Synthesis of 5-(Hydroxymethyl)pyrrolidin-2-ones by Cyclization of Amide Dianions with Epibromohydrin

Ilia Freifeld,[a] Holger Armbrust,[b] Peter Langer*[c,d]

[a] Institut für Biochemie, Universität Greifswald, Soldmannstr. 16, 17487 Greifswald, Germany

[b] Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany

[c] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax +381 4986412; E-mail: peter.langer@uni-rostock.de

[d] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

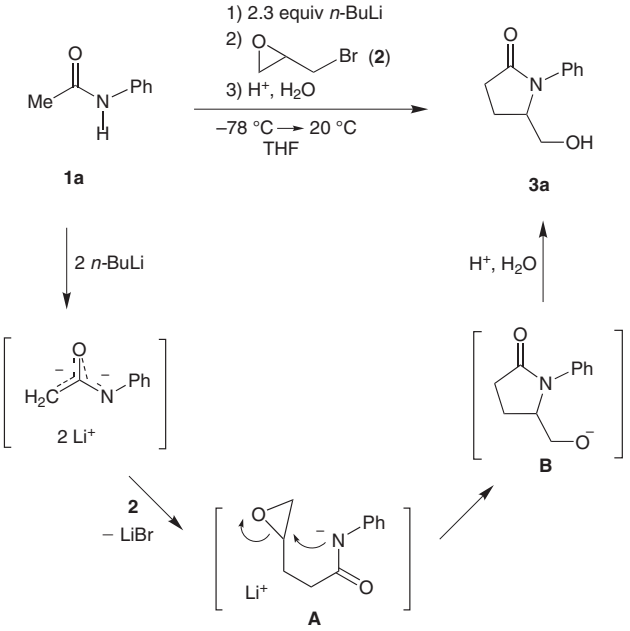
Received 16 November 2005; revised 27 January 2006

Abstract: The reaction of amide and thioamide dianions with epibromohydrin resulted in regioselective formation of 5-(hydroxymethyl)pyrrolidin-2-ones (pyroglutaminols) and -thiones. The cyclization of the dianion of *N*-(2-*tert*-butylphenyl)acetamide with epibromohydrin afforded racemic axially chiral 1-(2-*tert*-butylphenyl)-5-(hydroxymethyl)pyrrolidin-2-one with high diastereoselectivity.

Key words: cyclizations, dianions, epoxides, heterocycles, regioselectivity

Pyrrolidin-2-ones occur in several biologically relevant natural products.[1] In addition, they represent versatile synthetic building blocks.[1–3] 1-Arylpyrrolidin-2-ones represent an important subclass of pyrrolidin-2-ones which occurs in a number of natural products.[4] They have been used as synthetic building blocks[5] and represent potent influenza A sialidase inhibitors.[6] Axially chiral 1-(2-*tert*-butylphenyl)pyrrolidin-2-ones represent important building blocks for stereoselective syntheses.[7] For example, diastereoselective alkylations of axially chiral pyrrolidin-2-ones and diastereoselective reactions of pyrrolidin-2-one derived iminium salts have been reported. In recent years we developed a number of cyclization reactions[8] of ambident dianions with epibromohydrin.[9] Herein, we report what are, to the best of our knowledge, the first cyclizations of amide dianions[10,11] with epibromohydrin. These reactions allow an efficient and regioselective approach to 1-aryl-5-(hydroxymethyl)pyrrolidin-2-ones[12] (*N*-arylpyroglutaminols).

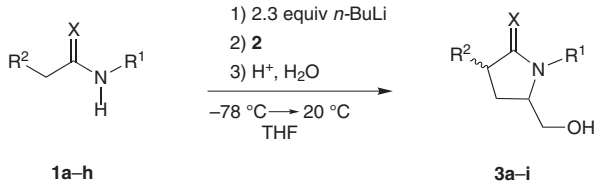
The reaction of epibromohydrin (**2**) with the dianion of *N*-phenylacetamide (**1a**), generated by treatment of a THF solution of **1a** with *n*-BuLi (2.3 equiv), afforded 1-phenyl-5-(hydroxymethyl)pyrrolidin-2-one (**3a**)[12b] (Scheme 1). Optimal yields (up to 81%) were obtained when the reaction was carried out at –78 °C → 20 °C (warming the mixture during 12 h and stirring at 20 °C for 5 h) and when 1.5 equivalents of the dianion (rather than only one) were used. Further variation of the temperature and the addition of a Lewis acid (LiCl, $LiClO_4$) did not result in an increase of the yield. The use of epichlorohydrin resulted in the formation of a complex mixture. The formation of **3a** can be explained by nucleophilic attack of the carbon atom of the dianion onto the CBr group and subsequent attack of the nitrogen atom onto the epoxide. Alternatively, the reaction may proceed by attack of the dianion onto the terminal carbon atom of the epoxide and subsequent Payne rearrangement. The regioselectivity is a result of the higher nucleophilicity of the nitrogen compared to the oxygen atom. The formation of other regioisomers was not observed.



Scheme 1 Cyclization of dilithiated *N*-phenylacetamide with epibromohydrin

The cyclization of epibromohydrin (**2**) with *N*-arylacetamides **1a–e** afforded the 1-aryl-5-(hydroxymethyl)pyrrolidin-2-ones **3a–e**[12b,c] in good yields (Scheme 2, Table 1). The cyclization of **2** with the dianion of *N*-(trimethylsilyl)acetamide[13] afforded the labile TMS-substituted pyrrolidin-2-one **3f**. The chromatographic purification (silica gel) of crude **3f** afforded parent pyroglutaminol (**3g**). The pyrrolidine-2-thione **3h** was prepared from dilithiated *N*-phenylthioacetamide in good yield and, despite the nu-

SYNTHESIS 2006, No. 11, pp 1807–1810
Advanced online publication: 05.05.2006
DOI: 10.1055/s-2006-942354; Art ID: T15705SS



Scheme 2 Synthesis of 5-(hydroxymethyl)pyrrolidin-2-ones **3a–i**

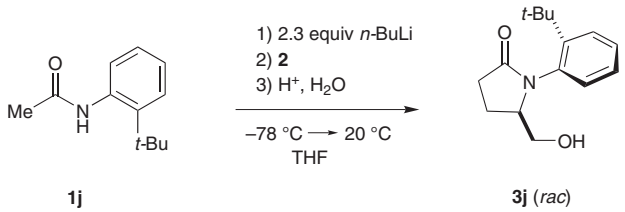
Table 1 Products and Yields Compounds **3**

3	R^1	R^2	X	Yield (%)[a]
a	Ph	H	O	81
b	4-MeC_6H_4	H	O	72
c	3-MeC_6H_4	H	O	76
d	4-$MeOC_6H_4$	H	O	78
e	4-$EtOC_6H_4$	H	O	67
f	$SiMe_3$	H	O	62[b]
g	H	H	O	98[c]
h	Ph	H	S	73
i	Ph	Me	O	64[d]

[a] Yield of isolated product.
[b] Crude product.
[c] By chromatography (silica gel) of **3f**.
[d] A 2:1 mixture of diastereomers (assignment arbitrary).

cleophilicity of the sulfur atom, with very good C/N-regioselectivity. The cyclization of **2** with the dianion of *N*-phenylpropionamide afforded **3i** as a 2:1 mixture of diastereomers.

The cyclization of the dianion of *N*-(2-*tert*-butylphenyl)acetamide (**1j**) with epibromohydrin afforded the axially chiral, configurationally stable pyrrolidin-2-one **3j** with very good diastereoselectivity (dr > 98:2) (Scheme 3). The other diastereomer could not be detected.



Scheme 3 Synthesis of racemic axially chiral pyrrolidin-2-one **3j**

In summary, we have reported the synthesis of 5-(hydroxymethyl)pyrrolidin-2-ones (glutaminols) and -thiones by regioselective cyclization of amide and thioamide dianions with epibromohydrin. The cyclization of the dianion of *N*-(2-*tert*-butylphenyl)acetamide with epibromohydrin afforded axially chiral 1-(2-*tert*-butylphenyl)-5-(hydroxymethyl)pyrrolidin-2-one with high diastereoselectivity.

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere using oven-dried (150 °C) glassware. THF was freshly distilled from Na. For the ^1H and ^{13}C NMR spectra (^1H NMR: 250 MHz, ^{13}C NMR: 62.9 MHz), the deuterated solvents indicated were used. The multiplicities of the ^{13}C NMR signals were determined with the DEPT 135 technique. Mass spectral data were obtained using the electron ionization (70 eV) or the chemical ionization technique (CI, H_2O). For preparative scale chromatography, silica gel (Merck, 60–200 mesh) was used.

5-(Hydroxymethyl)-1-phenylpyrrolidin-2-one (3a); Typical Procedure 1

To a THF solution (20 mL) of **1a** (0.67 g, 5.00 mmol) was added *n*-BuLi (0.01 mol, 4.23 mL, 15% solution in *n*-hexane) at 0 °C and the solution was stirred for 45 min. The solution was cooled to –78 °C and a THF solution (20 mL) of $LiClO_4$ (0.34 g) and, subsequently, epibromhydrin (0.33 g, 2.40 mmol) were added. The mixture was stirred for 5–8 h at –40 °C and for 10–12 h at 20 °C. A sat. aq solution of NH_4Cl was added to the mixture. The organic and the aqueous layers were separated and the latter was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, Et_2O) to give **3a** (0.37 g, 81%) as a colorless solid.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.17 (m, 2 H, 4-H), 2.54 (m, 2 H, 3-H), 3.58 (m, 2 H, CH_2OH), 4.26 (m, 1 H, 5-H), 7.17–7.38 (m, 5 H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.0, 31.4 (CH_2), 61.2 (CH), 62.1 (CH_2OH), 124.2, 126.1, 129.1 (CH_{arom}), 137.3 (C_{arom}), 175.3 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 191 (M^+, 22), 160 (100), 132 (10), 117 (6), 104 (9), 83 (9), 77 (12), 51 (3), 41 (4).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.11; H, 6.83.

5-(Hydroxymethyl-1-(4-methylphenyl)pyrrolidin-2-one (3b); Typical Procedure 2

To a THF solution (50 mL) of *N*-(4-methylphenyl)acetamide (**1b**; 746 mg, 5.00 mmol) was added *n*-BuLi (10.67 mmol, 4.51 mL, 3.2 M solution in hexane) under argon at 0 °C. After stirring for 60 min at 0 °C, the solution was cooled to –78 °C and epibromohydrin (0.29 mL, 3.33 mmol) was added. The solution was warmed to 20 °C during 12 h and was subsequently stirred for 6 h. A sat. aq NH_4Cl solution (40 mL) was added. The aqueous layer was extracted with Et_2O (2 ×) and with CH_2Cl_2 (2 ×) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, Et_2O) to give **3b** (492 mg, 72%) as a colorless solid.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.97–2.09 (m, 2 H, 4-H), 2.26 (s, 3 H, CH_3), 2.33–2.39 (m, 1 H, 3-H), 2.47–2.61 (m, 1 H, 3-H), 3.30–3.42 (m, 2 H, CH_2OH), 3.92 (br, 1 H, OH), 4.02–4.10 (m, 1 H, 5-H), 7.06 (d, *J* = 7.8 Hz, 2 H_{arom}), 7.16 (d, *J* = 7.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 21.90 (CH_3), 21.0 (C-4), 31.4 (C-3), 61.7 (C-5), 61.7 (CH_2OH), 124.4 (2 CH_{arom}), 129.6 (2 CH_{arom}), 135.9 (C_{arom}), 135.9 (C_{arom}), 175.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 205 (23, M^+), 174 (100), 132 (5), 118 (6), 91 (7).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{15}NO_2$ [M^+]: 205.1103; found: 205.1103 ± 2.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 69.95; H, 7.04.

5-(Hydroxymethyl)-1-(3-methylphenyl)pyrrolidin-2-one (3c)

The reaction was carried out according to the typical procedure 2. Starting with **1c** (0.741 g, 5.00 mmol) and *n*-BuLi (4.51 mL, 10.67

mmol, 3.2 M in hexane), **3c** was isolated as a pink solid; yield: 0.520 g (76%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.99–2.20 (m, 2 H, 4-H), 2.25 (s, 3 H, CH_3), 2.29–2.48 (m, 1 H, 3-H), 2.48–2.59 (m, 1 H, 3-H), 3.40–3.51 (m, 2 H, C*H*$_2$OH), 3.82 (br, 1 H, OH), 4.05–4.10 (m, 1 H, 5-H), 6.90–6.96 (m, 1 H_{arom}), 7.04–7.18 (m, 3 H_{arom}).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 21.0 (C-4), 21.4 (CH_3), 31.4 (C-3), 61.6 (C-5), 61.8 (CH_2OH), 121.5, 125.2, 127.1, 128.8, 137.2, 138.9 (Ar), 175.5 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 205 (21), 174 (100), 91 (9), 65 (3), 41 (3).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{17}NO_2$ [M$^+$]: 205.1203; found: 205.1203 ± 2.

5-(Hydroxymethyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (3d)
The reaction was carried out according to the typical procedure 2. Starting with **1d** (0.830 g, 5.00 mmol), *n*-BuLi (4.51 mL, 10.67 mmol, 3.2 M solution in hexane) and **2** (0.29 mL, 3.33 mmol), **3d** was isolated as a yellowish solid; yield: 0.611 g (78%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.03–2.30 (m, 2 H, 4-H), 2.38–2.51 (m, 1 H, 3-H), 2.57–2.67 (m, 1 H, 3-H), 3.47–3.66 (m, 2 H, C*H*$_2$OH), 3.76 (s, 3 H, OCH_3), 4.06–4.13 (m, 1 H, 5-H), 6.86 (d, 2 H_{arom}, *J* = 8.9 Hz), 7.22 (d, 2 H_{arom}, *J* = 8.9 Hz).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 21.01 (C-4), 31.26 (C-3), 55.43 (OCH_3), 61.87 (C-5), 62.15 (CH_2OH), 114.42 (CH_{arom}), 126.33 (CH_{arom}), 129.98 (C_{arom}), 157.89 (C_{arom}), 175.53 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 221 (39), 190 (100), 148 (4), 134 (7) 122 (6).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{15}NO_3$ [M$^+$]: 221.1642; found: 221.1642 ± 2.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 64.86; H, 6.64.

1-(4-Ethoxyphenyl)-5-(hydroxymethyl)pyrrolidin-2-one (3e)
The reaction was carried out according to the typical procedure 2. Starting with **1e** (0.896 g, 5.00 mmol), *n*-BuLi (4.51 mL, 10.67 mmol, 3.2 M solution in hexane) and **2** (0.29 mL, 3.33 mmol), **3e** was isolated as a brownish solid; yield: 0.556 g (67%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.31 (t, 3 H, *J* = 7.0 Hz, CH_3), 1.95–2.18 (m, 2 H, 4-H), 2.24–2.38 (m, 1 H, 3-H), 2.48–2.60 (m, 1 H, 3-H), 3.36–3.46 (m, 2 H, C*H*$_2$OH), 3.85–3.97 (m, 4 H, 5-H, OC*H*$_2$CH$_3$, OH), 6.86 (d, 2 H_{arom}, *J* = 8.8 Hz), 7.12 (d, 2 H_{arom}, *J* = 8.8 Hz).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.8 (CH_3), 21.0 (C-4), 31.2 (C-3), 61.7 (O*C*H$_2$CH$_3$), 62.0 (C-5), 62.5 (CH_2OH), 114.8 (CH_{arom}), 126.3 (CH_{arom}), 129.8 (C_{arom}), 157.2 (C_{arom}), 175.6 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 235 (19), 204 (100), 148 (11), 134 (11), 108 (15).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{13}H_{17}NO_3$ [M$^+$]: 235.2355; found: 235.2355 ± 2.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.64; H, 7.19.

5-(Hydroxymethyl)pyrrolidin-2-ones 3f and 3g
The reaction was carried out according to the typical procedure 1. The reaction of **1f** with **2** afforded **3f**, which was isolated as a crude product; yield: 62%.

3f
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.10 [s, 9 H, Si$(CH_3)_3$], 1.20–1.35 (m, 1 H, 4-H), 1.60–1.80 (m, 1 H, 4-H), 2.10–2.40 (m, 2 H, 3-H), 3.35–3.60 (m, 2 H, C*H*$_2$OH), 3.75 (m, 1 H, 5-H), 5.97 (br, 1 H, OH).

3g
Chromatographic purification (silica gel, Et_2O) of crude **3f** afforded the known desilylated product **3g** (98%). The spectroscopic data were identical with those of an authentic sample.

5-(Hydroxymethyl)-1-phenylpyrrolidin-2-thione (3h)
The reaction was carried out according to the procedure 2. Starting with **1h** (0.756 g, 5.00 mmol), *n*-BuLi (4.51 mL, 10.67 mmol, 3.2 M solution in hexane) and **2** (0.29 mL, 3.33 mmol), **3h** was isolated as a yellowish solid; yield: 0.511 g (73%).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.41–1.60 (m, 2 H, 4-H), 1.89–2.27 (m, 1 H, 3-H), 2.48–2.59 (m, 1 H, 3-H), 2.75–2.99 (m, 2 H, C*H*$_2$OH), 3.60–3.81 (m, 1 H, 5-H), 6.93–7.11 (m, 1 H_{arom}), 7.29–7.49 (m, 4 H_{arom}).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 26.1 (C-4), 29.6 (C-3), 53.1 (C-5), 65.0 (CH_2OH), 120.2, 124.4, 128.9 (CH_{arom}), 137.9 (C_{arom}), 170.8 (C=S).

MS (EI, 70 eV): *m*/*z* (%) = 207 (46), 174 (48), 115 (10), 106 (16), 93 (100).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{11}H_{13}NOS$ [M$^+$]: 207.0718; found: 207.0718 ± 2.

Anal. Calcd for $C_{11}H_{13}NSO$: C, 63.74; H, 6.32. Found: C, 63.52; H, 6.58.

5-(Hydroxymethyl)-3-methyl-1-phenylpyrrolidin-2-one (3i)
The reaction was carried out according to the procedure 2. Starting with **1i** (0.250 g, 1.68 mmol), *n*-BuLi (1.53 mL, 5.38 mmol, 3.2 M solution in hexane) and **2** (0.096 mL, 1.12 mmol), **3i** was isolated as a colorless solid; yield: 0.220 g 64%, dr = 2:1).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.23–1.35 (m, 1 H, 4-H), 1.22 (d, 3 H, *J* = 6.9 Hz, CH_3), 1.76–1.95 (m, 1 H, 4-H), 2.81–2.90 (m, 1 H, 3-H), 3.54–3.66 (m, 2 H, C*H*$_2$OH), 4.18 (m, 1 H, 5-H), 6.93–7.11 (m, 1 H_{arom}), 7.29–7.49 (m, 4 H_{arom}).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (major diastereomer) = 16.6 (CH_3), 30.4 (C-4), 36.8 (C-3), 59.2 (C-5), 62.3 (CH_2OH), 123.5, 125.8, 129.1 (CH_{arom}), 137.7 (C_{arom}), 177.7 (C=S).

MS (EI, 70 eV): *m*/*z* (%) = 205 (18), 171 (100), 141 (5), 121 (10), 107 (16).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{17}NO_2$ [M$^+$]: 205.1203; found: 205.1203 ± 2.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 69.88; H, 7.08.

***trans*-1-[2-(*tert*-Butylphenyl)]-5-(hydroxymethyl)pyrrolidin-2-one (3j)**
The reaction was carried out according to the procedure 1. Starting with **1j** (0.20 g, 1.00 mmol), **3j** was isolated as a colorless solid; yield: 0.13 g (77%, *cis*/*trans* < 2:98). The configuration was established by NOESY experiments.

IR (neat): 3347 (s), 2957 (s), 2929 (m), 2874 (w), 1665 (s), 1493 (m), 1462 (w), 1447 (s), 1414 (s), 1292 (w), 1114 (w), 1085 (w), 1050 (w), 782 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.37 [s, 9 H, $(CH_3)_3$], 2.06–2.77 (m, 4 H, 3-H, 4-H), 3.46 (dd, ^2J = 16.0 Hz, ^3J = 5.0 Hz, 1 H, C*H*$_2$OH), 3.60 (dd, ^2J = 16.0 Hz, ^3J = 7 Hz, 1 H, C*H*$_2$OH), 3.81 (m, 1 H, 5-H), 7.07 (dd, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1 H_{arom}), 7.20 (dt, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1 H_{arom}), 7.28 (dt, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1 H_{arom}), 7.49 (dd, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1 H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.0, 30.5 (CH_2), 31.7 [C(*C*H$_3$)$_3$], 35.7 [*C*(CH$_3$)$_3$], 62.1 (CH_2OH), 63.6 (CH), 126.9, 128.4, 128.6, 132.3 (CH_{arom}), 134.8, 148.1 (C_{arom}), 177.1 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 247 (M^+, 1), 216 (100), 190 (57), 160 (5), 144 (7), 130 (7), 118 (9), 91 (18), 77 (6), 57 (10), 41 (7).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{15}H_{21}NO_2$ [M^+]: 247.3328; found: 247.3328 ± 2.

Acknowledgment

Financial support from the Fonds der Chemischen Industrie and from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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