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Synthesis of γ-Hydroxy-α-amino Acids by Directed Hydroxylation via a Dihydro-1,3-oxazine Intermediate.

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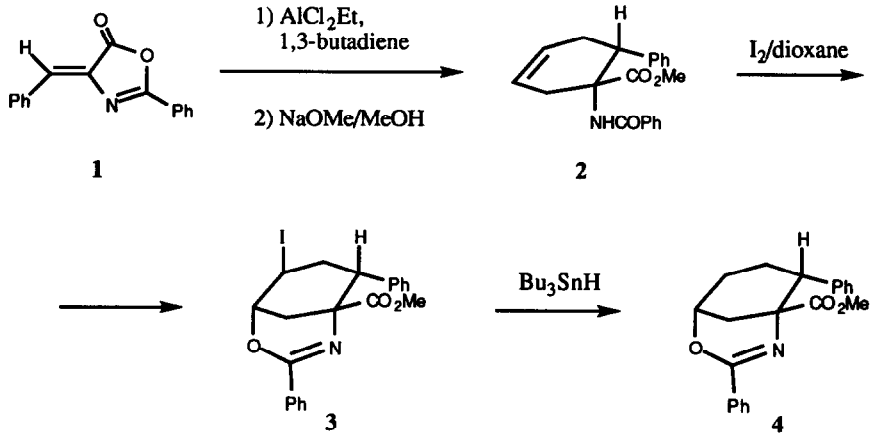
Abstract: The amide group of γ,δ-unsaturated amino acids can be used for the preparation of γ-hydroxy-α-amino acids. Product **2**, which is easily obtained by hydrolysis of the spiro-oxazolone-adduct formed in the Diels-Alder reaction between (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone **1** and 1,3-butadiene, was converted into the corresponding iodo-1,3-oxazine **3** with I_2/dioxane. Further deiodination and hydrolysis of this product allows the obtention of the free γ-hydroxy-α-amino acid **8**.

The incorporation of conformationally constrained amino acids into peptides is a powerful approach for generating structurally defined peptides as conformational probes and bioactive agents[1]. The description of new α-amino acids with this characteristic or of new synthetic procedures to obtain these compounds has therefore attracted the attention of numerous research groups[2]. In particular, the conformationally restricted cyclic amino acid analogues of phenylalanine have proved to be useful for determining the importance of the conformation of tyrosine in the enkephalins of analgesic activity and receptor recognition[3].

Because of the varied biological activities displayed by hydroxylated amino acids, in particular β- and γ-hydroxy-α-amino acids, which can be found in a number of natural products[4], their synthesis presents a challenging area for studies in stereocontrolled synthesis[5].

As part of our project on the synthesis of new non-proteinogenic as well as unusual amino acids, we have recently reported the synthesis of new conformationally rigid phenylalanine analogues through the Diels-Alder reaction between 1,3-butadiene and (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone **1**[6]. Due to the availability of product **2**, which is easily obtained in excellent yield by hydrolysis of the spiro-oxazolone-adduct, we now wish to report the iodo-oxazination reaction of this product with I_2/dioxane. The reaction occurs in very good yield and allows the direct hydroxylation in a syn relationship to the amide group through the iodo-oxazine intermediate **3**, which can be easily deiodinated to oxazine **4**, using tributyltin hydride in CH_2Cl_2 at room temperature for 10 h followed by the removal of organotin compounds with a silica gel column[7]. (Scheme 1)



Scheme 1

Electrophile-initiated cyclofunctionalization reactions involving oxygen nucleophiles, where the double bond attacked is in a constrained ring, occur with quite predictable stereochemical and regiochemical control. This kind of reaction has been extensively used in organic synthesis. In particular, the cyclization of heteroatom-tethered cyclic systems, involving a transient tether attached to a pre-existing group has been useful in stereoselective synthesis of amino sugars and aminocyclitols[8].

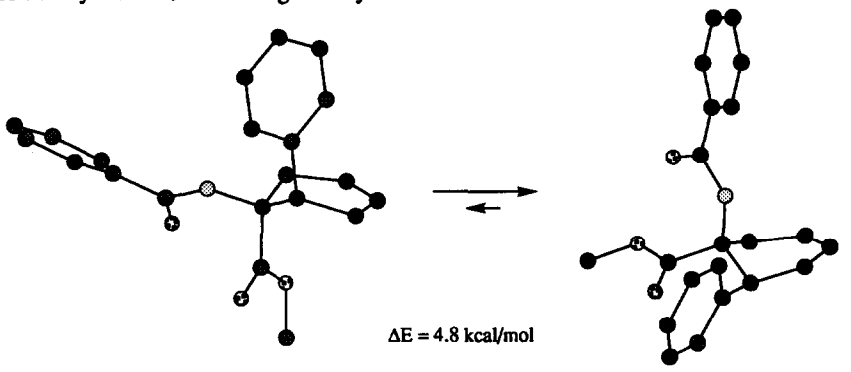
The commonly used oxygen nucleophiles in this strategy are carbamate derivatives of cyclic homoallylic amines[9], but there are only a few examples in the literature which describe the use of amide derivatives as oxygen nucleophiles[10] in intramolecular cyclization. Takano and co-workers described an efficient method for the synthesis of O-benzyl-4-benzoyloxyprolinol from a N-benzoyl-γ,δ-unsaturated amide by means of an iodine-mediated double cyclization. They propose that the key reaction in the cyclization mechanism proceeds through the initial formation of iododihydro-1,3-oxazonium salt, which cannot be isolated and under the reaction conditions is sequentially transformed into benzoyloxyprolinol[11].

Nevertheless, oxazine **4** is extraordinarily stable, presumably due to the presence of the phenyl group on the oxazine ring. In this context, it is important to point out the participation of the phenyl substituent on the amide group in the cyclization of the homoallylic amides to give 1,3-oxazines. The reaction is more favourable for the benzamides than for the acetamides. Moreover, 2-methyl-1,3-oxazine products are very unstable[12].

The only precedent in the literature for the generation of bicyclic systems uses carbamate derivatives as oxygen nucleophiles[13], and taking into account that the amide derivatives of homoallylic amines behave in such a way as to allow the intramolecular cyclization to generate bridged ring systems which are derivatives of 1,3-amino alcohols, this methodology will be useful to place a γ-hydroxy group on a α-amino acid in a syn relationship to the amino group

In the case described here, the phenyl group attached to the cyclohexene ring plays a very important role since the most favourable conformation places the benzamide group in an axial position, favouring attack on the double bond. In this way, we have made theoretical calculations and the lowest energy conformer of cycloadduct **2** was calculated by molecular mechanics, using the Chem 3D Plus™ program[14] and MM2 force field[15]. The geometry of the most favourable conformer of **2** is the half-chair conformation, where the phenyl and methyl

ester groups adopt equatorial positions. This conformer is more stable than that in which the same groups are in the axial position by 4.8 kcal/mol. This geometry is shown in Scheme 2.

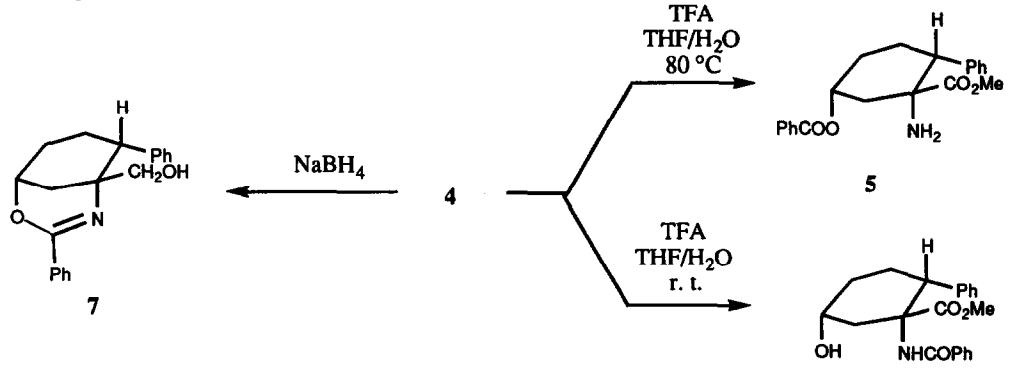


Scheme 2

After several unsuccessful attempts, we found that the hydrolysis reaction of dihydro-1,3-oxazine **4** can be efficiently carried out by stirring a solution of compound **4** with an excess of trifluoroacetic acid in THF-water at 80 °C for 12 h to afford the methyl γ-benzoyloxy-α-aminocarboxylate **5**, a direct precursor of the γ-hydroxy-α-amino acid **8** required. (Scheme 3)

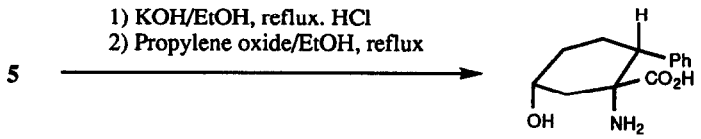
However, when the same reaction is carried out at room temperature, the cleavage of the oxazine is different and the product of hydrolysis is the corresponding methyl γ-hydroxy-α-benzamidocarboxylate **6**[16]. This compound is not a good precursor of γ-hydroxy-α-amino acid **8** because the hydrolysis of the benzamide group occurs in acid conditions at reflux and the hydroxy group would give elimination products. It can be supposed that compound **5** is the thermodynamically controlled product while compound **6** is the kinetically controlled product. (Scheme 3)

The dihydro-1,3-oxazine route has been extensively investigated by Meyers[17]. Normally, a controlled reduction to tetrahydro-1,3-oxazine, followed by hydrolysis, gives good yields of the corresponding aldehyde and amino alcohol, but in this case the imino linkage is not attacked by the hydride reducing agent. After 6 h at 50 °C only compound **7** is observed which corresponds to the reduction of the methyl carboxylate group to the alcohol group. This fact can be attributed to the 2-phenyl substituent on the 1,3-oxazine ring that stabilises the imino linkage. (Scheme 3)



Scheme 3

The hydrolysis of product **5** takes place without difficulty in an alkaline medium followed by the addition of HCl to give γ-hydroxy-α-amino acid hydrochloride, which is then converted into free γ-hydroxy-α-amino acid **8** by refluxing the salt in ethanol with an excess of propylene oxide. (Scheme 4)



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Scheme 4

Further studies to investigate the versatility of the methodology for the synthesis of other γ-hydroxy-α-amino acids are in progress.

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EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed by using Silica gel 60 (230-400 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Varian Unity-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values.

Methyl *cis*-1-Benzamido-6-phenyl-3-cyclohexen-1-carboxylate 2

A solution of 1 M $AlCl_2Et$ in hexane (2.25 mL) was added to a solution of (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone **1** (747 mg, 3 mmol) in dry CH_2Cl_2 (30 mL) kept under inert atmosphere. After 1 h stirring at 0° C, a solution of 1,3-butadiene (1.782 g, 33 mmol) in dry CH_2Cl_2 (5 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 72 h at 0° C. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was filtered and the solution was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (90:10) to afford 582 mg (64%) of spiro-oxazolone-adduct, which was dissolved in methanol and sodium methoxide (150 mg) was added. After 90 min stirring at room temperature, the solvent was eliminated and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (70:30) to afford cycloadduct **2** as an oil. Isolated yield 585 mg (91%).

Found C: 74.15, H: 6.20, N: 4.30

Anal. Calc. for $C_{21}H_{21}NO_3$ C: 75.19, H: 6.31, N: 4.36

^1H-NMR($CDCl_3$): δ= 2.49-2.76(m, 3H, $H_{2e'}$ + $H_{5a'}$ + $H_{5e'}$); 3.07(d, 1H, $J_{2a'\text{-}2e'}$=17.1, $H_{2a'}$ + $H_{2e'}$); 3.64(s, 4H, COOMe + H_{6a}); 5.81-5.92(m, 2H, H_3 + H_4); 6.18(brs, 1H, NH); 7.25-7.63(m, 10H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 29.0(C_5); 30.8(C_2); 43.8(C_6); 52.4(COOMe); 60.3(C_1); 124.3(C_3); 125.5(C_4); 126.8; 127.7; 128.3; 128.5; 128.8; 131.6; 134.1; 140.9(Arom.); 166.8(CONH); 172.7(COOMe).

Methyl *endo*-3,6-diphenyl-*exo*-8-iodo-2-oxa-4-azabicyclo[3.3.1]non-3-ene-5-carboxylate 3

A mixture of compound **2** (321 mg, 1.00 mmol) and iodine (952 mg, 3.75 mmol) in 50 mL of dioxane was stirred at room temperature. After 4 h, the reaction was diluted with ethyl ether, washed with 10% $Na_2S_2O_3$, dried over $MgSO_4$, filtered and evaporated to give compound **3**, which was purified by silica gel column chromatography using hexane-ethyl acetate (70:30) as an eluent. Isolated yield 401 mg of an oil (87%).

Found C: 54.73, H: 4.17, N: 2.91, I: 27.66

Anal. Calc. for $C_{21}H_{20}NO_3I$ C: 54.66, H: 4.37, N: 3.04, I: 27.53

^{1}H-NMR($CDCl_3$): δ= 2.00-2.16(m, 2H, H_{7n} + H_{7x}); 2.20(dd, 1H, J_{9s-1}=4.2, J_{9s-9a}=12.3, H_{9s}); 3.20(dd, 1H, J_{6x-7x}=1.5, J_{6x-7n}=13.5, H_{6x}); 3.56(s, 3H, COOMe); 3.85(dd, 1H, J_{9a-1}=4.2, J_{9a-9s}=12.3, H_{9a}); 4.76-4.84(m, 2H, H_1 + H_{8n}); 7.19-7.52(m, 8H, Arom.); 8.07-8.14(m, 2H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 28.4; 28.5; 35.7; 47.8(C_6, C_7, C_8, C_9); 52.2(COOMe); 61.6(C_5); 74.2(C_1); 127.2; 127.6; 128.1; 128.2; 129.0; 131.0; 132.9; 139.8(Arom.); 154.9(C_3); 172.9(COOMe).

Methyl *endo*-3,6-diphenyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-5-carboxylate 4

Tributyltin hydride (0.6 mL, 0.90 mmol) was added to a solution of iodo-oxazine **3** (346 mg, 0.75 mmol) in dry CH_2Cl_2 (25 mL) kept under inert atmosphere. After 10 h stirring at room temperature the solvent was evaporated and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (80:20) to afford 279 mg of compound **4** as a white solid. (93%). M. p. : 113-5 °C.

Found C: 75.27, H: 6.42, N: 4.31

Anal. Calc. for $C_{21}H_{21}NO_3$ C: 75.19, H: 6.31, N: 4.18

^{1}H-NMR($CDCl_3$): δ= 1.78-1.92(m, 3H, H_{7n} + H_{8n} + H_{8x}); 2.13(ddd, 1H, J_{7x-8n}=2.1, J_{7x-8x}=4.2, J_{7x-7n}=13.2, H_{7x}); 2.25-2.27(m, 1H, H_{9s}); 2.36(dd, 1H, J_{6x-7x}=1.2, J_{6x-7n}=13.2, H_{6x}); 3.38-3.44(m, 1H, H_{9a}); 3.53(s, 3H, CO_2Me); 4.78-4.82(m, 1H, H_1); 7.18-7.33(m, 5H, Ph-C_6); 7.38-7.52(m, 3H, m,p-Ph-C_3); 8.10-8.14(m, 2H, o-Ph-C_3).

^{13}C-NMR($CDCl_3$): δ= 25.4; 32.8; 33.2; 52.0(C_6, C_7, C_8, C_9); 52.4(COOMe); 61.4(C_5); 70.4(C_1); 126.8; 127.5; 127.9; 128.0; 128.7; 130.6; 133.6; 141.4(Arom.); 156.1(C_3); 174.0(COOMe).

Methyl 1-Amino-*t*-3-benzoyloxy-*t*-6-phenyl-*r*-1-cyclohexanecarboxylate 5

Trifluoroacetic acid (1.368 g, 12 mmol) was added to a solution of oxazine **4** (200 mg, 0.60 mmol) in 3:1 tetrahydrofuran-water (20 mL). The reaction was then heated at 80 °C and allowed to stand overnight. The solvent was evaporated and the residue was recrystallised in ethyl ether to afford 195 mg of compound **5** as a white solid (95%). M. p. : 130-2 °C.

Found C: 71.28, H: 6.48, N: 3.89

Anal. Calc. for $C_{21}H_{23}NO_4$ C: 71.36, H: 6.56, N: 3.90

^{1}H-NMR($CDCl_3$): δ= 1.79-1.95(m, 2H); 2.38-2.57(m, 3H); 2.75(d, 1H, J_{2e-2a}=15.6, H_{2e}); 3.31(dd, 1H, J_{6a-5e}=2.7, J_{6a-5a}=13.2, H_{6a}); 3.48(s, 3H, CO_2Me); 5.49(brs, 1H, H_{3e}); 6.64(brs, 2H, NH_2); 7.13-7.40(m, 8H, Arom.); 8.03-8.07(m, 2H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 20.9; 29.4; 35.5; 47.9; 53.2(C_2, C_4, C_5, C_6, COOMe); 63.5(C_1); 67.7(C_3); 128.1; 128.2; 128.4; 129.1; 129.5; 129.8; 133.1; 137.1(Arom.); 165.9(COPh); 170.4(COOMe).

Methyl 1-Benzamido-*t*-6-phenyl-*t*-3-cyclohexanol-*r*-1-carboxylate 6

Trifluoroacetic acid (200 mg, 1.75 mmol) was added to a solution of oxazine **4** (50 mg, 0.15 mmol) in 3:1 tetrahydrofuran-water (10 mL). After 38 h stirring at room temperature the solvent was evaporated and the residue was chromatographed on silica gel, eluting with hexane-ethyl acetate (70:30) to give 46 mg of compound **6** as an oil (91%).

Found C: 71.30, H: 6.49, N: 3.86

Anal. Calc. for $C_{21}H_{23}NO_4$ C: 71.36, H: 6.56, N: 3.97

^{1}H-NMR($CDCl_3$): δ= 1.65(dd, 1H, $J_{2e\text{-}3e}$=3.0, $J_{2e\text{-}2a}$=13.5, H_{2e}); 1.80-1.95(m, 3H); 2.19-2.31(m, 2H); 2.34-2.55(m, 2H); 3.23(dd, 1H, $J_{6a\text{-}5e}$=3.0, $J_{6a\text{-}5a}$=13.5, H_{6a}); 3.55(s, 3H, CO_2Me); 5.44-5.52(m, 1H, H_{3e}); 7.14-7.29(m, 5H, Ph-C_6); 7.46-7.58(m, 3H, m,p-Ph-CO); 8.06-8.10(m, 2 H, o-Ph-CO). ^{13}C-NMR($CDCl_3$): δ= 21.4; 30.2; 38.7; 49.8; 52.1(C_2, C_4, C_5, C_6, COOMe); 61.9(C_1); 69.2(C_3); 127.2; 128.2; 128.3; 128.5; 129.6; 130.5; 133.0; 140.8(Arom.); 165.7(CONH); 175.9(COOMe).

***endo*-3,6-Diphenyl-2-oxa-4-azabyciclo[3.3.1]non-3-ene-5-methanol 7**

A sodium borohydride solution (280 mg, 8.28 mmol) in water (1 mL) was added to another solution of compound **4** (130 mg, 0.39 mmol) in tetrahydrofuran (30 mL). The reaction mixture was then heated at 50 °C for 6 h. Water (15 mL) was added and the excess of sodium borohydride was destroyed by the dropwise addition of 10% HCl solution. Tetrahydrofuran was eliminated under reduced pressure and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give 92 mg of compound **7** as an oil (78%).

Found C: 78.22, H: 6.77, N: 4.42

Anal. Calc. for $C_{20}H_{21}NO_2$ C: 78.14, H: 6.89, N: 4.56

^{1}H-NMR($CDCl_3$): δ= 1.72-1.90(m, 4H, H_{6x} + H_{7n} + H_{8n} + H_{8x}); 2.13(ddd, 1H, $J_{7x\text{-}8n}$=2.1, $J_{7x\text{-}8x}$=6.6, $J_{7x\text{-}7n}$=13.2, H_{7x}); 2.22-2.25(m, 1H, H_{9s}); 2.87-2.96(m, 1H, H_{9a}); 3.36(d, 1H, $J_{a\text{-}b}$=10.8, CH_aH_bOH); 3.42(d, 1H, $J_{b\text{-}a}$=10.8, CH_aH_bOH); 4.84-4.87(m, 1H, H_1); 7.20-7.34(m, 5H, Ph-C_6); 7.41-7.52(m, 3H, m,p-Ph-C_3); 8.06-8.10(m, 2H, o-Ph-C_3).

^{13}C-NMR($CDCl_3$): δ= 26.6; 31.5; 33.5; 51.5(C_6, C_7, C_8, C_9); 55.8(C_5); 68.8(CH_2OH); 71.6(C_1); 126.6; 127.2; 128.0; 128.1; 128.9; 130.5; 133.7; 142.2(Arom.); 157.7(C_3).

1-Amino-*t*-6-phenyl-*t*-3-cyclohexanol-*r*-1-carboxylic Acid 8

Compound **5** (100 mg, 0.28 mmol) was refluxed with 10% potassium hydroxide-ethanol (6 mL). After 6 h, the solvent was eliminated under reduced pressure, the residue was diluted with water (5 mL) and extracted with ethyl ether (3 x 10 mL). The aqueous layer was acidified with conc. HCl and the water was evaporated. The residue was washed with ethanol and the filtrate was concentrated to 6 mL and propylene oxide (2 mL) was then added. The mixture was refluxed for 2 h and the free amino acid partially precipitated. After the removal of the ethanol, the white residue was dissolved in distilled water (5 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge, which after the removal of water gave 56 mg of amino acid **8** as a white solid (85%).

Found C: 66.29, H: 7.17, N: 5.83

Anal. Calc. for $C_{13}H_{17}NO_3$ C: 66.35, H: 7.29, N: 5.96

^{1}H-NMR(D_2O/TFA): δ= 1.58-1.81(m, 2H); 1.88-2.05(m, 2H); 2.14-2.31(m, 2H); 3.28(dd, 1H, $J_{6a\text{-}5e}$=3.0, $J_{6a\text{-}5a}$=14.1, H_{6a}); 4.14-4.22(m, 1H, H_{3e}); 7.13-7.32(m, 5H, Arom.).

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