Diastereoselective β-Hydroxyalkylation and β-Hydroxycarboxylation of Amides by a Diels–Alder Strategy

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Received 15 July 2002
Dedicated to Professor Dieter Seebach in recognition of his important contribution to synthetic methodology.

Abstract: Acid chlorides readily condensed with N-silylated imines in the presence of a base to generate 2-azadienes. These underwent Diels–Alder cycloadditions with a wide variety of aldehydes. In most cases the cycloadditions were diastereoselective in favor of the 3,4-cis-oxazinone adducts. Ethanolysis stereoselectively yielded products of hydroxyalkylation or hydroxycarboxylation of the primary amides derived from the initial acid chlorides.

Key words: amides, azadienes, heterocycles, oxazinones, aldehydes, Diels–Alder reactions

Diels–Alder reactions of 2-azadienes are of great value for the preparation of nitrogen-containing six membered rings.1 In recent years we have shown that 2-azadienes of type 1 could be efficiently prepared in a one-pot procedure from carboxylic acid chlorides and N-silylimines (Scheme 1).2 These 2-azadienes have been successfully reacted with olefinic and acetylenic dienophiles.3 The use of a chiral catalyst in these cycloadditions resulted in one of the most efficient route towards piperidine derivatives of high enantiomeric purities.4

We also examined the possibility of using 2-azadienes as carboxamide anion synthons. Thus asymmetric amination of carboxamides could be effected by cycloaddition of 1 with chiral acylnitroso compounds followed by reduction and hydrolysis.5 It was also shown by Panunzio’s,6 Barluenga’a’s and our group that 2-azadienes reacted with aldehydes to yield 1,3-oxazinone derivatives which were easily converted into useful intermediates. We now describe the details of our study of a stereoselective method of hydroxyalkylation and hydroxycarboxylation of carboxamides by a Diels–Alder strategy.

Azadienes 1 were prepared from the corresponding acid chlorides and N-trimethyl- or N-tert-butyldimethylsilylimines following the general procedure described earlier.2 The synthesis and characterization of the new azadienes are described in the experimental part. Scheme 2 and Table 1 summarize the results of the cycloaddition reactions of 1 with aldehydes after mild methanalysis to cleave the trialkysilyl group.

Scheme 1

Scheme 2

Examination of Table 1 leads to the following conclusions. (1) The cycloaddition works well with both aromatic and aliphatic aldehydes. As expected ethyl glyoxylate reacted faster as a result of the enhanced electrophilicity of its aldehyde group. (2) A wide variety of substituents at C-4 of the diene are allowed. However, the presence of a halogen atom required the use of high pressure.11 (3) Most cycloadditions took place with a significant preference for the cis-adduct resulting from an endo approach of the reactants (Figure 1). However, when the diene carried a phthalimido group at C-4, the trans isomer resulting from an exo-approach of the reactants was preferred. This could be the consequence of the large size of the phthalimido group.

The relative configurations of the 1,3-oxazin-4-ones 2 were maintained in the products 3.
Oxazinones 2 were ethanolyzed in 3 M HCl in EtOH–THF to yield the corresponding β-hydroxyamides 3 or succinic acid derivatives (Scheme 3, Table 2).

In summary, we have shown another example of the behavior of 2-azadienes 1 acting as synthetic equivalents of enolates derived from carboxamides. The cycloaddition of 1 with aldehydes stereoselectively yielded 1,3-oxazin-4-ones 2 carrying a wide variety of substituents. Ethanolysis of 2 led stereoselectively to the products 3 of β-hy-
**β-Hydroxyalkylation and β-Hydroxycarboxylation of Amides by a Diels–Alder Strategy**

Mps are uncorrected. ¹H spectra were recorded on Varian XL-200, VXR-200 or Gemini-300BB spectrometers. ¹³C NMR spectra were recorded at 50 MHz on Varian XL-200 or VXR-200 or at 75 MHz on Gemini 300BB. Data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ = 0.0). Coupling constants are given in Hertz. IR spectra were recorded with Perkin–Elmer 297 or 681 spectrometers. Mass spectra were obtained on Varian MAT-44 or Finnigan MAT-TS-TSQ-70 spectrometers (electronic impact 70eV or chemical ionisation 100 eV with 200 μbar isobutane as ionising gas). Elemental analyses were performed at the Microanalytic Service, University College, London.

2-Azadienes 1; General Procedure

Both known and unknown azadienes 1 were prepared by the procedure described earlier. Data for the new azadienes are as follows:

**2-Isopropoxy-4-N-phthalimido-3-tert-butyldimethylsilyloxy-2-aza-1,3-butadiene (1k)**

N-tert-Butyldimethylsilylisopropyl formimidade (4 g, 0.02 mmole), N-phthaloyl chloride (4.44 g, 0.02 mmol) and Et₃N (13.80 mL, 0.10 mmol) yielded 1k after flash chromatography (EtOAc–cyclohexane, 40:60).

Yield 4.6 g (60%); yellow solid; mp 84–85 °C.

**2-Hydroxylation and 2-Hydroxycarboxylation of Amides by a Diels–Alder Strategy**

The freshly distilled aldehyde was added to a solution of azadiene 1 (2 equiv) in toluene, MeCN or CH₂Cl₂. The resulting mixture was warmed to the selected temperature. When the reaction was over, MeOH was added at r.t. The crude product was purified by flash chromatography (EtOAc–cyclohexane). Products were recrystallized in Et₂O.

**2-Isopropoxy-5-methyl-6-phenyl-1,3-oxazin-4-one (2a)**

2-Azadiene 1a (0.75 g, 2.91 mmol) and benzaldehyde (0.148 mL, 5.05 mmol) yielded 2a after flash chromatography (EtOAc–cyclohexane, 80:20).

Yield: 0.301 g (83%) endo product and 0.028 g (8%) exo product; endo product 2a mp 104–105 °C.

IR (KBr): 3400, 3092, 1694 cm⁻¹.

**3.2.2.1**

**Scheme 3**

**Table 2 Ethanolysis of 1,3-Oxazin-4-ones**

<table>
<thead>
<tr>
<th>Substrate 2°</th>
<th>Product 3</th>
<th>Yield b (%)</th>
</tr>
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<tbody>
<tr>
<td>a-cis</td>
<td>Me</td>
<td>R²</td>
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<tr>
<td>b-cis</td>
<td>Me</td>
<td>2-furyl</td>
</tr>
<tr>
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<tr>
<td>d-cis</td>
<td>Me</td>
<td>ρ-ClC₆H₄</td>
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<tr>
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<td>Me</td>
<td>ρ-NO₂C₆H₄</td>
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<tr>
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<td>Me</td>
<td>n-C₆H₄</td>
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<td>F</td>
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<td>k-trans</td>
<td>FN</td>
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<td>l-cis</td>
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</tr>
<tr>
<td>r-cis</td>
<td>AcO</td>
<td>CO₂Et</td>
</tr>
</tbody>
</table>

° Single stereoisomer.

b Pure compounds.

*droxyalkylation or β-hydroxycarboxylation of a carboxylic amide. Of particular interest is the possibility of introducing a functionality α to the amide group with high diastereoselectivity.*
2-Azadiene (2c) 59.80; H, 7.05; N, 5.71.

Yield: 0.23 g (73%) endo product; mp 110–111 °C.

IR (film): 3198, 2917, 1683, 1521, 1348 cm⁻¹.

Found: C, 58.96; H, 6.32; Cl, 12.20; N, 4.93.

2-Isopropoxy-5-methyl-6-(4-chlorophenyl)-1,3-oxazin-4-one (2e) 64.73; H, 7.70; N, 5.00. Found: C, 62.85; H, 10.54; N, 6.11.

1H NMR (300 MHz, CDCl₃): δ = 7.37 (d, 2 H, J = 8.5), 7.24 (d, 2 H, J = 8.5), 6.67 (br s, 1 H), 5.84 (s, 1 H), 5.04 (d, 1 H, J = 3.4), 4.20 (sept, 1 H, J = 6.3), 2.63 (qd, 1 H, J = 3.1, 7.3), 1.31 (t, 6 H, J = 6.3), 0.97 (d, 3 H, J = 6.3).

13C NMR (75 MHz, CDCl₃): δ = 173.6, 135.9, 133.4, 128.6, 126.6, 99.9, 74.1, 69.7, 41.5, 23.6, 23.0, 12.09.

MS (EI): m/z (%) = 224 (23), 181 (22), 179 (65), 152 (100), 143 (95), 117 (91), 101 (83), 91 (10), 56 (17), 45 (21).

Analytical Calcd for C₁₉H₁₈NO₅: C, 79.26; H, 6.39; Cl, 12.49; N, 4.94. Found: C, 78.96; H, 6.32; Cl, 12.20; N, 4.93.

2-Isopropoxy-5-methyl-6-(4-nitrophenyl)-1,3-oxazin-4-one (2f) 2-Azadiene 1a (0.75 g, 2.91 mmol) and 4-nitrobenzaldehyde (0.219 g, 1.45 mmol) yielded 2f after flash chromatography (EtOAc–cyclohexane, 60:40).

Yield: 0.28 g (73%) endo 2e and 0.027 g (8%) exo product; endo product mp 110–111 °C.

IR (film): 3422, 1654 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 6.84 (s, 1 H), 6.54 (s, 1 H), 4.09 (sept, 1 H, J = 6.2), 4.02 (m, 1 H, J = 3.3, 7.3), 1.64 (s, 1 H), 1.44 (s, 1 H), 1.25 (d, 3 H, J = 7.3), 1.18 (d, 3 H, J = 6.2), 1.17 (d, 3 H, J = 6.2), 0.95 (t, 3 H, J = 7.0).

13C NMR (75 MHz, CDCl₃): δ = 174.8, 99.6, 73.2, 69.3, 39.6, 32.7, 23.2, 22.6, 18.6, 13.6, 11.2.

MS (EI): m/z (%) = 215 (M⁺, 2), 214 (130), 213 (100), 172 (21), 156 (100), 111 (83), 89 (22), 83 (15), 55 (15), 43 (28).

Analytical Calcd for C₁₉H₁₈NO₅: C, 63.17; H, 9.83; N, 6.50. Found: C, 62.10; H, 9.80; N, 6.49.

2-Isopropoxy-5-methyl-6-isobutyryl-1,3-oxazin-4-one (2g) 2-Azadiene 1a (0.75 g, 2.91 mmol) and butyraldehyde (0.13 mL, 1.46 mmol) yielded 2f after flash chromatography (EtOAc–cyclohexane, 60:40).

Yield: 0.28 g (84%) endo product and 0.027 g (8%) exo product; endo product mp 70–71 °C.

IR (film): 3351, 2929, 1653 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 6.53 (s, 1 H), 5.64 (s, 1 H), 4.09 (sept, 1 H, J = 6.2), 3.87 (ddd, 1 H, J = 3.4, 7.4), 1.75 (s, 1 H), 1.59 (s, 1 H), 1.26 (d, 3 H, J = 6.2), 1.23 (d, 3 H, J = 6.2), 1.18 (d, 3 H, J = 7.4), 0.96 (d, 3 H, J = 6.7), 0.93 (d, 3 H, J = 6.7).

13C NMR (75 MHz, CDCl₃): δ = 173.6, 97.1, 68.4, 66.4, 40.5, 39.8, 24.3, 23.3, 23.2, 22.2, 21.8, 10.8.

MS (EI): m/z (%) = 228 (2), 214 (12), 170 (100), 125 (27), 101 (10), 97 (24), 56 (13).

Analytical Calcd for C₁₉H₁₈NO₅: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.92; H, 10.25; N, 6.05.
2-Isopropoxy-5,6-diphenyl-1,3-oxazin-4-one (2h)

2-Azadiene 1h (0.75 g, 2.56 mmol) and benzaldehyde (0.18 mL, 1.19 mmol) yielded 2h after flash chromatography (EtOAc–cyclohexane, 40:60).

Yield: 0.20 g (35%) endo product and 0.034 g (6%) exo product; endo-product 2h mp 165–166 °C.

IR (film): 3194, 2983, 1673 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.15–7.04 (m, 2 H), 7.0–6.96 (m, 8 H), 6.80 (br s, 1 H), 5.94 (s, 1 H), 5.23 (d, 1 H, J = 3.5), 4.23 (sept, 1 H, J = 6.2), 3.76 (d, 1 H, J = 3.5), 1.36 (d, 3 H, J = 6.2). 13C NMR (75 MHz, CDCl₃): δ = 167.9, 138.4, 128.9, 128.7, 127.9, 127.0, 127.5, 75.4, 50.5, 43.2, 24.1, 23.7, 22.7.

3.97 (sept, 1 H, J = 3.6), 4.27 (sept, 1 H, J = 3.6, 7.1) .

5-Acetoxy-2-isopropoxy-6-phenyl-1,3-oxazin-4-one (2l)

2-Azadiene 1l (0.75 g, 2.49 mmol) and benzaldehyde (0.19 mL, 1.91 mmol) yielded 2l after flash chromatography (EtOAc–cyclohexane, 60:40).

Yield: 0.40 g (72%) endo product 2l; mp 168–169 °C.

IR (film): 3190, 2975, 2929, 1694 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.78–7.38 (m, 5 H), 6.67 (s, 1 H), 5.85 (s, 1 H), 5.65 (d, 1 H, J = 3.0), 5.04 (d, 1 H, J = 3.0), 4.23 (sept, 1 H, J = 6.2), 1.81 (s, 3 H), 1.32 (d, 3 H, J = 6.2), 1.30 (d, 3 H, J = 6.2).

IR (film): 3212, 2980, 1760, 1649 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.78–7.38 (m, 5 H), 6.67 (s, 1 H), 5.85 (s, 1 H), 5.65 (d, 1 H, J = 3.0), 5.04 (d, 1 H, J = 3.0), 4.23 (sept, 1 H, J = 6.2), 1.81 (s, 3 H), 1.32 (d, 3 H, J = 6.2), 1.30 (d, 3 H, J = 6.2).

1H NMR (300 MHz, CDCl₃): δ = 7.78–7.38 (m, 5 H), 6.67 (s, 1 H), 5.85 (s, 1 H), 5.65 (d, 1 H, J = 3.0), 5.04 (d, 1 H, J = 3.0), 4.23 (sept, 1 H, J = 6.2), 1.81 (s, 3 H), 1.32 (d, 3 H, J = 6.2), 1.30 (d, 3 H, J = 6.2).

1H NMR (300 MHz, CDCl₃): δ = 7.78–7.38 (m, 5 H), 6.67 (s, 1 H), 5.85 (s, 1 H), 5.65 (d, 1 H, J = 3.0), 5.04 (d, 1 H, J = 3.0), 4.23 (sept, 1 H, J = 6.2), 1.81 (s, 3 H), 1.32 (d, 3 H, J = 6.2), 1.30 (d, 3 H, J = 6.2).
MS (El): m/z (%) = 307 (16), 248 (43), 247 (17), 205 (78), 192 (19), 176 (100), 163 (49), 147 (68), 131 (99), 118 (78), 91 (44), 77 (16), 43 (52).

Anal. Calcld for C_{10}H_{16}NO_{5}: C, 48.19; H, 6.47; N, 5.62. Found: C, 48.22; H, 6.48; N, 5.60.

**exo-Product 2n**

IR (film): 3263, 2976, 1726, 1684 cm⁻¹.

**endo-Product 2n**

IR (film): 3220, 2987, 1747, 1700 cm⁻¹.

**2-Azadiene (2p)**

5-Chloro-2-methoxy-4-oxo-1,3-oxazin-6-ethyl Carboxylate (2o)

HRMS: m/z calcd for C_{10}H_{16}FNO_{5}: 308.149798; found: 308.149806.

Anal. Calcd for C_{12}H_{19}NO_{7}: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.45; H, 6.84; N, 4.89.

**5-Chloro-2-methoxy-4-oxo-1,3-oxazin-6-ethyl Carboxylate (2o)**

IR (KBr): 3340, 3196 (NH), 2960, 1769, 1702 cm⁻¹.

**5-Fluoro-2-isopropoxy-4-oxo-1,3-oxazin-6-ethyl Carboxylate (2q)**

IR (film): 3224, 2979, 1755, 1700 cm⁻¹.

**endo-Product 2o**

IR (film): 3263, 2976, 1726, 1684 cm⁻¹.

**exo-Product 2o**

IR (film): 3210, 3119, 2971, 1736, 1722, 1692 cm⁻¹.

**2-Isopropoxy-5-phthalimido-4-oxo-1,3-oxazin-6-ethyl Carboxylate (2q)**

IR (film): 3340, 3196 (NH), 2960, 1769, 1702 cm⁻¹.

2-Azadiene 1k (0.75 g, 1.93 mmol) and ethyl glyoxylate (0.10 g, 0.96 mmol) yielded 2q after flash chromatography (EtOAc–cyclohexane, 60:40).

**Yield:** 0.30 g (83%) *exo* product; mp 211–212 °C.

**endo-Product 2r**

IR (film): 3210, 3119, 2971, 1736, 1722, 1692 cm⁻¹.

**exo-Product 2r**

IR (film): 3263, 2976, 1726, 1684 cm⁻¹.

**5-Acetoxy-2-isopropoxy-4-oxo-1,3-oxazin-6-ethyl Carboxylate (2r)**

IR (KBr): 3340, 3196 (NH), 2960, 1769, 1702 cm⁻¹.

2-Azadiene 1i (0.75 g, 2.48 mmol) after flash chromatography (EtOAc–cyclohexane, 60:40).

**Yield:** 0.34 g (60%) *endo* product and 0.09 g (15%) *exo* product.
**endo-Product 2s**

Mp 135–136 °C.

1H NMR (300 MHz, CDCl3): δ = 7.51–7.42 (m, 5 H), 6.14 (s, 1 H), 5.75 (s, 1 H), 4.68 (d, 1 H, J = 3.8), 4.30 (q, 2 H, J = 7.1), 2.92 (qd, 1 H, J = 3.8, 7.2), 1.35 (d, 3 J, J = 7.2), 1.32 (t, 3 H, J = 7.1).

13C NMR (50 MHz): δ = 171.7, 168.0, 137.1, 130.1, 128.9, 127.0, 85.4, 85.3, 61.5, 14.2, 13.2.

MS (CI): m/z (%) = 264 (22), 234 (15), 176 (14), 157 (36), 143 (16), 122 (38), 99 (21), 89 (92), 75 (100), 73 (36).

Anal. Calcd for C14H17NO4: C, 63.86; H, 6.50; N, 5.32. Found: C, 63.82; H, 6.56; N, 5.14.

**exo-Product 2s**

 Mp 122–123 °C.

1H NMR (300 MHz, CDCl3): δ = 7.49–7.35 (m, 5 H), 6.56 (s, 1 H), 6.56 (s, 1 H), 4.29 (q, 2 H, J = 7.1), 4.18 (d, 1 H, J = 8.4), 2.94 (qd, 1 H, J = 8.4, 7.1), 1.35 (d, 3 J, J = 7.1), 1.33 (t, 3 J, J = 7.1).

13C NMR (75 MHz): δ = 171.3, 170.6, 136.7, 129.8, 128.9, 126.7, 81.9, 81.2, 61.7, 37.8, 14.1, 13.1.

MS (EI): m/z (%) = 262 (1), 194 (40), 178 (5), 149 (3), 121 (100), 105 (55), 77 (38), 44 (21).

HRMS: calcd for C14H17NO4: 262.109793; found: 262.108592.

**2-tet-Butyl-5-methyl-1,3-oxazin-6-ethyl Carboxylate (2t)**

A solution of the cycloadduct 2 in THF was mixed with HCl (3 M) in EtOH (5–10 equiv) and stirred at r.t. for 16–24 h. The crude product was purified by flash chromatography (silica gel; EtOAc–cyclohexane). Solids were recrystallized.

**3a-cis**

Yield: 0.27 g (74%); mp 84–85 °C.

IR (KBr): 3383, 3192, 2971, 2922, 1630 cm−1.

**3b-cis**

Yield: 0.22 g (63%); mp 114–115 °C.

IR (KBr): 3385, 2909, 3187, 2987, 2974, 2933, 1507, 1459, 1421, 1283, 1233 cm−1.

**3c-cis**

Yield: 0.27 g (72%); mp 118–119 °C.

IR (KBr): 3453, 2909, 2835, 1899, 1695, 1518 cm−1.

**3d-cis**

Yield: 0.29 g (77%); mp 72–83 °C.

IR (KBr): 3385, 3095, 2988, 2977, 2267, 1798, 1609, 1507, 1459, 1283, 1233 cm−1.

**Ethanolysis of 2; General Procedure**

A solution of the cycloadduct 2 in THF was mixed with HCl (3 M) in EtOH (5–10 equiv) and stirred at r.t. for 16–24 h. The crude product was purified by flash chromatography (silica gel; EtOAc–cyclohexane). Solids were recrystallized.

Yield: 0.27 g (74%); mp 84–85 °C.

IR (KBr): 3383, 3192, 2971, 2922, 1630 cm−1.
3c-cis
2c-cis (0.5 g, 1.70 mmol), THF (3 mL), and HCl–EtOH (3 M; 3 mL) yielded 3c-cis after 16 h and recrystallization in MeCN.
Yield: 0.32 g (84%); mp 157–158 °C.
IR (KBr): 3465, 3045 cm⁻¹.
1H NMR (200 MHz, CD2OD): δ = 7.98 (d, 2 H, J = 8.8), 7.40 (d, 2 H, J = 8.8), 4.71 (d, 1 H, J = 6.6), 5.24 (qd, 1 H, J = 6.6, 6.9), 1.00 (d, 3 H, J = 6.9).
13C NMR (50 MHz, CD2OD): δ = 180.8, 151.9, 148.7, 128.7, 124.5, 74.8, 48.7, 13.3.
MS (EI): m/z (%) = 224 (27), 209 (86), 192 (5), 152 (23), 115 (8), 105 (11), 73 (100), 44 (14).
HRMS: m/z calcd for C10H12N: 171.096907.

Synthesis 2002, No. 14, 2043–2052 ISSN 0039-7881 © Thieme Stuttgart · New York
3r-cis
2r-cis (0.5 g, 1.73 mmol), THF (2 mL) and HCl–EtOH (3 M; 3 mL) yielded 3r-cis after recrystallization in i-PrOH.
Yield: 0.28 g (74%); mp 130–131 °C.

IR (KBr): 3462, 2365, 2342, 1739, 1653 cm⁻¹.
1H NMR (300 MHz, DMSO-δ6): δ = 7.31 (s, 1 H), 7.17 (s, 1 H), 5.47 (d, 1 H, J = 1.4), 5.27 (dd, 1 H, J = 1.4, 1.2), 4.36 (d, 1 H, J = 1.2), 4.09 (q, 2 H, J = 7.1), 1.19 (t, 3 H, J = 7.1).

13C NMR (75 MHz, DMSO-δ6): δ = 173.5, 172.3, 73.0, 72.0, 60.3, 42.0, 38.5.
MS (EI): m/z (%): = 178 (27), 133 (98), 116 (100), 88 (100), 75 (15), 61 (12), 60 (15), 44 (35).
Anal. Calcd for C6H11NO5: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.89; H, 6.32; N, 7.86.

Acknowledgements
This work was generously supported by the Republic of Burundi (fellowship to D.N.) and the ‘Ministère de l’Éducation et de la Recherche Scientifique de la Communauté Française de Belgique (Action concertée 96/01-197)’. We thank Dr R. Touillaux for the help in the NMR analyses and Prof. J.-P. Declercq and Dr B. Tinant for X-ray diffraction analyses.

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