Pergamon

Tetrahedron Vol. 50, No. 45, pp. 12989-12998, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00823-X

A New Efficient Synthesis of 2-Phenyl-4-oxo-1-amino-cyclohexanecarboxylic Acids

Alberto Avenoza[a], Jesús H. Busto[a], Carlos Cativiela[b]* and Jesús M. Peregrina[a]

[a] Department of Chemistry (Organic Chemistry). Edificio Científico-Técnico. Sección Ciencias. Universidad de La Rioja. 26001 Logroño. Spain.

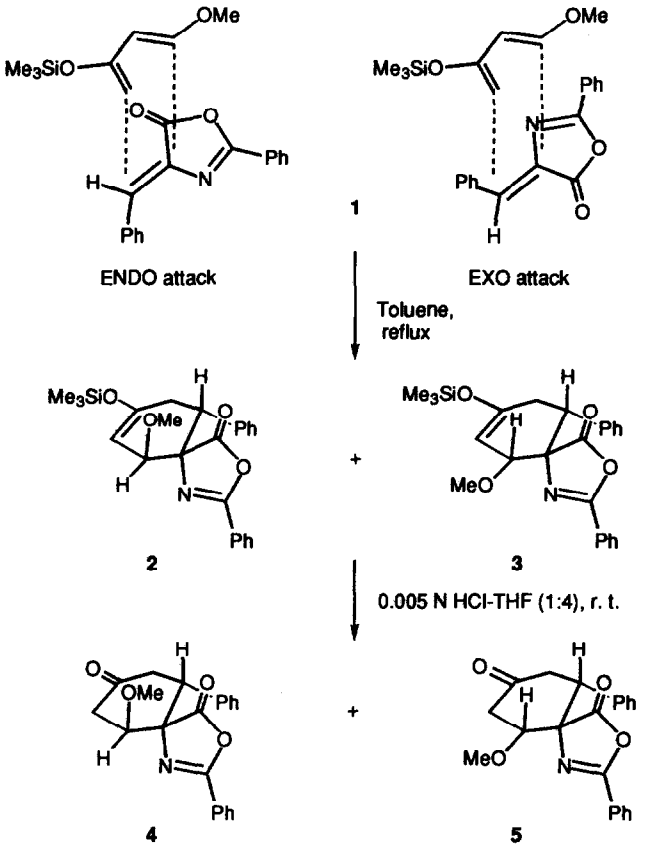
[b] Department of Organic Chemistry. Instituto de Ciencia de Materiales de Aragón. Universidad de Zaragoza-C.S.I.C. 50009 Zaragoza. Spain.

Abstract: The adducts obtained through the Diels-Alder cycloadditions of (Z)-2-phenyl-4-benzyliden-5(4H)-oxazolone **1** with Danishefsky's diene and of methyl (E)-2-cyanocinnamate **9** with 2-methoxy-1,3-butadiene, were subsequently transformed allowing the synthesis of both stereoisomers of 2-phenyl-4-oxo-1-aminocyclohexanecarboxylic acid (**8** and **20**).

Whereas the synthesis of α-amino acids has been a matter of continual interest[1], the synthesis of new conformationally constrained α-amino acids has only attracted significant attention during the last few years[2] when it was recognised that their incorporation into peptides is a powerful approach for generating structurally defined peptides as conformational probes and bioactive agents[3]. In this context, and as part of our project on the synthesis of new non-proteinogenic and unusual conformationally restricted α-amino acids, we have published the synthesis of new conformationally rigid phenylalanine analogues using the Diels-Alder reaction between unsaturated 5(4H)-oxazolones and several dienes[4] such as cyclopentadiene, 1,3-butadiene or 2,3-dimethyl-1,3-butadiene. We now wish to extend the versatility of the Diels-Alder reaction to Danishefsky's diene, allowing the synthesis of 2-phenyl-4-oxo-1-aminocyclohexanecarboxylic acids, which are valuable intermediates in the synthesis of new δ-substituted conformationally restricted α-amino acids. This significant reaction, a key step in the synthesis of important natural products[5], was attempted some years ago[6] although the results were quite poor since the yields were very low, even when working at high temperatures, and the stereochemical results were not determined.

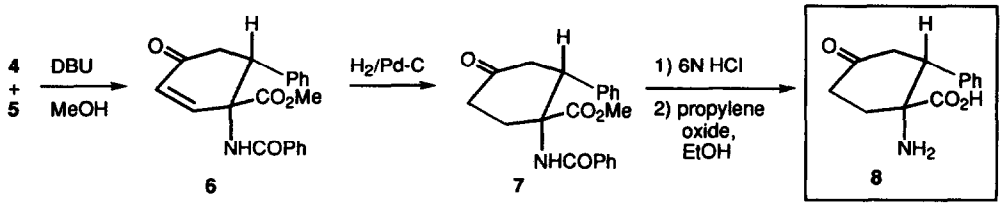
The direct diene precursor of 2-phenyl-4-oxo-1-aminocyclohexanecarboxylic acids is 2-methoxy-1,3-butadiene, but the results obtained in the Diels-Alder reaction with (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone **1** were poor. Consequently, we were obliged to use Danishefsky's diene and in our experiments the cycloaddition with oxazolone **1** worked with excellent results when the reaction was carried out in toluene at reflux during 48 h using two equivalents of the diene, allowing the obtention of the mixture of *c*-2-methoxy and *t*-2-methoxy-4-trimethylsilyloxy-*t*-6-phenylcyclohex-*r*-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]}-3-ene **2** and **3**, corresponding to *endo* and *exo* attack respectively. This mixture of products was treated with a 0.005 N

HCl-THF (1:4) solution to afford a mixture of *c*-2-methoxy and *t*-2-methoxy-*t*-6-phenylcyclohexan-*r*-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]}-4-one **4** and **5** in a ratio of 45:55[7].(Scheme 1).



Scheme 1

The methoxy group of the *endo*-cycloadduct **4** was easily eliminated to give enone **6** when Et_3N in MeOH was added to the mixture of **4** and **5**, while the *exo*-cycloadduct **5** remained unaltered[8]. Nevertheless, both methoxy groups of compounds **4** and **5** were eliminated by the action of DBU in MeOH at 0 °C to generate enone **6** in excellent yield. Typical heterogeneous hydrogenation of the double bond of this enone, using 10% palladium-carbon as a catalyst, yielded ketone **7** quantitatively, which was hydrolysed in an acid medium and the free δ-oxo-α-amino acid **8** was obtained with propylene oxide using a typical procedure[9]. (Scheme 2)

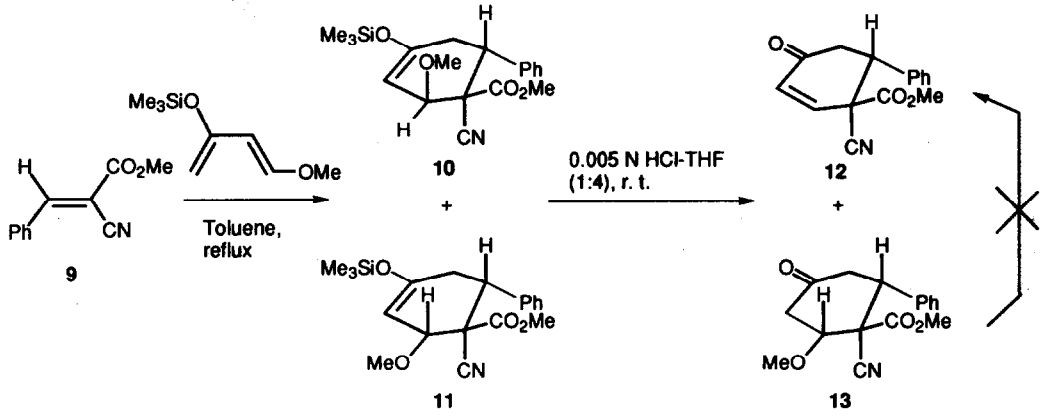


Scheme 2

On the other hand, all attempts to use the same methodology with (E)-2-phenyl-4-benzylidene-5(4H)-oxazolone to obtain the other δ-oxo-α-amino acid stereoisomer by repeating the same sequence of reactions were unsuccessful since, under these reaction conditions, the partial isomerization of (E)-5(4H)-oxazolone to the thermodynamically more stable (Z)-5(4H)-oxazolone takes place and the mixture of all four spiroxazolones was always obtained.

Recently, we reported the excellent behaviour of several derivatives of (E)-2-cyanocinnamic acid as dienophiles in the Diels-Alder reaction with different dienes such as cyclopentadiene[10], 2,3-dimethyl-1,3-butadiene[11] and 1,3-butadiene[12], which allowed the synthesis of various cycloaliphatic α-amino acids, even in enantiomerically pure form when chiral (E)-2-cyanocinnamates were used.

In this case the Diels-Alder reaction between methyl (E)-2-cyanocinnamate **9** and Danishefsky's diene under the same conditions as described previously occurred with excellent yield, giving a mixture of methyl 1-cyano-*c*-2-methoxy-4-trimethylsilyloxy-*t*-6-phenyl-3-cyclohexen-*r*-1-carboxylate **10** and methyl 1-cyano-*t*-2-methoxy-4-trimethylsilyloxy-*t*-6-phenyl-3-cyclohexen-*r*-1-carboxylate **11** in the ratio 1:1, which was then treated with 0.005 N HCl-THF (1:4) solution. Under these conditions the axial methoxy group attached to the C_2 in the adduct **10** was eliminated to give enone **12**, while the equatorial methoxy group in the adduct **11** could not be eliminated, affording the corresponding methoxy ketone **13**. Several different conditions, including DBU in MeOH, were employed in order to eliminate the methoxy group in ketone **13**, but in all cases unreacted starting material was recovered. (Scheme 3).

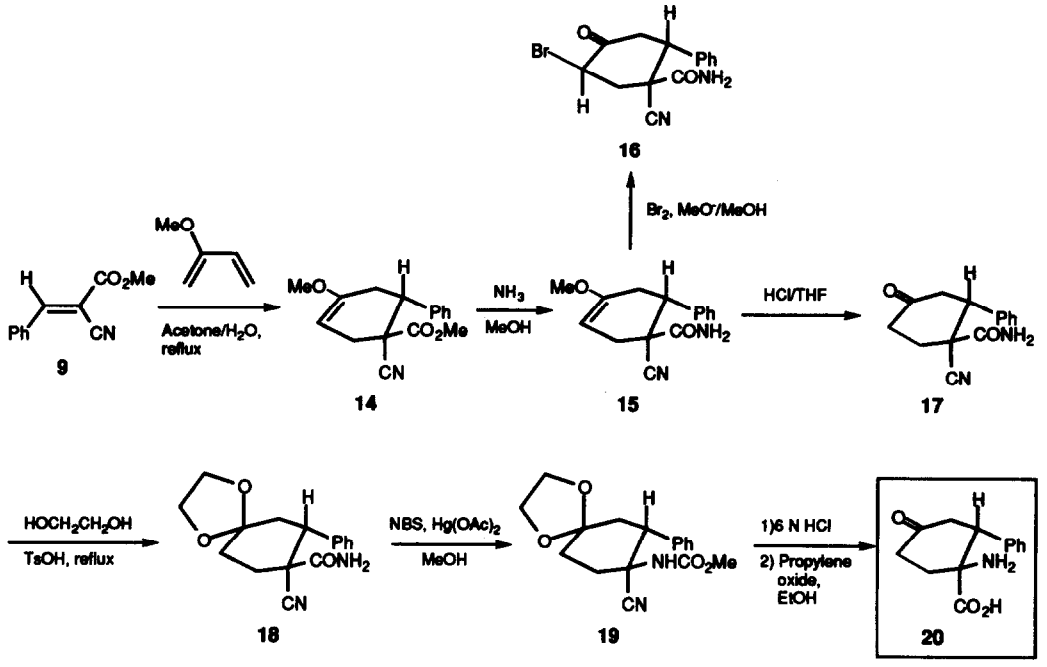


Scheme 3

Consequently, we decided to use 2-methoxy-1,3-butadiene in the Diels-Alder cycloaddition with methyl (E)-2-cyanocinnamate as precursor of the other δ-oxo-α-amino acid. Although this diene is less reactive than Danishefsky's diene[13], dienophile **9** did react in acetone-water after two days at reflux to give compound **14** in 65% yield, which was then converted into the cyano amide **15** by addition of ammonia.(Scheme 4)

Selective Hofmann rearrangement of the cyano amide **15** by treatment with Br_2 in MeONa/MeOH[14] gave the α-bromo ketone **16** rather than the corresponding carbamate, so the methyl enol ether **15** was initially transformed into the ketone **17** which was protected by means of ethane-1,2-diol using TsOH as a catalyst[15] to afford compound **18**. Further Hofmann rearrangement of the protected ketone **18** gave the corresponding protected cyano carbamate **19**, which was hydrolysed in an acid medium at reflux to obtain the required free

δ-oxo-α-amino acid **20** according to the protocol described for the synthesis of the other δ-oxo-α-amino acid **8**. (Scheme 4)



Scheme 4

In summary, the Diels-Alder cycloadditions of (Z)-2-phenyl-4-benzyliden-5(4H)-oxazolone with Danishefsky's diene and of methyl (E)-2-cyanocinnamate with 2-methoxy-1,3-butadiene open the way for the synthesis of both stereoisomers of 2-phenyl-1-aminocyclohexanecarboxylic acid functionalised in the δ-position[16] as a key product to the synthesis of a great variety of new conformationally constrained non-proteinogenic α-amino acids.

Acknowledgements: We are indebted to the *Dirección General de Investigación Científica y Técnica*, project PB91-0696 for its generous support. J. H. B. thanks the *Ministerio de Educación y Ciencia* for a doctoral fellowship.

EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230-400 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 melting point apparatus and are

uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values.

_c_-2-Methoxy and _t_-2-Methoxy-_t_-6-phenylcyclohexan-_r_-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]}-4-one. 4 and 5

Danishefsky's diene (488 mg, 4.00 mmol) was added to a solution of (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone[17] **1** (498 mg, 2.00 mmol) in dry toluene (30 mL). After 2 days stirring at reflux, the solvent was evaporated *in vacuo* and a solution of 0.005 N HCl-THF (1:4) (20 mL) was added to the residue. The reaction mixture was stitrred for 7 h, the solvent was eliminated and the mixture was diluted with CH_2Cl_2 (30 mL). This solution was washed with brine (2 x 20 mL) and an aqueous solution of 5% $NaHCO_3$ (2 x 20 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a mixture of compounds **4** and **5** in a ratio of 45:55, which was used in the next step without purification; yield 647 mg (93%).

^{1}H-NMR($CDCl_3$): δ = 2.52-2.68(m, 2H); 2.82-2.90(ddd, 1H, J=15.0, J=3.3, J=1.8); 2.98-3.02(m, 2H); 3.10-3.18(dd, 1H, J=13.8, J=3.0); 3.20-3.42(m, 6H); 3.47(s, 3H); 3.74-3.78(m, 1H); 4.00-4.11(m, 2H); 7.10-8.00(m, 20H).

Methyl _cis_-1-Benzamido-6-phenyl-4-oxo-2-cyclohexen-1-carboxylate. 6

Method A: To a solution of the crude mixture **4, 5** (100 mg, 0.28 mmol) in MeOH (6 mL) was added Et_3N (0.1 mL) and the mixture was stirred for 2 days at reflux. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane-ethyl acetate (7:3) as eluent, to yield 35 mg of compound **6** (36%) as an oil. Compound **5** was recovered as a pure oily product (36 mg).

Compound **5**:

Found C: 72.26, H: 5.55, N: 3.89

Anal. Calc. for $C_{21}H_{19}NO_4$ C: 72.18, H: 5.48, N: 4.01

^{1}H-NMR($CDCl_3$): δ = 2.56(dd, 1H, $J_{5e\text{-}5a}$=13.8, $J_{5e\text{-}6a}$=3.0, H_{5e}); 2.98-3.02(m, 2H, H_{3e} + H_{3a}); 3.22-3.36(m, 4H, H_{5a} + OMe); 3.42(dd, 1H, $J_{6a\text{-}5a}$=14.4, $J_{6a\text{-}5e}$=3.0, H_{6a}); 4.01(dd, 1H, $J_{2a\text{-}3a}$=9.6, $J_{2a\text{-}3e}$=7.5, H_{2a}); 7.10-7.20(m, 5H, Arom.); 7.40-7.55(m, 3H, Arom.); 7.90-7.94(m, 2H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 43.1, 43.5, 45.4, 57.7(C_1, C_3, C_5, C_6); 81.1(C_2); 128.1, 128.2, 128.4, 128.5, 128.7, 132.8, 135.4, 135.5 (Arom.); 161.9(C=N); 177.8(COO); 205.6(CO).

Compound **6**:

Found C: 72.30, H: 5.57, N: 3.91

Anal. Calc. for $C_{21}H_{19}NO_4$ C: 72.18, H: 5.48, N: 4.01

^{1}H-NMR($CDCl_3$): δ = 2.78(dd, 1H, $J_{5e\text{-}5a}$=16.8, $J_{5e\text{-}6a}$=4.8, H_{5e}); 3.22(dd, 1H, $J_{5a\text{-}5e}$=16.8, $J_{5a\text{-}6a}$=10.8, H_{5a}); 3.78(s, 3H, COOMe); 4.02(dd, 1H, $J_{6a\text{-}5a}$=10.8, $J_{6a\text{-}5e}$=4.8, H_{6a}); 6.29(brd, 1H, $J_{2\text{-}3}$=10.2, H_2); 6.57(brs, 1H, NH); 7.10-7.60(m, 11H, H_3 + Arom.).

^{13}C-NMR($CDCl_3$): δ = 39.4, 47.5, 53.7, 61.7(C_1, C_5, C_6, COOMe); 126.9, 128.2, 128.6, 128.7, 128.8, 129.3, 129.8, 132.1, 137.1, 137.7 (Arom., C_2, C_3); 167.7(CONH); 171.5(COOMe); 197.4(CO).

Method B: To a solution of the crude mixture **4, 5** (100 mg, 0.28 mmol) in MeOH (6 mL) was added DBU (42 mg, 0.28 mmol) and the mixture was stirred for 3 days at 0 °C. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane-ethyl acetate (1:1) as eluent, to yield 75 mg of enone **6** (75%) as an oil.

Methyl *cis*-1-Benzamido-2-phenyl-4-oxo-1-cyclohexanecarboxylate. 7

A solution of compound **6** (91 mg, 0.26 mmol) in dry CH_2Cl_2 (20 mL) was hydrogenated at atmospheric pressure for 24 h using 10% palladium-carbon (10 mg) as a catalyst. Removal of the catalyst and the solvent gave compound **7** quantitatively as an oil.

Found C: 71.62, H: 5.15, N: 3.86

Anal. Calc. for $C_{21}H_{21}NO_4$ C: 71.76, H: 6.03, N: 3.99

^{1}H-NMR($CDCl_3$): δ = 2.50-2.70(m, 3H, H_{5e} + H_{6a} + H_{6e}); 2.82(dd, 1H, J_{3e-3a}=15.6, J_{3e-2a}=5.4, H_{3e}); 3.04(dd, 1H, J_{3a-3e}=15.6, J_{3a-2a}=10.2, H_{3a}); 3.11-3.18(m, 1H, H_{5a}); 3.68(s, 3H, COOMe); 3.94(dd, 1H, J_{2a-3a}=10.2, J_{2a-3e}=5.4, H_{2a}); 6.24(brs, 1H, NH); 7.14-7.70(m, 10H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 30.2, 36.8, 41.9, 48.2(C_2, C_3, C_5, C_6); 52.7(COOMe); 62.2(C_1); 126.7, 127.7, 128.4, 128.6, 129.1, 131.9, 134.1, 137.7 (Arom.); 168.2(CONH); 172.5(COOMe); 208.8(CO).

***cis*-2-Phenyl-4-oxo-1-aminocyclohexane-1-carboxylic Acid. 8**

Compound **7** was dissolved in 6 N HCl (20 mL) and refluxed for 24 h. The solvent was evaporated, the residue of aminoacid hydrochloride was dissolved in EtOH (6 mL) and propylene oxide (2 mL) was added. The mixture was refluxed for 1 h and partially precipitated. After removal of the EtOH, the residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge which, after removal of water, gave 45 mg (73%) of α-amino acid **8** as a white solid.

Found C: 66.88, H: 6.37, N: 5.88

Anal. Calc. for $C_{13}H_{15}NO_3$ C: 66.92, H: 6.49, N: 6.01

^{1}H-NMR(D_2O/TFA): δ = 1.82-2.68(m, 4H, H_{3e} + H_{5e} + H_{6a} + H_{6e}); 2.96-3.12(m, 1H, H_{3a}); 3.48-3.64(m, 1H, H_{5a}); 3.86(dd, 1H, J_{2a-3a}=15.0, J_{2a-3e}=1.2, H_{2a}); 7.05-7.40(m, 5H, Arom.).

Methyl *trans*-1-Cyano-6-phenyl-4-oxo-2-cyclohexen-1-carboxylate. 12 and Methyl 1-Cyano-*t*-2-methoxy-*t*-6phenyl-4-oxo-*r*-1-cyclohexanecarboxylate. 13

Starting from methyl (E)-2-cyanocinnamate[18] **9** (187 mg, 1.00 mmol) and following the same procedure as described above for **4** and **5**, a mixture of compounds **12** and **13** was obtained. Three fractions were separated by silica gel column chromatography eluting with hexane-ethyl acetate (3:2), the first fraction yielded 80 mg (30%) of compound **12** as an oil, the second yielded 75 mg of a mixture of compounds **12** and **13** and the third yielded 50 mg (18%) of **13** as an oil.

Compound **12**

Found C: 70.72, H: 5.25, N: 5.43

Anal. Calc. for $C_{15}H_{13}NO_3$ C: 70.56, H: 5.14, N: 5.49

^{1}H-NMR($CDCl_3$): δ = 2.80(dd, 1H, J_{5e-5a}=17.1, J_{5e-6a}=3.4, H_{5e}); 3.23(dd, 1H, J_{5a-5e}=17.1, J_{5a-6a}=14.4, H_{5a}); 3.69(s, 3H, COOMe); 3.89(dd, 1H, J_{6a-5a}=14.4, J_{6a-5e}=3.4, H_{6a}); 6.34(d, 1H, J_{3-2}=9.6, H_3); 6.83(d, 1H, J_{2-3}=9.6, H_2); 7.26-7.31(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 40.3, 47.4, 51.6, 54.1(C_1, C_5, C_6, COOMe); 114.2(CN); 128.0, 129.0, 129.2, 131.8, 136.0, 140.5(Arom., C_2, C_3,); 167.0(COOMe); 195.6(CO).

Compound **13**

Found C: 66.72, H: 5.85, N: 4.96

Anal. Calc. for $C_{21}H_{21}NO_4$ C: 66.87, H: 5.97, N: 4.88

^{1}H-NMR($CDCl_3$): δ = 2.58(ddd, 1H, $J_{5e\text{-}5a}$=15.0, $J_{5e\text{-}6a}$=3.6, $J_{5e\text{-}3e}$=1.8, H_{5e}); 2.79(dd, 1H, $J_{3a\text{-}3e}$=14.7, $J_{3a\text{-}2a}$=12.0, H_{3a}); 3.05(ddd, 1H, $J_{3e\text{-}3a}$=14.7, $J_{3e\text{-}2a}$=4.8, $J_{3e\text{-}5e}$=1.8, H_{3e}); 3.14('t', 1H, $J_{5a\text{-}5e}$~$J_{5a\text{-}6a}$=15.0, H_{5a}); 3.32(dd, 1H, $J_{6a\text{-}5a}$=14.7, $J_{6a\text{-}5e}$=3.6, H_{6a}); 3.36(s, 3H, OMe); 3.53(s, 3H, COOMe); 4.07(dd, 1H, $J_{2a\text{-}3a}$=12.0, $J_{2a\text{-}3e}$=4.8, H_{2a}); 7.24-7.35(m, 5H, Arom.).
^{13}C-NMR($CDCl_3$): δ = 42.9, 43.1, 44.4, 53.4, 57.5, 59.1(C_1, C_3, C_5, C_6, OMe, COOMe); 80.0(C_2); 115.0(CN); 127.5, 128.7, 128.8, 135.1(Arom.); 167.2(COOMe); 202.9(CO).

Methyl *trans*-1-Cyano-4-methoxy-6-phenyl-3-cyclohexen-1-carboxylate. 14

2-Methoxy-1,3-butadiene (4.03 g, 48.00 mmol) was added to a solution of dienophile **9** (1.50 g, 8.00 mmol) in acetone-water (2:1) (120 mL). After 2 days stirring at 80 °C, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with toluene-$CHCl_3$ (1:4) to yield 1.41 g (65%) of compound **14** as an oil.

Found C: 70.72, H: 6.41, N: 5.03
Anal. Calc. for $C_{16}H_{17}NO_3$ C: 70.83, H: 6.32, N: 5.16

^{1}H-NMR($CDCl_3$): δ = 2.41(dd, 1H, $J_{5e\text{-}5a}$=16.8, $J_{5e\text{-}6a}$=5.4, H_{5e}); 2.70(dd, 1H, $J_{2e\text{-}2a}$=16.2, $J_{2e\text{-}3}$=5.7, H_{2e}); 2.88(dd, 1H, $J_{5a\text{-}5e}$=16.8, $J_{5a\text{-}6a}$=12.3, H_{5a}); 2.98(d, 1H, $J_{2a\text{-}2e}$=16.2, H_{2a}); 3.37(dd, 1H, $J_{6a\text{-}5a}$=12.3, $J_{6a\text{-}5e}$=5.4, H_{6a}); 3.47(s, 3H, COOMe); 3.60(s, 3H, OMe); 4.66(d, 1H, $J_{3\text{-}2e}$=5.7, H_3); 7.26-7.40(m, 5H, Arom.).
^{13}C-NMR($CDCl_3$): δ = 31.9, 33.4, 45.7, 50.1, 53.1, 54.5(C_1, C_2, C_5, C_6, OMe, COOMe); 88.1(C_3); 118.1(CN); 127.9, 128.2, 128.7, 138.1(Arom.), 154.6(C_4); 168.9(COOMe).

***trans*-1-Cyano-4-methoxy-6-phenyl-3-cyclohexen-1-carboxamide. 15**

Ammonia was bubbled through a methanolic solution (40 mL) of methyl ester **14** (500 mg, 1.83 mmol) until the solution was saturated. After 2 days stirring at room temperature, the solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (1:1) as eluent to give 451 mg (96%) of carboxamide **15** as an oil.

Found C: 70.15, H: 6.19, N: 11.01
Anal. Calc. for $C_{15}H_{16}N_2O_2$ C: 70.29, H: 6.29, N: 10.93

^{1}H-NMR($CDCl_3$): δ = 2.40(dd, 1H, $J_{5e\text{-}5a}$=17.1, $J_{5e\text{-}6a}$=5.4, H_{5e}); 2.60(dd, 1H, $J_{2e\text{-}2a}$=16.5, $J_{2e\text{-}3}$=5.7, H_{2e}); 2.86(dd, 1H, $J_{5a\text{-}5e}$=17.1, $J_{5a\text{-}6a}$=12.6, H_{5a}); 3.06(d, 1H, $J_{2a\text{-}2e}$=16.5, H_{2a}); 3.40(dd, 1H, $J_{6a\text{-}5a}$=12.6, $J_{6a\text{-}5e}$=5.4, H_{6a}); 3.59(s, 3H, OMe); 4.67(d, 1H, $J_{3\text{-}2e}$=5.7, H_3); 5.49(brs, 1H, NH); 5.92(brs, 1H, NH); 7.26-7.42(m, 5H, Arom.).
^{13}C-NMR($CDCl_3$): δ = 31.8, 33.2, 44.9, 50.1, 54.4(C_1, C_2, C_5, C_6, OMe); 88.5(C_3); 120.3(CN); 128.1, 128.2, 128.7, 138.3(Arom.), 154.3(C_4); 168.8($CONH_2$).

1-Cyano-*c*-3-bromo-*t*-6-phenyl-4-oxo-*r*-1-cyclohexanecarboxamide. 16

Sodium methoxide (21.6 mg, 0.90 mmol) was added to a methanolic solution (15 mL) of carboxamide **15** (50 mg, 0.20 mmol). The solution was cooled to -45 °C and bromine (16 mg, 0.20 mmol) was added. The reaction mixture was warmed to -15 °C and after a few minutes was heated to 55 °C for 15 minutes. After evaporation of the solvent, water (20 mL) was added and this mixture was extracted with diethyl ether (2 x 20 mL). The organic

layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to give 47 mg (73%) of carboxamide **16** as an oil.

Found C: 52.41, H: 4.13, N: 8.64, Br: 24.79

Anal. Calc. for $C_{14}H_{13}N_2O_2Br$ C: 52.36, H: 4.08, N: 8.72, Br: 24.88

^{1}H-NMR(CD_3COCD_3): δ = 2.76(dd, 1H, J_{5e-5a}=14.4, J_{5e-6a}=3.6, H_{5e}); 2.88('t', 1H, J_{2a-2e}~J_{2a-3a}=13.5, H_{2a}); 3.07(dd, 1H, J_{2e-2a}=13.5, J_{2e-3a}=6.0, H_{2e}); 3.46('t', 1H, J_{5a-5e}~J_{5a-6a}=14.4, H_{5a}); 3.84(dd, 1H, J_{6a-5a}=14.4, J_{6a-5e}=3.6, H_{6a}); 5.28(dd, 1H, J_{3a-2a}=13.5, J_{3a-2e}=6.0, H_{3a}); 6.90-7.00(m, 1H, NH_2); 7.30-7.45(m, 5H, Arom.).

^{13}C-NMR(CD_3COCD_3): δ = 41.6, 43.0, 46.8, 50.3, 52.8(C_1, C_2, C_3, C_5, C_6); 116.7(CN); 126.9, 127.2, 127.4, 136.0(Arom.); 164.9($\underline{C}ONH_2$); 195.1(CO).

***trans*-1-Cyano-2-phenyl-4-oxo-1-cyclohexanecarboxamide. 17**

2N HCl solution (10 mL) was added to a solution of compound **15** (400 mg, 1.56 mmol) in THF (50 mL). After 12 h stirring at room temperature the THF was eliminated *in vacuo* and the aqueous solution was extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried, filtered and the solvent eliminated to give 375 mg (99%) of compound **17** as a white solid. Mp: 177-9 °C.

Found C: 69.37, H: 5.95, N: 11.45

Anal. Calc. for $C_{14}H_{14}N_2O_2$ C: 69.41, H: 5.82, N: 11.56

^{1}H-NMR($CDCl_3$): δ = 2.44(ddd, 1H, J_{5e-5a}=13.8, J_{5e-6a}=6.3, J_{5e-6e}=2.4, H_{5e}); 2.50-2.71(m, 3H, H_{3e} + H_{5a} + H_{6e}); 2.80('t'd, 1H, J_{6a-5a}~J_{6a-6e}=13.8, J_{6a-5e}=6.3, H_{6a}); 3.11('t', 1H, J_{3a-3e}~J_{3a-2a}=14.7, H_{3a}); 3.60(dd, 1H, J_{2a-3a}=14.7, J_{2a-3e}=3.6, H_{2a}); 5.36(brs, 1H, NH); 5.88(brs, 1H, NH); 7.31-7.39(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 33.3, 37.3, 43.6, 48.2, 51.9(C_1, C_2, C_3, C_5, C_6); 118.9(CN); 127.8, 128.7, 128.9, 136.8(Arom.); 167.5($\underline{C}ONH_2$); 205.5(CO).

***trans*-1-Cyano-2-phenyl-4-spiro-{2'[1',3'-dioxolane]}-1-cyclohexanecarboxamide. 18**

Ethane-1,2-diol (100 mg, 1.55 mmol), compound **17** (340 mg, 1.40 mmol), toluene-*p*-sulphonic acid and dry toluene (50 mL) were placed in a round-bottomed flask fitted with a Dean-Stark water separator and a reflux condenser. The reaction mixture was heated at reflux for 24 h (until no more water was collected). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (30 mL). This solution was dried over anhydrous $MgSO_4$, filtered and evaporated to afford 386 mg (96%) of compound **18** as a white solid. Mp: 170-2 °C.

Found C: 66.98, H: 6.46, N: 9.81

Anal. Calc. for $C_{16}H_{18}N_2O_3$ C: 67.10, H: 6.34, N: 9.79

^{1}H-NMR($CDCl_3$): δ = 1.90-2.57(m, 6H, H_{3a} + H_{3e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}); 3.53(dd, 1H, J_{2a-3a}=12.0, J_{2a-3e}=3.0, H_{2a}); 3.94-4.05(m, 4H, 2 OCH_2); 5.59(brs, 1H, NH); 5.85(brs, 1H, NH); 7.23-7.35(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 31.4, 32.1, 37.4, 45.8, 52.5(C_1, C_2, C_3, C_5, C_6); 64.6, 64.7(2 OCH_2); 107.1(C_4); 119.4(CN); 128.1, 128.2, 128.6, 138.2(Arom.); 169.1($\underline{C}ONH_2$).

***trans*-1-Methoxycarbonylamino-2-phenyl-4-spiro-{2'[1',3'-dioxolane]}-1-cyclohexane-nitrile. 19**

To a solution of compound **18** (350 mg, 1.22 mmol) and $Hg(OAc)_2$ (468 mg, 1.47 mmol) in dry DMF (10 mL) were added MeOH (1.17 g, 36.60 mmol) and a solution of NBS (285 mg, 1.60 mmol) in dry DMF (3 mL) at room temperature. The reaction was stirred for 14 h and the solvent was evaporated *in vacuo*. The solid residue was diluted with diethyl ether (20 mL), washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed and the residue purified by silica gel column chromatography eluting with hexane-ethyl acetate (1:1) to afford 234 mg (61%) of carbamate **19** as a white solid. Mp: 125-7 °C.

Found C: 69.57, H: 6.49, N: 8.70

Anal. Calc. for $C_{17}H_{20}N_2O_4$ C: 64.53, H: 6.38, N: 8.86

^{1}H-NMR($CDCl_3$): δ = 1.86-1.99(m, 3H); 2.10-2.19(m, 1H); 2.43('t', 1H, J=13.8); 3.00-3.16(m, 2H); 3.61(s, 3H, COOMe);3.90-4.08(m, 4H, 2 OCH_2); 4.88(brs, 1H, NH); 7.35-7.46(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 31.46, 38.4, 48.5, 52.4, 53.4, 56.2(C_1, C_2, C_3, C_5, C_6, COO<u>Me</u>); 64.5, 64.8(2 OCH_2); 106.9(C_4); 117.9(CN); 128.4, 128.8, 129.5, 136.9(Arom.); 154.9(<u>C</u>OOMe).

***trans*-2-phenyl-4-oxo-1-aminocyclohexanecarboxylic acid. 20**

In a similar way to that described for **8**, starting from carbamate **19** (200 mg, 0.63 mmol), δ-oxo-α-amino acid **20** was obtained as a white solid in 66% yield.

Found C: 66.82, H: 6.55, N: 5.97

Anal. Calc. for $C_{13}H_{15}NO_3$ C: 66.92, H: 6.49, N: 6.01

^{1}H-NMR(D_2O/TFA): δ = 1.90-2.53(m, 4H); 2.60-2.80(m, 1H); 2.81-3.00(m, 1H); 3.01-3.16(m, 1H); 7.25-7.48(m, 5H, Arom.).

REFERENCES AND NOTES

1. (a) Barrett, G. C.; *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) O'Donnell, M. J. *"Symposia-in-Print Nº 33" Tetrahedron* **1988**, *44*, 5253. (c) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (d) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
2. See e. g.: (a) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 2243. (b) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243. (c) Schöllkopf, U.; Westphalen, K.-O.; Scröder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (d) Zydowski, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. (e) Ojima, T.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. (f) Seebach, D.; Burger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669. (g) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (h) Ihiara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Nitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. I* **1991**, 525. (i) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800. (j) O'Donnell, M. J.; Shengde, W. *Tetrahedron: Asymmetry* **1992**, *3*, 591. (k) Roos, E. C.; López, M. C.; Brook, M. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1993**, *58*, 3259. (l) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1. (m) Boteju, L. W.; Wegner, K.; Qian, X.; Hruby, V. J. *Tetrahedron* **1994**, *50*, 2391. (n)

Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733. (o) Dharanipragada, R.; Nicolas, E.; Toth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6841.

3. (a) DeGrado, W. F. *Adv. Protein Chem.* **1988**, *39*, 51. (b) Hruby, V. J. *Life Sciences* **1982**, *31*, 189. (c) Gupta, S.; Krasnoff, S. B.; Roberts, D. W.; Renwick, J. A. A.; Brinen, L. S.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 707. (d) Kleinkauf, H.; von Döhren, H. *Biochemistry of Peptide Antibiotics*; Walter de Gruyter: Berlin, New York, 1990. (e) Hruby, V. J. *The Peptides: Analysis, Synthesis, Biology*; Academic Press: Orlando, 1985.
4. (a) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; González, M.; Roy, M. A. *Synthesis* **1990**, 114. (b) Cativiela, C.; Díaz-de-Villegas, M. D.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 677. (c) Cativiela, C.; Díaz-de-Villegas, M. D.; Avenoza, A.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 10987.
5. Keck, G. E.; Boden, E.; Sonnewald, U. *Tetrahedron Lett.* **1981**, *2615*.
6. Kraus, G. A.; Yu, F. *Synth. Commun.* **1989**, *19*, 2401.
7. The ratio of the *endo* and *exo* adducts was determined by the integration of the signals corresponding to the H_{3e} proton of product **4** and H_{5e} proton of product **5** in the ^{1}H-NMR spectrum of the mixture **4**, **5**. H_{3e} (**4**): 2.48(ddd, 1H, $J_{3e\text{-}3a}$=15.0, $J_{3e\text{-}2e}$=3.3, $J_{3e\text{-}5e}$=1.8). H_{5e} (**5**): 2.56(dd, 1H, $J_{5e\text{-}5a}$=13.8, $J_{5e\text{-}6a}$=3.0).
8. Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.
9. See experimental section.
10. (a) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Roy, M. A. *Tetrahedron* **1989**, *45*, 3923. (b) Cativiela, C.; Avenoza, A.; Mayoral, J. A.; Roy, M. A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3766. (c) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Sinou, D. *Tetrahedron: Asymmetry* **1990**, *1*, 765. (d) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Lahoz, F. J.; Gimeno, S. *J. Org. Chem.* **1992**, *57*, 4664.
11. Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1992**, *3*, 913.
12. Cativiela, C.; París, M.; Avenoza, A.; Peregrina, J. M. *J. Org. Chem.* **in press.**
13. Fringelli, F.; Tatcchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley and Sons, Inc.: New York. 1990.
14. Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.
15. Daignault, R. A.; Eliel, E. L. *Organic Syntheses, Coll.* **1973**, *5*, 303.
16. (a) Scholtz, J. M.; Bartlett, P. A. *Synthesis* **1989**, 542. (b) Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091. (c) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodríguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 4989. (d) Belokon', Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B.; Tsyryapkin, V. A.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. I* **1988**, 2075.
17. Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2815.
18. Lapworth, A.; Baker, W. *Org. Synth. Coll. Vol. I* **1942**, 181.

(*Received in UK* 26 *July* 1994; *revised* 21 *September* 1994; *accepted* 23 *September* 1994)