Abstract: A useful microwave-assisted synthesis of γ-nitro-α-amino esters and corresponding acids, under mild conditions and without solvent, is described. The desired products were obtained via Michael addition from methyl N-(diphenylmethylene)-2,3-didehydroalaninate and commercially available nitroalkanes.

Key words: microwave-assisted synthesis, α-amino acids, methyl N-(diphenylmethylene)-2,3-didehydroalaninate, nitroalkanes

The protected derivatives of unnatural γ-nitro-α-amino acids are effective intermediates in the syntheses of natural and synthetic bioactive substances.1–3 They are also versatile starting materials for the preparation of unusual α-amino acids due to the many interconversions offered by the chemistry of nitro group (a ‘synthetic chameleon’). For these reasons, three leading synthetic approaches have been reported: (i) addition of glycine equivalent anions to nitroethylene templates (Schöllkopf,10 Leeson3), (ii) nucleophilic substitution of iodine with NaNO2/DMF in N-Boc-α-amino-γ-iodobutanoic acid (Prochazka11), and (iii) addition of α-nitroalkyl anions to 2,3-didehydro-α-amino acid esters (Wieland,12 Crossley13).

From this literature survey, we observed that Schöllkopf only developed a general asymmetric synthesis of γ-nitro-α-amino esters. The Crossley work was general but addressed to N-Cbz or N-acyl protected compounds.13,14 Since only few alkyl γ-nitro-α-amino acids were prepared in the free form,11,12,15,16 we decided to further investigate the Wieland procedure, in order to obtain a general and robust synthesis of fully or partially deprotected amino acids. The presence of nitro and ester functions may interfere with the N-deprotection because of their reactivity in strong acidic, nucleophilic or reductive conditions. To overcome this problem, we chose the O’Donnell’s N-diphenylmethylene protection,17 that is known as strong activator in Michael additions, and requires only mild acidic conditions for deprotection.3,17–21 Therefore we tried the addition of α-nitro carbanions to methyl N-(diphenylmethylene)-2,3-didehydroalaninate (Scheme 1).

The starting compound 1 was prepared from serine methyl ester, following a previously reported two-step procedure.19 We tested different reaction conditions reported in the literature for such reactions,12,13 and found that the ‘old dog’ Triton B (benzyltrimethylammonium hydroxide, 40% in MeOH) was an excellent catalyst to use in a ‘new trick’ microwave-assisted, solvent-free procedure, leading to compounds 2–9 in good yields (Table 1).22

<table>
<thead>
<tr>
<th>Table 1 Michael Addition of 1 with Nitro Compounds</th>
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<tbody>
<tr>
<td>Nitro Compounds</td>
</tr>
<tr>
<td>NO2</td>
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<td>NO₂</td>
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</table>

The microwave-induced reactions were performed in a cooking microwave oven at 200 W, and the open reaction vessels were placed in a fixed position halfway on the radius of the rotating plate. The molar ratio of catalyst/substrate/nitroalkane was optimized at 0.25:1:2. In the case of

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primary nitroalkanes, this ratio provided better yields of 2, 3, 5, 8 and 9, minimizing the quantities of by-products from addition of the newly formed nitro compound to the C=C bond of 1, as it is known for such reactions.\textsuperscript{13}

The primary nitroalkanes gave rise to the diastereomers labeled \( a, b \) in about 1:1 ratio (\(^1\)H NMR, the compounds \( 2a, b \) were separated by flash chromatography, while the compounds \( 3a, b \) were separated by crystallization, see experimental). The diastereomeric mixtures \( 2a, b \) and \( 3a, b \) were resolved in their racemic components. In both cases the less polar isomers, \( 2a \) and \( 3a \), were assigned as \( 2RS,4RS \), while the more polar \( 2b \) and \( 3b \) as \( 2RS,4SR \). The configuration \( 2RS,4RS \) of \( 2a \) was given on the basis of chemical correlation with a compound described by Crossley and co-workers. The nitrogen of \( 2a \) was deprotected (0.5 N HCl, H\(_2\)O-MeOH, 1:1, r.t.) and the intermediate ester was reacted with benzyl chlorocarbonate/Et\(_3\)N/NH\(_3\)+CH\(_2\)Cl\(_2\) at reflux. After workup, the methyl 2-(N-benzyl-oxy carbonylamino)-4-nitropentanoate (55% overall yield) was obtained, having identical spectroscopical data (\(^1\)H NMR, MS) with those reported in the literature for the \( 2RS,4RS \) diastereomer.\textsuperscript{13} The configuration assignments were completed on the basis of the close similarity in the pattern of coupling constants of compounds \( 2a, b \) and \( 3a, b \) with those reported by Crossley for the \( N \)-phthalyl or \( N \)-Boc protected analogues. The \(^1\)H NMR based assignments were possible since the structure of methyl (2RS,4RS)-4-nitro-2-phthalimidopentanoate had been determined by X-ray crystallography.\textsuperscript{13}

It is important to point out that the selective deblocking under mild acidic conditions of our secondary nitro derivatives \( 2a \) underpins the synthetic advantages of the use of the \( N \)-diphenylmethylene protection. A further example is depicted in Table 2, where \( 4a \) was \( N \)-deprotected by stirring in 0.1 N HCl at r.t. for 3 hours, giving the 2-amino-4-methyl-4-nitropentanoic acid methyl ester (11) in quantitative yield. By using different conditions (0.5 N HCl, reflux, 3 h), compound \( 4a \) gave the 4-methyl-4-nitro-\( a \)-aminopentanoic acid 12 in 82% yield.

The reaction of nitromethane anion with 1, carried out under conditions described in Scheme 1, afforded diastereo-

**Table 2** Deprotection of \( N \)-Diphenylmethylen Compounds \( 2a \) and \( 4a \)

<table>
<thead>
<tr>
<th>Protected Compound</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>( \pm 2a )</td>
<td>0.5 N HCl, H(_2)O-MeOH (1:1), r.t.</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>( 4a )</td>
<td>0.1 N, HCl, r.t., 3 h</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>( 4a )</td>
<td>0.5 N HCl, H(_2)O-EtOH (1:1) reflux, 3 h</td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

selectively the 4-nitro-5,5-diphenyl pyrrolidine-2-carboxylic acid methyl ester (10) (47%). Ester 10 resulted from the addition of the nitro anion to the C=C bond, followed by a second carbanionic addition to the C=N bond of the \( N \)-diphenylmethylen protection. The stereochemistry depicted in Scheme 2 was assigned on the basis of \(^1\)H NMR experiments.\textsuperscript{23}

In conclusion, we have demonstrated that the synthesis of \( \gamma \)-nitroalkyl-\( \alpha \)-amino esters (and corresponding acids) from \( N \)-(diphenylmethylen)-2,3-didehydroalanine \( 1 \) can be chosen as an alternative to established methods, especially when there are needs for easy, fast, economic reactions, and when selectivity and mildness of deprotection conditions are critical factors. The reactions described in general, with the exception of the reaction of \( 1 \) with nitromethane in which a cyclization takes place leading to the pyrrolidine derivative 10.

The combination Triton B/microwave has no precedent. This technique, easy to perform and reproducible despite the use of a domestic microwave oven, gives very fast results and it is inexpensive in terms of catalyst and solvent, being practically solvent-free. Moreover, the reactions employ a favorable 2:1 nitroalkane/Michael acceptor ratio. All these findings are substantial improvements to the Wieland method.

\(^1\)H NMR and \(^13\)C NMR spectra were recorded on a Bruker AC 200 spectrometer; chemical shifts (\( \delta \) scale) are reported in parts per million (ppm) respective to the central peak of the solvent. Coupling constants (\( J \) values) are given in Hertz (Hz) and were determined for compounds \( 2a, 2b, 3a \) and \( 3b \) by decoupling experiments. EI-MS spectra (70 eV) were taken on a Fisons Trio 1000. Only molecular ions (\( M^+ \)) and base peaks are given. IR spectra were obtained on a Bruker FT-48 spectrometer. Melting points were determined on a Büchi SMP-510 capillary melting point apparatus and are uncorrected. Column chromatography purifications were performed under flash condition using Merck 230–400 Mesh silica gel. TLC was carried out with silica gel plates. The reagents employed were used directly without further purification. Reactions were carried out in a domestic microwave oven in an open vessel. Satisfactory elemental analyses (C, H, N ± 0.4) were obtained for all new compounds (Carlo Erba analyzer).

The starting methyl \( N \)-(diphenylmethylen)didehydroalaninate (1) was prepared using a literature procedure.\textsuperscript{19}

**Microwave/Triton B-Induced Reaction of 1 with Nitro Compounds; General Procedure**

The respective nitro derivative (2 mmol) and Triton B (40% MeOH, 0.25 equiv) were introduced in a round-bottomed flask and left to react for 2 min. Then, methyl \( N \)-(diphenylmethylen)-2,3-didehydroalaninate (1; 0.53 g, 2 mmol) was added, and the flask was gently heated at 40 °C for 3 min, in order to obtain a homogeneous

![Scheme 2](image-url)
mixture. The reaction vessel was placed inside a microwave oven (halfway on the radius of the rotating plate) and irradiated at 200 W for 3 min. After cooling, the vitreous pale yellow or yellow-brown solids obtained were dissolved in EtOAc (20–80 mL), and the EtOAc layer was quickly washed with 0.1 N HCl (8 mL) and H2O (3 × 10 mL). The combined organic phases, after drying (Na2SO4), were evaporated under reduced pressure. The residues were purified using flash chromatography (eluent: cyclohexane–EtOAc, 9:1), to give compounds 2–9.

**Methyl 2-(Diphenylmethyleneamino)-4-nitropentanoates (2a,b)**

Yield: 85% diastereomeric mixture (1:1 from 1H NMR). The mixture was separated by flash chromatography (cyclohexane–EtOAc, 9:1).

**Structures and Data**

- **2a**: Mp 68 °C (EtO-O-pentane).
- **2b**: Mp 79 °C (cyclohexane).

**Spectral Data**

- **IR (Nujol)**: 3056, 1745, 1546, 1459 cm⁻¹.
- **1H NMR (200 MHz, CDCl₃)**: 6 = 1.46 (d, 3 H, 3 J_HH = 6.0 Hz, CH₃), 2.3–2.4 (m, 1 H, H-3), 2.6–2.8 (m, 1 H, H-3), 3.72 (s, 3 H, OCH₃), 4.11 (dd, 1 H, J_HH = 3.8, 3 J_HH = 9.1 Hz, H-2), 4.7–4.8 (m, 1 H, H-4), 7.2–7.4 (m, 10 H, Ar).
- **13C NMR (50 MHz, CDCl₃)**: δ = 19.83 (CH₃), 38.20 (CH₃), 52.55 (OCH₃), 62.35 (CH₂), 80.85 (CH₄), 127.69 (2 CH, Ar), 128.19 (2 CH, Ar), 128.27 (2 CH, Ar), 129.87 (2 CH, Ar), 129.13 (CH, Ar), 130.89 (CH, Ar), 135.62 (C, Ar), 138.85 (C, Ar), 171.37 (C=N), 172.29 (C-1).
- **MS (EI)**: m/z = 341 (M⁺ + 1), 310, 294, 235, 180, 165.

**Anal. Calcd for C₁₉H₂₀N₂O₄ (340.37): C, 65.02; H, 5.92; N, 8.23.** Found: C, 65.22; H, 6.17; N, 8.27.

**Methyl 2-(Diphenylmethyleneamino)-4-nitroheptanoates (5a,b)**

Yield: 77%; mp 76 °C (EtO-O-light petroleum).

**IR (Nujol)**: 3056, 1739, 1533, 1446 cm⁻¹.

**1H NMR (200 MHz, CDCl₃)**: δ = 1.43 (s, 3 H, CH₃), 1.58 (s, 3 H, CH₃), 2.63 (dd, 1 H, J_HH = 4.3, J_HH = 14.8 Hz, H-3), 2.82 (dd, 1 H, J_HH = 7.4, J_HH = 14.8 Hz, H-3), 3.73 (s, 3 H, OCH₃), 4.22 (dd, 1 H, J_HH = 4.3, J_HH = 14.8 Hz, H-4), 7.2–7.5 (m, 10 H, Ar).

**13C NMR (50 MHz, CDCl₃)**: δ = 20.53 (CH₃), 38.20 (CH₃), 52.45 (OCH₃), 61.63 (CH₂), 80.22 (CH₄), 127.60 (2 CH, Ar), 128.18 (2 CH, Ar), 128.61 (2 CH, Ar), 128.92 (2 CH, Ar), 130.08 (CH, Ar), 130.85 (CH, Ar), 135.64 (C, Ar), 138.96 (C, Ar), 171.44 (C=N), 173.04 (C-1).

**MS (EI)**: m/z = 356 (M⁺ + 1), 308, 248, 180, 165.


**Methyl 2-(Diphenylmethyleneamino)-4-methyl-4-nitropentanoate (4a)**

Yield: 83% diastereomeric mixture (1:1 from 1H NMR).

**IR (Nujol)**: 3056, 1748, 1628, 1541, 1461 cm⁻¹.

**1H NMR (200 MHz, CDCl₃)**: δ = 0.9–1.0 (m, 6 H, H-7), 1.2–1.5 (m, 4 H, H-6), 1.5–2.1 (m, 5 H, H-5), 2.3–2.5 (m, 2 H, H-3), 2.6–2.7 (m, 2 H, H-3), 3.71 (s, 3 H, OCH₃), 4.1–4.2 (m, 2 H, H-2), 4.5–4.8 (m, 2 H, H-4), 7.2–7.7 (m, 10 H, Ar).

**13C NMR (50 MHz, CDCl₃)**: δ = 13.35 (CH₃), 13.39 (CH₃), 18.91 (CH₂), 19.00 (CH₂), 36.22 (CH₂), 36.72 (CH₂), 36.92 (CH₂), 37.02 (CH₂), 52.42 (OCH₃), 61.69 (CH₂), 62.66 (CH₂), 84.95 (CH₂), 85.88 (CH₂), 127.64 (CH, Ar), 127.73 (CH, Ar),
12.8.18 (CH, Ar), 128.61 (CH, Ar), 128.74 (CH, Ar), 128.92 (CH, Ar), 128.97 (CH, Ar), 130.81 (CH, Ar), 135.66 (CH, Ar), 135.70 (C), 139.02 (C), 171.36 (C), 171.42 (C), 171.12 (C), 172.99 (C).

MS (EI): m/z = 369 (M⁺ + 1), 322, 262, 180, 165.


Methyl 2-(Diphenylmethyleneamino)-3-(1-nitrocyclopent-yl)propanoate (6a)

Yield: 93% mp 89 °C (Et₂O–light petroleum).

1H NMR (200 MHz, CDCl₃); δ = 1.6–2.5 (m, 8 H, cyclohexyl H), 2.73 (dd, 1 H, JHH = 3.9, JHH = 14.8 Hz, H-3), 2.91 (dd, 1 H, JHH = 8.7 Hz, H-3), 3.72 (s, 3 H, OCH₃), 4.17 (dd, 1 H, JHH = 3.9, 8.7 Hz, H-2), 7.2–7.6 (m, 10 H, Ar).

13C NMR (50 MHz, CDCl₃); δ = 25.30 (CH-6), 23.97 (CH-7), 36.86 (CH₃-C₅), 38.29 (CH-8), 42.51 (CH₂-3), 52.54 (OCH₃), 62.62 (CH₂-2), 97.94 (CH), 127.83 (CH, Ar), 128.14 (CH, Ar), 128.51 (CH, Ar), 130.92 (CH, Ar), 130.69 (CH, Ar), 135.70 (C), 139.09 (C), 171.73 (C), 172.23 (C).

MS (EI): m/z = 381 (M⁺ + 1), 334, 274, 180, 165.


2-(Diphenylmethyleneamino)-4-nitroheptanedioic Acid Dimethyl Esters (9a,b)

Yield: 65% diastereometric mixture (1:1 from 1H NMR).

IR (Nujol): 3059, 1738, 1622, 1597, 1576, 1551, 1438 cm⁻¹.

1H NMR (200 MHz, CDCl₃); δ = 2.0–2.7 (m, 12 H, H-3, H-5 and H-6), 3.60 (s, 3 H, OCH₃), 3.65 (s, 3 H, OCH₃), 3.67 (s, 3 H, OCH₃), 4.0–4.2 (m, 1 H, H-2), 4.2–4.4 (m, 1 H, H-2), 4.4–4.6 (m, 1 H, H-4), 4.6–4.7 (m, 1 H, H-4), 7.2–7.6 (m, 20 H, Ar).

13C NMR (50 MHz, CDCl₃); δ = 29.03 (CH-6), 29.48 (CH-8), 29.76 (CH-5), 30.16 (CH-5), 36.78 (CH₃-C₅), 36.91 (CH₂-3), 51.79 (OCH₃), 51.81 (OCH₃), 52.41 (OCH₃), 52.43 (OCH₃), 61.56 (CH₂-2), 62.44 (CH₂-2), 84.14 (CH-4), 84.97 (CH-4), 126.84 (CH, Ar), 127.79 (CH, Ar), 127.64 (CH, Ar), 128.12 (CH, Ar), 128.14 (CH, Ar), 128.58 (CH, Ar), 128.72 (CH, Ar), 128.89 (CH, Ar), 129.91 (CH, Ar), 129.97 (CH, Ar), 129.05 (CH, Ar), 130.79 (CH, Ar), 135.60 (C), 135.68 (C), 138.92 (C), 138.95 (C), 171.14 (C), 171.21 (C), 171.99 (C), 172.04 (C), 172.29 (C), 172.97 (C).

MS (EI): m/z = 413 (M⁺ + 1), 381, 366, 353, 306, 180, 165.

Anal. Calcld for C₂₂H₂₄N₂O₄ (412.44): C, 64.07; H, 5.87; N, 6.79. Found: C, 64.10; H, 6.00; N, 7.01.

Methyl (2RS,4RS)-2-(Benzyloxy carbamoylino)-4-nitropropanoates from 2a

Diastereomer 2a (mp 68 °C; 0.170 g, 0.5 mmol) was placed in a round-bottomed flask with MeOH (10 mL) and 1 N HCl (1 mL) under stirring at r.t. under N₂. After 0.5 h, the solution was concentrated at r.t. in order to eliminate most of the MeOH. From the residue, diluted with H₂O (4 mL), benzophenone was extracted with CH₂Cl₂ (2 × 4 mL), then pH was adjusted to about 10 by addition of solid NaHCO₃. The solution was extracted with CH₂Cl₂ (4 × 20 mL) and the combined organic phases were washed with a small portion of H₂O. After drying (Na₂SO₄) and evaporation of the solution using a rotary evaporator, a pale yellow oil was obtained. This oil was taken in CH₂Cl₂ (5 mL) and treated with Et₂N (0.121 g, 1.2 mmol) and benzyl chlorocarbonate (0.170 g, 1 mmol). After 2 h reflux under N₂, the solution was evaporated at r.t., the residue was taken in EtOAc (20 mL). The organic phase was washed with aq sat. solution of NaHCO₃ (2 × 4 mL), then pH was adjusted to about 10 by addition of solid NaHCO₃. The solution was extracted with CH₂Cl₂ (4 × 20 mL) and the combined organic phases were washed with a small portion of H₂O. After drying (Na₂SO₄) and evaporation of the solution using a rotary evaporator, a pale orange oil. TLC: cyclohexane–EtOAc (7:3), spray reagent ninhydrin, yellow spot at Rₗ 0.6. Flash chromatography (cyclohexane–EtOAc, 8:2) gave 0.086 g (55% overall yield) of pure methyl 2-(benzyl carbamoylamo)-4-nitropropanoate with spectroscopic data (1H NMR, MS) identical to those reported in the literature for the diastereomer (2RS,4RS).

2-Amino-4-methyl-4-nitrophenoxycetic Acid Methyl Ester (11)

Aq 0.1 N HCl (15 mL) was added to a solution of 4a (0.354 g, 1 mmol) in Et₂O (15 mL) kept in an ice-bath. The mixture, monitored by TLC (cyclohexane–EtOAc, 7:3), was vigorously stirred for 3 h at r.t. under N₂. The solution was diluted with H₂O (20 mL), the aqueous phase was washed with Et₂O (3 × 20 mL), basified with solid NaHCO₃ and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phases were dried (Na₂SO₄) and evaporated under reduced pressure giving 11 as an oil in quantitative yield.

1H NMR (200 MHz, CDCl₃); δ = 1.57 (s, 3 H, CH₃), 1.63 (s, 3 H, CH₃), 2.33 (dd, 1 H, JHH = 4.8, JHH = 15.7 Hz, H-3), 2.77 (dd, 1 H, JHH = 8.6, and JHH = 15.7 Hz, H-3), 3.66 (s, 3 H, OCH₃), 4.22 (dd, 1 H, JHH = 4.8, JHH = 8.6 Hz, H-2).

13C NMR (50MHz, CDCl₃); δ = 25.45 (CH₃), 28.61 (CH₃), 40.36 (CH₃), 50.50 (CH₃), 54.70 (OCH₃), 88.12 (C), 171.10 (C).

Anal. Calcld for C₆H₁₂NO₄ (190.20): C, 44.20; H, 7.42; N, 14.73. Found: C, 44.26; H, 7.83; N, 14.70.

4-Methyl-4-nitro-o-aminopentanoic Acid (12)
The crude oil obtained from the reaction of 1 (1 mmol) with 2-nitropropane was dissolved in EtOH (10 ml), then 1 N HCl (10 ml) was added. TLC monitoring (propan-2-ol/conc. NH₄OH/CHCl₃, 80:15:5) showed a yellow spot of the ester 11 at Rf 0.8 (gradually fading) and a yellow spot of 12 at Rf 0.4 (gradually increasing in time). The reaction mixture was refluxed for 3 h under N₂, then the solution was concentrated to half the volume at reduced pressure. The aqeous solution was washed with EtOAc (2 x 5 ml). For the reaction mixture, the pH was adjusted to 7 by adding solid NaHCO₃, and then it was kept overnight in refrigerator. The white crystals formed were filtered off and washed on the filter with a small amount of cold water. After drying, 12 was obtained; yield: 0.159 g (82% yield from 1); mp 195–200 °C (dec.) (lit. 12 mp 196–200 °C (dec.).

1H NMR (200 MHz, CDCl₃): δ = 1.89 (s, 3 H, CH₃), 1.91 (s, 3 H, CH₃), 2.46 (dd, 1 H, 3JH,H = 6.3 Hz, -H-3), 2.73 (dd, 1 H, 3JH,H = 15.8 Hz, -H-3), 3.81 (s, 3 H, OCH₃), 3.83 (br, 1 H, NH), 3.94 (d, 1 H, 3JH,H = 10.4 Hz, -H-2), 5.98 (d, 1 H, 3JH,H = 6.3 Hz, -H-2).

13C NMR (50 MHz, CDCl₃): δ = 25.11 (CH₃), 25.92 (CH₃), 43.08 (CH₃), 51.70 (CH), 87.54 (C), 174.43 (C).

Anal. Calcd for C₈H₁₄N₂O₄ (176.17): C, 40.91; H, 6.87; N, 15.90.

References

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(20) Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. Synthesis 1988, 514.
(22) The nitroalkyl additions to 1 can be alternatively run in the classic way: i.e. in THF at r.t. With little change in the stoichiometry (substrate/nitroalkane ratio = 1:1.5), but with much longer reaction times (3–5 h), we obtained the adducts in yields close to those from microwave-induced reactions.
(23) The stereochemistry depicted in Scheme 2 was assigned on the base of 1H NMR measurements, as follows. In the decoupled spectrum the H-2 proton shows two coupling constants (JH-4 = 10.4 Hz and JH-9 = 4.9 Hz) consistent with a pseudo-axial conformation. A coupling between H-3a and H-4 (JH-3a = 6.1 Hz) and the absence of coupling between H-4 and H-3b are suitable for a structure, where the H-4 proton is eclipsed with H-3a, and where H-4 had a dihedral angle of about 90° with H-3b. This hypothesis is furthermore supported by NOE values that are higher between H-3b and H-4 than between H-4 and H-3. Finally, no NOE was observed between H-4 and H-2, a finding in accord to the given structure.