128.7, 128.2, 125.9, 120.7, 102.4, 102.2, 59.8, 59.7, 40.8, 33.6, 28.9, 19.5, 19.3, 19.0, 14.3, 13.3, 10.1; IR 3391, 3064, 2978, 2933, 1732, 1682, 1625, 1495, 1210; MS 453 (35, M + 1), 379 (16.2), 338 (11), 301 (35), 252 (100), 91 (17). An analytical sample was obtained by preparative TLC ($SiO_2$, hexane/ethyl acetate, 4:1), $R_f$ 0.16. Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.75; H, 7.21; N, 6.33.

The racemic mixture was separated on a Daicel CHIRALCEL OJ column using 2% ethanol in hexane solvent with a flow rate of 1 mL/min. The enantiomers eluted approximately at 32 and 50 min, at ca. 50 °C. Enantiomeric purity was checked by reinjection after fraction collection. Within the limits of detection, the fractions were single enantiomers.

The procedures for X-ray crystallography[4,25,26] and radioligand binding[3,27] have been described previously, and are detailed in the supplementary material.

**Acknowledgment.** We wish to thank the Herman Frasch Foundation, administered by the American Chemical Society (Grant Number 0150-HF), and the National Institutes of General Medical Sciences (Grant Number 1-R15-GM42029-01) for generous support of our program. We thank Dr. Roger Willett and Brian Scott of the Washington State University X-ray facility. We also thank the NSF (Grant CHE-8408407) and the Boeing Co. for funds which helped establish the WSU X-ray facility.

**Supplementary Material Available:** 2D NOESY spectrum of 1, molecular mechanics calculations (including Cartesian coordinates) of *Z*- and *E*-1, tables of X-ray data for IDHP 5 (atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, and anisotropic thermal parameters, H atom coordinates), molecular mechanics calculation for 5, and NOESY spectrum of 5 (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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# A New Approach to Kainoids through Tandem Michael Reaction Methodology: Application to the Enantioselective Synthesis of (+)- and (−)-α-Allokainic Acid and to the Formal Synthesis of (−)-α-Kainic Acid†

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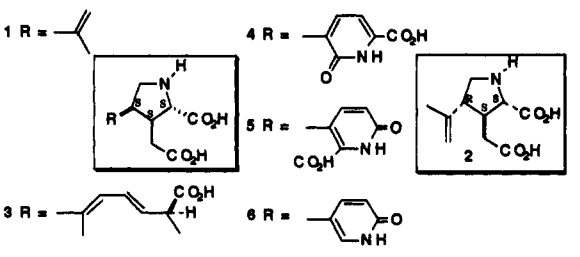
A convergent, one-pot construction of functionalized pyrrolidine ring systems has been developed. The method is based on a tandem Michael reaction initiated by an intermolecular conjugate addition of a nitrogen nucleophile to an electrophilic olefin followed by trapping of the generated enolate by a built-in α,β-unsaturated acceptor. After model studies verified the feasibility of the process and gave information about its stereochemical outcome, the strategy was successfully applied to kainoid synthesis. The construction of the basic pyrrolidine skeleton of all the members of the family requires coupling of a suitable electrophilic subunit with a common donor–acceptor fragment containing the nitrogen nucleophile. Thus, the enantioselective synthesis of (+)-α-allokainic acid (2) and the formal synthesis of its C-4 epimer (−)-α-kainic acid (1), have been accomplished using methyl vinyl ketone and 2-nitro-3-methyl-1,3-butadiene, respectively, as electrophilic partners of (*S*)-4-(benzylamino)-5-hydroxy-2-pentenoic acid ethyl ester (17), easily derived in six steps from D-serine. Although the acetyl group of methyl vinyl ketone is a logical precursor to the isopropenyl moiety of 2, the use of the nitrobutadiene is more appropriate for the synthesis of 1 because of the startling degree of control of the cyclization stereochemistry exerted by the nitro group.

## Introduction

The term kainoid refers to a group of naturally occurring, nonproteinogenic amino acids possessing a pyrrolidine dicarboxylic acids nucleus as a common structural feature.[1] Certain members of this family (Chart I), such as α-kainic acid (1) and its C-4 epimer α-allokainic acid (2),[2] domoic acid (3),[3] and acromelic acids A (4), B (5),[4] and C (6),[5] are of considerable interest since they have been found to exhibit powerful biological properties, principally neuroexcitatory, which can be ascribed to their acting as conformationally restricted analogues of glutamic acid.

Chart I




From a synthetic viewpoint, these compounds present a considerable challenge,[6] most notably because the pyr-

† Taken in part from the thesis of "Dottorato di Ricerca in Scienze Chimiche" of G. Spalluto, Parma, Modena and Ferrara Universities, 1989–1991.

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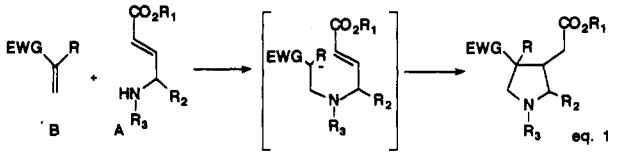
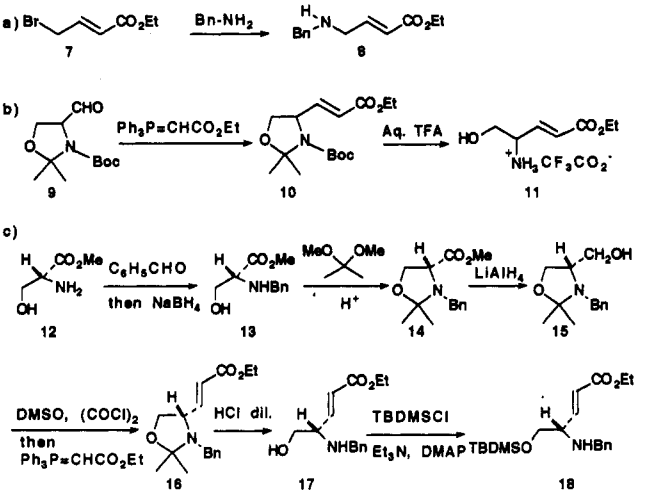
rolidine ring system contains three contiguous chiral centers, all but one with a trans arrangement between the C-2 and C-3 substituents and a cis arrangement of the C-3 and C-4 substituents. The first enantioselective synthesis of (−)-α-kainic acid (1) was achieved by Oppolzer[7] in 1982 starting from L-glutamic acid, thus establishing unequivocally the absolute configuration. Synthetic efforts in this area are being directed to the development of general methodologies adaptable to the synthesis of kainoids with side chains other than those leading to kainic acid. This concept is well illustrated by the cobalt-mediated enantioselective route to kainoids recently disclosed by J. Baldwin et al.[8]

**General Strategy.** With the aim of developing a general approach to kainoids that would allow a ready incorporation of a variety of different side chains, we were attracted by the possibility of constructing functionalized pyrrolidine ring systems through a one-pot tandem Michael reaction sequence. Although efficient variants[9-11] of such multicomponent annulation reactions have been widely applied for the construction of carbocyclic structures, usually by carbon nucleophile-initiated Michael additions, less attention has been paid to nitrogen nucleophile-initiated multiple bond formation in a single step as a tool for the preparation of substituted nitrogen heterocycles.

Our own synthetic strategy, illustrated in its simplest version for preparing 3,4-disubstituted pyrrolidines in eq 1, requires two subunits, namely the fragment A (Michael donor–acceptor), containing both the nitrogen nucleophile and a suitably placed Michael acceptor able to trap the initially generated anion, and the electrophilic olefin B (Michael acceptor–donor). In order to extend the methodology to the construction of 2,3,4-trisubstituted pyrrolidines, and thence to kainoids, an additional substituent serving as precursor of a carboxyl group is required at the carbon carrying the nitrogen nucleophile. Moreover, depending on the length of the tether joining the nitrogen nucleophile and on the nature of the built-in α,β-unsaturated acceptor, the method could be easily adapted to the preparation of substituted piperidine ring systems.




**Scheme I**




A number of electrophilic olefins are commercially available or easily prepared by simple methodologies. At the outset of this study, we selected methyl vinyl ketone (MVK) and nitroolefins, being aware of their ability to function as Michael reagents. We also considered the versatility and flexibility of the electron-withdrawing functionalities, which, of course, not only activate the double bond but also may serve as precursors of required substituents or be removable after having completed their function. Therefore, our first task was the preparation of fragments containing both the nitrogen nucleophile and the suitably placed Michael acceptor.

## Results and Discussion

**Preparation of Donor–Acceptor Subunits.** In order to verify the feasibility of the protocol, we used the standard chemistry outlined in Scheme I to prepare subunits 8, 11, and 18, which contain the required moieties. Unit 8 was easily obtained by nucleophilic substitution of the allylic bromine of ethyl 4-bromo-2-butenoate with benzylamine (path a). Building blocks 11, 17, and 18 were prepared from protected serine derivatives, in both racemic (path b) and optically active forms (path c). Thus, the α,β-unsaturated hydroxy ester 11 was obtained in 90% yield from the readily available aldehyde 9[12] in a two-step sequence involving transformation of 9 to ester 10 by reaction with (carbethoxymethylene)triphenylphosphorane followed by aqueous trifluoroacetic acid-promoted removal of the protecting groups. A serine-derived aldehyde analogous to 9, which was not isolated, was the key intermediate for the preparation of the N-benzylated derivatives 17 and 18. The benzyl protecting group, which preserves the nucleophilic character of the nitrogen atom, was easily introduced by reductive amination of D-serine methyl ester 12 to yield 13, which was further converted to isopropylidene derivative 14. Disappointingly, we were unable to convert the ester group of 14 directly into the required aldehyde by reduction with diisobutylaluminum hydride in spite of previous successes on similar substrates. Therefore, we were forced to use a reduction–oxidation sequence to perform this transformation. Lithium aluminum hydride reduction of 14 gave the primary alcohol 15, which was submitted to Swern oxidation and Wittig reaction (carbethoxymethylene)triphenylphosphorane in a single operation[13] to afford α,β-unsaturated ester 16. The

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(4) (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939–942. (b) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *100*, 4807–4815.

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(6) For recent developments in the area of α-amino acid synthesis, see: Williams, R. M. *The Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

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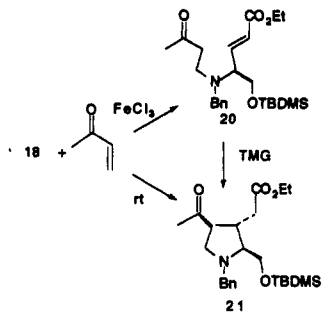
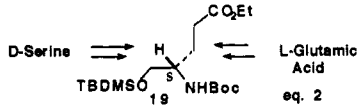
**Scheme II**




acid-promoted opening of the oxazolidine ring produced γ-amino-α,β-unsaturated hydroxy ester **17**, which was easily transformed into the corresponding silyl ether **18** by DMAP-catalyzed reaction with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of triethylamine. The optical integrity of **18**, obtained in six steps in 40% overall yield starting from D-serine, has been unambiguously established through its conversion by catalytic hydrogenation over 10% Pd/C in the presence of $(Boc)_2O$ to the known **19**, prepared by Oppolzer[7] from (*S*)-glutamic acid as a key intermediate in the total synthesis of (−)-α-kainic acid (eq 2).

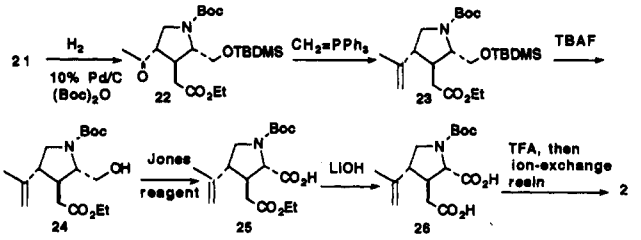



**Coupling Reactions.** Having in hand suitably designed nitrogen nucleophiles, we were prepared to study their coupling reaction with electrophilic olefins such as MVK and nitroolefins.

**(a) Coupling with MVK: Enantioselective Synthesis of (+)-α-Allokainic Acid (2).** The reaction of MVK with the Michael donor–acceptor γ-amino-α,β-unsaturated ester **18** in ethanol solution proceeded rather slowly at room temperature (Scheme II), producing after 15 days pyrrolidine **21** as the sole reaction product. Interestingly, we found that the cyclization of the initially formed intermolecular adduct **20** could be significantly accelerated by the addition of a few drops of tetramethylguanidine (TMG) after the disappearance of the starting materials. The reaction can also be carried out in two separate steps by adding $FeCl_3$, which acts both as a catalyst for the intermolecular Michael addition and as an inhibitor of the intramolecular process.[14] The subsequent cyclization step was promoted by TMG, as well as other bases such as sodium ethoxide, and afforded **21** in 90% yield. The formation of a pyrrolidine ring system possessing anti substituents at C-2–C-3 and at C-3–C-4, the arrangement of lower steric interactions, can be accounted for by a transition state with a favorable antiperiplanar orientation between the acceptor side chain and the acetyl group in the intramolecular reaction.

Since the structure of trisubstituted pyrrolidine **21** could not be unequivocally established either by decoupling or by NOE experiments, we decided to elaborate **21** to kainoids,[15] the acetyl group being a logical precursor of the isopropenyl side chain that is present in both (−)-α-kainic acid (**1**) and its C-4 epimer (+)-α-allokainic acid (**2**). The

**Scheme III**




synthetic sequence is depicted in Scheme III. Thus, the nitrogen protective benzyl group of **21** was hydrogenolytically removed and replaced by a *tert*-butyloxycarbonyl moiety in a single operation,[16] affording a practically quantitative yield of **22**. Ketone **22** underwent Wittig olefination with methylenetriphenylphosphorane to produce **23** in 60% yield. Treatment of **23** with tetrabutylammonium fluoride (TBAF) gave the primary alcohol **24**. The all-trans relationship of the C-2, C-3, and C-4 protons was unequivocally demonstrated by comparison of the $^1H$ NMR of **24** with that of a similar compound recently described by Baldwin[8] and by the occurrence of the olefinic protons as a singlet. The presence of a singlet is indicative of a trans relationship between the acetic chain and the isopropenyl side chain, as suggested by Kozikowski.[17] The structure of **24** allowed us to draw conclusions about the stereochemical outcome of the tandem Michael cyclization and about the key role played by the C-2 substituent in controlling the C-3 stereochemistry. Oxidation of the primary alcohol to the corresponding carboxylic acid with Jones reagent afforded **25**, which was converted to diacid **26** by lithium hydroxide saponification. Removal of the remaining protective group with trifluoroacetic acid, ion-exchange resin chromatography, and crystallization from water led to the isolation of enantiomerically pure (+)-α-allokainic acid (**2**).

Starting from the enantiomer of **18**, in turn derived from L-serine methyl ester **12**, we were able to synthesize (−)-α-allokainic acid in a similar fashion. This result supported the validity of the tandem Michael approach for the synthesis of stereochemically defined trisubstituted pyrrolidine systems and for the creation of three contiguous stereogenic centers in a single stage. However, it was apparent that this approach would not afford compounds with the requisite cis relationship between the acetic chain at C-3 and a substituent at C-4 suitable for the synthesis of kainoids.

**(b) Coupling with Nitroethylenes.** To expand the scope of our protocol, we decided to investigate the reactivity of nitroethylenes toward nitrogen nucleophiles. The Michael acceptor properties of these compounds are well-known. However, despite a pertinent body of literature on their chemistry,[18] we were forced to take a preliminary look at a suitable device to overcome the propensity of nitroethylenes for anionic polymerization in the presence of aliphatic amines. We overcame this obstacle by generating nitroalkenes in situ from 1-(benzoyloxy)-2-nitroethanes in the presence of the nitrogen-containing subunits,[19] which act both as Michael donors and as basic catalysts to promote the formation of the nitroalkenes. Nitroalkene precursors **27–30** were prepared from the

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(15) Preliminary communication: Barco, A.; Benetti, S.; Casolari, A.; Pollini, G. P.; Spalluto, G. *Tetrahedron Lett.* **1990**, *31*, 4917–4920.
(16) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654–4660.
(17) Kozikowski, A. P.; Fauq, A. H. *Tetrahedron Lett.* **1990**, *31*, 2967–2970.
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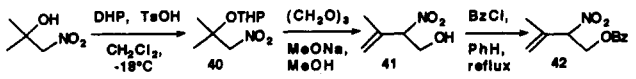
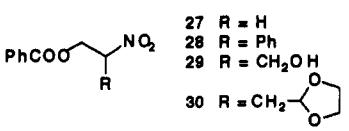
**Scheme IV**

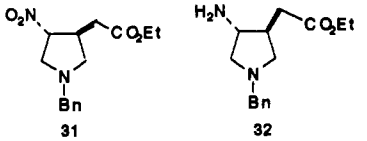


corresponding nitro alcohols and benzoyl chloride following reported directions.[20]



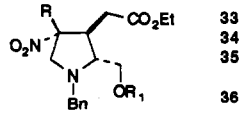
27 R = H
28 R = Ph
29 R = $CH_2OH$
30 R = $CH_2$-(dioxolane)

To establish appropriate conditions for preparing disubstituted pyrrolidine and piperidine ring systems by the tandem Michael reaction methodology, our preliminary efforts[21] were directed toward the simple model compound derived from the reaction of **27** with subunit **8**. The use of benzylated secondary amines instead of primary ones prevented the formation of mono- and bisadducts in the intermolecular step. Thus, treatment of equimolecular amounts of **27** and **8** at room temperature led directly to formation of cyclized products in good yield. $^1H$ NMR analysis of the crude mixture revealed the presence of two products: trans pyrrolidine **31** and small quantities of the cis isomer (ratio 20:1), where were separated by careful flash chromatography. The stereospecific course of the heterocyclization leading to a preferential trans arrangement of the substituents agreed with the results described for similar carbocyclizations.[10] Indirect evidence supporting the assigned trans relationship of the nitro group and the acetic side chain came from the reluctance of the derived amino ester **32** to undergo intramolecular lactamization, in sharp contrast with the facile aminolysis of $\gamma$-amino ester to form $\gamma$-butyrolactams.



31 32

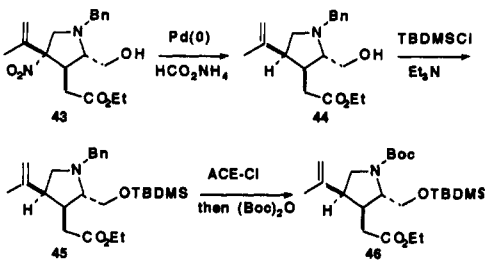
Analogously, the reactions of racemic amino esters **17** with the nitroethylenes generated from **27** and **28** produced the cyclized products **33** and **34**, respectively, and the reaction of amino ester **18** with the nitroethylenes generated from **29** and **30** produced **35** and **36**, respectively. Only in the reaction of subunit **17** with **28** was the formation of a minor amount (10%) of the C-4 epimer observed. Interestingly, the presence of a free hydroxyl group, as in **17**, did not affect the stereochemical outcome of the process, excluding possible interaction between the nitro and hydroxyl group in the transition state leading to the heterocycle formation. Most of these cyclic compounds might



33 R = H; $R_1$ = H
34 R = Ph; $R_1$ = H
35 R = $CH_2OH$; $R_1$ = TBDMS
36 R = $CH_2$-(dioxolane); $R_1$ = TBDMS

in principle be considered useful intermediates for kainoid synthesis provided it was possible to stereospecifically replace the nitro group with a hydrogen. This operation was initially performed on substrates **34–36** under radical conditions ($n$-$Bu_3SnH$ in the presence of AIBN). In the case of **34** and **35**, $^1H$ NMR analysis of the reaction products revealed the presence of an inseparable mixture

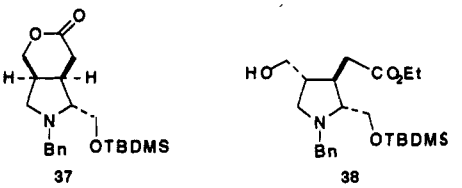
**Scheme V**





43 44 45 46

of the denitrated compounds. Flash chromatography of the mixture derived from **35** allowed the separation of the lactone **37** and trans hydroxy ester **38** in 1:1 ratio. The latter result was indirect evidence for the stereochemical assignment of the cyclized products.



37 38

Although not unexpected, the lack of stereospecificity of the radical denitration process called for an alternative method for effecting this pivotal operation. The methodology introduced by Ono[22] for denitration of allylic nitro compounds, based on activation through initial complexation with a Pd(0) derivative followed by nitrite ion expulsion, seemed well suited for our purposes. The regiochemistry is secured by the use of ammonium formate as the hydride source, while the stereoselectivity is provided by expulsion of nitrite ion from the $\pi$-allylpalladium complex through hydride attack. Of course, this tactical solution required the preparation of a trisubstituted pyrrolidine having an allylic nitro group at the C-4 position. A logical solution was the utilization of 2-nitro-1,3-butadienes instead of simple nitroolefins as Michael acceptors.

**(c) Coupling with 2-Nitro-1,3-butadienes: Formal Enantioselective Synthesis of (−)-$\alpha$-Kainic Acid (1).** In planning to carry out this fascinating hypothesis, we were immediately faced with the apparently trivial problem of preparing the nitro diene **39** or an equivalent thereof

39

in useful yield. The pyrolysis of 3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxide is the only reported[23] preparation of **39**. In view of the instability of **39** and its propensity for anionic polymerization, this preparation was unsatisfactory in terms of both practicality and yield. Fortunately, we were able to develop an efficient preparation of 1-(benzoyloxy)-3-methyl-2-nitro-3-butene (**42**) starting from commercially available 2-hydroxy-2-methyl-1-nitropropane (Scheme IV). Thus, protection of the tertiary hydroxyl gave tetrahydropyranyl ether **40**. Hydroxymethylation gave **41**, and subsequent benzoylation with benzoyl chloride gave **42**, a suitable precursor for electrophilic component **39** in the crucial coupling reaction with **17**. Compound **17** acts both as the donor–acceptor partner and as a basic catalyst for generating **39**.

Having in hand convenient sources of the required subunits, we were prepared to apply our tandem Michael

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(22) Ono, N.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 3734–3736.
(23) Berestovitskaya, V. M.; Speranskii, E. M.; Perekalin, V. V. *Zh. Org. Khim.* **1979**, *15*, 164–172.

reaction protocol. We were delighted to find[24] that a quantitative yield of the desired pyrrolidine **43** could be obtained as the sole reaction product simply by stirring equimolecular quantities of **17** and **42** in ethanol at room temperature for 15 h! The startling extent to which the nitro group served as a stereo- and regiochemical control element during the cyclization came as an unexpected bonus. The $^1$H NMR spectrum of **43** exhibits two broad singlets for the olefinic protons, indicating the cis relationship between the acetic acid chain and the isopropenyl appendage.[17] This assignment was supported by formal conversion of **43** to (−)-α-kainic acid (**1**) as depicted in Scheme V.

Having served its stereochemical controlling role, the allylic nitro group was now removed regio- and stereoselectively by a palladium-catalyzed hydride-transfer reaction following the Ono procedure. Compound **44** was produced in practically quantitative yield. The formal synthesis of (−)-α-kainic acid was completed by standard protection of the hydroxyl group of **44** as the *tert*-butyldimethylsilyl ether **45**. Subsequent replacement of the nitrogen benzyl protective group by *tert*-butyloxy in a single operation[25] afforded a 50% overall yield of intermediate **46**, already converted by Oppolzer et al.[7] into (−)-α-kainic acid (**1**).

## Experimental Section

**General Remarks.** Melting points are uncorrected. Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates $F_{254}$ (Merck) and visualized with iodine, aqueous potassium permanganate, or methanolic ninhydrin. Nuclear magnetic resonance ($^1$H NMR) spectra were recorded in $CDCl_3$ unless otherwise noted; peak positions are given in parts per million downfield from tetramethylsilane as an internal standard, and $J$ values are given in hertz. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Petroleum ether refers to the fractions boiling in the range 40–60 °C. Flash chromatography was carried out with Merck silica gel (230–400 mesh). All reactions were carried out under $N_2$. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

**Ethyl 4-(Benzylamino)-2-butenoate (8).** A solution of ethyl 4-bromo-2-butenoate (3.86 g, 20 mmol) and benzylamine (4.28 g, 40 mmol) in $CH_2Cl_2$ (50 mL) was stirred at rt for 3 h and then washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried, and concentrated. The residue was purified by flash chromatography (4:1 ether–petroleum ether) to afford **8** (3.5 g, 80%) as an oil: IR (neat) 3350, 1720 cm$^{-1}$; $^1$H NMR δ 1.2 (t, 3 H, $J$ = 7), 1.6 (bs, 1 H), 3.42 (dd, 2 H, $J$ = 5, 1.6), 3.8 (s, 2 H), 4.2 (q, 2 H, $J$ = 7), 6.04 (d, 1 H, $J$ = 15), 7.06 (dt, 1 H, $J$ = 15, 5), 7.35 (m, 5 H).

**2,2-Dimethyl-4-(3-ethoxy-3-oxo-1-propenyl)-3-oxazolidinecarboxylic Acid 1,1-Dimethylethyl Ester (10).** [(Ethoxycarbonyl)methylene]triphenylphosphorane (3.65 g, 10.5 mmol) was added to a solution of racemic protected serinal (**9**)[12] (2 g, 8.73 mmol) in anhydrous benzene (12 mL), and the mixture was stirred at rt for 6 h. The precipitated solid was removed by filtration, and the filtrate was concentrated. The residue was purified by flash chromatography (1:4 EtOAc–petroleum ether) to give **10** as an oil in quantitative yield: IR (neat) 1730, 1710, 1670 cm$^{-1}$; $^1$H NMR δ 1.25 (t, 3 H, $J$ = 7), 1.45 (s, 9 H), 1.55 (s, 3 H), 1.65 (s, 3 H), 3.7 (m, 1 H), 4.1 (m, 1 H), 4.2 (q, 2 H, $J$ = 7), 4.4–4.55 (m, 1 H), 5.9 (m, 1 H), 6.85 (m, 1 H). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.32; H, 8.24; N, 4.63.

**4-Ammonio-5-hydroxy-2-pentenoic Acid Ethyl Ester Trifluoroacetate (11).** A mixture of **10** (2 g, 6.69 mmol) in TFA (5 mL) containing few drops of $H_2O$ was stirred at rt for 1 h. The solvent was removed to leave crude **11** as a waxy solid, which was used in the next step without further purification. A sample of the waxy solid was treated with $NaHCO_3$ solution, extracted with AcOEt, dried, and evaporated. The residue was flash chromatographed (1:9 MeOH–AcOEt) to give the free amino compound as an oil: IR (neat) 3500, 3300, 1725, 1660 cm$^{-1}$; $^1$H NMR δ 1.1 (t, 3 H, $J$ = 7), 3.5–3.75 (m, 2 H), 3.91 (m, 1 H), 4.2 (q, 2 H, $J$ = 7), 6.1 (d, 1 H, $J$ = 15), 6.85 (dd, 1 H, $J$ = 15, 4).

**(*RS*)- or (*R*)-*N*-Benzylserine Methyl Ester (13).** To a solution of racemic or D-serine methyl ester hydrochloride (**12**) (7.87 g, 50.4 mmol) in anhydrous $CH_2Cl_2$ (50 mL) were added $Et_3N$ (7.26 mL), benzaldehyde (5.14 mL), and anhydrous $MgSO_4$ (5 g). After 24 h, the mixture was filtered, the filtrate was concentrated, and the residue was dissolved in MeOH (100 mL) and treated portionwise with $NaBH_4$ (1.9 g) at 0 °C. After 4 h, $H_2O$ and EtOAc (50 mL each) were added, and the organic layer was separated, washed with brine, and dried. Removal of the solvent afforded **13** (10.4 g), which was utilized without further purification: IR (neat) 3500, 3300, 1740, 1600 cm$^{-1}$; $^1$H NMR δ 2.62 (bs, 2 H), 3.42 (dd, 1 H, $J$ = 6, 4), 3.62 (dd, 1 H, $J$ = 14, 6), 3.73 (s, 3 H), 3.8 (AB system, 2 H, $J$ = 15), 3.82 (dd, 1 H, $J$ = 14, 4), 7.31 (m, 5 H).

**(*R*)-3-Benzyl-2,2-dimethyl-4-oxazolidinecarboxylic Acid Methyl Ester (14).** A solution of **13** (10 g, 47.8 mmol), 2,2-dimethoxypropane (60 mL) in dry benzene (60 mL) containing *p*-TSA (0.3 g), and molecular sieves (4 Å) was refluxed for 24 h. The reaction mixture was filtered and concentrated, and the residue was partitioned between saturated $NaHCO_3$ and ether. The dried organic extracts were concentrated, and the residue was purified by distillation to give **14** as a colorless oil in quantitative yield: bp 101 °C (0.5 mmHg); $[\alpha]^{20}_D$ = −7.8° (*c* 3.06, $CHCl_3$); IR (neat) 1750 cm$^{-1}$; $^1$H NMR δ 1.3 (s, 3 H), 1.4 (s, 3 H), 3.4 (s, 3 H), 3.65 (m, 1 H), 3.7 (d, 1 H, $J$ = 13.2), 4.0 (m, 1 H), 4.11 (t, 1 H, $J$ = 8), 7.3 (m, 5 H). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.40; H, 7.59; N, 5.67.

**(*S*)-3-Benzyl-2,2-dimethyl-4-oxazolidinemethanol (15).** To an ice-cooled suspension of $LiAlH_4$ (0.27 g, 7.1 mmol) in dry ether was added dropwise a solution of ester **14** (3 g, 12 mmol) in ether (20 mL). The rate of addition was adjusted so as to keep the internal temperature below 3 °C. After 1 h, water was cautiously added, and the supernatant was decanted from the aluminum salts, which were washed three times with ether. The combined extracts were dried and concentrated to leave quantitatively **15**, which was used without further purification: IR (neat) 3500, 3300 cm$^{-1}$; $^1$H NMR δ 1.28 (s, 3 H), 1.33 (s, 3 H), 2.28 (bs, 1 H), 3.1 (m, 3 H), 3.55 (d, 1 H, $J$ = 15), 3.8–3.97 (m, 1 H), 3.9 (d, 1 H, $J$ = 15), 4.0 (m, 1 H), 7.32 (m, 5 H).

**(*S*)-3-Benzyl-2,2-dimethyl-4-oxazolidinepropenoic Acid Ethyl Ester (16).** To a stirred −78 °C solution of oxalyl chloride (1.26 mL, 14.64 mmol) in dry $CH_2Cl_2$ (20 mL) was added DMSO (2.26 mL, 32.34 mmol). After stirring of the reaction mixture for 15 min, alcohol **15** (2.7 g, 12.21 mmol) in $CH_2Cl_2$ (15 mL) was added over 5 min. After the solution stirred for an additional 20 min, $Et_3N$ (8.8 mL) was added, followed by a solution of (carbethoxymethylene)triphenylphosphorane (8.5 g, 35.6 mmol) in $CH_2Cl_2$ (30 mL). The reaction mixture was allowed to warm to rt over 1 h and then treated with brine (10 mL). The separated organic layer was dried, the solvent removed, and the residue flash chromatographed (1:1 ether–petroleum ether) to afford **16** (2.15 g, 61%) as a colorless oil: $[\alpha]^{20}_D$ = +8.3° (*c* 1.72, $CHCl_3$); IR (neat) 1715, 1650 cm$^{-1}$; $^1$H NMR δ 1.23 (t, 3 H, $J$ = 6.8), 1.25 (s, 3 H), 1.27 (s, 3 H), 3.54 (d, 1 H, $J$ = 13.7), 3.57 (m, 2 H), 3.77 (d, 1 H, $J$ = 13.7), 4.03 (m, 1 H), 4.1 (q, 2 H, $J$ = 6.8), 5.72 (d, 1 H, $J$ = 15.6), 6.61 (dd, 1 H, $J$ = 15.6, 7.6), 7.3 (m, 5 H). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.65; H, 7.91; N, 4.98.

**(*S*)-4-(Benzylamino)-5-hydroxy-2-pentenoic Acid Ethyl Ester (17).** A solution of **16** (2.89 g, 10 mmol) in EtOH (20 mL) containing few drops of diluted HCl was stirred at rt for 18 h and then concentrated. The residue was treated with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (4 × 25 mL). The dried organic extracts were evaporated to leave **17** in quantitative yield as an oil: $[\alpha]^{20}_D$ = +2.4° (*c* 0.49, $CHCl_3$); IR (neat) 3500–3300, 1715, 1650 cm$^{-1}$; $^1$H NMR δ 1.3 (t, 3 H, $J$ = 7.5), 2.0 (s, 2 H), 3.4 (m, 2 H), 3.69 (m, 1 H), 3.7 (d, 1 H, $J$ = 15), 3.89 (d, 1 H, $J$ = 15), 4.21 (q, 2 H, $J$ = 7.5), 6.01 (d, 1 H, $J$ = 15.6),

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6.81 (dd, 1 H, $J$ = 15.6, 7.6), 7.32 (m, 5 H). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.38; H, 7.72; N, 5.37.

**(*S*)-4-(Benzylamino)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-pentenoic Acid Ethyl Ester (18).** $Et_3N$ (1.04 mL) was added to a rapidly stirred solution of **17** (1.5 g, 6.02 mmol) in dry $CH_2Cl_2$ (20 mL). TBDMS-Cl (1.1 g) and DMAP (40 mg) were then added. After 4 h, the reaction mixture was diluted with $H_2O$ (15 mL), and the organic phase was separated and dried. Removal of the solvent and flash chromatography of the residue (1:1 ether–petroleum ether) afforded **18** (1.53 g, 70%) as an oil: $[\alpha]^{20}_D$ = +5.96° (*c* 0.95, $CHCl_3$); IR (neat) 1720, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 0.033 (s, 3 H), 0.039 (s, 3 H), 0.87 (s, 9 H), 1.3 (t, 3 H, $J$ = 7), 2.0 (s, 1 H), 3.5–3.7 (m, 3 H), 3.65 (d, 1 H, $J$ = 15), 3.85 (d, 1 H, $J$ = 15), 4.2 (q, 2 H, $J$ = 7), 6.05 (d, 1 H, $J$ = 15), 6.82 (dd, 1 H, $J$ = 15.6, 7.6), 7.3 (m, 5 H). Anal. Calcd for $C_{20}H_{33}NO_3Si$: C, 66.08; H, 9.15; N, 3.85. Found: C, 66.35; H, 9.02; N, 4.03.

**(*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]pentanoic Acid Ethyl Ester (19).** Di-*tert*-butyl dicarbonate (0.75 g, 3.42 mmol) was added to a solution of **18** (0.5 g, 1.37 mmol) in MeOH (60 mL). 10% Pd/C (0.3 g) was then added, and the resulting suspension was hydrogenated at 50 psi for 4 h. The catalyst was filtered off and washed with MeOH, and the combined filtrates were concentrated. The residue was diluted with ether (40 mL), washed with saturated $NaHCO_3$, dried, and evaporated. The residue was flash chromatographed (1:1 ether–petroleum ether) to give **19** (0.41 g, 80%), $[\alpha]^{20}_D$ = −22.5° (*c* 0.88, $CH_2Cl_2$), with physical properties identical to those previously reported:[7] IR (neat) 1740, 1690 $cm^{-1}$; $^1H$ NMR $\delta$ 0.088 (s, 6 H), 0.91 (s, 9 H), 1.3 (t, 3 H, $J$ = 7), 1.47 (s, 9 H), 2.1 (m, 2 H), 2.5 (t, 3 H, $J$ = 7), 3.2–3.4 (m, 3 H), 4.2 (q, 2 H, $J$ = 7), 4.4 (bs, 1 H). Anal. Calcd for $C_{18}H_{37}NO_5Si$: C, 57.57; H, 9.93; N, 3.73. Found: C, 57.53; H, 10.04; N, 3.79.

**[2*S*-(2$\alpha$,3$\beta$,4$\alpha$)]-4-Acetyl-1-benzyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-pyrrolidineacetic Acid Ethyl Ester (21). Method A.** A mixture of **18** (3.63 g, 10 mmol) and MVK (4.06 mL, 50 mmol) in EtOH (20 mL) was stirred for 12 h in the presence of $FeCl_3$, filtered through Celite, and evaporated to give quantitatively **20** as an oil. A sample was flash chromatographed (1:1 ether–petroleum ether) to afford pure **20** as an oil: IR (neat) 1730, 1710, 1650, $cm^{-1}$; $^1H$ NMR $\delta$ 0.05 (s, 6 H), 0.84 (s, 9 H), 1.3 (t, 3 H, $J$ = 7), 2.02 (s, 3 H), 2.53 (m, 2 H), 2.7–3.05 (m, 2 H), 3.45 (m, 1 H), 3.6 (d, 1 H, $J$ = 15), 3.8 (d, 1 H, $J$ = 15), 3.58–3.9 (m, 2 H), 4.2 (q, 2 H, $J$ = 7), 5.93 (d, 1 H, $J$ = 14), 6.95 (dd, 1 H, $J$ = 14, 6), 7.3 (m, 5 H). Anal. Calcd for $C_{24}H_{39}NO_4Si$: C, 66.48; H, 9.07; N, 3.23. Found: C, 66.51; H, 9.03; N, 3.31.

Crude **20** in EtOH (20 mL) containing a few drops of TMG was stirred for 2 h at rt. Removal of the solvent and flash chromatography of the residue (1:1 ether–petroleum ether) afforded **21** (4.33 g), as an oil: $[\alpha]^{20}_D$ = −81.3° (*c* 0.91, $CHCl_3$); IR (neat) 1750, 1710, 1400 $cm^{-1}$; $^1H$ NMR $\delta$ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.9 (s, 9 H), 1.24 (t, 3 H, $J$ = 6.8), 2.1 (s, 3 H), 2.3–2.85 (m, 5 H), 3.1 (m, 1 H), 3.33 (d, 1 H, $J$ = 15), 3.6–3.9 (m, 2 H), 4.11 (q, 2 H, $J$ = 6.8), 4.15 9d, 1 H, $J$ = 15), 4.0–4.25 (m, 1 H), 7.3 (m, 5 H).

**Method B.** A mixture of **18** (3.63 g, 10 mmol) and MVK (4.06 mL, 50 mmol) in EtOH (20 mL) was stirred at rt until complete disappearance of **18** (ca. 3 days), a few drops of TMG were then added, and stirring was continued for 2 h. The reaction mixture was processed as described above to yield **21** in essentially quantitative yield.

**[2*S*-(2$\alpha$,3$\beta$,4$\alpha$)]-4-Acetyl-1-[(1,1-dimethylethoxy)carbonyl]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-pyrrolidineacetic Acid Ethyl Ester (22).** Compound **21** (1.58 g, 3.64 mmol), $(Boc)_2O$ (2.73 g, 10.92 mmol) in MeOH (53 mL), and 10% Pd/C (0.27 g) were hydrogenated for 48 h at rt under 3 atm of $H_2$ with a Parr shaker. The mixture was filtered through a pad of Celite, and the solvent was then evaporated. Flash chromatography of the residue (1:2 ether–petroleum ether) gave **22** as an oil in quantitative yield: $[\alpha]^{20}_D$ = −4.64° (*c* 1.68, $CHCl_3$); IR (neat) 1740, 1700 $cm^{-1}$; $^1H$ NMR $\delta$ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.25 (t, 3 H, $J$ = 7), 1.45 (s, 9 H), 2.23 (s, 3 H), 2.3–2.6 (m, 2 H), 2.8–3.2 (m, 2 H), 3.25–4.0 (m, 5 H), 4.12 (q, 2 H, $J$ = 7). Anal. Calcd for $C_{22}H_{41}NO_6Si$: C, 59.57; H, 9.32; N, 3.16. Found: C, 59.55; H, 9.45; N, 3.21.

**[2*S*-(2$\alpha$,3$\beta$,4$\alpha$)]-1-[(1,1-Dimethylethoxy)carbonyl]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (23).** A solution of **22** (1.1 g, 2.48 mmol) in dry ether (25 mL) was added to a cooled (0 °C) solution of methylenetriphenylphosphorane (1.33 g, 3.72 mmol of triphenylphosphonium bromide and 3.2 mmol of *n*-BuLi 1 M in hexane) in dry ether (50 mL). The mixture was stirred for 2 h at 0 °C and then left to warm at rt. The mixture was then filtered, and the filtrate was evaporated. Flash chromatography of the yellow, oily residue (1:2 ether–petroleum ether) afforded **23** (0.7 g, 60%): $[\alpha]^{20}_D$ = −8.4° (*c* 1.07, $CHCl_3$); IR (neat) 1740, 1700, 1680, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 0.041 (s, 6 H), 0.88 (s, 9 H), 1.24 (t, 3 H, $J$ = 7), 1.45 (s, 9 H), 1.72 (s, 3 H), 2.42 (m, 3 H), 2.82 (m, 1 H), 3.1 (m, 1 H), 3.5–4.0 (m, 4 H), 4.12 (q, 2 H, $J$ = 7), 4.84 (s, 2 H). Anal. Calcd for $C_{23}H_{43}NO_5Si$: C, 62.60; H, 9.75; N, 3.17. Found: C, 62.44; H, 9.96; N, 3.13

**[2*S*-(2$\alpha$,3$\beta$,4$\alpha$)]-1-[(1,1-Dimethylethoxy)carbonyl]-2-(hydroxymethyl)-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (24).** To a solution of **23** (0.65 g, 1.47 mmol) in THF (20 mL) was added *n*-$Bu_4NF$ (1.5 g, 5.74 mmol). The mixture was stirred at rt for 1 h, diluted with $H_2O$ (25 mL), and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with brine (20 mL), dried, and evaporated. Flash chromatography of the residue with ether gave **24** (0.4 g, 83%) as an oil: $[\alpha]^{20}_D$ = −9.4° (*c* 1.04, $CHCl_3$); IR (neat) 3400, 1740, 1700–1650 $cm^{-1}$; $^1H$ NMR: $\delta$ 1.25 (t, 3 H, $J$ = 6.8), 1.48 (s, 9 H), 1.71 (s, 3 H), 2.1 (m, 1 H), 2.38–2.6 (m, 3 H), 3.11 (t, 1 H, $J$ = 11), 3.5–3.9 (m, 5 H), 4.11 (q, 2 H, $J$ = 6.8), 4.9 (s, 2 H). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C 62.29; H, 9.03; N, 4.39.

**[2*S*-(2$\alpha$,3$\beta$,4$\alpha$)]-2-Carboxy-1-[(1,1-dimethoxyethoxy)carbonyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (25).** To a cooled (0 °C) solution of **24** (0.4 g, 1.22 mmol) in acetone (100 mL) was added dropwise 8 N Jones reagent (1.4 mL), and the mixture was stirred at the same temperature for 1 h. After the remaining oxidant was decomposed by the addition of 2-propanol (0.5 mL), the mixture was diluted with ether and $H_2O$ (50 mL each). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine (20 mL), dried, and evaporated to leave a residue, which was flash chromatographed (8:2 AcOEt–ether) to give **25** (0.25 g, 60%) as an oil: $[\alpha]^{20}_D$ = −8.75° (*c* 0.41, $CHCl_3$); IR (neat) 3500–3300, 1730, 1680–1640 $cm^{-1}$; $^1H$ NMR $\delta$ 1.21 (t, 3 H, $J$ = 6.8), 1.42 (s, 9 H), 1.71 (s, 3 H), 2.3–2.8 (m, 3 H), 2.8–3.7 (m, 4 H), 4.11 (q, 2 H, $J$ = 6.8), 4.83 (s, 2 H), 13.4 (bs, 1 H). Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.79; H, 7.91; N, 4.13.

**(+)-$\alpha$-Allokainic Acid (2).** A solution of **25** (0.4 g, 1.17 mmol) in 3:1 MeOH–$H_2O$ (15 mL) was treated with LiOH (0.25 g, 11.7 mmol), allowed to stir at rt for 40 h, cooled (0 °C), brought to pH 2 by the addition of 10% HCl, and concentrated to give crude **26**, which was added to a cooled (0 °C) mixture of 1:1 TFA–$CHCl_3$. After the reaction mixture was stirred at rt for 1 h, the solvent was removed, and the residue was purified through columns of ion-exchange resin (Dowex 50WX-8, 100–200 mesh; Amberlite CG-50) to afford **2** (0.14 g, 56%) as a solid: mp 241–244 °C dec; $[\alpha]^{20}_D$ = +7.77° (*c* 0.18, $H_2O$) [lit.[26] mp 238–242 °C (dec)]; $[\alpha]^{23}_D$ = +7.4° (*c* 0.7, $H_2O$); IR (KBr) 3440, 3135, 1725, 1635, 1580 $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$ 1.75 (s, 3 H), 2.5–3.0 (m, 4 H), 3.33 (t, 1 H, $J$ = 11), 3.55 (dd, 1 H, $J$ = 7.8, 11), 3.93 (d, 1 H, $J$ = 8.5), 4.99 (s, 2 H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.29; H, 7.08; N, 6.61.

**2-(Benzoyloxy)-1-nitroethane (27).** A solution of nitroethanol (9.1 g, 100 mmol) and benzoyl chloride (11.6 mL, 100 mmol) in dry benzene (100 mL) was heated at reflux for 24 h and then concentrated. Flash chromatography of the residue (1:1 ether–petroleum ether) gave **27** (13.65 g, 70%) as an oil: IR (neat) 1735, 1550 $cm^{-1}$; $^1H$ NMR $\delta$ 4.75 (m, 2 H), 4.77 (m, 2 H), 7.55 (m, 5 H). Anal. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.47; H, 4.52; N, 7.15.

**2-(Benzoyloxy)-1-phenyl-1-nitroethane (28).** 1-Phenyl-1-nitroethanol[20] (8.35 g, 50 mmol) was treated under the conditions described for **27** to produce **28** (8 g, 70%) as a solid after flash

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chromatography (1:1 ether–petroleum ether): mp 80–81 °C; IR (Nujol) 1735, 1550 $cm^{-1}$; $^1H$ NMR $\delta$ 4.8 (dd, 1 H, $J$ = 3.5, 12.5), 5.2 (dd, 1 H, $J$ = 9.8, 12.5), 5.9 (dd, 1 H, $J$ = 3.5, 9.8), 7.4–7.6 (m, 10 H). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.40; H, 4.85; N, 5.19.

**3-(Benzoyloxy)-2-nitro-1-propanol (29).** 2-Nitro-1,3-propanediol[27] (1.21 g, 10 mmol) was treated under the conditions described for **28** to produce **29** (1.8 g, 80%) as an oil after flash chromatography (1:1 AcOEt–ether): IR (neat) 3500, 1735, 1550, 1350 $cm^{-1}$; $^1H$ NMR $\delta$ 4.15 (m, 3 H), 4.82 (m, 3 H), 7.47 (m, 5 H). Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.45; H, 5.06; N, 6.17.

**2-[3-(Benzoyloxy)-2-nitropropyl]-1,3-dioxolane (30).** 2-(2-Nitro-3-hydroxypropyl)-1,3-dioxolane (1.77 g, 10 mmol) (prepared from 2-(2-nitroethyl)-1,3-dioxolane[28] following reported directions[20]) was treated under the conditions described above to produce after flash chromatography (1:1 ether–petroleum ether) **30** (1.8 g, 64%) as an oil: IR (neat) 1730, 1550 $cm^{-1}$; $^1H$ NMR $\delta$ 2.2 (m, 1 H), 2.61 (m, 1 H), 3.7–4.1 (m, 4 H), 4.6–4.9 (m, 2 H), 5.05 (m, 1 H), 5.1 (m, 1 H), 7.5 (m, 3 H), 8.0 (m, 2 H). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.88. Found: C, 55.59; H, 5.42; N, 5.06.

***trans*-4-Nitro-1-(phenylmethyl)-3-pyrrolidineacetic Acid Ethyl Ester (31).** A solution of **8** (3.3 g, 15 mmol) and **27** (2.92 g, 15 mmol) in EtOH (30 mL) was stirred at rt for 15 h and then concentrated. The residue was treated with ether and saturated aqueous $NaHCO_3$ (40 mL each), and the organic layer was separated and dried. Removal of the solvent and flash chromatography of the residue (1:1 ether–petroleum ether) afforded **31** (3.15 g, 90%) as an oil: IR (neat) 1740, 1550, 1350 $cm^{-1}$; $^1H$ NMR $\delta$ 1.24 (t, 3 H, $J$ = 7), 2.25 (dd, 1 H, $J$ = 9, 6.4), 2.62 (dd, 2 H, $J$ = 6.4, 1.5), 2.95 (dd, 1 H, $J$ = 11, 7.6), 3.05–3.5 (m, 3 H), 3.64 (s, 2 H), 4.2 (q, 2 H, $J$ = 7), 4.77 (m, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.48; H, 7.02; N, 9.49.

***trans*-4-Amino-1-(phenylmethyl)-3-pyrrolidineacetic Acid Ethyl Ester (32).** A solution of **31** (1.46 g, 5 mmol) in EtOH (50 mL) was stirred with 10% Pd/C (0.5 g) for 7 h at rt under 40 psi of hydrogen. The mixture was filtered through a pad of Celite, and the solvent was then evaporated to give **32** (0.9 g, 78%) as an oil: IR (neat) 3350, 1740 $cm^{-1}$; $^1H$ NMR $\delta$ 1.28 (t, 3 H, $J$ = 7), 2.3 (m, 1 H), 2.35–2.54 (m, 5 H), 2.62 (dd, 2 H, $J$ = 11, 6.8), 2.72 (m, 1 H), 3.15 (bs, 1 H), 3.38 (d, 1 H, $J$ = 15), 3.98 (d, 1 H, $J$ = 15), 4.15 (q, 2 H, $J$ = 7), 7.3 (m, 5 H). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.63; H, 8.49; N, 10.66.

**1-Benzyl-2α-(hydroxymethyl)-4α-nitro-3β-pyrrolidineacetic Acid Ethyl Ester (33).** A solution of **17** (2.49 g, 10 mmol) and **27** (2.71 g, 10 mmol) in EtOH (30 mL) was left at rt for 20 h and then worked up as described above for **31** to afford, after flash chromatography (1:1 ether–petroleum ether), **33** (3.58 g, 90%) as an oil: IR (neat) 3500–3300, 1730, 1550, 1350 $cm^{-1}$; $^1H$ NMR $\delta$ 1.3 (t, 3 H, $J$ = 7), 2.3 (dd, 1 H, $J$ = 17, 9.4), 2.7 (bs, 1 H), 3.05 (m, 2 H), 3.4 (d, 1 H, $J$ = 15), 3.55 (dd, 1 H, $J$ = 11, 1.6), 3.57–3.9 (m, 3 H), 3.95 (d, 1 H, $J$ = 15), 4.11 (d, 1 H, $J$ = 11), 4.2 (q, 2 H, $J$ = 7), 7.35 (m, 10 H). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.18; H, 6.66; N, 7.11. A small amount of the C-4 epimer (0.4 g, 10%) was also isolated.

**1-Benzyl-2α-(hydroxymethyl)-4α-nitro-4β-phenyl-3β-pyrrolidineacetic Acid Ethyl Ester (34).** A solution of **17** (1.25 g, 5 mmol) and **28** (1.13 g, 5 mmol) in EtOH (15 mL) was stirred at rt for 2 h and then worked up as described above to give, after flash chromatography with AcOEt, **34** as a solid: mp 82–83 °C (ether); IR (Nujol) 3500–3300, 1740, 1530, 1360 $cm^{-1}$; $^1H$ NMR $\delta$ 1.29 (t, 3 H, $J$ = 7), 2.4 (m, 2 H), 2.5 (bs, 2 H), 2.89 (m, 2 H), 3.25 (d, 1 H, $J$ = 10), 3.35 (d, 1 H, $J$ = 10), 3.5 (dd, 1 H, $J$ = 13, 1.0), 3.6 (d, 1 H, $J$ = 13), 3.78 (dd, 1 H, $J$ = 13, 3), 3.85 (d, 1 H, $J$ = 12.5), 4.1 (d, 1 H, $J$ = 15), 4.17 (q, 2 H, $J$ = 7), 7.3 (m, 5 H). Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.95. Found: C, 57.90; H, 6.85; N, 7.98.

**1-Benzyl-2α-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4β-[(1,3-dioxolan-2-yl)methyl]-4α-nitro-3β-pyrrolidineacetic Acid Ethyl Ester (36).** A solution of **18** (1 g, 2.75 mmol) and **30** (0.77 g, 2.75 mmol) in EtOH (10 mL) was stirred at rt for 48 h and then worked up as described above to give, after flash chromatography (1:2 ether–petroleum ether), **36** (1.09 g, 76%) as an oil: IR (neat) 1730, 1535, 1370 $cm^{-1}$; $^1H$ NMR $\delta$ 0.037 (s, 6 H), 0.87 (s, 9 H), 1.26 (t, 3 H, $J$ = 7), 2.1–2.6 (m, 4 H), 2.65–2.9 (m, 3 H), 3.29 (d, 1 H, $J$ = 10), 3.4 (d, 1 H, $J$ = 10), 3.6–3.9 (m, 6 H), 4.0–4.25 (m, 3 H), 4.84 (t, 1 H, $J$ = 3), 7.3 (m, 5 H). Anal. Calcd for $C_{26}H_{42}N_2O_7Si$: C, 59.77; H, 8.04; N, 5.36. Found: C, 59.65; H, 7.99; N, 5.30.

**1-Benzyl-2α-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4β-(hydroxymethyl)-4α-nitro-3β-pyrrolidineacetic Acid Ethyl Ester (35).** A solution of **18** (1.81 g, 5 mmol) and **29** (1.13 g, 5 mmol) in EtOH (15 mL) was stirred at rt for 3 h and then processed as described above to afford after flash chromatography (1:1 ether–petroleum ether) **35** (1.75 g, 75%) as an oil: IR (neat) 3500–3300, 1735, 1540, 1360 $cm^{-1}$; $^1H$ NMR $\delta$ 0.088 (s, 6 H), 0.9 (s, 9 H), 1.25 (t, 3 H, $J$ = 7), 2.75 (m, 4 H), 3.14 (d, 1 H, $J$ = 14), 3.34 (d, 1 H, $J$ = 11.2), 3.53 (d, 1 H, $J$ = 14), 3.68 (dd, 1 H, $J$ = 12.6, 6.8), 3.80 (dd, 1 H, $J$ = 12.6, 6.8), 3.88 (d, 1 H, $J$ = 14), 4.15 (q, 2 H, $J$ = 7), 4.0–4.2 (m, 2 H), 7.3 (m, 5 H). Anal. Calcd for $C_{23}H_{38}N_2O_6Si$: C, 59.20; H, 8.21; N, 4.00. Found: C, 59.02; H, 8.33; N, 4.12.

**(1α,3aα,7aα)-Octahydro-2-benzyl-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-6-oxopyrano[3,4-*c*]pyrrole (37) and (2α,3β,4α)-1-Benzyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(hydroxymethyl)-3-pyrrolidineacetic Acid Ethyl Ester (38).** A solution of **35** (2 g, 4.29 mmol) and $Bu_3SnH$ (1.6 mL, 6 mmol) in dry benzene (20 mL) containing AIBN (0.15 g) was heated at reflux for 4 h and then concentrated. The residue was treated with ether and water (40 mL each) and stirred for 18 h in the presence of KF (1 g). The organic layer was separated, dried, and concentrated. The residue was flash chromatographed (4:1 ether–petroleum ether) to give a 1:1 mixture of **37** and **38** in 80% yield. Compound **37**: oil; IR (neat) 1750, 1470, 1450 $cm^{-1}$; $^1H$ NMR $\delta$ 0.055 (s, 3 H), 0.07 (s, 3 H), 0.9 (s, 3 H), 2.17 (m, 1 H), 2.34 (m, 1 H), 2.58 (m, 4 H), 3.02 (m, 1 H), 3.23 (d, 1 H, $J$ = 13), 3.61 (dd, 1 H, $J$ = 10, 5), 3.85 (dd, 1 H, $J$ = 10, 5), 4.05 (dd, 1 H, $J$ = 10.5, 2.5), 4.1 (d, 1 H, $J$ = 13), 4.2 (dd, 1 H, $J$ = 10.5, 2.5), 7.3 (m, 5 H). Anal. Calcd for $C_{21}H_{33}NO_3Si$: C, 67.17; H, 8.86; N, 3.73. Found: C, 67.35; H, 9.01; N, 3.99. Compound **38** oil; IR (neat) 3500–3300, 1730, 1600 $cm^{-1}$; $^1H$ NMR: $\delta$ 0.064 (s, 3 H), 0.067 (s, 3 H), 0.89 (s, 9 H), 1.16 (bs, 1 H), 1.25 (t, 3 H, $J$ = 7), 1.95 (m, 1 H), 2.2–2.55 (m, 4 H), 2.6–2.9 (m, 2 H), 3.15 (d, 1 H, $J$ = 13), 3.55 (m, 2 H), 3.65 (dd, 1 H, $J$ = 10, 5), 3.9 (dd, 1 H, $J$ = 10, 5), 4.1 (q, 2 H, $J$ = 7), 4.15 (d, 1 H, $J$ = 13), 7.3 (m, 5 H). Anal. Calcd for $C_{23}H_{39}NO_4Si$: C, 65.52; H, 9.33; N, 3.32. Found: C, 65.47; H, 9.39; N, 3.44.

**2-Methyl-2-[(tetrahydro-2*H*-pyranyl)oxy]nitropropane (40).** A few crystals of *p*-TSA were added to a cooled (−18 °C) solution of 2-hydroxy-2-methyl-1-nitropropane (12 g, 100 mmol) and dihydropyran (18.6 g, 200 mmol) in $CH_2Cl_2$ (40 mL). After the reaction mixture stirred for 1 h, saturated aqueous $NaHCO_3$ (20 mL) was added, and the organic layer was separated, dried, and concentrated. The residue was distilled at 20 mmHg to give a quantitative yield of **40**: bp 115–120 °C; IR (neat) 1550, 1370 $cm^{-1}$; $^1H$ NMR $\delta$ 1.45 (s, 3 H), 1.49 (s, 3 H), 1.5–2.0 (m, 6 H), 3.5 (m, 1 H), 3.95 (m, 1 H), 4.5 (AB system, 2 H, $J$ = 11), 4.88 (m, 1 H). Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.46; N, 6.89. Found: C, 53.31; H, 8.29; N, 7.0.

**3-Methyl-2-nitro-3-buten-1-ol (41).** A solution of **40** (2.03 g, 10 mmol) and paraformaldehyde (0.3 g, 10 mmol) in MeOH (3 mL) was added to a cooled (0 °C) solution of MeONa (0.23 g of Na) in MeOH (3 mL), and the mixture was stirred for 18 h at the same temperature. The solid sodium nitronate was filtered, suspended in an ethereal solution of salicylic acid (1.38 g in 200 mL of ether), and stirred for 1 h at rt and for 2 h at 40 °C. After filtration, the organic layer was concentrated, and the residue was flash chromatographed (2:1 ether–petroleum ether) to afford **41** (1 g, 76%) as an oil: IR (neat): 3500, 1650, 1550 $cm^{-1}$; $^1H$ NMR $\delta$ 1.82 (s, 3 H), 2.92 (bs, 1 H), 3.86 (dd, 1 H, $J$ = 12.5, 3.5), 4.32 (dd, 1 H, $J$ = 12.5, 9.7), 5.1 (dd, 1 H, $J$ = 9.7, 3.5), 5.19 (m, 2 H). Anal. Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.69; H, 6.99; N, 10.58.

**4-(Benzoyloxy)-2-methyl-3-nitro-1-butene (42).** A solution of **41** (2 g, 15 mmol) and BzCl (1.74 g, 15 mmol) in dry benzene

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(30 mL) was heated at reflux for 24 h and then worked up as described above for **27** to give after flash chromatography (1:2 ether–petroleum ether) **42** (3.45 g, 91%) as an oil: IR (neat) 1735, 1550 $cm^{-1}$; $^1H$ NMR $\delta$ 1.92 (s, 3 H), 4.72 (dd, 1 H, $J$ = 12, 3.8), 4.92 (dd, 1 H, $J$ = 12, 9.8), 5.28 (m, 2 H), 5.36 (dd, 1 H, $J$ = 9.8, 3.8), 7.4 (m, 5 H). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.25; H, 5.64; N, 6.05.

**(2*S*)-1-Benzyl-2α-(hydroxymethyl)-4β-(1-methylethenyl)-4α-nitro-3β-pyrrolidineacetic Acid Ethyl Ester (43).** A solution of **17** (1.25 g, 5 mmol) and **42** (1.25 g, 5 mmol) in EtOH (20 mL) was stirred at rt for 15 h and then processed as described above for **31** to give after flash chromatography (2:1 ether–petroleum ether) **43** (1.6 g, 88%) as a pale yellow oil: $[\alpha]^{20}_D$ −1.11° (*c* 2.19, $CHCl_3$); IR (neat) 3500–3300, 1735, 1530 $cm^{-1}$; $^1H$ NMR $\delta$ 1.28 (t, 3 H, $J$ = 7), 1.64 (s, 3 H), 2.1 (dd, 1 H, $J$ = 16.5, 9.7), 2.65 (bs, 1 H), 2.83 (dd, 1 H, $J$ = 16.5, 2.4), 2.9 (m, 1 H), 3.2 (d, 1 H, $J$ = 13), 3.43 (dd, 1 H, $J$ = 9.7, 2.4), 3.59 (d, 1 H, $J$ = 13), 3.75 (dd, 1 H, $J$ = 12.4, 5.6), 3.8 (d, 1 H, $J$ = 13.5), 4.05 (d, 1 H, $J$ = 13.5), 4.2 (q, 2 H, $J$ = 7) 5.15 (s, 1 H), 5.28 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; N, 7.23; N, 7.73. Found: C, 62.88; H, 7.31; N, 7.79.

**[2*S*-(2α,3β,4β)]-1-Benzyl-2-(hydroxymethyl)-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (44).** A solution of **43** (1.81 mmol), ammonium formate (0.378 g, 6 mmol), $Ph_3P$ (0.131 g), and $Pd(PPh_3)_4$ (0.29 g) in THF (30 mL) was heated at reflux for 48 h and then concentrated. The residue was flash chromatographed (2:1 ether–petroleum ether) to give quantitatively **44** as an oil: $[\alpha]^{20}_D$ −3.66° (*c* 0.75, $CHCl_3$); IR (neat) 3500–3300, 1730, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 1.26 (t, 3 H, $J$ = 7), 1.69 (s, 3 H), 2.11 (dd, 1 H, $J$ = 16, 9.5), 2.25 (dd, 1 H, $J$ = 16, 6), 2.4–3.0 (m, 6 H), 3.5 (d, 1 H, $J$ = 13.5), 3.6 (m, 1 H), 3.95 (d, 1 H, $J$ = 13.5), 4.12 (q, 2 H, $J$ = 7), 4.56 (s, 1 H), 4.81 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.83; H, 8.62; N, 4.50.

**[2*S*-(2α,3β,4β)]-1-Benzyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (45).** A solution of **44** (0.8 g, 2.5 mmol), TBDMS-Cl (0.45 g, 3 mmol) and $Et_3N$ (0.38 g, 3 mmol) in $CH_2Cl_2$ (10 mL) containing DMAP (61 mg) was stirred at rt for 15 h. The solvent was removed, and the residue was dissolved in ether–$H_2O$ (25 mL each). The aqueous layer was extracted with ether, and the combined organic layers were washed with 1 M HCl and $H_2O$. After drying, the solvent was evaporated, and the residue was flash chromatographed (1:4 ether–petroleum ether) to afford **45** (0.9 g, 81%) as an oil: $[\alpha]^{2}10_D$ −27.2° (*c* 0.99, $CHCl_3$); IR (neat) 1735, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 0.045 (s, 6 H), 0.88 (s, 9 H), 1.25 (t, 3 H, $J$ = 7), 1.7 (s, 3 H), 2.07 (dd, 1 H, $J$ = 16, 9.4), 2.21 (dd, 1 H, $J$ = 16, 6), 2.4–2.6 (m, 2 H), 2.62–2.72 (m, 1 H), 2.78–2.98 (m, 2 H), 3.54 (d, 2 H, $J$ = 5.6), 3.58 (d, 1 H, $J$ = 15), 4.08 (d, 1 H, $J$ = 15), 4.12 (q, 2 H, $J$ = 7), 4.56 (s, 1 H), 4.8 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{25}H_{41}NO_3Si$: C, 69.57; H, 9.58; N, 3.24. Found: C, 69.51; H, 9.48; N, 3.35.

**[2*S*-(2α,3β,4β)]-1-[(1,1-Dimethylethoxy)carbonyl]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (46).** To a cooled (0 °C) solution of **45** (1.07 g, 2.5 mmol) in dry 1,2-dichloroethane (10 mL) was added α-chloroethyl chloroformate (ACE-Cl) (0.27 mL, 2.5 mmol). After being stirred at 0 °C for 30 min and then refluxed for 2 h, the mixture was concentrated. The residue was dissolved in dioxane (10 mL) containing $Et_3N$ (0.38 mL, 2.5 mmol) and $(Boc)_2O$ (0.545 g, 2.5 mmol), stirred at rt for 24 h, and then evaporated. Flash chromatography of the residue (1:4 ether–petroleum ether) afforded **46** (1 g, 90%) as an oil: $[\alpha]^{20}_D$ −33.07° (*c* 0.61, $CH_2Cl_2$) [lit.[7] $[\alpha]^{20}_D$ −31.8° (*c* 0.6, $CH_2Cl_2$)]; IR (neat) 1735, 1690, 1645, 1470, 1400 $cm^{-1}$; $^1H$ NMR $\delta$ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.28 (t, 3 H, $J$ = 7), 1.47 (s, 9 H), 1.72 (s, 3 H), 2.05–2.3 (m, 2 H), 2.83 (m, 1 H), 3.05–3.25 (m, 1 H), 3.3–3.5 (m, 2 H), 3.5–3.63 (m, 1 H), 3.2 (dd, 1 H, $J$ = 5.4, 1.6), 4.15 (q, 2 H, $J$ = 7), 4.66 (s, 1 H), 4.87 (s, 1 H). Anal. Calcd for $C_{23}H_{43}NO_5Si$: C, 62.60; H, 9.75; N, 3.17. Found: C, 62.55; H, 9.71; N, 3.25.

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# Synthesis of (Optically Active) Sulfur-Containing Trifunctional Amino Acids by Radical Addition to (Optically Active) Unsaturated Amino Acids

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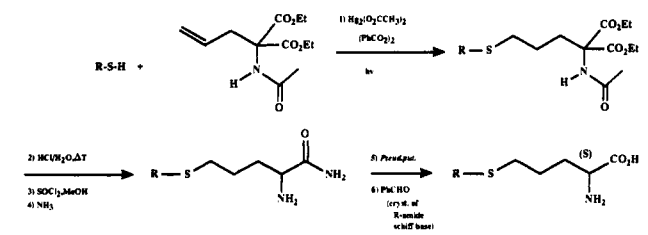
Sulfur-based radicals, generated from R–S–H-type precursors (R = alkyl, acyl) with AIBN, smoothly add to α-allylglycines protected at none, one, or both of the amino acid functions ($NH_2$ and/or $CO_2H$). Sulfur-containing trifunctional amino acids were obtained in good to excellent yields (64–100%). The solvent used for the reaction is critical. Optimal results were obtained when both the unsaturated amino acid and RSH dissolve completely in the medium (dioxane/water or methanol/water are good solvent systems). The scope of the reaction includes α-substituted α-allylglycine and derivatives as well as β-substituted β-allyl-β-amino alcohols. In the case of optically active α-allylglycine derivatives, radical addition is accompanied by a small amount of racemization, the amount depending on the type of protection and R–S–H. The products are easily optically enriched by crystallization. Addition of sulfur-based radicals to α-allylglycine is believed to be an example of a general method for synthesizing optically active trifunctional amino acids from unsaturated amino acids.

## Introduction

We regard (optically active) trifunctional amino acids as versatile tools enabling medicinal chemists and agrochemists to synthesize new drugs and pesticides. The advent of rational design methods for bioactive molecules capable of a desired interaction with a selected target receptor aims at compounds acting as, e.g., a suicide inhibitor or a transition-state analog.[1] The recent revival of peptide/peptidomimetic chemistry is connected with this broad trend. Trifunctional amino acids contain not only an amino group and a carboxyl group but also a third

**Scheme I**



(1) See, for example: *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: New York, 1989.

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