Synthesis and Spectroscopic Studies of Optically Active *N*-Acetyl Butenoates and *N*-Acetyl-2-alkyl-pyrrolin-4-ones

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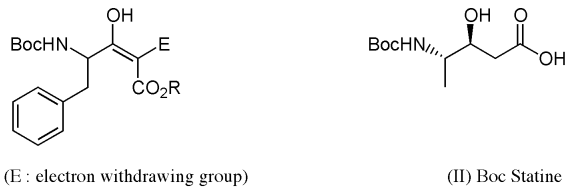
Received July 25, 2001

The synthesis of a series of optically active *N*-acetyl butenoates **3**-**5** is described using a facile methodology. These butenoates undergo cyclization to the corresponding *N*-acetyl-2-alkyl-pyrrolin-4-ones **6,7** retaining their stereochemical integrity. The structure of the newly synthesized compounds has been elucidated through ^{1}H-^{13}C NMR, IR spectroscopy and their enantiomeric excesses have been measured by chiral HPLC analysis.

J. Heterocyclic Chem., **39**, 185 (2002).

Introduction.

Chiral α-substituted γ-amino-β-ketoesters (I) are important precursors of α-substituted "statine analogues" and constitute interesting building blocks for the construction of nitrogen heterocycles containing the pyrrolinone nucleus [1]. β-Hydroxy-γ-amino acids derivatives have been widely used for the synthesis of statine (II) (Figure 1), a nonproteogenic amino acid which is recognised as a key component of some low molecular weight peptides such as the aspartic protease inhibitor pepstatin [2-4]. It has been accepted that the hydroxyl residues are important, given that they will generally be within hydrogen bonding distance of both aspartate carboxyls [5].



(1) (E : electron withdrawing group) (II) Boc Statine

Figure 1. α-Substituted-γ-amino-β–ketoesters (I) and Boc Statine (II).

On the other hand, difunctionalized enols of type (I) possess topographical similarities with Boc-statine (II), therefore they can be effective as inhibitors of HIV-1 protease [6,7].

In the course of our research program on the synthesis of nitrogen heterocycles containing the pyrrolidine-2,4-dione nucleus [8-10], we have developed a facile and convenient approach to highly functionalized, optically active *N*-acetyl tetramic acids [11,12]. We report herein a simple and efficient preparation of optically active *N*-protected α-acyl-β-hydroxy butenoates from the corresponding L-α-amino acids with the additional requirement that the proposed methodology should allow for the synthesis of **3**-**5** (Scheme 1) in enantiopure form. It is known that the diastereoselective hydrogenation of *N*-protected γ-amino-β-ketoesters utilizing chiral Rh(I) and Ru(II) catalysts provides an efficient entry to "statine series" with high enantiomeric purities [13].

Having access to a convenient source of the γ-amino-β-hydroxy butenoates we then investigated their conversion to pyrrolinone derivatives under different experimental conditions. A smooth transformation of the desired derivatives **6,7** (Scheme 1) was eventually achieved *via* an intramolecular nucleophilic attack of the *N*H group to the acyl carbonyl, leading ultimately to the formation of the five-membered heterocyclic ring system, with the retention of configuration about the asymmetric γ-carbon atom.

Owing to their role as intermediates for synthesizing more complex biologically important molecules, optically active functionalized pyrrolinones have received considerable attention in the last decades. Those methodologies that can lead to chiral pyrrolinones with functional groups are still greatly pursued by synthetic chemists.

Results and Discussion.

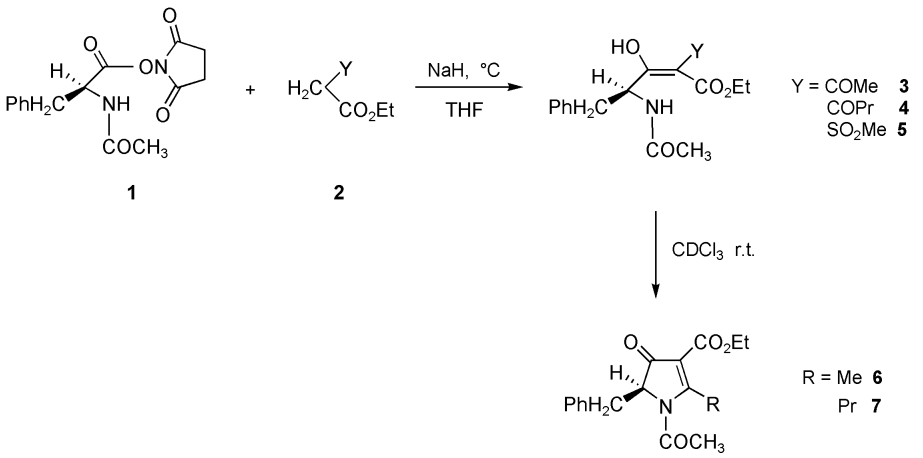
A series of experiments were necessary to establish an optimal procedure for our synthetic protocol. Thus in the C-acylation reaction 2 equivalents of the active methylene compound were treated with 1 equivalent of the *N*-hydroxysuccinimide ester of *N*-acetyl-L-phenylalanine in the presence of 2 equivalents of NaH, in anhydrous THF at 0 °C, for 2-5 hours. The reaction mixture was concentrated *in vacuo* and the obtained solid was diluted with water and washed with diethyl ether. The aqueous layer was separated, acidified with 10% hydrochloric acid in an ice-water bath giving a solid that was filtered off. The obtained optically active butenoates **3**-**5** were isolated in good yields. In deuteriochloroform solution, the butenoates undergo cyclization, generating the optically active pyrrolinones in 70% overall yield.

An important feature of the proposed strategy has been the use of optically active *N*-hydroxysuccinimide ester of *N*-acetyl-L-phenylalanine as acylating agent. This chiral starting material is easily prepared and maintains the stereochemical integrity of the corresponding α-amino acid. Moreover this compound proved to be very stable under

the mild reaction conditions (NaH in THF, 0 °C, short reaction time) allowing the isolation of the corresponding butenoates **3-5** in satisfactory yields.

The IR spectra of the C-acylation compounds **3-5** show absorptions at 3270-3430 and 3030-3090 cm^{-1} which are assigned to O-H and N-H stretching, respectively. In the

Scheme 1



1 2

Synthesis of *N*-Acetyl Butenoates **3-5** and *N*-Acetyl-2-alkyl-pyrrolin-4-ones **6-7**.

Additionally, intramolecular condensation was also possible since compounds **3-5** could be smoothly converted (deuteriochloroform solution, room temperature) into the optically active pyrrolin-4-ones **6,7**. The structures of the newly prepared compounds **3-7** have been elucidated with elemental analysis, FT-IR, and NMR spectral data. A complete assignment of the ^{1}H-^{13}C NMR has been made possible with two-dimensional NMR experiments (COSY, HETCOR).

While the *N*-acetyl butenoates **3,4** exist in their enolic tautomeric form, compound **5** has been found to exist completely in deuteriochloroform solution in the keto form as disclosed by the existence of a methine –CH hydrogen signal at 5.25 ppm (Figure 2).

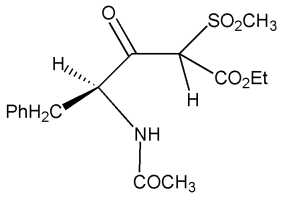


Figure 2. Keto form of compound **5**.

Surprisingly, the ^{1}H and ^{13}C NMR spectra of the optically active compound **5** which is found to exist in its keto form, exhibits 'self-induced' anisochrony for certain proton and carbon signals. This otherwise unexpected phenomenon can be explained if it is supposed that hydrogen bonding 'cross-association' between the amide and keto carbonyl is favorable, in a non polar solvent such as deuteriochloroform (see experimental) [14].

carbonyl region, the CO absorption of the urethane group appears at 1690-1740 cm^{-1} whereas the intramolecular hydrogen bonded carbonyl of the enol form of the β-keto ester, C(OH)=C-CO_2Et, absorbs at 1646-1652 cm^{-1}. The strong band at 1515-1555 cm^{-1} is attributed to the carbon-carbon double bond of this system. Taking everything into account, it appears that the enolic form of the C-acylation compounds is predominating in the solid state.

Attempts to achieve the cyclization of the *N*-acetyl butenoates **3-5** towards the 3-substituted tetramic acids (pyrrolidine-2,4-diones) by removal of the acetyl group by EtONa/EtOH or *t*-BuOK/*t*-BuOH, resulted in the synthesis of the appropriate tetramic acids but with complete racemisation.

Table 1

Optical Rotations and Enantiomeric Excess of compounds **3-7**

	Enantiomeric Ratio (t, min)	$[\alpha]_D$	e.e.
3	97(8.37):3(11.13)	+30.5 (c2, MeOH)	94
4	96(8.50):4(11.73)	+53.4 (c3, MeOH)	92
5	95(7.75):5(9.23)	-20.1 (c3, MeOH)	90
6	95(6.05):5(8.23)	+5.6 (c4, MeOH)	90
7	95(5.95):5(7.67)	+19.7 (c4, MeOH)	90

Determination of the optical purity of compounds **3-7** was done by HPLC analysis using a CHIRALPAK AS column and, all the analogs were found to have enantiomeric excess > 90%. The absence of strongly basic or thermal conditions did not promote removal of the acidic α-proton of the α-amino acid backbone in these products and as a result the epimerization of the stereogenic center was minimized although not completely avoided.

Conclusion.

The synthesis of a series of *N*-acetyl butenoates **3-5** has been achieved with a facile and practical method. Chiral HPLC analysis of the newly synthesized compounds revealed that they retain the enantiopurity of the *N*-acetyl-α-amino acid, used as starting material. The above mentioned butenoates undergo cyclization under mild conditions to afford *N*-acetyl-2-alkyl-pyrrolin-4-ones **6,7** in good yields and enantiomeric purity. The new compounds have been extensively studied by ^{1}H, ^{13}C NMR and IR spectroscopy as well as 2D NMR and the results are fully in accord with the proposed structures.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Magna 560R FT-IR in KBr. The ^{1}H-^{13}C, 2D HETCOR NMR spectra were recorded on a Gemini-2000 300 MHz spectrometer. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained with a EuroVector EA3000 elemental analyser. The enantiomeric ratios were determined by HPLC analysis with a CHIRALPAK AS column (4.6x250mm), [254nm, 0.50 ml/minute, *i*-propanol-hexane (90:10)]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter and the $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

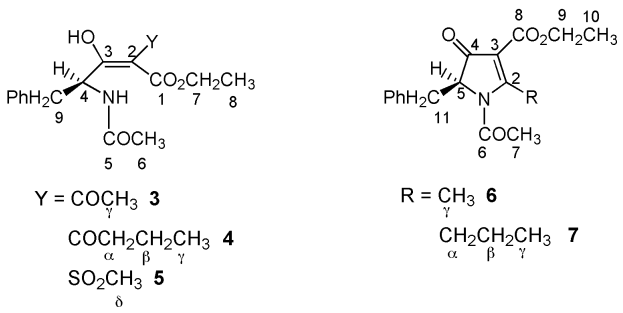


Figure 3. Atom numbering of compounds **3-7**.

General Procedure for the Synthesis of *N*-acetyl Butenoates **3-5**.

The active methylene compound **2** (2.0 mmol) was added dropwise to a mixture of sodium hydride (2.0 mmol, 60% sodium hydride in oil) in anhydrous tetrahydrofuran (15 ml) and the yellow solution thus formed was stirred at room temperature for 1 hour. The *N*-hydroxysuccinimide ester of *N*-acetyl-L-phenylalanine **1** (1.0 mmol) was added to the solution and stirring continued for 2-5 hours in an ice-water bath (temperature 0°C). The mixture was concentrated *in vacuo*, the residue was dissolved in the minimum amount of water *ca* 5 ml, extracted once with diethyl ether, the aqueous layer was separated and acidified with 10% hydrochloric acid in an ice-water bath. Compounds **3-5** were isolated as crystalline solids formed directly in the acidified solution.

Ethyl 4-Acetylamino-2-acetyl-4-benzyl-3-hydroxybutenoate (*4S*-**3**).

This compound was obtained as a white solid (0.22 g, 69%), mp 77-78 °C; ^{1}H-nmr (deuteriochloroform): δ 1.19 (3H, t, *J* = 7.1, $CO_2CH_2CH_3$), 1.95 (3H, s, *N*-$COCH_3$), 2.26 (3H, s, $COCH_3$), 2.93-2.99 (1H, dd, J_1 = 5, J_2 = 14.3, -$CH_2C_6H_5$), 3.22-3.27 (1H, dd, J_1 = 9.8, J_2 = 14.3, -$CH_2C_6H_5$), 4.15 (2H, q, *J* = 7.1, $CO_2CH_2CH_3$), 5.45 (1H, m, -CH), 6.05 (1H, two br, -NH), 7.21-7.35 (5H, m, -$CH_2C_6H_5$), 17.3 (1H, br, -OH); ^{13}C nmr (deuteriochloroform): δ C(3) 196.8, C(5) 170.5, C(1) 165.7, (phenyl group) 138.7/131.3/127.0/124.2, C(2) 111.2, C(7) 60.1, C(4) 48.3, C(9) 38.3, C(γ) 23.1, C(6) 20.2, C(8) 14.1; ir (potassium bromide): 3274 (OH), 3083 (NH), 1705, 1652 (C=O), 1553 (C=C) cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58; N, 4.39. Found: C, 63.83; H, 6.48; N, 4.65.

Ethyl 4-Acetylamino-4-benzyl-2-butanoyl-3-hydroxybutenoate (*4S*-**4**).

This compound was obtained as a white solid (0.26 g, 75%), mp 91-92.5 °C; ^{1}H nmr (deuteriochloroform): δ 0.97 (3H, t, *J* = 7.0, $COCH_2CH_2CH_3$), 1.36 (3H, t, *J* = 7.0, $CO_2CH_2CH_3$), 1.69 (2H, m, $COCH_2CH_2CH_3$), 1.93 (3H, s, *N*-$COCH_3$), 2.64 (2H, t, *J* = 7.5, $COCH_2CH_2CH_3$), 2.83-2.9 (1H, dd, J_1 = 7.7 , J_2 = 15.7, -$CH_2C_6H_5$), 3.19-3.26 (1H, dd, J_1 = 6.3, J_2 = 15.7, -$CH_2C_6H_5$), 4.29 (2H, q, *J* = 7.0, $CO_2CH_2CH_3$), 5.64 (1H, m, -*CH*), 6.01 (1H, d br, *J* = 9.3, -*NH*), 7.10-7.13 and 7.23-7.30 (5H, m, -$CH_2C_6H_5$), 17.4 (1H, br, -O*H*); ^{13}C nmr (deuteriochloroform): δ C(3) 197.4, C(5) 169.5, C(1) 166.4, C(2) 107.6, C(7) 61.2, C(4) 54.0, C(α) 38.8, C(9) 38.7, C(6) 22.9, C(β) 19.5, C(8) 13.9, C(γ) 13.7; ir (potassium bromide): 3288 (OH), 3085 (NH), 1694, 1647 (C=O), 1553 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.71; H, 7.20; N, 4.03. Found: C, 65.92; H, 7.35; N, 4.15.

Ethyl 4-Acetylamino-4-benzyl-3-hydroxy-2-methylsulfonyl-butenoate (4S-**5**).

This compound was obtained as a white solid (0.28 g, 79%), mp 100-101 °C; ^{1}H nmr (deuteriochloroform): δ 1.27 and 1.31 (3H, two t, *J* = 7.1, $CO_2CH_2CH_3$), 1.94 and 1.97 (3H, two s, *N*-$COCH_3$), 2.93-3.0 (1H, dd, J_1 = 8.5, J_2 = 14.3, -$CH_2C_6H_5$), 3.21-3.28 (1H, dd, overlapping with –SO_2CH_3, -$CH_2C_6H_5$), 3.23 and 3.26 (3H, two s, -SO_2CH_3), 4.24 and 4.29 (2H, two q, *J* = 7.1, $CO_2CH_2CH_3$), 4.61 and 5.06 (1H, two m, -*CH*), 5.22 and 5.28 (1H, two s, CO-*CH*), 5.98 and 6.07 (1H, two d br, *J* = 6.9 - *NH*), 7.17-7.19 and 7.28-7.35 (5H, m, -$CH_2C_6H_5$); ^{13}C nmr (deuteriochloroform): δ C(3) 195.0/193.7, C(5) 170.7, C(1) 161.4/160.8, (phenyl group) 136.0/135.5, 129.3/129.2, 129.0/128.9, 127.5/127.4, C(2) 75.1/ 74.2, C(7) 63.5/63.4, C(4) 60.7/60.0, C(γ) 41.6/39.9, C(δ) 35.6/34.7, C(6) 22.7/22.3, C(8) 13.8/13.7; ir (potassium bromide): 3424 (OH), 3028 (NH), 1737, 1646 (C=O), 1515 (C=C) cm^{-1}.

Anal. Calcd. for $C_{16}H_{21}NO_6S$: C, 54.08; H, 5.92; N, 3.94; S, 9.01. Found: C, 53.89; H, 5.75; N, 4.17; S, 8.92.

General Procedure for the Synthesis of *N*-Acetyl-2-alkyl-3-ethoxycarbonylpyrrolin-4-ones **6,7**.

The appropriate *N*-acetyl butenoate **3,4** is dissolved in $CDCl_3$ and stirred at room temperature for several days. After completion of the cyclization reaction, as monitored by ^{1}H NMR, the solvent was evaporated *in vacuo* to yield almost quantitatively the respective *N*-acetyl-2-alkyl-pyrrolin-4-ones.

N-Acetyl-5-benzyl-3-ethoxycarbonyl-2-methylpyrrolin-4-one (*5S*-**6**).

This compound was obtained as a yellow oil (0.14 g, 93%), ^{1}H nmr (deuteriochloroform): δ 1.29 (3H, t, *J* = 7.0, $CO_2CH_2CH_3$), 2.32 (3H, s, *N*-$COCH_3$), 2.65 (3H, s -CH_3), 3.32 (2H, d, *J* = 4.1, -$CH_2C_6H_5$), 4.23 (2H, q, *J* = 7.0, $CO_2CH_2CH_3$), 4.39 (1H, t, *J* = 4.6, -C*H*), 7.01-7.21 (5H, m, -$CH_2C_6H_5$); ^{13}C nmr (deuteriochloroform): δ C(4) 194.5, C(2) 178.3, C(6) 168.5, C(8) 162.9, (phenyl group) 133.5/129.5/128.4/127.6, C(3) 113.9, C(9) 66.7, C(5) 60.5, C(11) 37.8, C(7) 25.2, C(γ) 17.1, C(10) 14.1.

N-Acetyl-5-benzyl-3-ethoxycarbonyl-2-propylpyrrolin-4-one (*5S*-**7**).

This compound was obtained as a yellow oil (0.16g, 97%), ^{1}H nmr (deuteriochloroform): δ 0.78 (3H, t, *J* = 7.0, CH_2-CH_2CH_3), 1.28 (3H, t, *J* = 7.0, $CO_2CH_2CH_3$), 1.69 (2H, m, $CH_2CH_2CH_3$), 2.35 (3H, s, *N*-$COCH_3$), 3.10 (2H, t, *J* = 7.0, $CH_2CH_2CH_3$), 3.32 (2H, dd, J_1 = 3.3, J_2 = 6.0, J_3 = 16.0, -$CH_2C_6H_5$), 4.23 (2H, q, *J* = 7.0, $CO_2CH_2CH_3$), 4.33 (1H, dd, J_1 = 3.3, J_2 = 6.0, -C*H*), 7.0-7.19 (5H, m, -$CH_2C_6H_5$); ^{13}C nmr (deuteriochloroform): δ C(4) 194.7, C(2) 182.7, C(6) 168.0, C(8) 162.7, (phenyl group) 133.1/129.7/128.4/127.6, C(3) 113.5, C(9) 66.5, C(5) 60.4, C(11) 38.1, C(α) 30.8, C(7) 25.1, C(β) 21.8, C(10) 14.1, C(γ) 13.9.

Acknowledgements.

We would like to thank the Committee of Research of the National Technical University of Athens, Greece, for a doctoral assistantship (E.G.).

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