Enzymatic Kinetic Resolution of α-Nitro α-Methyl Carboxylic Acids

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Received November 17, 1987

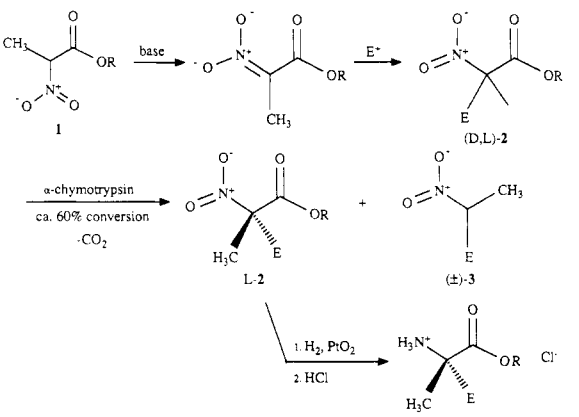
Synthetic routes to various quaternary α-nitro α-methyl carboxylic acid esters from simpler nitroalkanes and nitroalkane derivatives are described. These quaternary α-amino acid precursors can be kinetically resolved by using α-chymotrypsin. It was found that partial hydrolysis of these α-nitro α-methyl esters and recovery of the unhydrolyzed ester proceeds preferentially by hydrolysis of the D enantiomer. Reduction of the α-nitro group thus then affords highly enantiomerically enriched L-α-methyl α-amino acids.

The synthesis of optically pure α-methyl α-amino acids has recently been a goal of many workers due to the unique biological activity of these nonproteinogenic α-amino acids.[1,2] α-Methyl α-amino acids have been employed in the pharmaceutical industry as reversible inhibitors of amino acid decarboxylases. The increased steric bulk at the α-position of these amino acids leads to conformational rigidity as well as resistance to hydrolysis by peptidases for peptides containing α-methyl α-amino acids in place of natural α-amino acids. These two properties have led to an increase in importance of α-methyl α-amino acids in structure–activity relationship studies of peptide hormones. α-Methyl α-amino acids have also been found to be constituents of peptides having antibiotic activity.[2]

Two practical procedures exist for preparation of enantiomers of α-amino acids containing an α-methyl group. First, classical resolution of the amino acid is often possible.[3] A more modern approach exemplified by the work of Schöllkopf and others is to use asymmetric organic synthesis with an appropriate chiral auxiliary.[1] In such cases, the quaternary center is formed stereoselectively by an alkylation reaction. A third approach would be some sort of kinetic resolution. Indeed, kinetic resolution of α-amino acid derivatives using enzymatic catalysts is an established application of enzymes in synthesis. However, unlike common α-amino acid derivatives that contain chiral tertiary centers, α-methyl α-amino acid derivatives containing chiral quaternary centers are often not good substrates for hydrolytic enzymes. Thus, enzymatic resolution, which is a very effective procedure for obtaining pure enantiomeric forms of natural α-amino acids, is of only limited utility in preparation of homochiral α-methyl α-amino acids.[4]

We have found that α-nitropropanoate esters are good substrates for enantioselective hydrolysis using chymotrypsin. Thus, by combining the rich chemistry of α-nitro carboxylic acid esters with an enzymatic hydrolysis, we have developed a method to prepare α-nitropropanoic acid esters in high enantiomeric purity. These esters, potentially interesting themselves as amino acid analogues and as chiral starting materials, can easily be reduced to the corresponding α-methyl α-amino acid using Adam's catalyst (PtO_2). The overall scheme outlined in Scheme I summarizes this approach for preparation of optically active α-methyl α-amino acids.

Scheme I



The highly acidic (pK_a = 5.7)[5] α-nitropropanoate ester 1 was found to be useful as a substrate in several reactions in which the rather acidic proton was replaced by a carbon-bonded substituent. Thus, this simple precursor can serve as a common starting material for several different types of α-methyl α-amino acids. While simple electrophilic alkylation of the ambident anion derived from 1 with alkyl halides yields mixtures of products because of competing O- and C-alkylation, the reactions in eq 1–4 all proceeded to give high yields of products. The tetrakis(triphenylphosphine)palladium(0)-catalyzed allylation of 1 using allyl acetate or methallyl acetate (eq 1) gave excellent yields of the nitro analogues of α-methylnorvaline (**2a**) and of α-methylleucine (**2b**), respectively.[6] While a recent report by Tsuji describes problems with O-allylation in rearrangements of allyl esters of α-nitro carboxylic acids,[7] O-allylation was not observed and was evidently not a problem in these reactions using allylic acetates. Michael additions of 1 to butyl acrylate and methyl vinyl ketone

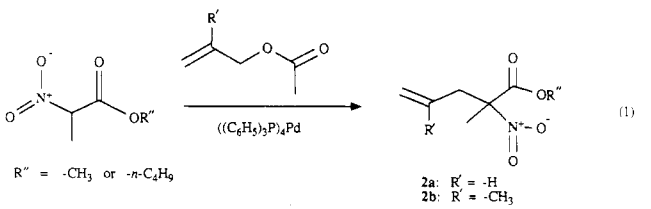


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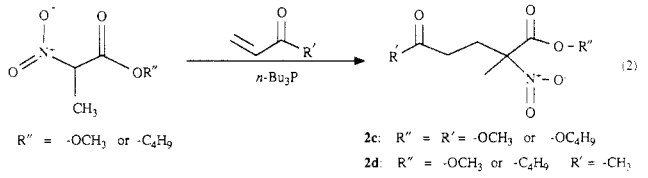
Table I. Formation of α-Methyl α-Amino Acid Precursors from 2-Nitropropanoate Esters

electrophile	reagent[a]	yield (%)[b]	analogous α-methyl α-amino acid after reduction
gramine	*c*	93[d]	α-methyl-tryptophan
allyl acetate	$Pd(PPh_3)_4$	62	α-methyl-γ,δ-dehydronorvaline
allyl acetate	$Pd(PPh_3)_4$[f]	94[e]	α-methylnorvaline
isobutenyl acetate	$Pd(PPh_3)_4$	94[e]	α-methylleucine
methyl vinyl ketone	$(C_4H_9)_3P$	92	δ-keto-α-amino-α-methylhexanoic acid
butyl acrylate	$(C_4H_9)_3P$	92[g]	α-methylglutamic acid
C_6H_5	Ph_3BiCl_2	81	α-methyl-α-phenylglycine

[a] Butyl 2-nitropropanoate was used as the starting material. [b] Isolated yields of products characterized by NMR, IR, and mass spectroscopy (see Experimental Section). [c] Reference 11. [d] Substitution of methyl 2-nitropropanoate produced the analogous methyl ester in 91% yield. [e] Pd/C was used to selectively hydrogenate the γ,δ double bond of **2a** with minimal reduction or cleavage of the α-nitro group. [f] Substitution of methyl 2-nitropropanoate produced the analogous methyl ester in 72% yield.

were both successful. These reactions were carried out both with tri-*n*-butylphosphine and KF/basic alumina as catalysts.[8,9] Although the latter catalyst works well in similar reactions of simple nitroalkanes, tri-*n*-butylphosphine was preferred in this case because it was a more reactive catalyst and because **1** can only react once with the α,β-unsaturated Michael acceptor. The products of these reactions were nitro analogues of δ-keto-α-methyl-α-aminohexanoic acid (**2d**) and α-methylglutamic acid (**2c**),



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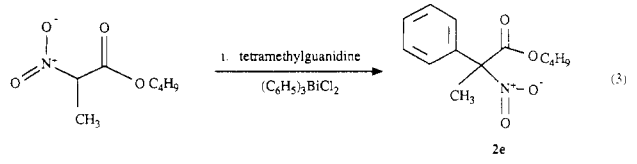

(3)

respectively. The α-methylphenylglycine analogue (**2e**) was obtained from **1** by using the recently developed Barton phenylation reaction.[10] Treatment of **1** with tetramethylguanidine followed by triphenylbismuth dichloride gave the α-methylphenylglycine precursor **2e** in good yield. Finally, the condensation of gramine with **1** gave the α-methyltryptophan analogue **2f**.[11] The results of these reactions are summarized in Table I.

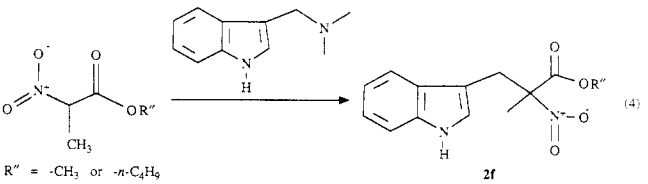

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Table II. Kinetic Resolution of α-Methyl α-Nitro Carboxylic Acid Esters

α-nitro carboxylic acid ester	ester group	enantiomeric excess[a] (% ee)
2a	butyl	>95
2b	butyl	85
2c	methyl	39[b]
2c	butyl	*c*
2d	butyl	75
2e	butyl	>95
2f	butyl	>95
2f	methyl	>95[d]
2f	butyl	90[e]
1	butyl	0

[a] The enantiomeric excess of the product α-nitro α-methyl carboxylic acid ester was measured by ^1H NMR spectroscopy using a chiral shift reagent, $Eu(hfc)_3$. [b] The dimethyl ester **2c** was used as a substrate in this case. [c] The dibutyl ester of **2c** used in this case was not hydrolyzed. [d] This reaction was carried out on a larger scale and the final product eventually hydrogenated to yield the methyl ester of optically active L-α-methyltryptophan (see Experimental Section). [e] This reaction was carried out to 52% conversion.

Enzymatic resolutions were carried out by using α-chymotrypsin. Other lipases and esterases were ineffective. The α-chymotrypsin-catalyzed hydrolyses were performed in a 0.25 M pH 7.1 phosphate buffer, using a 2:1 mixture of buffer and dimethyl sulfoxide as a cosolvent. The substituted α-nitropropanoate esters (**2a–f**) were suspended in the solvent mixture along with an internal standard, hexadecane. The enzyme was then added to the suspension and the suspension was mechanically shaken to facilitate reaction in the resulting two-phase system. The course of the hydrolysis was monitored by analyzing diethyl ether extracts of aliquots of the suspension by capillary gas chromatography. In a typical procedure, 480 mg of the methyl ester **2f** was suspended in 60 mL of the above-mentioned solvent mixture along with 180 mg of α-chymotrypsin. After 6 h of shaking, the hydrolysis was 60% complete. At this point the reaction mixture was extracted with diethyl ether. The unreacted ester **2f** isolated from this ether solution was found to be optically pure by ^1H NMR spectroscopy (ee >98%) using $Eu(hfc)_3$ as a chiral shift reagent.

Hydrolysis of the esters **2** with lipases derived from *Candida cylindracea* (CCL) and from porcine pancreas (or porcine pancreatic lipase) (PPL) failed. However, we were able to successfully transesterify **1** using 1-octanol with CCL as a catalyst in anhydrous heptane. In this case there was a significant decrease in reaction rate after 50% reaction, indicating that kinetic resolution might be feasible. However, unreacted **1** isolated in such a case after 60% reaction had no rotation, probably because of racemization of the stereochemically labile chiral center. A similar result was obtained in α-chymotrypsin hydrolysis of **1**.

In all cases, the rate of hydrolysis of **2** decreased significantly at 50% reaction. Under the conditions for hydrolysis described in the Experimental Section, the products were as shown in Scheme I. In each case a mixture of resolved α-nitro ester and the nitroalkane **3** was obtained. However, this mixture of the α-nitro ester and nitroalkane were easily separated by chromatography or distillation as noted. Table II lists examples of isolated products whose enantiomeric excess is also listed. The enantiomeric excesses of the product α-nitro esters kinetically resolved in this way were generally quite high, typically >95%. The major exception to this generalization was the ester **1**, which contained an acidic proton on the chiral center. In this case, after 60% reaction the isolated unreacted ester was racemic. Apparently the

unreacted ester racemizes in the aqueous medium. Kinetic resolution of **2c** was also minimally successful. We also examined the stereochemistry of recovered chiral nitroalkanes formed by decarboxylation of the hydrolyzed α-nitro α-methyl carboxylic acid. However, these nitroalkanes were, as expected, racemic.

The enantioselectivity of the kinetic destruction of the starting ester **2** was generally highest in cases where the substituent group was unsaturated (i.e. **2a**, **2b**, **2e**, and **2f**) as might have been predicted considering the natural substrate selectivity of α-chymotrypsin. The α-methyltryptophan precursor **2f** was also transformed further to form the amino ester. Reduction of **2f** under 40 psi of H_2 using Adam's catalyst (PtO_2) proceeded in quantitative yield. The amino ester was isolated (86%) as the hydrochloride and was found to be >97% optically pure. This reaction further established the stereochemistry of the product as being L-methyl α-methyltryptophan hydrochloride. This indicated that the D isomer of the α-methyl α-nitro carboxylic acid was preferentially hydrolyzed by the protease.

Experimental Section

General Methods. All reactions of air- or water-sensitive reagents were performed in flame-dried glassware flushed with dry argon by using standard techniques.[12] Argon was dried by passing it through a Drierite tower. Ether and hydrocarbon solvents were dried over solutions or suspensions of potassium or sodium benzophenone ketyl and were freshly distilled before use. Dichloromethane was dried by distillation from phosphorus pentoxide. Methanol, ethanol, and 2-propanol were distilled from their magnesium alkoxides before use. α-Chymotrypsin used in the hydrolyses was obtained as the triply recystallized enzyme. All enzymes used were obtained from Sigma Chemical Co. and were stored in a dessicator at 5 °C prior to use. Unless noted otherwise, all other reagents were obtained from Aldrich Chemical Co. as reagent grade materials and were used without further purification. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ using a Varian XL 200E (200 MHz) spectrometer. Isolated products were >95% pure by capillary GC and by ^1H and ^{13}C NMR spectroscopy unless otherwise indicated and were also characterized by high resolution mass spectroscopy where appropriate. A Varian 3900 gas chromatograph with a fused silica Megabore capillary column was used to monitor reactions. Routine gas chromatography/mass spectrometry (GC/MS) analyses were performed on a HP 5790 gas chromatograph using a HP 5970A mass selective detector and high resolution MS data were obtained on a VG Model 70S high resolution mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium D line) in either a 10.00-mm or 5.00-cm cell in chloroform at room temperature. Column chromatography was performed by using standard gravity or flash chromatography techniques on E. Merck 230–400-mesh silica gel or 70–230-mesh neutral alumina. Radial chromatography was performed on 1-, 2-, or 4-mm silica coated glass plates by using a gravity fed solvent system for elution. The radial chromatography was performed under a N_2 atmosphere on an apparatus obtained from Harrison Research. All melting points and boiling points are reported in degrees Celsius (°C) and are uncorrected.

Preparation of Esters of 2-Nitropropanoic Acid. Methyl and butyl esters of 2-nitropropanoic acid were prepared on large scale by carboxylation of the magnesium salt of nitroethane and acid-catalyzed esterification of the product acid following a literature procedure.[13] Both the esters were purified by vacuum distillation with care being taken not to evaporate to dryness. In the case of the methyl ester, 32 g (37%) of a clear liquid was obtained: bp 101–105 °C (30 Torr); ^1H NMR δ 5.13 (q, 1 H, J = 6.9 Hz), 3.76 (s, 3 H), 1.77 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 165.53, 82.95, 53.39, 15.48; MS, m/e (relative abundance) 101.95 (2.7), 58.95 (100.0), 56.05 (12.4), 55.05 (14.9). Butyl 2-nitropropanoate was similarly prepared on a 37-g scale in 35% yield and purified by distillation: bp 72–76 °C (0.5 Torr); ^1H NMR δ 5.20 (q, 1 H, J = 7.0 Hz), 4.20 (t, 2 H, J = 6.9 Hz), 2.75 (d, 3 H, J = 7.0 Hz), 1.2–1.80 (m, 4 H), 0.9 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 165.11, 83.20, 66.78, 30.32, 18.92, 15.77, 13.61; MS, m/e (relative abundance) 129.15 (2.2), 102.05 (17.1), 101.15 (7.1), 75.05 (6.4), 74.05 (7.1), 73.05 (13.1), 58.15 (6.0), 57.15 (100.0), 56.15 (92.9), 55.15 (36.1); IR (neat) cm^{-1} 2850–2950 (s), 1695 (s), 1555 (s), 1445 (m), 1190–1400 (br s), 1080 (m). Small-scale preparations of the methyl and butyl esters of 2-nitropropanoic acid were more conveniently accomplished by substitution of nitrite for bromide by using the corresponding 2-bromopropanoic acid esters using the method of Kornblum and Blackwood.[14]

Butyl 2-methyl-2-nitro-4-pentenoate was prepared by the allylation of butyl 2-nitropropanoate catalyzed by $(Ph_3P)_4Pd$. A modification of the procedure of Ferrod, Genet, and Muzart was used.[6] Allyl acetate (2.0 g, 20 mmol), butyl 2-nitropropionate (1.1 g, 6.3 mmol), and $(Ph_3P)_4Pd$ (0.1 g, 0.09 mmol) were dissolved in 20 mL of dry THF and the resulting yellow solution was stirred under nitrogen for 6 h after which time the ester had been completely consumed as evidenced by GC. The solvent and excess allyl acetate were then removed at reduced pressure on a rotary evaporator and the product ester was purified by bulb-to-bulb distillation (90 °C (0.05 Torr)). A clear colorless liquid was obtained (1.23 g, 91% yield): ^1H NMR δ 5.05–5.95 (m, 3 H), 4.20 (t, 2 H, J = 7.1 Hz), 2.80–3.15 (m, 2 H), 1.80 (s, 3 H), 1.20–1.80 (m, 4 H), 0.9 (t, 3 H, J = 7.7 Hz); ^{13}C NMR δ 167.1, 121.4, 92.0, 68.5, 40.9, 30.2, 21.0, 18.9, 13.5; MS, m/e (relative abundance) 113.15 (62.0), 112.15 (37.9), 83.15 (21.6), 69.15 (18.0), 68.15 (18.0), 67.15 (39.0), 57.15 (100.0), 56.15 (15.6), 55.15 (19.6); exact mass calcd for $C_{10}H_{16}O_2$ 168.1150 (M – NO_2H), found 168.1148.

Methyl 2-methyl-2-nitro-4-pentenoate was prepared from methyl 2-nitropropanoate and allyl acetate in a manner analogous to that described above for the butyl ester. The product ester was isolated after bulb-to-bulb distillation (50–60 °C, 0.5 Torr) as a clear colorless liquid in 95% yield (1.23 g) and had the following: ^1H NMR δ 5.50–5.72 (m, 1 H), 5.05–5.20 (m, 2 H), 3.80 (s, 3 H), 2.70–3.05 (m, 2 H), 1.80 (s, 3 H); ^{13}C NMR δ 167.5, 129.5, 121.6, 92.0, 53.4, 40.1, 21.0.

Methyl 2-methyl-2-nitropentanoate was prepared by hydrogenation of methyl 2-methyl-2-nitro-4-pentenoate (30 mg, 0.173 mmol) using 10% Pd/C under 15 psi of H_2 in methanol. Reduction of the carbon–carbon double bond under these conditions proceeded without reduction of the nitro group to yield 19 mg (62%) of an oily product after bulb-to-bulb distillation (40 °C at 0.3 Torr): ^1H NMR δ 3.80 (s, 3 H), 2.00–2.35 (m, 2 H), 1.75 (s, 3 H), 1.15–1.45 (m, 2 H), 0.95 (t, 3 H, J = 7.7 Hz); ^{13}C NMR δ 168.0, 92.7, 53.4, 38.5, 21.3, 17.1, 13.9.

Butyl 2,4-Dimethyl-2-nitro-4-pentenoate. Methallyl acetate (0.4 g, 3.5 mmol) and butyl 2-nitropropanoate (0.51 g, 2.9 mmol) were allowed to react in the presence of $(Ph_3P)_4Pd$ (0.1 g, 0.09 mmol) in the manner described above to yield the crude product, which was purified by bulb-to-bulb distillation (55 °C, 0.4 Torr) to give 0.63 g (94.4%) of pure product: ^1H NMR δ 4.98 (m, 1 H), 4.75 (m, 1 H), 4.20 (t, 2 H, J = 7.0 Hz), 2.98 (m, 2 H), 1.75 (s, 3 H), 1.65 (s, 3 H), 1.55–1.70 (m, 2 H), 1.25–1.45 (m, 2 H), 0.95 (t, 3 H, J = 7.5 Hz); ^{13}C NMR δ 167.5, 138.0, 117.6, 92.2, 66.6, 43.6, 30.2, 23.1, 21.2, 18.9, 13.5; MS, m/e (relative abundance) 212.25 (2.6), 127.2 (2.7), 113.1 (4.4), 85.25 (25.1), 71.15 (49.3), 69.15 (7.8), 57.15 (100.0), 56.15 (15.3), 55.05 (18.8); exact mass calcd for $C_{11}H_{18}NO_3$ (M – OH) 212.1287, found 212.2496; calcd for $C_7H_{10}NO_3$ (M – C_4H_9O) 156.0660, found 156.1824.

Butyl 2-Nitro-2-phenylpropanoate. Triphenylbismuth dichloride was prepared from triphenylbismuth according to the procedure of Wittig and Claus and was then used in Barton's method to phenylate butyl 2-nitropropanoate.[15] Thus, butyl 2-nitropropanoate (0.18 g, 1 mmol) and tetramethylguanadine (0.21 g, 2 mmol) were dissolved in 10 mL of dry benzene under nitrogen. Then the triphenylbismuth dichloride (0.56 g, 1.1 mmol) was added in one portion to the solution and the faintly yellow suspension was stirred under nitrogen for an additional 3 h. Then

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the benzene was removed at reduced pressure on a rotary evaporator. The residue was purified by bulb-to-bulb distillation. A lower boiling impurity was first removed (40 °C, 0.05 Torr) after which the product was distilled from triphenylbismuth (70 °C, 0.05 Torr) to give 0.21 g (81% yield) of a clear liquid: ^{1}H NMR δ 7.45 (br, 5 H), 4.3 (t, 2 H, J = 7.1 Hz), 2.25 (s, 3 H), 1.55–1.75 (m, 2 H), 1.40–1.20 (m, 2 H), 0.9 (t, 3 H, J = 7.5 Hz); ^{13}C NMR δ 167.3, 134.1, 129.9, 128.6, 127.5, 95.1, 67.0, 30.2, 23.1, 18.9, 13.5; MS, m/e (relative abundance) 205.12 (77.5), 181.0 (15.9), 169.0 (19.4), 149.0 (51.2), 121.1 (66.0), 104.1 (31.0), 103.05 (67.8), 69.0 (100.0); exact mass calcd for $C_{13}H_{17}O_2$ 205.1228, found 205.1217.

Butyl 2-methyl-2-nitro-1,5-pentanedicarboxylate was prepared both by KF/basic alumina and by tri-*n*-butylphosphine-catalyzed Michael additions of butyl 2-nitropropanoate to butyl acrylate (PBu_3: 0.75 g (4.3 mmol) of butyl 2-nitropropanoate, 1.0 g (7.8 mmol) of butyl acrylate, and 3 drops of PBu_3; KF/basic Al_2O_3: 2.0 g (11.4 mmol) of butyl 2-nitropropanoate, 4.0 g (31.2 mmol) of butyl acrylate, and 5.0 g of KF/basic Al_2O_3).[8,9] The product diester was isolated by distillation (80 °C, 0.05 Torr) as a clear colorless oil ($PPBu_3$, 0.93 g (72%); KF/basic Al_2O_3, 0.94 g (27%)) and had the following: ^{1}H NMR δ 4.2 (t, 2 H, J = 7.0 Hz), 4.05 (t, 2 H, J = 7.0 Hz), 2.30–2.60 (m, 4 H), 1.75 (s, 3 H), 1.20–1.70 (m, 8 H), 0.95 (t, 3 H, J = 7.5 Hz), 0.90 (t, 3 H, J = 7.5 Hz); ^{13}C NMR δ 171.6, 166.9, 91.8, 66.8, 64.8, 31.6, 30.6, 29.0, 21.6, 19.2, 19.0, 13.7, 13.6; MS, m/e (relative abundance) 230.25 (6.1), 183.15 (7.3), 174.10 (47.5), 145.10 (17.5), 128.10 (8.7), 127.10 (100.0), 100.15 (27.0), 99.15 (57.5), 57.15 (48.7), 56.15 (24.2), 55.05 (24.7); exact mass calcd for $C_{10}H_{16}NO_5$ (M – C_4H_9O) 230.1028, found 230.1054.

Methyl 2-methyl-2-nitro-1,5-pentanedicarboxylate was also prepared by using a tri-*n*-butylphosphine-catalyzed Michael addition and yielded after purification by radial chromatography (2-mm silica gel plate, hexanes) 1.15 g (91.5% yield) of product as a colorless oil: ^{1}H NMR δ 3.75 (s, 3 H), 3.65 (s, 3 H), 2.20–2.60 (m, 4 H), 1.75 (s, 3 H); ^{13}C NMR δ 172.1, 167.4, 91.6, 53.6, 52.0, 31.5, 28.7, 21.7; MS, m/e (relative abundance) 188.05 (13.2), 173.05 (0.4), 141.0 (100.0), 114.05 (24.2), 113.05 (78.6), 99.05 (24.3), 85.0 (17.5), 55.0 (32.1), 53.0 (26.0).

Butyl 2-methyl-2-nitro-5-oxohexanoate was prepared by using a tri-*n*-butylphosphine (3 drops) catalyzed Michael reaction between butyl 2-nitropropanoate (0.56 g, 3.2 mmol) and methyl vinyl ketone (0.24 g, 3.4 mmol). The product was isolated by bulb-to-bulb distillation at 75 °C and 0.5 Torr as a clear colorless oil (0.72 g, 91.8% yield): ^{1}H NMR δ 4.2 (t, 2 H, J = 6.9 Hz), 2.25–2.55 (m, 4 H), 2.15 (s, 3 H), 1.75 (s, 3 H, J = 7.3 Hz), 1.55 (m, 2 H), 1.35 (m, 2 H) 0.90 (t, 3 H); ^{13}C NMR δ 205.7, 167.1, 91.8, 66.7, 37.8, 30.2, 29.9, 21.9, 18.9, 14.5, 13.6; MS, m/e (relative abundance) 199.2 (11.8), 125.1 (32.8), 115.1 (21.6), 99.1 (23.9), 97.1 (17.5), 87.1 (14.1), 71.1 (100.0), 57.1 (18.5), 55.1 (12.5); exact mass calcd for $C_{10}H_{19}O_3$ 199.1334, found 199.1312.

Methyl 3-(3-indolyl)-2-methyl-2-nitropropanoate and butyl 3-(3-indolyl)-2-methyl-2-nitropropanoate were prepared by using the reaction of either butyl or methyl 2-nitropropanoate with gramine.[11] Reaction of 1.0 g (7.5 mmol) of methyl 2-nitropropanoate with 1.8 g (10 mmol) of gramine yielded 1.6 g (81%) of product while reaction of 4.5 g (26 mmol) of butyl 2-nitropropanoate with 4.9 g (28 mmol) of gramine yielded 7.36 g (93%) of product. Radial chromatography of the methyl ester product yielded a clear colorless oil in 81% yield having the following: ^{1}H NMR δ 8.10 (br, 1 H), 7.50 (dd, 1 H, J = 1.9 Hz and 7.5 Hz), 7.05–7.20 (m, 3 H), 6.90 (d, 1 H), 3.75 (s, 3 H), 3.70 (m, 2 H), 1.70 (s, 3 H); ^{13}C NMR δ 168.2, 135.9, 127.9, 124.2, 122.4, 120.0, 118.5, 111.4, 107.3, 93.8, 53.5, 32.2, 21.4; MS, m/e (relative abundance) 216.05 (33.8), 215.05 (56.5), 206.95 (61.2), 132.0 (20.6) 130.0 (100.0), 129.00 (27.4), 89.0 (16.1). The butyl ester was isolated in 93% yield as a yellow oil after evaporation of solvent and was of sufficient purity to be used in the α-chymotrypsin hydrolyses without further purification. The butyl ester was characterized spectroscopically and had the following: ^{1}H NMR δ 8.15–8.22 (br, 1 H), 7.40–7.52 (m, 1 H), 7.05–7.42 (m, 3 H), 6.95–7.00 (m, 1 H), 4.12 (t, 2 H, J = 7.1 Hz), 3.72 (m, 2 H), 1.75 (s, 3 H), 1.52–1.75 (m, 2 H), 1.25–1.45 (m, 2 H), 0.90 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 167.8, 135.8, 127.9, 124.1, 122.2, 118.5, 111.3, 107.3, 93.8, 66.6, 32.1, 30.2, 21.3, 18.9, 13.5.

Methyl α-methyltryptophan hydrochloride was prepared from the α-nitro ester (31 mg, 0.13 mmol) by using a literature procedure with Adam's catalyst in methanol.[11] The product was isolated after addition of dry hydrogen chloride to precipitate the product as a white, hygroscopic solid in 86% yield (27.2 mg); mp 158–159 °C (lit.[4a] mp 160 °C); ^{1}H NMR (DMSO-d_6) δ 7.50 (dd, 1 H, J = 1.75 Hz and 7.5 Hz), 7.30 (d, 1 H), 6.85–7.05 (m, 3 H), 3.50 (s, 3 H), 3.00–3.40 (br, 4 H), 2.95 (m, 2 H), 1.25 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 177.1, 135.8, 127.8, 124.0, 118.5, 111.2, 109.3, 58.7, 51.5, 40.5, 25.7.

General Procedure for the α-Chymotrypsin-Catalyzed Hydrolyses of 2-Nitro Esters. The appropriate substituted α-nitropropanoate ester and an equal weight of an *n*-alkane hydrocarbon internal standard (typically C_{10}–C_{14} depending on the molecular weight of the α-nitro ester) were dissolved in 10 mL of DMSO. The DMSO solution was then added to 20 mL of pH 7.1 0.25 M phosphate buffer. The aqueous buffer was swirled during the addition of the DMSO solution to insure that an even suspension was formed. The suspension was then shaken vigorously and a 0.5-mL aliquot was removed as rapidly as possible. The 0.5-mL aliquot was placed in a capped 2-mL polyethylene centrifuge tube along with 1.5 mL of diethyl ether. The mixture was shaken and the ether layer was analyzed by GC. The enzyme was then added to the suspension and the suspension was shaken mechanically on a wrist action shaker. Aliquots were removed periodically and analyzed as above for the disappearance of the α-nitro ester and the appearance of nitroalkane (from decarboxylation of the hydrolyzed ester). When the reaction was 60% complete, Celite was added to the reaction mixture and the enzyme was removed by filtration. The filtrate was then extracted with five 20-mL portions of diethyl ether. The combined ether extracts were then washed five times with 10-mL portions of saturated brine to remove any DMSO in the ether layer. The ether was then dried (Na_2SO_4) for 30 min. The solution was filtered and the ether was removed under reduced pressure to give a clear colorless oil which was found by ^{1}H NMR to contain the hydrocarbon standard, the unreacted ester, and the nitroalkane resulting from decarboxylation of the α-nitro carboxylic acid hydrolysis product. The extent of hydrolysis was confirmed by NMR integration. The residue obtained was directly analyzed for optical activity and the ester was examined for enantiomeric purity by the use of Eu(hfc)$_3$. The results from these hydrolyses are listed in Table II.

(−)-L-Methyl 3-(3-Indolyl)-2-methyl-2-nitropropanoate Kinetic Resolution. The racemic methyl ester was treated with α-chymotrypsin as discussed in the general procedure above. Thus 480 mg (1.58 mmol) of this ester was suspended in 60 mL of the above-mentioned solvent mixture along with 180 mg of α-chymotrypsin. After shaking for 6 h, the hydrolysis was 60% complete. The unreacted ester (0.13 g, 27% yield) was isolated by radial chromatography and was found to be optically pure by ^{1}H NMR using Eu(hfc)$_3$ and both the methoxy and α-methyl singlets: $[\alpha]_D$ −65.8° (*c* 5.7 g in 100 mL of $CDCl_3$). The other product isolated as a clear oil by radial chromatography was the decarboxylation product 2-nitro-3-(3-indolyl)propane (0.15 g, 48% yield): ^{1}H NMR δ 8.05–8.20 (br, 1 H), 7.55–7.60 (m, 1 H), 6.95–7.40 (m, 4 H), 4.87 (m, 1 H), 3.35 (m, 2 H), 1.55 (d, 3 H); ^{13}C NMR δ 136.2, 127.0, 122.2, 122.3, 119.8, 118.3, 111.5, 109.8, 84.0, 31.3, 19.0; MS, m/e (relative abundance) 204.1 (66.1), 158.1 (54.1), 157.1 (61.2), 130.0 (100.0), 117.05 (22.3), 77.05 (12.2).

(+)-L-Methyl α-methyltryptophan hydrochloride was prepared by reduction of the corresponding ester (50 mg, 0.19 mmol) using the procedure described above for the racemic ester using Adam's catalyst. The hydrochloride salt was isolated in 81% yield (41.3 mg): mp 157–158 °C dec (lit.[4a] mp 159 °C); $[\alpha]_D$ +27.5° (*c* 0.84 ($CDCl_3$)) at 25 °C (lit.[4a] $[\alpha]_D$ +27.3).

Acknowledgment. Support of this work by the Robert A. Welch foundation and a Biomedical Sciences Support grant from Texas A&M University and from the Board of Regents of Texas A&M University is gratefully acknowledged.

Registry No. 1 (R = C_4H_9), 113747-70-9; 1 (R = CH_3), 62013-44-9; **2a** (R = C_4H_9), 113747-71-0; **2a** (R = CH_3), 113747-72-1; **2b** (R″ = C_4H_9), 113747-73-2; **2c** (R″ = R′ = OCH_3), 113747-74-3; **2c** (R″ = R′ = OC_4H_9), 113747-75-4; **2d** (R′ = CH_3R″ = C_4H_9), 113747-76-5; **2e**, 113747-77-6; **2f** (R″ = CH_3), 113747-78-7;

2f (R″ = C_4H_9), 113747-79-8; methyl α-methyltryptophan·HCl, 84120-83-2; nitroethane, 79-24-3; 2-nitropropanoic acid, 113747-80-1; allyl acetate, 591-87-7; methyl 2-methyl-2-nitropentanoate, 113747-81-2; methallyl acetate, 820-71-3; butyl acrylate, 141-32-2; methyl vinyl ketone, 78-94-4; gramine, 87-52-5; (–)-L-methyl 3-(3-indolyl)-2-methyl-2-nitropropanoate, 113829-15-5; α-chymotrypsin, 9004-07-3; (+)-L-methyl α-methyltryptophan·HCl, 84120-86-5.

General Approach to the Synthesis of Polyquinenes via the Weiss Reaction. 6. Progress toward the Synthesis of Dicyclopentapentalenes

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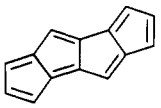
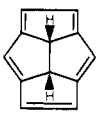
Received September 23, 1987

The synthesis of the three tetraquinanes tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecanetetraol (**27**), tetracyclo[6.6.0.$0^{2,6}$.$0^{9,13}$]tetradecanediol (**36**), and tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradecanediol (**39**) has been achieved via the Weiss reaction. Reaction of glyoxal (**4a**) with di-*tert*-butyl 3-oxoglutarate (**5b**) gave tetra-*tert*-butyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**6b**) in excellent yield. This was converted, regiospecifically, into bisenol ether **20b** with diazomethane. The bisalkylation of **20b** was effected with allyl iodide/KH to provide a mixture of the 2,6-diallyl regioisomer **23b** (64%) and the corresponding 2,8-diallyl dione **24b** (36%); the former compound crystallized from the reaction mixture. Hydrolysis of tetraester **23b** furnished 2,6-diallyl dione **7**, which was oxidized and cyclized to diketo diol **26**, isolated as a mixture of diexo and diendo stereoisomers **26a** and **26b**, both of which were reduced with borane–tetrahydrofuran to provide the desired tetraol **27** in 80% yield. The HMPA-mediated dehydration of **27** gave the tetracyclotetradecadiene **28**. Furthermore, the 2,6-diallyl diones **7a** and **7b** were converted with HBr–peroxides into dibromides **35a,b**, and this mixture of epimers was cyclized to the tetracyclotetradecanediol **36** on stirring with samarium diiodide (80% yield). Analogous to the chemistry developed for preparation of **36**, the 2,8-diallyl tetra-*tert*-butyl ester **24b** was converted into the 2,8-bis(3-bromopropyl) dione **38**, which cyclized on treatment with SmI_2 to the desired tetracyclic tetradecanediol **39** in 68% yield.

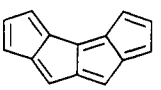
The preparation of highly strained polyunsaturated cyclopentanoid compounds (polyquinenes) has received a great deal of attention in recent years. Katz[1a] reported the formation of the dianion of pentalene in 1964. This was followed by studies on the synthesis of pentalene and its derivatives by Hafner[1b] and others.[1c] Moreover, de Meijere has detailed attempts to prepare acepentalene and has recently reported the preparation of dihydroacepentalenediide.[2] To date, the 14π-annulenes dicyclopenta[*a*,*e*]pentalene (**1**) and dicyclopenta[*a*,*d*]pentalene (**3**), as well as the 10π-annulene *cis*-tetracyclo-



1

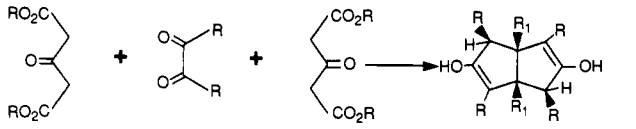


2



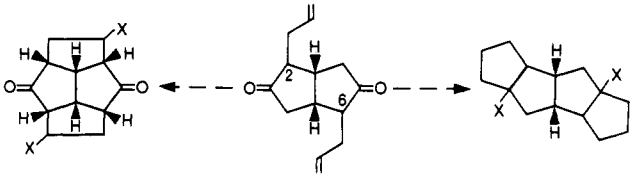
3

Scheme I



5a, R=CH_3 5b, R=t-Bu | 4a, R=H 4b, R=CH_3 | 5a, R=CH_3 5b, R=t-Bu | 6a, R_1=H, R=CO_2CH_3 6b, R_1=H, R=CO_2tBu; 84%

Scheme II



9 7 8

[7.2.1.$0^{4,11}$.$0^{6,10}$]dodeca-1,3,5,7,9(12)-pentaene (**2**) have been discussed only from a theoretical point of view despite the preparation of the carbon skeletons of these molecules by several groups.[3-5]

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