SHORT SYNTHESIS OF (±)-CORYNANTHEIDOL AND (±)-3-EPICORYNANTHEIDOL

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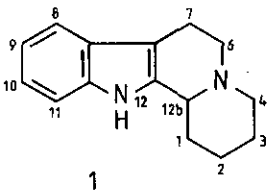
Abstract - A short synthesis for (±)-corynantheidol and (±)-3-epicorynantheidol is described.

Recent reports from our laboratory have described a new general method,[1-5] which permits the preparation of 1-, 2- and 3-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (1) derivatives possessing the C(12b)H-C(1)H, C(12b)H-C(2)H and C(12b)H-C(3)H relationship [corresponding to the C(3)H-C(14)H, C(3)H-C(15)H and C(3)H-C(20)H relationship, respectively, when the biogenetic numbering of indole alkaloids is used[6]] cis or trans at will.

Our method appeared to be ideally suited for a short synthesis of both (±)-corynantheidol (2) and (±)-3-epicorynantheidol (3) (biogenetic numbering[6]) of which the former is the racemic form of the known indole alkaloid (-)-corynantheidol found in Mitragyna parvifolia (Roxb.) Korth. (Rubiaceae).[7] In the present paper we describe the results obtained.



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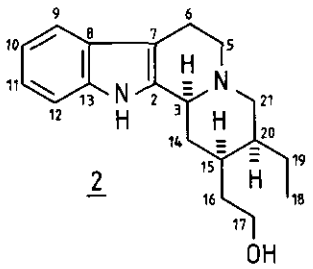

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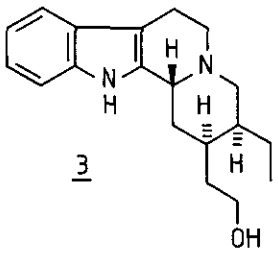

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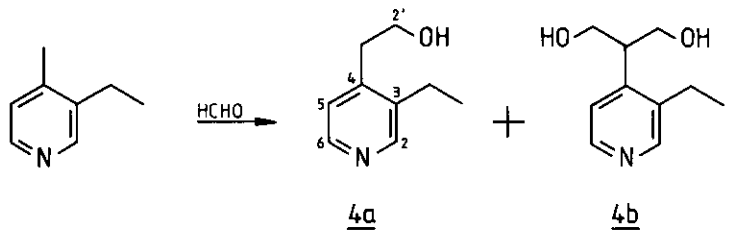
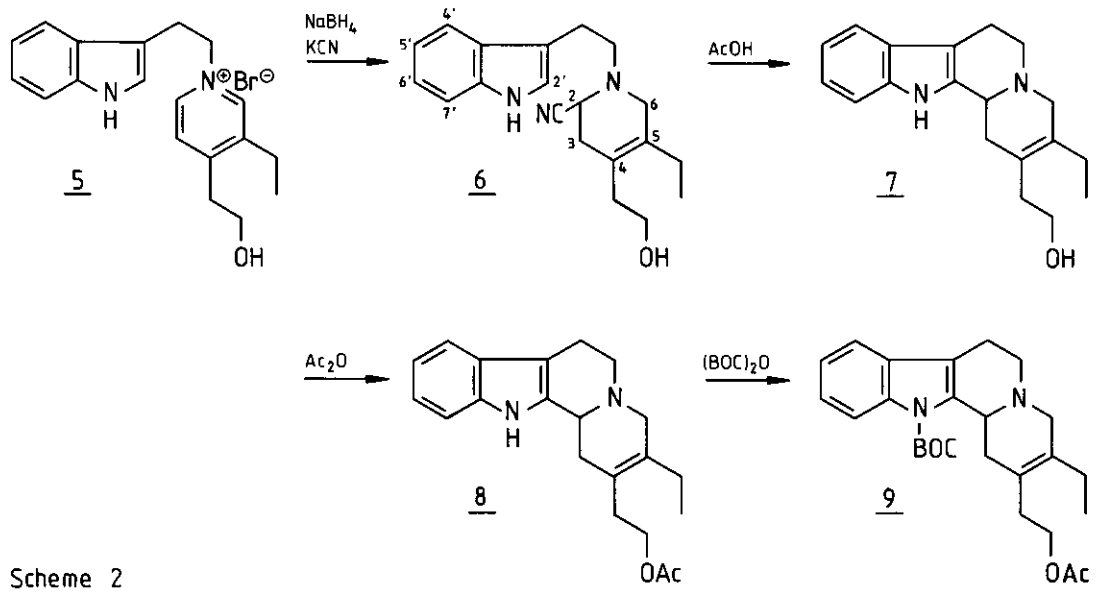
RESULTS AND DISCUSSION

Alkylation of 3-ethyl-4-(2'-hydroxyethyl)pyridine (4a) [prepared together with compound (4b) from 3-ethyl-4-methylpyridine[8] and formaldehyde; Scheme 1] with tryptophyl bromide[9] yielded the pyridinium salt (5).



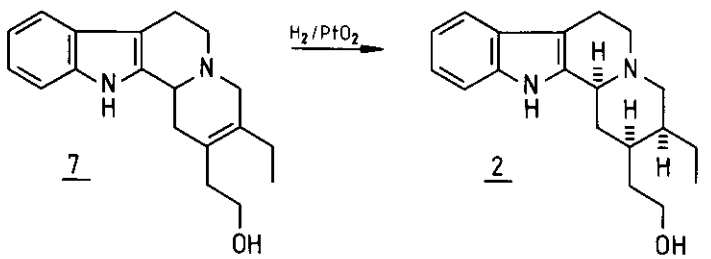
Scheme 1

The pyridinium salt (5) was transformed by $NaBH_4$ reduction and cyanide trapping[10-13] to α-aminonitrile (6), which by AcOH treatment[14-16] afforded compound (7). A part of compound (7) was acetylated to compound (8) which was then transformed with di-t-butyl dicarbonate [$(BOC)_2O$] to the corresponding BOC-protected compound (9) (Scheme 2).[13,17,18]



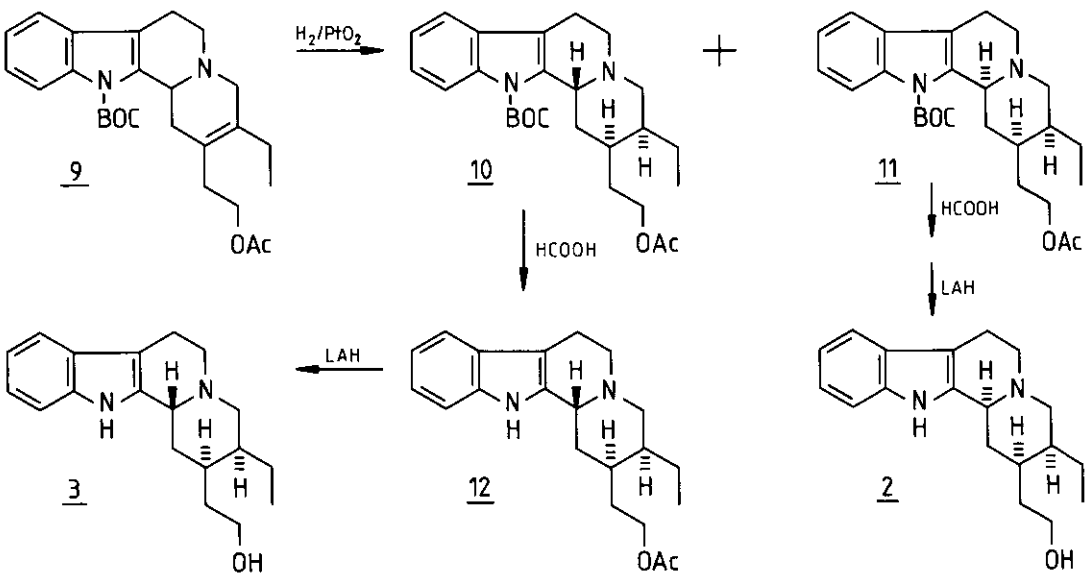
Scheme 2

Catalytic hydrogenation (PtO_2) of compound (7) led directly to (±)-corynantheidol (2) [C(3)H-C(15)H cis; C(3)H-C(20)H cis]. Thus a very short stereoselective synthesis of (±)-corynantheidol (2) was in hand (Scheme 3).



Scheme 3

Catalytic hydrogenation (PtO_2) of the BOC-protected compound (9) instead of compound (7) led to a 60/40 mixture of compound (10) [C(3)H-C(15)H trans; C(3)H-C(20)H trans] and compound (11) [C(3)H-C(15)H cis; C(3)H-C(20)H cis], which were separated by tlc. Acid-induced cleavage (HCOOH) of compound (10) afforded compound (12), which by LAH treatment yielded (±)-3-epicorynantheidol (3). Compound (11) was transformed by consecutive HCOOH and LAH treatments to (±)-corynantheidol (2) without the isolation of the acetate intermediate [cf. compound (12)] (Scheme 4[19]).



Scheme 4

^{13}C Nmr data of all the compounds formed are given in Figure 1. The proper shift assignment was confirmed by recording single frequency, off-resonance decoupled (sford) spectra.

Comparison of the chemical shifts found for compounds (2), (3), (7), (8), (9), (10), (11) and (12) with those given earlier,[1,3,20] taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines, provides clear evidence of the stereostructures depicted in the formulae.

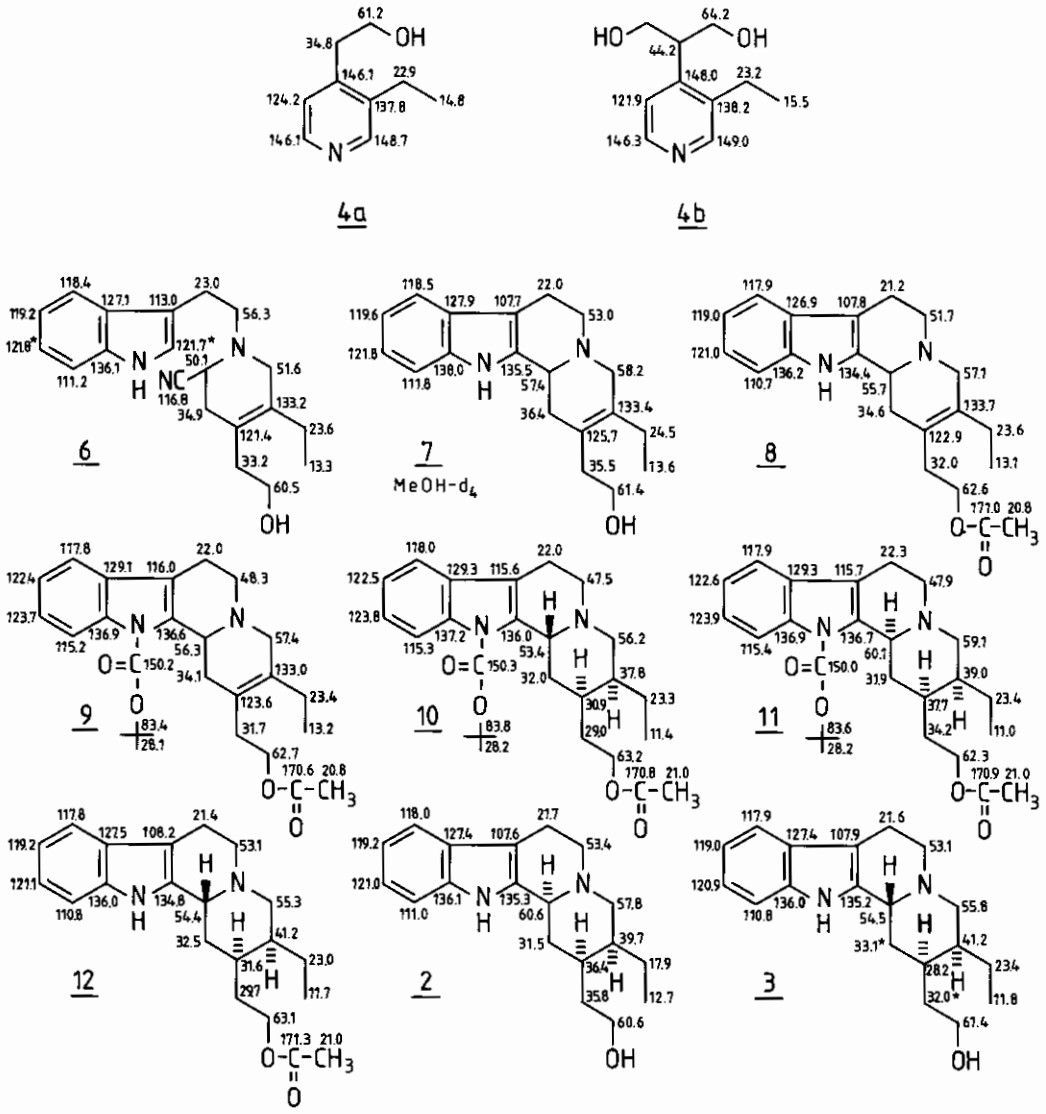


Figure 1

CONCLUSIONS

The results clearly demonstrate that our recently developed method[1-5] can successfully be applied to a short synthesis of both (±)-corynantheidol (2) and (±)-3-epicorynantheidol (3). Compared with some earlier syntheses[21-27] our method affords an easier access to these compounds.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer. Absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^{1}H and ^{13}C nmr spectra were recorded in $CDCl_3$ (if not otherwise stated) with a JEOL JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H nmr) and 15.04 MHz (^{13}C nmr). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m and br are used to designate singlet, doublet, triplet, multiplet and broad, respectively. For ^{13}C nmr data see Figure 1. Mass spectrometry was done on a JEOL DX 303/DA 5000 instrument.

Compounds (4a) and (4b)

Commercial 3-ethyl-4-methylpyridine[8] (10.00 g, 82.64 mmol) and formaldehyde (35%, 15 ml) were refluxed for 60 h (Ar-atm). The crude product was purified by column chromatography (alumina, first CH_2Cl_2, then increasing the polarity of the eluent with gradual MeOH addition). Three compounds were isolated: unreacted starting compound, monoalcohol (4a) and dialcohol (4b).

Compound (4a). Yield: 2.50 g (20%). Oil. Ir 3300 (OH), pmr 1.20 (3H, t, J=7.0 Hz, $-CH_3$), 2.67 (2H, q, J=7.0 Hz, $-C\underline{H}_2-CH_3$), 2.89 (2H, t, J=7.0 Hz, $-C\underline{H}_2-CH_2OH$), 3.87 (2H, t, J=7.0 Hz, $-C\underline{H}_2OH$), 4.83 (1H, s, -OH), 7.14 (1H, d, J=6.0 Hz, H-5), 8.20 (1H, d, J=6.0 Hz, H-6), 8.23 (1H, s, H-2), m/z 151 (M^+), 132, 120, 118 (100%), 106; exact mass: 151.1010 (calcd for $C_9H_{13}NO$: 151.0997).

Compound (4b). Yield: 3.74 g (25%). mp 102-103°C (MeOH). Ir 3200 (OH), pmr 1.18 (3H, t, J=7.0 Hz, $-CH_3$), 2.67 (2H, q, J=7.0 Hz, $-C\underline{H}_2-CH_3$), 3.88 (4H, 2xd, J=6.0 Hz, $-C\underline{H}_2OH$), 4.71 (1H, s, -OH), 7.12 (1H, d, J=5.0 Hz, H-5), 8.12 (1H, d, J=5.0 Hz, H-6), 8.17 (1H, s, H-2), m/z 182 (M + 1 peak[28]), 181 (M^+), 145, 133, 118 (100%), 106; exact mass: 181.1110 (calcd for $C_{10}H_{15}NO_2$: 181.1103).

Compound (5)

Alkylation of compound (4a) (1.21 g, 8.01 mmol) with tryptophyl bromide (1.80 g, 8.04 mmol) afforded salt (5). Yield: 2.79 g (93%).

Compound (6)

Hydrochloric acid (6N, 4 ml) was added dropwise to a cooled (0°C) stirred solution of KCN (3.02 g, 46.46 mmol) in H_2O (4 ml) and layered with Et_2O (20 ml). MeOH (7 ml) and the salt (5) (2.79 g, 7.44 mmol) were added, after which $NaBH_4$ (0.37 g, 9.78 mmol) was added during 0.5 h keeping the solution at 0°C. Stirring was continued for 4 h at room temerature. The ethereal layer was separated and the aqueous layer was extracted several times with ether. The combined organic layers were dried over Na_2SO_4 and evaporated to yield nitrile (6), which was used without purification in the next step. Yield: 2.35 g (98%). Amorphous material. Ir 3420 (NH), 3300 (OH), 2280 (CN), pmr 0.99 (3H, t, J=7.5 Hz, $-CH_3$), 6.94 (1H, d, J=2.4 Hz, H-2'), 7.19-7.66 (4H, m, H-4', 5', 6', 7'), 8.26 (1H, br s, NH), m/z 323 (M^+), 308, 296, 168, 144 (100%), 130; exact mass: 323.1984 (calcd for $C_{20}H_{25}N_3O$: 323.1998).

Compound (7)

Compound (6) (2.17 g, 6.72 mmol) in 50% AcOH (200 ml) was stirred (at room temperature) for 68 h. After evaporation and neutralization (2N Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. The product was purified by column chromatography (alumina, first CH_2Cl_2, then increasing the polarity of the eluent with gradual MeOH addition) to yield compound (7). Yield: 1.18 g (59%). mp 223-224°C (MeOH). Ir 3410 (NH), 3210 (OH), pmr 0.97 (3H, t, J=7.5 Hz, $-CH_3$), 7.04-7.53 (4H, m, H-9, 10, 11, 12), 8.64 (1H, m, NH), m/z 296 (M^+), 295, 170 (100%), 169; exact mass: 296.1906 (calcd for $C_{19}H_{24}N_2O$: 296.1889).

(±)-Corynantheidol (2)

Catalytic hydrogenation (PtO_2, 24 h) of compound (7) (180 mg, 0.61 mmol) in MeOH afforded crude compound (2), which was purified by tlc (silica gel, CH_2Cl_2/MeOH; 95:5). Yield: 100 mg (55%) (after recycling the unreacted starting material). mp 163-165°C (CH_2Cl_2) (lit. 158-162°C;[21] 158-160°C;[22] 157-159°C;[23] 160-161°C;[25] 162-164°C[26]). Ir 3430 (NH), 3280 (OH), 2830 and 2780 (Bohlmann bands), pmr 0.88 (3H, t, J=7.0 Hz, $-CH_3$), 6.96-7.56 (4H, m, H-9, 10, 11, 12), 8.54 (1H, br s, NH), m/z 298 (M^+), 297 (100%), 170, 169; exact mass: 298.2061 (calcd for $C_{19}H_{26}N_2O$: 298.2041).

Compound (8)

Compound (7) (0.60 g, 2.03 mmol), Ac_2O (6.2 ml) and two drops of pyridine were stirred (room temperature, Ar-atm) for 20 h. The solution was poured into ice water, neutralized with aq. NH_4OH and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 to afford pure compound (8). Yield: 0.64 g (93%). Amorphous material. Ir 3400 (NH), 1740 (C=O), pmr 1.00 (3H, t, J=7.0 Hz, $-CH_3$), 2.00 (3H, s, AcO-), 7.02-7.55 (4H, m, H-9, 10, 11, 12), 8.40 (1H, br s, NH), m/z 338 (M^+), 170 (100%), 169; exact mass: 338.1981 (calcd for $C_{21}H_{26}N_2O_2$: 338.1990).

Compound (9)

To compound (8) (310 mg, 0.92 mmol) in dry CH_2Cl_2 (2 ml) were added 4-dimethylaminopyridine (DMAP) (12 mg, 0.1 equiv.) and di-t-butyl dicarbonate [$(BOC)_2O$] (242 mg, 1.2 equiv.) with stirring (room temperature, Ar-atm). After 2 h the mixture was evaporated and purified by column chromatography (silica gel, CH_2Cl_2/MeOH/Et_3N; 99:0.75:0.25) to afford pure compound (9). Yield: 361 mg (90%). Viscous oil. Ir 1740 (2 x C=O), pmr 1.03 (3H, t, J=7.0 Hz, $-CH_3$), 1.66 (9H, s, $-C(CH_3)_3$), 2.02 (3H, s, AcO-), 4.10 (1H, t, J=6.0 Hz, H-3), 7.14-7.42 (3H, m, H-9, 10, 11), 8.06 (1H, m, H-12), m/z 438 (M^+), 383, 382, 214 (100%), 170, 169; exact mass: 438.2516 (calcd for $C_{26}H_{34}N_2O_4$: 438.2519).

Compounds (10) and (11)

Catalytic hydrogenation (PtO_2, 20 h) of compound (9) (344 mg, 0.79 mmol) in MeOH afforded a mixture of compounds [(10) and (11) (60:40)] and unreacted compound (9), which was recyclized. Compounds (10) and (11) were separated by tlc (silica gel,

CH_2Cl_2/MeOH; 95:5).
Compound (10). Yield: 198 mg (57%). Amorphous material. Ir 1730 (2 x C=O), pmr 0.93 (3H, t, J=6.0 Hz, $-CH_3$), 1.68 (9H, s, $-C(CH_3)_3$), 2.05 (3H, s, AcO-), 4.35 (1H, m, H-3), 7.14-7.50 (3H, m, H-9, 10, 11), 7.98 (1H, m, H-12), m/z 440 (M^+), 384, 383 (100%), 339; exact mass: 440.2663 (calcd for $C_{26}H_{36}N_2O_4$: 440.2675).
Compound (11). Yield: 132 mg (38%). Amorphous material. Ir 1730 (2 x C=O), pmr 0.98 (3H, t, J=6.0 Hz, $-CH_3$), 1.67 (9H, s, $-C(CH_3)_3$), 2.04 (3H, s, AcO-), 4.09 (1H, m, H-3), 7.14-7.43 (3H, m, H-9, 10, 11), 8.07 (1H, m, H-12), m/z 440 (M^+), 384, 383 (100%), 339; exact mass: 440.2666 (calcd for $C_{26}H_{36}N_2O_4$: 440.2675).

Compound (12)
Compound (10) (92 mg, 0.21 mmol) was stirred in HCOOH (2 ml) for 70 h (room temperature, Ar-atm). After evaporation and neutralization (10% Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to yield compound (12). Yield: 57 mg (80%). Amorphous material. Ir 3400 (NH), 1730 (C=O), pmr 0.93 (3H, t, J=5.0 Hz, $-CH_3$), 2.06 (3H, s, AcO-), 4.20 (1H, m, H-3), 7.05-7.53 (4H, m, H-9, 10, 11, 12), 8.28 (1H, m, NH), m/z 340 (M^+, 100%), 339, 170, 169; exact mass: 340.2153 (calcd for $C_{21}H_{28}N_2O_2$: 340.2151).

(±)-3-Epicorynantheidol (3)
LAH treatment of compound (12) (57 mg, 0.17 mmol) in dry THF for 2.5 h (room temperature, Ar-atm) afforded crude product (3), which was purified by tlc (silica gel, CH_2Cl_2/MeOH; 90:10). Yield: 25 mg (50%). mp 189-191°C (CH_2Cl_2) (lit.191-192°C;[21,22] 192-194°C[23]). Ir 3350-3200 (NH and OH), pmr 0.90 (3H, t, J=5.0 Hz,-CH_3), 3.74 (1H, m, H-3), 7.01-7.42 (4H, m, H-9, 10, 11, 12), 8.49 (1H, m, NH), m/z 298 (M^+), 297 (100%), 170, 169; exact mass: 298.2019 (calcd for $C_{19}H_{26}N_2O$: 298.2041).

(±)-Corynantheidol (2)
Consecutive HCOOH and LAH treatments (vide supra) of compound (11) (60 mg, 0.14 mmol) led to crude compound (2), which was purified by tlc (silica gel, CH_2Cl_2/MeOH; 90:10). Yield: 18 mg (45%). mp 163-165°C (CH_2Cl_2) (lit. 158-162°C;[21] 158-160°C;[22] 157-159°C;[23] 160-161°C;[25] 162-164°C[26]).
Spectral data were identical with those described above.

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