalline compounds.

The enantiomeric purities of (2*R*,3*R*)- and (2*S*,3*S*)-[2,3-$^2H_2$]oxirane were determined by ^2H NMR analysis of a derivative.[16,17] A small quantity of each enantiomer was reacted with phenyllithium, and the resulting 2-phenylethanol was esterified with (1*S*)-(−)-camphanyl chloride (Scheme II). Eu(dpm)$_3$-shifted 61.39-MHz deuterium NMR spectra of the camphanate esters were obtained (and are available as supplementary material). Integration of the phenethyl C-1 deuteron signals showed that

Scheme III



the enantiomeric excess of (2*R*,3*R*)-[2,3-$^2H_2$]oxirane was 92%, and that of (2*S*,3*S*)-[2,3-$^2H_2$]oxirane was 94%. In each case, the *pro-S* deuteron resonated downfield relative to the *pro-R* deuteron,[16] supporting the assigned absolute configurations.

Synthesis and Analysis of Chirally Labeled Homoserine Lactone. The synthesis and resolution of (2*RS*,3*S*,4*S*)-[3,4-$^2H_2$]homoserine lactone are summarized in Scheme III. The trianion of hippuric acid[18] was generated with 3 equiv of lithium diisopropylamide in a mixed, cation-complexing solvent and was allowed to react with (2*S*,3*S*)-[2,3-$^2H_2$]oxirane (produced from (2*R*,3*S*)-2-(triphenylsilyl)[2,3-$^2H_2$]oxirane). The reaction mixture was acidified and heated briefly at reflux, providing a mixture of C-2 epimers of chirally labeled *N*-benzoylhomoserine lactone, in 60% yield based on the amount of oxirane generated.

The method of choice for determining the stereochemical integrity of the lactone deuterium atoms was high-field proton NMR spectroscopy, since it was assumed that a bulky lactone ring substituent (such as the benzamide group) would assume a quasiequatorial orientation and serve as a conformational anchor. Since the absolute configurations of the deuterium atoms (and *not* the configurations relative to the chiral center at lactone C-2) were fixed, it was necessary to resolve the labeled lactone. Unfortunately, attempts to use a chiral HPLC column to resolve *N*-benzoylhomoserine lactone, itself, failed. At this time a paper[19] by Pirkle and co-workers appeared in print, describing the resolution by HPLC of the enantiomers of *N*-(3,5-dinitrobenzoyl)-homoserine lactone, using a commercially available[20] column with a chiral stationary phase derived from *N*-(2-naphthyl)alanine.

In the event, *N*-benzoylhomoserine lactone was hydrolyzed with aqueous sodium hydroxide, and the lactone ring was reclosed, by treatment with acid and heat. The resulting labeled homoserine lactone was acylated with 3,5-dinitrobenzoyl chloride, affording the desired amido lactone in high yield. The chromatographic resolution of this material worked cleanly on an analytical scale; however, the preparative separation proved extremely tedious since only a 4.6 mm (i.d.) column was available in our lab. This column was easily overloaded, resulting in substantial peak tailing. Not surprisingly, the enantiomeric purity of the slower eluting 2*R* enantiomer was the lower of the two, since it was contaminated

(12) For the synthesis of the trimethylsilyl analogue, see: Katsuki, T. *Tetrahedron Lett.* **1984**, *25*, 2821–2822.
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(20) Pierce Chemical Co.

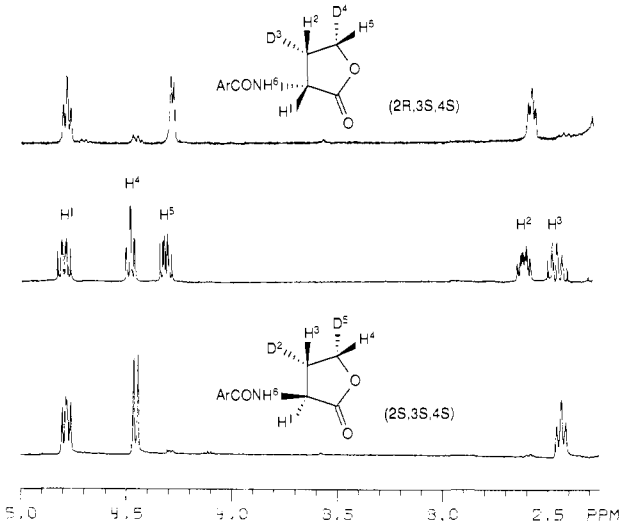
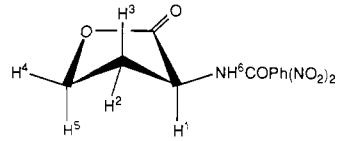


Figure 1. ^{1}H NMR (470 MHz) spectra of unlabeled and labeled samples of *N*-(3,5-dinitrobenzoyl)homoserine lactone (**10**) made by the route shown in Scheme III.

with a small amount of the 2*S* enantiomer.

The ^{1}H NMR spectrum of unlabeled *N*-(3,5-dinitrobenzoyl)-homoserine lactone was run at 470 MHz (Figure 1 (middle)), and a set of approximate coupling constants was determined by inspection. (Single-frequency decoupling and 2-D COSY experiments provided general coupling information.) Application of Schatz's RACCOON spectral simulation program[21] gave the coupling constants and chemical shifts shown below, affording remarkably accurate simulated spectra (data not shown). The NMR data were interpreted in terms of the conformation and assignments shown for *N*-(3,5-dinitrobenzoyl)homoserine lactone.



$J_{1,6}$ =	8.03 Hz	$J_{2,5}$ =	6.50 Hz
$J_{1,2}$ =	9.10 Hz	$J_{3,4}$ =	9.08 Hz
$J_{1,3}$ =	10.93 Hz	$J_{3,5}$ =	10.63 Hz
$J_{2,3}$ =	12.40 Hz	$J_{4,5}$ =	9.06 Hz
$J_{2,4}$ =	1.83 Hz		

It is predicted that in the ^{1}H NMR spectrum of (2*R*,3*S*,4*S*)-*N*-(3,5-dinitrobenzoyl)[3,4-^{2}H$_2$]homoserine lactone, the signals at 2.45 and 4.47 ppm should be missing (i.e., substituted with deuterium), and to a first approximation, this was so (Figure 1, top). Similarly, the signals at 2.61 and 4.30 ppm were essentially missing from the spectrum of the 2*S*,3*S*,4*S* compound (Figure 1, bottom). The stereochemical contamination of these samples could come from two sources: incomplete resolution by HPLC and the lack of enantiomeric purity of the deuterated oxirane.

The following calculations are for the 2*S* enantiomer, since the signal-to-noise ratio of its NMR spectrum was higher than that of the 2*R* enantiomer. The integrals of the residual 3*S* and 4*S* proton signals (H^2 and H^5, respectively) were each approximately 3.5% of those of the 3*R* and 4*R* proton signals. Analytical HPLC analysis showed that the sample contained 0.6% of the 2*R* enantiomer. The difference, i.e. 2.9%, could therefore be attributed to the presence of the 2*S*,3*R*,4*R* species. Thus, the diastereomeric excess value of the 2*S*,3*S*,4*S* lactone was (100 − (2.9 × 2))% = 94.2%. As mentioned above, the minimum ee value that we had

(21) We thank Prof. John Moore, Eastern Michigan University, and Project Seraphim for access to the RACCOON program.

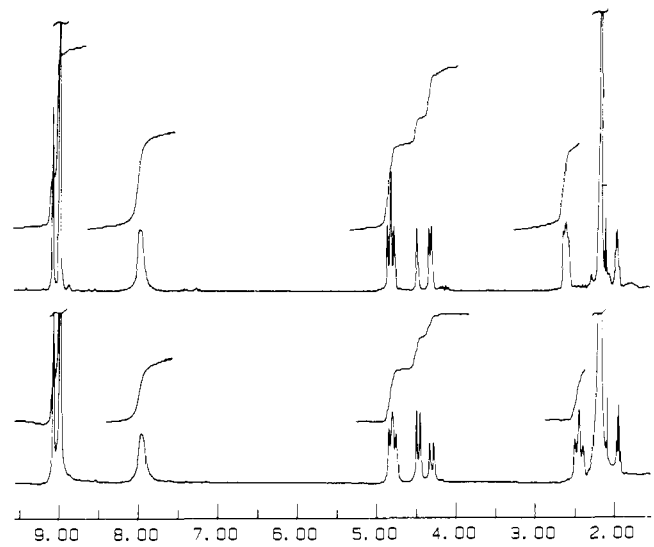


Figure 2. ^{1}H NMR (200 MHz) spectra of *N*-(3,5-dinitrobenzoyl)-homoserine lactone (**10**) made from (2*RS*,3*S*,4*S*)-*N*-benzoyl[3,4-^{2}H$_2$]-homoserine lactone that had been hydrolyzed in 6 N HCl and then acylated. Upper spectrum, (2*R*)-**10**; lower spectrum, (2*S*)-**10**.

determined previously for (2*S*,3*S*)-[2,3-^{2}H$_2$]oxirane was 94%, and so the two values agree closely.

Acid-Catalyzed Epimerization at C-4 of the Lactone. The original plan had been to debenzoylate *N*-benzoylhomoserine lactone in a single step, by acid hydrolysis. Since the reaction worked well on unlabeled lactone, it was repeated with a chirally labeled sample. The *N*-(3,5-dinitrobenzoyl) derivative of the resulting homoserine lactone was then resolved chromatographically. ^{1}H NMR spectra (200 MHz) of the labeled amido lactones are shown in Figure 2. The spectra indicate substantial epimerization of the C-4 label. There is no evidence for epimerization at C-3.

Three mechanisms for C-4 epimerization were considered (Scheme IV): (A) lactone hydrolysis, elimination of the C-4 hydroxyl with participation by the benzamide group, imidate hydrolysis, ester hydrolysis, and lactone reclosure; (B) lactone hydrolysis via an $A_{AL}2$ mechanism, amide hydrolysis, and lactone reclosure through initial attack of the C-4 hydroxyl at the carbonyl carbon; (C) lactone hydrolysis via nucleophilic attack of water at the carbonyl carbon, amide hydrolysis, and lactone reclosure with displacement of the C-4 hydroxyl by the carboxyl group (the reverse of $A_{AL}2$ hydrolysis). Mechanisms B and C are closely related. Mechanism A is fundamentally different.

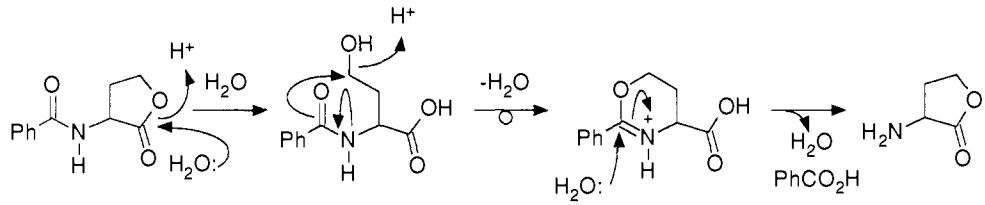
To evaluate epimerization mechanism A, the following experiment was performed (Scheme V). *N*-[*benzoyl*-^{18}O]-Benzoylhomoserine lactone was synthesized (from homoserine lactone and [^{18}O]benzoyl chloride) and subjected to the same acid-hydrolysis conditions used on the deuterated amido lactone. The resulting homoserine lactone was converted to the *N*-(3,5-dinitrobenzoyl) derivative, which was purified by HPLC. Analysis of this amido lactone by mass spectrometry indicated that no ^{18}O had been incorporated. Mechanism A predicts the incorporation of ^{18}O for each epimerization event. Since no label was incorporated, although the same hydrolysis conditions had been shown to result in extensive epimerization, mechanism A is eliminated.

Discussion

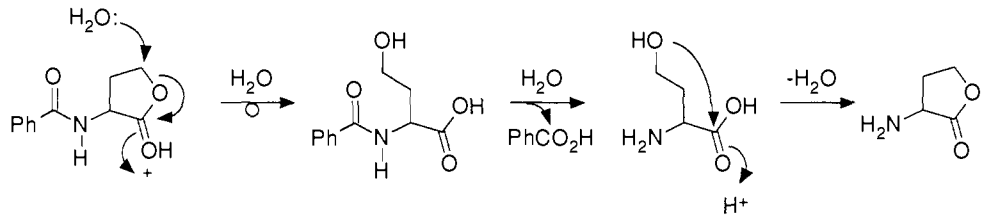
It is clear from integration of the signals in the ^{2}H NMR spectra of the phenethyl camphanates that the enantiomeric purity of chirally deuterated oxirane provided by our synthetic route is quite high. Though our samples were not of 100% enantiomeric purity, the values that we obtained (92% and 94% ee for (*R*)- and (*S*)-oxirane, respectively) are typical of those reported by Wang et al.[10] for their variant of the asymmetric epoxidation reaction. There is therefore no reason to suspect that either the decarbonylation or the desilylation compromises the stereochemical integrity of the product.

Scheme IV

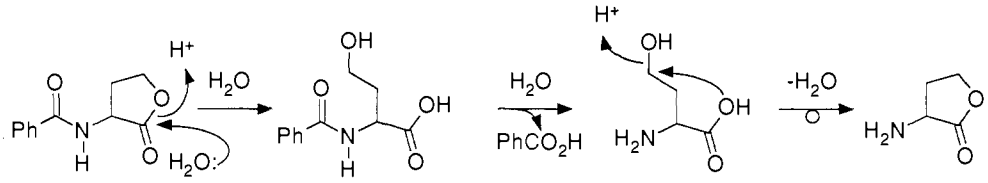
(A) Neighboring group participation:



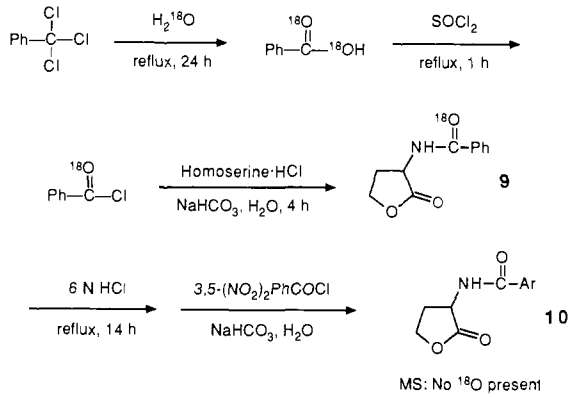
(B) Lactone hydrolysis via $A_{AL}2$ mechanism:



(C) "Normal" lactone hydrolysis; aberrant reclosure:



Scheme V



MS: No ^{18}O present

The procedures for synthesis and analysis of chirally deuterated oxirane as reported herein were improved somewhat over those that we had reported previously.[4] The most significant improvement is in the oxidation of 3-(triphenylsilyl)glycidol. Previously, silver carbonate on Celite[22] had been used for this purpose, but the yield proved variable (as low as 30%), and the reaction tended to be very sluggish. A variety of alternative methods were investigated before freshly prepared, activated manganese dioxide was found to work reliably,[13] although only providing fair-to-good yields. The analysis of our oxirane was facilitated by reacting it with phenyllithium, giving 2-phenylethanol, rather than with *n*-butyllithium, which gave 1-hexanol. Not only is 2-phenylethanol considerably less volatile (hence, easier to handle in small amounts) than 1-hexanol, but 2-phenylethanol and its (1*S*)-camphanic acid ester have UV chromophores, aiding their chromatographic identification.

Our original idea for the synthesis of chirally labeled oxirane was to reduce propargyl alcohol to (*E*)-2-[2,3-$^2H_2$]propenol, which would be asymmetrically epoxidized to [$^2H_2$]glycidol. Oxidation to [$^2H_2$]glycidal and decarbonylation of the latter would give [$^2H_2$]oxirane. This route was not even attempted, however, since it had been reported[11] that glycidol's water solubility rendered it very difficult to isolate from the epoxidation reaction mixture. We then envisioned a revised scheme that was the same as the successful scheme portrayed in Scheme I, except that trimethylsilyl, rather than triphenylsilyl, auxiliaries were employed. While the epoxidation of 3-(trimethylsilyl)-2-propenol proceeds smoothly,[12] we had no success with the desilylation reaction. The substitution of the triphenylsilyl group, as suggested by Prof. Chan,[23] led to smooth desilylation.[24] An incidental benefit of this modification is that all of the triphenylsilyl-substituted intermediates are water-insoluble, crystalline solids, and their molecular weights are high enough that manipulation of millimolar quantities is extremely straightforward.

The weakest step of the oxirane synthesis is the decarbonylation,[14] which is stoichiometric, not catalytic, and which proceeds in only fair yield.

We anticipate a number of applications for chirally labeled oxirane. For instance, the vibrational circular dichroism (VCD) spectra of the C–H and C–D stretching regions of (2*S*,3*S*)-[2,3-$^2H_2$]oxirane have recently been assigned,[25] and very recent theoretical calculations[26] have verified the assignments and led to extremely accurate modeling of the observed spectra. These results are of fundamental importance in that successful testing of theoretical predictions provides a framework for the interpretation of experimental VCD spectra of molecules of unknown stereochemistry.

A second application of chirally labeled oxirane is of more immediate relevance to our own interests. Since oxiranes are extremely versatile synthetic building blocks,[27] a wide variety of chirally labeled compounds can be produced with chirally labeled oxirane, or intermediates in our synthetic scheme, as the starting

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(23) Personal communication from Prof. T.-H. Chan.

(24) Infrared absorption spectra run by Prof. Nafie's group indicated that a small amount of benzene is formed as a byproduct.

(25) Freedman, T. B.; Paterlini, M. G.; Lee, N.-S.; Nafie, L. A.; Schwab, J. M.; Ray, T. *J. Am. Chem. Soc.* **1987**, *109*, 4727–4728.

(26) Jalkanen, K. J.; Stephens, P. J.; Amos, R. D.; Handy, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 2012–2013.

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material. The synthesis of (2*RS*,3*S*,4*S*)-[3,4-$^2H_2$]homoserine lactone in high diastereomeric purity is a case in point. Although chirally labeled homoserine has been made before,[28-31,54,55] the current synthesis is by far the shortest (considering oxirane or (triphenylsilyl)oxirane as the starting point).

The assignment of the sites of deuterium substitution in our labeled homoserine lactone amides was based on determination of the coupling constants of the ring protons (by inspection, with confirmation and refinement by spectral simulation). Several of these coupling constants, especially $J_{1,3}$, $J_{3,5}$, and $J_{2,4}$, led us to propose the conformation that is shown in the Results section. This interpretation is supported by the observation that the C-3 and C-4 axial protons resonate at higher field than do their equatorial counterparts.[32] As this stage of our work was being concluded (a preliminary communication[5] had already been submitted), a paper by Baldwin et al.[33] appeared in which the ^1H NMR spectrum of *N*-tritylhomoserine lactone was described and assigned. According to their assignments, if the conformation of this compound were similar to that of the *N*-(3,5-dinitrobenzoyl) derivative, with the nitrogen substituent in a quasiequatorial orientation, then the C-4 axial proton would resonate *downfield* relative to the C-4 equatorial proton. When the discrepancy between his results and ours was brought to his attention, Prof. Baldwin responded with a revised assignment,[34] based on NOE difference spectra. Indeed, *both* his original C-4 *and* C-3 proton assignments had been incorrect. Thus, the C-3 axial proton actually resonates at 1.6 ppm, downfield relative to the equatorial proton at 1.2 ppm. This assignment has recently been confirmed by Prof. R. W. Woodard,[35] by conversion of homoserine chirally labeled at C-3[30] to Baldwin's compound. The expected ^1H NMR signals were found to be absent.

The observed acid-catalyzed epimerization at C-4 of the lactone, while entirely unexpected, could be rationalized by one of the three mechanisms shown in Scheme IV. Of these, mechanism A is well-precedented.[36,37] According to both Gould[38] and March,[39] $A_{AL}2$ lactone hydrolyses (as in mechanism B) have not been observed. Since mechanism C proposes a lactone ring closure that is formally the reverse of an $A_{AL}2$ hydrolysis, it, too, is unlikely. We therefore expected that acidic hydrolysis of *N*-[*benzoyl*-^{18}O]benzoylhomoserine lactone would result in the labeling of the lactone ring oxygen, as predicted by mechanism A. Since this was not the case, we are left with the latter two mechanisms. The trivial explanation for the loss of ^{18}O is that the starting amide has itself undergone carbonyl oxygen exchange. Bender has shown, however, that amide oxygens do not exchange under acid-hydrolysis conditions.[40,41] Experiments designed to detect an $A_{AL}2$ lactone-hydrolysis mechanism (or the reverse mechanism, in the cyclization of a hydroxy acid) in a simpler system are currently being carried out.

There are many examples of nucleophilic lactone opening via S_N2 mechanisms.[42-50] Although imidate esters have been shown to hydrolyze by an $A_{AL}2$ mechanism in sulfuric acid solution,[51] the reaction described herein appears to be the first example of an $A_{AL}2$ oxygen ester hydrolysis.

Experimental Section

3-(Triphenylsilyl)-2-propynol (1).[6,7,52] To a solution of 2-propyn-1-ol (2.24 g, 40 mmol) in tetrahydrofuran (15 mL), in a flame-dried 500-mL three-necked flask at 0 °C, was added slowly, with stirring, a 2 M solution of ethylmagnesium bromide in tetrahydrofuran (44 mL). When the addition was complete, the mixture was allowed to warm to room temperature, and it was stirred for 1 h. Triethylamine (13 mL) was added along with a solution of chlorotriphenylsilane (25.9 g, 88 mmol) in tetrahydrofuran (40 mL), and the mixture was stirred overnight at room temperature. Tetrahydrofuran was removed in vacuo, and the residue was dissolved in ether. This solution was washed with dilute hydrochloric acid and then water, dried, and concentrated in vacuo. The residue was dissolved in tetrahydrofuran (10 mL) and treated with a mixture of acetic acid (20 mL) and water (10 mL) at 70 °C for 3 h. The reaction mixture was then cooled, and ether was added. This solution was washed with water, saturated aqueous sodium bicarbonate, and finally with water and was then dried and concentrated, giving a white solid. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes, affording compound **1** as colorless needles (9.4 g; 75% yield), mp 125–6 °C: ^1H NMR δ 1.67 (t, J = 5.5 Hz, 1 H, OH), 4.41 (d, J = 5.5 Hz, 2 H, CH_2O), 7.34–7.44 (m, 9 H, ArH), 7.62–7.66 (m, 6 H, ArH); IR (KBr) 3295 (br); 3060, 3009, 2998, 2900, 2848, 2170, 1431, 1125, 1100 (sh), 1048 (sh), 1035, 990, 981, 968 (sh), 731, 708, 698 cm^{-1}; HRMS (CI, isobutane) calcd for [$C_{21}H_{18}OSi$ + H − H_2O] 297.1099, found 297.1095.

(*E*)-3-(Triphenylsilyl)-2-[2,3-$^2H_2$]propenol (2).[6,9] To a suspension of lithium aluminum deuteride (42 mg, 1.0 mmol) in dry tetrahydrofuran (10 mL) was added a solution of **1** (314 mg, 1.0 mmol) in tetrahydrofuran (5 mL) at room temperature. The mixture was stirred for 2 h, until the reaction was complete. At this time, deuterium oxide (0.5 mL) was carefully added, and the mixture was stirred for 1 h before being diluted with ether (50 mL) and filtered. The organic phase was dried, and the solvent was removed, leaving a white residue of **2**, which was crystallized from ether/hexanes as colorless needles (310 mg: 98% yield), mp 145 °C: ^1H NMR δ 1.5 (t, J = 5.95 Hz, 1 H, OH), 4.28 (d, J = 5.95 Hz, 2 H, CH_2O), 7.34–7.42 (m, 9 H, ArH), 7.50–7.55 (m, 6 H, ArH); IR (KBr) 3320 (br), 3081, 3026, 3005, 2880 (br), 1602, 1490, 1457, 1440, 1381, 1346 (sh), 1335, 1308, 1264, 1186, 1157, 1117, 1088, 1042, 1030, 1004, 705 cm^{-1}; HRMS (CI, isobutane) calcd for [$C_{21}H_{18}D_2OSi$ + H − H_2O] 301.1381, found 301.1379.

(2*R*,3*R*)-3-(Triphenylsilyl)[2,3-$^2H_2$]oxiranemethanol (3a).[10-12] A mixture of titanium(IV) isopropoxide (5.68 g, 20 mmol), calcium hydride (0.08 g, 2.0 mmol), and silica gel (0.12 g, 2.0 mmol) in dry dichloromethane (100 mL) was stirred under nitrogen at −20 °C, while (−)-diisopropyl D-tartrate (5.85 g, 25 mmol) was added slowly via syringe. After the mixture had been stirred for 10 min, a solution of compound **2** (6.2 g, 20 mmol) in dichloromethane (40 mL) was added, and the reaction mixture was stirred for another 10 min. Anhydrous *tert*-butyl hydroperoxide (13 mL of a 3 M solution in toluene, 40 mmol) was then added. The reaction mixture was stirred at −20 °C for 16 h, after which time 10% aqueous tartaric acid (50 mL) was added, and the mixture was stirred at −20 °C for 30 min and then at room temperature for 1 h. The organic and aqueous layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic phase was dried and concentrated. The residue was diluted with ether and 1 N sodium hydroxide (50 mL) was added, and the resulting mixture was stirred for 30 min at 0 °C. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether extracts were washed with water and then dried. Concentration afforded a white solid, which was crystallized from a mixture of ether and hexanes, providing compound **3** as colorless needles (mp 127–8 °C, 6.3 g: 96% yield): ^1H NMR δ 1.75 (br t, 1 H, OH_C), 3.7 (dd, J_{AB} = 12.3 and J_{BC} = 6.5 Hz, 1 H,

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CH_AH_BOH), 4.0 (dd, J_{AB} = 12.3 and J_{AC} = 5.2 Hz, 1 H, $CH_AH_BOH_C$), 7.40–7.47 (m, 9 H, ArH), 7.50–7.61 (m, 6 H, ArH); IR (KBr) 3430 (br), 3065, 3045, 3000, 2910, 2860, 1480, 1428, 1180, 1100, 1070, 980, 960, 920 cm^{-1}; HRMS (CI, isobutane) calcd for $[C_{21}H_{18}D_2O_2Si + H]$ 317.1361, found 317.1358.

(2*R*,3*R*)-3-(Triphenylsilyl)[2,3-$^2H_2$]oxiranecarboxaldehyde (4a).[13] Alcohol **3a** (0.686 g, 2.04 mmol) was dissolved in dry benzene (75 mL) in a round-bottomed flask, and freshly prepared, activated manganese dioxide (1.8 g, 20.5 mmol) was added. The mixture was heated at reflux for 16 h and then was cooled and filtered, and the filter cake was washed thoroughly with ether. The filtrate was concentrated, leaving a white solid, which was partially purified by flash chromatography. Further purification was effected by careful crystallization of the impurities from hexanes/ether, in which they were less soluble. The mother liquor was concentrated to dryness, affording aldehyde **4a** (ca. 0.4 g, 60%) in a form sufficiently pure for the next step (mp 127–9 °C, for material recrystallized from EtOAc/hexanes): ^1H NMR δ 7.35–7.56 (m, 15 H, ArH), 8.76 (s, 1 H, CHO); IR (KBr) 3070, 3050, 3010, 2812, 1731, 1431, 1143, 1120, 1102 (sh), 1031, 995, 854, 816, 735, 714, 701 cm^{-1}; HRMS (CI, isobutane) calcd for $[C_{21}H_{18}O_2Si + H]$ (an analogous unlabeled sample) 331.1154, found 331.1150.

(2*R*,3*S*)-2-(Triphenylsilyl)[2,3-$^2H_2$]oxirane (5a). To a solution of **4a** (0.996 g, 3.00 mmol) in dry benzene (50 mL) was added tris(triphenylphosphine)rhodium(I) chloride (3.05 g, 3.30 mmol). The reaction mixture was heated at reflux for 4 h, cooled, filtered through Celite, and concentrated. The residue was purified by flash chromatography using 10% ethyl acetate in hexanes as eluent. Oxirane **5a** was obtained as colorless crystals (mp 61–2 °C, 0.36 g: 40% yield): ^1H NMR δ 3.00 (s, 1 H, CH), 7.56–7.60 (m, 15 H, ArH); IR (KBr) 3070, 3012, 1650, 1432, 1113, 733, 709, 697 cm^{-1}. For HRMS of the enantiomer **5b**, see the preparation of **6b**, below.

(2*S*,3*S*)-[2,3-$^2H_2$]Oxirane (6a) and Its Conversion to (2*S*,3*S*)-2-Phenyl-1-[1,2-$^2H_2$]ethanol (7a). A gentle stream of nitrogen was bubbled through a solution of **5a** (470 mg, 1.55 mmol) in dimethyl sulfoxide (5 mL) in a 50-mL three-necked flask. The gas outlet tube was dipped into anhydrous ether (2 mL), which was cooled to −20 °C. Tetraethylammonium fluoride (300 mg) was added quickly to the reaction mixture, which was stirred for 2 h. By this time the reaction was finished, and oxirane **6a** had been collected in the ether. A solution of phenyllithium (1.5 mL of a 1.7 M solution in hexanes/ether) was added slowly by syringe to the ethereal solution of the oxirane with constant stirring. After 10 min the temperature was allowed to rise to room temperature, and the mixture was stirred for an additional 0.5 h. The excess phenyllithium was then destroyed by the slow addition of water. The reaction mixture was acidified with cold 0.1 N hydrochloric acid and was extracted repeatedly with ether. The combined ether extracts were washed with water, dried, and concentrated, affording alcohol **7a** as a colorless oil (115 mg, 60% yield from **5a**): ^1H NMR δ 1.66 (s, 1 H, OH), 2.82 (br d, J = 6.1 Hz, 1 H CHPh), 3.81 (br d, J = 6.1 Hz, 1 H C*H*OH), 7.20–7.31 (m, 5 H, ArH).

(2*R*,3*R*)-[2,3-$^2H_2$]Oxirane (6b) and (2*R*,3*R*)-2-Phenyl-1-[1,2-$^2H_2$]-ethanol (7b). These compounds were prepared by the same procedures as described above for **6a** and **7a**. The IR and ^1H NMR data of **7b** were the same as those of **7a**. HRMS (CI, isobutane) calcd for **5b** $[C_{20}H_{16}D_2OSi + H]$ 305.1330, found 305.1333.

(1*S*)-Camphanate Ester Derivatives of Alcohols 7a and 7b. A solution of each alcohol (**7a** and **7b**) (30 mg, 0.25 mmol) in dry benzene (0.5 mL) with pyridine (0.03 mL) was added to 60 mg of freshly prepared (1*S*)-(−)-camphanic acid chloride (made by reaction of (1*S*)-camphanic acid with thionyl chloride) in a 10-mL round-bottomed flask. The reaction mixture was heated at reflux for 2 h and was then cooled, diluted with ether (5 mL), and washed with cold dilute hydrochloric acid, water, aqueous sodium bicarbonate, and finally with water. The organic phase was dried and concentrated, providing the camphanate ester, which was purified by flash chromatography.

8a (66 mg; colorless needles, mp 62–3 °C): ^1H NMR δ 0.85 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.6–1.7 (m, 1 H), 1.8–2.05 (m, 2 H), 2.3–2.4 (m, 1 H), 2.99 (br d, J = 7.2 Hz, 1 H, CHPh), 4.45 (br d, J = 7.2 Hz, 1 H, CHO), 7.22–7.32 (m, 5 H, ArH); IR (neat film) 2960, 2920, 2860, 1770, 1730, 1450, 1390, 1370, 1350, 1310, 1260, 1150, 1100, 1050, 1000, 980, 950, 920 cm^{-1}.

8b (68 mg; colorless needles, mp 62–3 °C): ^1H NMR δ 0.85 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 1.58–1.70 (m, 1 H), 1.8–2.02 (m, 2 H), 2.28–2.37 (m, 1 H), 2.98 (br d, J = 7 Hz, 1 H, CHPh), 4.45 (br d, J = 7 Hz, 1 H, CHO), 7.21–7.30 (m, 5 H, ArH).

(2*RS*,3*S*,4*S*)-*N*-Benzoyl[3,4-$^2H_2$]homoserine Lactone (9). To a stirred mixture of diisopropylamine (0.303 g; 3.00 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (0.5 mL) at 0 °C was slowly added *n*-butyllithium (2.1 mL of a 1.6 M solution in hexane; 3.36 mmol), under an atmosphere of nitrogen. After 10 min the mixture was cooled to −78 °C, and a solution of hippuric acid (0.179 g, 1.00 mmol) in tetrahydrofuran (1.0 mL) and TMEDA (1.0 mL) was added slowly, leading to the evolution of a deep yellow-orange color. This trianion solution was stirred for 15 min, and a solution of (2*S*,3*S*)-[2,3-$^2H_2$]oxirane (generated from 1.7 mmol of **5a**) in tetrahydrofuran (1 mL) plus hexamethylphosphoramide (1 mL) was added. The mixture was stirred for 1 h at −78 °C after which it was allowed to warm to room temperature and was stirred for an additional 1 h. It was then acidified with an equal volume of 6 N hydrochloric acid and heated at reflux for 15 min. After the reaction mixture had cooled to room temperature, it was extracted with ethyl acetate, and the extracts were washed sequentially with water, saturated aqueous sodium bicarbonate, and water. The solvent was removed, and the residual lactone was purified by flash chromatography (1:1, ethyl acetate/hexanes) to give **9** (0.124 g, 60%), which crystallized from $CHCl_3$/hexanes as colorless needles, mp 136–8 °C: ^1H NMR δ 2.28 (t, J = 9 Hz, 1 H, C*H*DCHDO), 2.85 (dd, J = 8.7, 5.9 Hz, 1 H, C*H*DCHDO), 4.3 (d, J = 9 Hz, 1 H, CHDO), 4.47 (d, J = 5.9 Hz, 1 H, CHDO), 4.76 (m, 1 H, C*H*NH), 7.1 (d, J = 6 Hz, 1 H, NH), 7.40–7.49 (m, 3 H, ArH) 7.7 (m, 2 H, ArH). NMR data and assignments of protons of undeuterated **9** are tabulated below for [*benzoyl*-^{18}O]-**9**.

***N*-(3,5-Dinitrobenzoyl)homoserine Lactone (10).** A solution of homoserine (0.12 g, 1 mmol) in 3 N hydrochloric acid (4 mL) was heated at reflux for 30 min and was then cooled. The resulting lactone solution was neutralized with aqueous sodium bicarbonate, and then an additional amount of sodium bicarbonate (0.20 g, 2.4 mmol) was added. To this solution was added 3,5-dinitrobenzoyl chloride (0.276 g, 1.2 mmol), and the mixture was stirred overnight. The white precipitate was removed by filtration, and it was washed with dilute aqueous sodium bicarbonate, and then with water. It was dried and then crystallized from acetone as colorless needles (0.176 g, 90%), mp 221–3 °C: ^1H NMR (CD_3CN; see Figure 1) δ 2.45 (dddd, J = 12.4, 10.9, 10.6, 9.1 Hz, 1 H, C-3 H cis to NH), 2.61 (dddd, J = 12.4, 9.1, 6.5, 1.8 Hz, 1 H, C-3 H trans to NH), 4.3 (ddd, J = 10.6, 9.1, 6.5 Hz, 1 H, C-4 H trans to NH), 4.47 (ddd, J = 9.1, 9.1, 1.8 Hz, 1 H, C-4 H cis to NH), 4.78 (ddd, J = 10.9, 9.1, 8.0 Hz, 1 H, C-2 H), 7.98 (d, J = 8.0 Hz, 1 H, NH), 8.95 (d, J = 1.9 Hz, 2 H, C-2′ and 6′ H), 9.04 (t, J = 1.9 Hz, 1 H, C-4′ H).

(2*RS*,3*S*,4*S*)-*N*-(3,5-Dinitrobenzoyl)[3,4-$^2H_2$]homoserine Lactone. To a solution of **9** (0.103 g, 0.5 mmol) in tetrahydrofuran (0.5 mL) was added 1.0 mL of 6 M sodium hydroxide. The resulting mixture was heated at reflux for 16 h and was then cooled and acidified with cold 3 N hydrochloric acid. This solution was heated at reflux for 15 min and then cooled in ice. The benzoic acid that separated was removed by filtration, and the homoserine lactone in the filtrate was acylated directly. The filtrate was neutralized with aqueous sodium bicarbonate, and then an additional amount of sodium bicarbonate (0.101 g, 1.2 mmol) was added. To the resulting solution was added 3,5-dinitrobenzoyl chloride (0.138 g, 0.6 mmol), and the mixture was stirred overnight. The product, a white solid, was removed by filtration and was washed with dilute aqueous sodium bicarbonate and then with water. It was dried and crystallized from acetone as colorless needles (0.118 g, 80%), mp 221–3 °C.

Resolution of 10 by HPLC.[19] Separation of the C-2 epimers of compound **10** was effected by HPLC using a column with a covalently bonded D-naphthylalanine stationary phase. The instrument was operated isocratically, using as the mobile phase 40% isopropyl alcohol in hexanes, with a flow rate of 2 mL/min. Under these conditions, the 2*S* (**10a**) and 2*R* (**10b**) isomers had retention times of 17.2 and 29.2 min, respectively. The order of elution was confirmed by comparing the observed retention times to that of *N*-(3,5-dinitrobenzoyl)homoserine lactone prepared from authentic, unlabeled L-homoserine. Twelve 10-μL injections were made of a 5 mg/mL solution of **10** in acetone. Due to overloading of the column, the resolved samples were contaminated with one another. The extent of this contamination, evaluated by analytical HPLC on the same column, was 0.6% for (2*S*)-**10** and 1.8% for (2*R*)-**10**.

(2*S*)-**10**: ^1H NMR (CD_3CN; see Figure 1) δ 2.43 (dd, J = 10.9, 9 Hz, 1 H, axial C-3 H), 4.45 (d, J = 9 Hz, 1 H, equatorial C-4 H), 4.78 (dd, J = 10.9, 7.7 Hz, 1 H, C-2 H), 7.99 (br, 1 H, NH), 8.96 (d, J = 1.9 Hz, 2 H, C-2′,6′ H), 9.04 (t, J = 1.9 Hz, 1 H, C-4′ H).

(2*R*)-**10**: ^1H NMR (CD_3CN; see Figure 1) δ 2.58 (dd, J = 8.9, 6 Hz, 1 H, equatorial C-3 H), 4.28 (d, J = 6 Hz, 1 H, axial C-4 H), 4.78 (dd, J = 8.9, 7.7 Hz, 1 H, C-2 H), 7.97 (br, 1 H, NH), 8.96 (d, J = 1.9 Hz, 2 H, C-2′,6′ H), 9.04 (t, J = 1.9 Hz, 1 H, C-4′ H).

Acid Hydrolysis of Benzamide 9. Derivatization and Resolution of the Resulting Labeled Homoserine Lactone. A suspension of **9** (0.103 g, 0.5 mmol) in 6 N hydrochloric acid (2 mL) was heated at reflux for 14 h. The mixture was then cooled in ice, and the benzoic acid that separated was removed by filtration. The homoserine lactone in the filtrate was converted without further manipulation to its *N*-(3,5-dinitrobenzoyl) derivative, as described above. The crude product was purified by flash

chromatography (1:1, ethyl acetate/hexanes), giving **10** as a white solid (0.118 g, 80% from 9), which was crystallized from acetone, affording colorless needles, mp 221-3 °C. The isomers ((2*S*)-**10** and (2*R*)-**10**) were separated by HPLC, as described above.

(2*S*)-**10**: ^{1}H NMR (CD_3CN; see Figure 2) δ 2.43 (dd, J = 10.9, 9 Hz, 1 H, axial C-3 H, overlapped with dd, J = 10.9, 10.6 Hz, 0.38 Hz, axial C-3 H of minor C-4 epimer), 4.28 (d, J = 10.6 Hz, 0.38 H, axial C-4 H of minor epimer), 4.45 (d, J = 9 Hz, 0.63 H, equatorial C-4 H of major epimer), 4.78 (dd, J = 10.9, 8 Hz, 1 H, C-2 H), 7.94 (br d, 1 H, NH), 8.96 (d, J = 1.9 Hz, 2 H, C-2',6' H), 9.04 (t, J = 1.9 Hz, 1 H, C-4' H).

(2*R*)-**10**: ^{1}H NMR (CD_3CN; see Figure 2) δ 2.58 (m, 1 H, overlapping equatorial C-3 H of both epimers), 4.28 (d, J = 6.5 Hz, 0.63 H, axial C-4 H), 4.44 (s, 0.38 H, equatorial C-4 H of the minor epimer), 4.78 (dd, J = 9.1, 8 Hz, 1 H, C-2 H), 7.94 (br d, 1 H, NH), 8.95 (d, J = 2 Hz, 2 H, C-2',6' H), 9.04 (t, J = 2 Hz, 1 H, C-4' H).

***N*-[*benzoyl*-^{18}O]Benzoylhomoserine Lactone (9).** A solution of homoserine (0.13 g, 1.1 mmol) in 3 N hydrochloric acid (4 mL) was heated at reflux for 30 min and then was cooled. The resulting lactone solution was neutralized with aqueous sodium bicarbonate and was then added to [^{18}O]benzoyl chloride (0.16 g, 1.1 mmol; made from [$^{18}O_2$]benzoic acid[53] by reaction with thionyl chloride). Sodium bicarbonate (0.42 g, 5.0 mmol) was added, and the mixture was stirred at room temperature for 1 h. The white solid that separated during the reaction was removed by filtration and dissolved in ethyl acetate. The organics were washed with water, dried, and concentrated, providing [*benzoyl*-^{18}O]**9**: ^{1}H NMR δ 2.27 (dddd, J = 12.6, 11.2, 9, 11.5 Hz, 1 H, C-3 H, cis to NH), 2.86 (dddd, J = 12.6, 5.9, 8.7, 1.3 Hz, 1 H, C-3 H, trans to NH), 4.30 (ddd, J = 11.2, 5.9, 9 Hz, 1 H, C-4 H, trans to NH), 4.47 (ddd, J = 9, 9, 1.3 Hz, 1 H, C-4 H, cis to NH), 4.75 (ddd, J = 11.5, 8.7, 6.2 Hz, 1 H, C-2 H), 7.08 (d, J = 6.2 Hz, 1 H, NH), 7.4-7.9 (m, 5 H, ArH); MS (70 eV, EI), m/z (% of base peak) 208 (10), 207 (10), 198 (1), 188 (5), 179 (1), 163 (3), 149 (2), 123 (4), 107 (100). Authentic, unlabeled **9**: MS (70 eV, EI), m/z (% of base peak) 206 (8), 205 (10), 196 (1), 188 (4), 176 (1), 161 (3), 147 (2), 121 (4), 105 (100).

Acid Hydrolysis of [*benzoyl*-^{18}O]-9. Derivatization and Analysis of the Resulting Homoserine Lactone. [*benzoyl*-^{18}O]-**9** was subjected to acid hydrolysis, as described above. The resulting homoserine lactone was converted to the 3,5-dinitrobenzamide **10**, which was crystallized from acetone (mp 222-3 °C). The ^{1}H NMR spectrum (CD_3CN) was identical with that of unlabeled **10**, described above. MS (CI, isobutane), m/z 298 (4), 296 (100), 282 (2), 266 (4). Authentic unlabeled **10**: MS (CI, isobutane), m/z 298 (2), 296 (100), 282 (3), 266 (5).

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Supplementary Material Available: Deuterium NMR spectrum of the chirally labeled 2-phenylethyl (1*S*)-camphanate ester derivatives of the chirally labeled oxirane enantiomers; a summary of general experimental procedures; a modification of the published procedure for the preparation of [^{18}O]benzoyl chloride (5 pages). Ordering information is given on any current masthead page.

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The Total Syntheses of the Isodityrosine-Derived Cyclic Tripeptides OF4949-III and K-13. Determination of the Absolute Configuration of K-13

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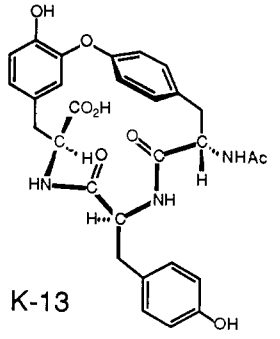
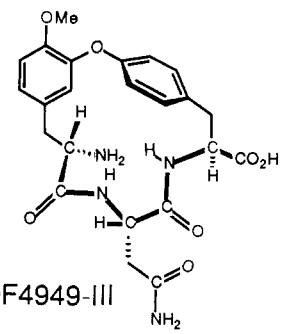
Abstract: The asymmetric syntheses of the two cyclic tripeptides OF4949-III and K-13 have been completed. The absolute stereochemical assignment of the former compound has been confirmed, while the absolute configuration of the latter has been established for the first time. The expedient bidirectional synthesis of a fully differentiated isodityrosine, a common



K-13



OF4949-III

intermediate to both molecules, was achieved by employing the recently developed direct electrophilic azidation of chiral imide enolates. In completing these syntheses, the utility of the azide as an amine-protecting group in peptide-coupling reactions and in peptide cyclizations was also evaluated. These studies have established that α-azido carboxylic acids are practical N-protected α-amino acid synthons and may be used as such in "racemization-free" peptide synthesis.

A diverse array of amino acids and peptides containing oxidatively coupled aromatic nuclei exist in nature. These compounds range from the tyrosine-derived peptides (thyroxine,[2] dityrosine,[3] isodityrosine,[4] trityrosine,[5] isotrityrosine,[6] piperazinomycin,[7]

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