SYNTHESES IN THE GROUP OF NUPHAR ALKALOIDS. VII. AN EASY ACCESS TO (—)-NUPHARAMINE

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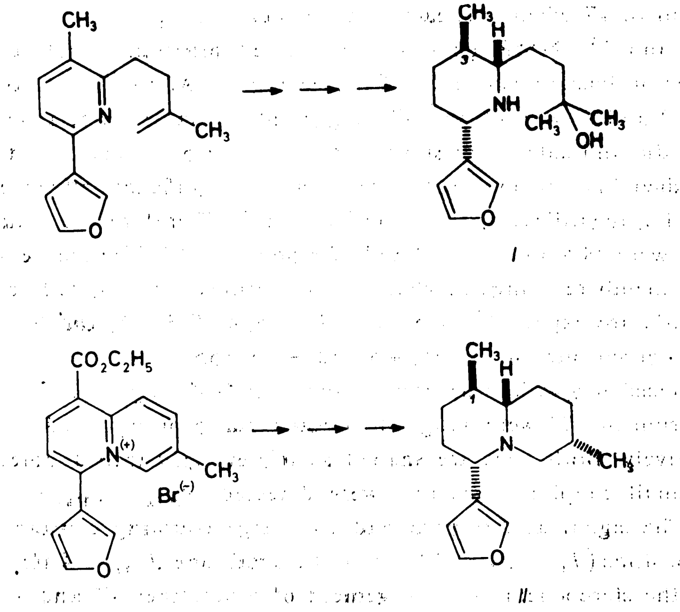
A simple and effective approach to the total synthesis of (—)-nupharamine (*I*) is presented, which allows to control the stereochemistry at C-3 by epimerization of the ethoxycarbonyl function. The key steps are reductive amination of the respective substituted 1,5-diketone *V* and enantiomer resolution of piperidine *VI* using (1*S*)-(—)-camphanic acid.

Three general ideas connected with our investigations in the field of Nuphar alkaloid[1] total synthesis should be emphasized: (i) simultaneous formation of all chiral centers in one synthetic step, (ii) full stereochemical control, and (iii) simplification and generalization in the sense of finding a uniform approach for synthesis of all struc-



Scheme 1

tural types, i.e. piperidine, quinolizidine and thiaspirane dimeric derivatives. The last idea is tied with the necessity (in our opinion) of isolation the right enantiomeric form of an intermediate, which could be profitable when approaching the dimeric sulfur alkaloids.

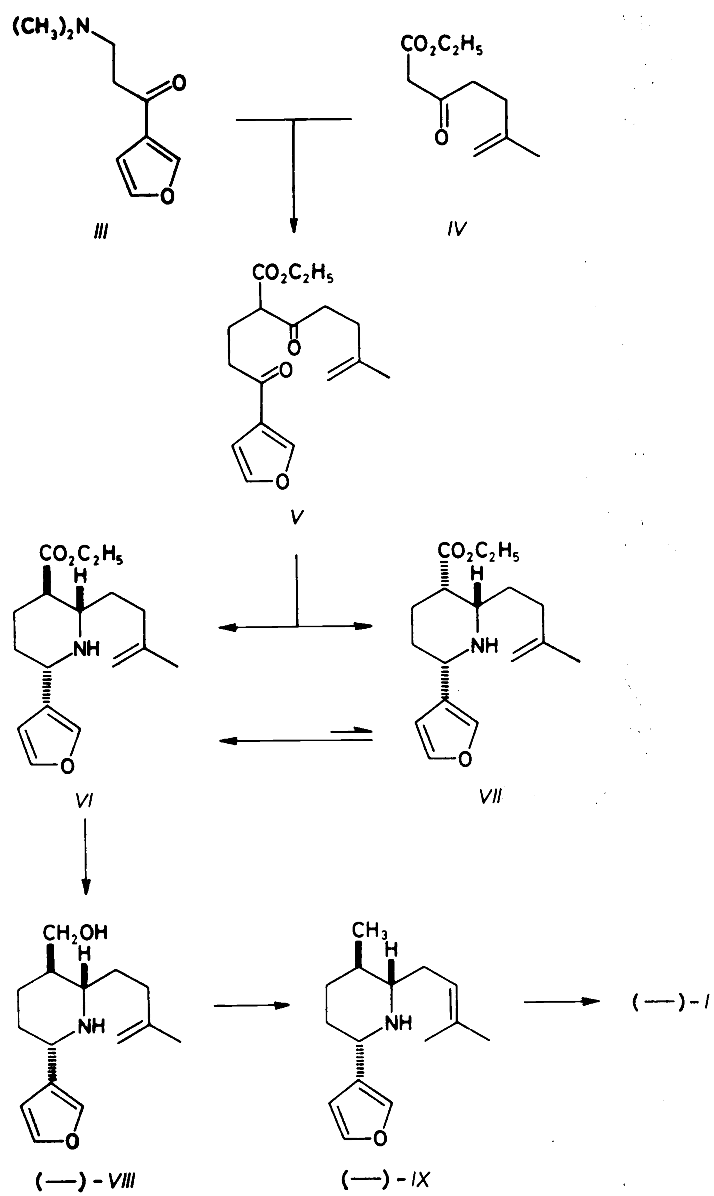
Our previous approaches to the total syntheses of some piperidine and quinolizidine nuphar alkaloids showed that reduction of suitable substituted aromatic precursors (Scheme 1) can serve as a source of (±)-nupharamine[2] (*I*) and (±)-deoxynupharidine[3,4] (*II*). Stereochemical control at C-3 (in piperidine *I*) and at C-1 (in quinolizidine *II*) chiral centers is necessary to achieve good stereoselectivity of performed transformations. In order to fulfill that condition a quinolizinium salt has been used for the synthesis of racemic deoxynupharidine (*II*) (ref.[3]). An ethoxycarbonyl substituent served for epimerization at C-1 also as the source of the equatorial methyl group.

Here we report a quite different route to the stereoselective total synthesis of (−)-nupharamine (*I*) which demonstrates that epimerization can also occur at C-3 of the piperidine ring in a way similar to that mentioned above.

The key intermediate *V* is easily available by condensation (Scheme 2) between Mannich base *III* and 6-methyl-3-oxo-6-heptenoate (*IV*). Simultaneous formation of all three chiral centers takes place at the reductive amination step of 1,5-diketoester *V* with cyanoborohydride anion in the presence of ammonium acetate in a weakly acidic medium. Two epimeric piperidines *VI* and *VII* have been found to be the major components in basic fraction of reduction products. The compounds formed in a 1 : 3 ratio under shown conditions. We observed changes in the product distribution in favour of *VI* when the reaction time was prolonged.

Both ^1H and ^{13}C NMR data of the isolated piperidines indicated differences characteristic of diastereoisomers at C-3 (see Fig. 1). Almost identical values of ^{13}C shifts for C-2 and C-6 in *VI* and *VII* suggested the same *cis* relative configuration of the aromatic and side chain substituents at these positions[5]. On the other hand it is established that carboxy substituent has no significant influence on β-carbon chemical shifts, regardless of their configuration[6]. Therefore the assumed chemical shifts in *VII* were 28·6 ppm for C-4 and 27·8 ppm for C-5. The theoretical differences in rigid, six-membered rings in chair conformations for C-3, C-5, and C-2—CH_2 chemical shifts are expected[7] to be 8·56 ± 0·36, 4·55 ± 0·1, and 0·0 ppm, respectively. The observed ones were: 7·6, 4·6 and −0·9 ppm.

For the consistency with these circumstances ^1H NMR signals at 2·60 and 2·80 ppm in the spectrum of *VII* were assigned to equatorial proton at C-3 and axial one at C-2, respectively. Both ones are shaped as triplets split into doublets. In the first one three small coupling constants were detected: $J_{H2a} = J_{H4a} = 4$, and $J_{H4e} = 2·5$ Hz. The signal at 2·80 ppm had two large coupling constants with vicinal methylene protons ($J_1 = J_2 = 7·5$ Hz) and a small one $J_{H3e} = 4$ Hz. In conclusion, we assume the stereochemical arrangement of piperidines *VI* and *VII* in the form shown in Fig. 1.



SCHEME 2

Some impurities present in a crude mixture of basic products isolated after the reductive aminocyclization reaction did not interfere in performing epimerization in the presence of sodium ethoxide (Scheme 2). The equilibrium ratio of *VI* to *VII* reached about 9 : 1 after 38 h of heating at the temperature 80°C.

The enantiomer resolution of *VI* has been done in four consecutive crystallizations using (*S*)-(−)-camphanic acid and the crude mixture after epimerization. The optical rotation of final fraction was −37·3. Using this fraction as a crystallization site it was possible to confine the resolution procedure to two steps.

Reduction of the enatiomer (−)-*VI* with lithium aluminium hydride gave aminoalcohol (−)-*VIII* which was transformed to (−)-*IX* in two steps: (i) substitution of the hydroxymethyl to bromomethyl group in the presence of phosphorous tribromide, and (ii) reduction of bromide with zinc dust in acetic acid.

The compound (−)-*IX* containing isomerized side chain double bond proved to be identical with the natural (−)-anhydronupharamine isolated by Arata and Ohashi[8].

The final step of our synthesis was the addition of water to the isolated double bond in the presence of diluted hydrochloric acid. The reaction conditions were analogous to the transformation of (−)-nuphenine to (−)-3-epinupharamine described by Forrest and Ray[9]. It gave (−)-nupharamine (*I*) and a mixture of (−)-*VIII* and (−)-*IX* after chromatographic separation. Our synthetic (−)-*I* was compared

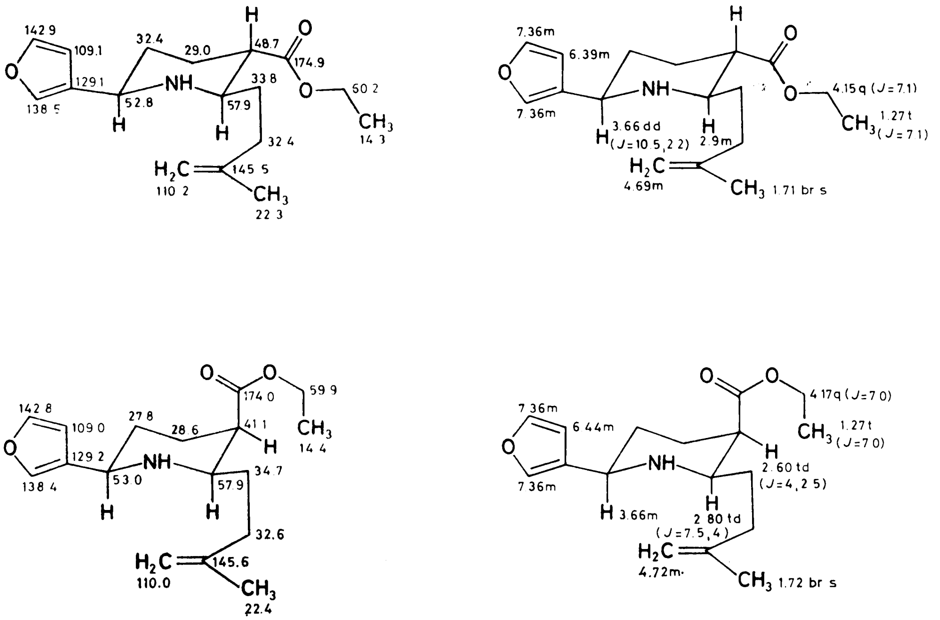


FIG. 1

^{13}C and ^{1}H NMR data of epimers *VI* and *VII* (chemical shifts in ppm; coupling constants (in Hz) in parentheses) with an authentic sample of the natural alkaloid, showing full spectral and chromatographic identity. The optical rotations were −33·6 and −32·0, respectively.

In summary, this work resulted in a short total synthesis of (−)-anhydronupharamine and (−)-nupharamine, thus opening a simple and general route to the synthesis of not only piperidine-shaped nuphar alkaloids. Replacing the component *IV* (Scheme 2) by the commercially available diethyl 3-oxo-pimelate it is possible to approach some optically active quinolizidine nuphar alkaloids. Results of these investigations will be shown in a forthcoming publication.

EXPERIMENTAL

Apparatus, Methods and Materials

The IR spectra were determined on a Zeiss UR-20 spectrophotometer in chloroform solutions. The ^{1}H NMR were run at 100 MHz on a Jeol JNM-4H or at 80 MHz on a Tesla BS-487B instruments. Natural abundance ^{13}C NMR were recorded on a Jeol FX 90Q Fourier transform spectrometer at 22·5 MHz and a probe temperature of +35°C. Noise-decoupled and off-resonance spectra were obtained at 5 kHz width and 1·0 s acquisition time, using $CDCl_3$ as a solvent and TMS as an internal standard. Coupling constants (*J*) are given in Hz. Mass spectra were recorded on an LKB 9000 spectrometer at an ionizing voltage of 80 eV and a source temperature of 150—200°C and are reported as *m*/*z* values with relative intensities in brackets. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at the Na-D line in absolute chloroform (*c* 1·0) at 25·0°C. Anhydrous (1*S*)-(−)-camphanic acid was prepared using the described method[10]. Its optical rotation was −19·3 and m.p. 206—206·5°C. Ethyl 6-methyl-3-oxo-6-heptenoate (*IV*) was prepared in two steps: by methallylation of acetylacetone[11] and ethoxycarbonylation of the resulting 5-methyl-5-hexen-2-one[12]. Melting points were taken using a Kofler apparatus (Boetius type) and are uncorrected. The purity of all samples was checked by TLC chromatography in several solvent systems. Silica gel 60F-254 (Merck) was used for analytical TLC and Kieselgel 60 (230—400 mesh) for column chromatography. Aluminium oxide GF-254 (type 60/E, Merck) was used for analytical TLC and Fluka neutral alumina (type 507C, activity III) for column chromatography.

Condensation of Ethyl 6-Methyl-3-oxo-6-heptenoate (*IV*) with 2-(3-Furoyl)-dimethylethylamine (*III*)

Mannich base *III*: A solution of *III*.HCl (12·1 g, 59·5 mmol) in water (25 ml) was poured into a mixture of aqueous 1M sodium carbonate (70 ml) and chloroform (50 ml) in a funnel separator. The organic layer was separated and the aqueous one shaken twice with chloroform (30 ml). The combined extracts were washed with water (30 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure using a water bath at temperature below 45°C. After 1—2 day air-drying the oily residue solidified giving 9·7 g (yield, 97%) of the crude Mannich base *III*. M.p. 78°C.

From a 55% dispersion of sodium hydride (0·39 g) an oil was removed by shaking with two 10 ml portions of anhydrous toluene. The hydride suspension in toluene (5 ml) was added to a solution of Mannich base *III* (9·7 g, 58 mmol) and ketoester *IV* (10·15 g, 55 mmol) in toluene (100 ml). The red solution was refluxed for 2 h. After cooling it was washed with 2M HCl (25 ml) and twice with water. Toluene was removed under reduced pressure and a light yellow oily residue was dried at 0·6 Torr for 4 h. The crude product contained only traces of the starting ketoester (TLC using benzene–chloroform (1 : 2) on alumina and hexane–ethyl acetate (2 : 3) on silica). Yield 14·6 g (82%, calculated on the Mannich base used). For $C_{17}H_{22}O_5$ (306·4) calculated: 66·65% C, 7·24% H; found: 66·41% C, 7·44% H, IR: 3 463 br (enol), 3 142 and 873 (3-furyl), 3 084 and 1 665 ($C{=}CH_2$), 1 726 and 1 714 ($C{=}O$), 1 165 ($C{-}O$) cm^{-1}. ^1H NMR: 1·26 t, 3 H ($CH_3{-}CH_2$, $J = 8$); 2·3 m, 4 H ($CH_2{-}C{=}CH_2$ and $CH_2{-}CH_2{-}C{=}O$); 1·72 br s, 3 H ($H_3CC{=}CH_2$); 2·7 m, 4 H ($CH_2{-}C{=}O$); 3·64 t, 1 H ($CH{-}C{=}O$, $J = 6·5$); 4·21 q, 2 H ($O{-}CH_2$, $J = 8$); 4·72 m, 2 H ($C{=}CH_2$); 6·77 m, 1 H (H-4, furan); 7·45 m, 1 H (H-5, furan); 8·04 m, 1 H (H-2, furan) ppm. ^{13}C NMR: 14·1 q (CH_3-ester); 22·3 t (CH_3CH); 22·6 q ($CH_3C{=}$; ${=}C$); 31·1 t ($CH_2C{=}C$); 37·3 t (C-4); 40·4 t (CH_2—3-furoyl); 57·4 d (C-2); 61·5 t (OCH_2); 108·5 d (C-4, furan); 110·4 t (C-7); 127·4 s (C-3, furan); 144·1 s (C-6); 144·2 d (C-5, furan) 147·4 d (C-2, furan); 169·4 s (C-1), 193·8 s (CO-furyl); 204·4 s (C-3) ppm.

Reductive Aminocyclization of Ethyl 2-[2-(3-Furoyl)ethyl]-6-methyl-3-oxohept-6-enoate (*V*)

To a stirred solution of diketoester *V* (14·0 g, 45·7 mmol), ammonium acetate (18·0 g, 233 mmol), and glacial acetic acid (2 ml) in absolute etanol (150 ml) sodium cyanoborohydride was added in three portions (3·55 g at the beginning of reaction, 2·4 g and 4 ml of AcOH after 4 h, and 2·4 g and 4 ml of AcOH after 24 h). Overall reaction time was 45 h at 21°C. The solvent was removed under reduced pressure. Benzene (100 ml) was added to the residue followed by 1M aqueous sodium carbonate solution (portionwise 120 ml). The inorganic layer was extracted with additional two portions of benzene, and from combined fractions basic products were removed by extraction with diluted hydrochloric acid. After common work-up an oily fraction of neutral products (3·4 g) was discarded. Basic products weighed 9·3 g and contained mainly two compounds *VI* and *VII* (yield c. 70%; ratio c. 1 : 3; TLC in hexane–ethyl acetate (2 : 3) on silica). Pure samples of both epimers were obtained by column chromatography on silica using petroleum ether–ether (5 : 1) as eluent.

Data for *VI*: For $C_{17}H_{25}NO_3$ (291·4) calculated: 70·07% C, 8·65% H, 4·81% N; found: 70·32% C, 9·10% H, 5·01% N. MS: 291 (31), 222 (39), 121 (61), 107 (100), 98 (11), 94 (97), 81 (37), 55 (37)%. IR: 3 333 (NH), 3 160 and 876 (3-furyl), 3 083 and 1 654 ($C{=}CH_2$), 1 729 ($C{=}O$), 1 166 ($C{-}O$) cm^{-1}. The ^1H and ^{13}C NMR data are shown in Fig. 1.

Data for *VII*: MS: 291 (26), 222 (21), 121 (40), 107 (43), 94 (100), 81 (23), 55 (16)%. IR: 3 311 (NH), 3 150 and 877 (3-furyl), 3 085 and 1 653 ($C{=}CH_2$), 1 726 ($C{=}O$), 1 167 ($C{-}O$) cm^{-1}. ^1H and ^{13}C NMR data are shown in Fig. 1.

Epimerization of *VII* to *VI*

To a solution of sodium ethoxide (prepared from 3·8 g of sodium and 130 ml of absolute ethanol) crude basic products from the reductive aminocyclization reaction (9·5 g in 50 ml of ethanol) were added and resulting red solution was refluxed for 38 h. The course of transformation was checked by TLC. After cooling, glacial acetic acid (11 ml) was added and the solvent removed under reduced pressure. The solid residue was dissolved in water (100 ml) and basified with 1M sodium carbonate followed by extraction with benzene. The extract was washed wiht water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 7·4 g of *VI* (yield c. 77%, purity c. 90%).

Enantiomer Resolution

(1*S*)-(−)-Camphanic acid (5·0 g) was dissolved in a solution of crude epimerization products (7·4 g) in absolute ether (50 ml). After 70 h at 0°C crystals that separated (5·5 g) were collected and recrystallized four times from ethyl acetate. Optical rotation values changed from −10·4 for the crude salt to maximum −37·3 for the last fraction (m.p. 175·5—178°C). The free base (−)-*VI* liberated from the purest salt had $[\alpha]_D$ −68·1 and m.p. 173—176°C (diethyl ether).

Reduction of (−)-*VI* with Lithium Aluminium Hydride

Reduction was performed in a conventional manner (LAH in ether) but using abs. THF for dissolving the ester. Starting from 737 mg of (−)-*VI* 572 mg of aminoalcohol was obtained (yield 91%). M.p. 60—61°C (hexane–ethyl acetate), $[\alpha]_D$ −65·8. MS: 249 (M^+, 28), 218 (13), 194 (12), 180 (100), 162 (10), 121 (11), 107 (68), 96 (15), 95 (11), 94 (70), 81 (22), 79 (18), 77 (11), 67 (11), 56 (12), 55 (12), 41 (20)%. IR: 3 623 (OH), 3 330 (NH), 3 155 and 878 (3-furyl), 3 088, 1 651 and 893 ($C{=}CH_2$), 1 166 (C—O) cm^{-1}. ^1H NMR: 1·69 br s, 3 H ($H_2C{=}C{-}CH_3$); 2·0 m, 2 H (OH and NH); 2·53 m, 1 H (H-2); 3·6 m, 3 H (OCH_2 and H-6); 4·72 m, 2 H ($C{=}CH_2$); 6·33 m, 2 H (H-4, furan); 7·30 m, 2 H (H-2 and H-5, furan) ppm. ^{13}C NMR: 22·4 q ($CH_3C{=}C$); 28·6 t (C-4); 31·2 t ($CH_2C{=}C$); 33·2 t ($C\text{-}2{-}CH_2$); 33·8 t (C-5); 43·1 d (C-3); 53·3 d (C-6); 58·4 d (C-2); 64·4 t (OCH_2); 109·1 d (C-4, furan); 110·1 t ($CH_2{=}C$); 129·2 s (C-3, furan); 138·4 d (C-2, furan); 142·8 d (C-5, furan); 145·7 s ($C{=}CH_2$) ppm.

(−)-Anhydronupharamine (*IX*)

Dry hydrogen bromide was passed over a stirred solution of aminoalcohol (−)-*VIII* (548 mg, 2·2 mmol) in absolute chloroform (10 ml) for a few minutes. To an oily suspension phosphorous tribromide (0·2 ml) was added and the resulting homogeneous mixture was refluxed for 1·5 h. Evaporation of the solvent gave a glass-like light yellow material which was dissolved in glacial acetic acid (10 ml) and then heated with zinc dust (1·0 g) on a hot water bath for 30 min. Excess of zinc was removed by filtration, washed with AcOH, and the solvent was evaporated under vacuum. The resulting semi-solid was dissolved in concentrated ammonia (10 ml) and extracted with ether (3 × 5 ml). The combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and a crude liquid product (290 mg) was chromatographed on alumina (20 g) using benzene and benzene–chloroform systems as eluent. It gave pure (−)-anhydronupharamine (−)-*IX*, 204 mg, yield 40% as a colorless liquid, $[\alpha]_D$ −62·5. Ref.[13] $[\alpha]_D$ −59 (solvent not specified). ^1H NMR: (see incomplete data[14]) 0·92 d, 3 H ($C\text{-}3{-}CH_3$, $J = 5·5$); 1·67 br s, 3 H (*cis* $CH_3C{=}C$); 1·74 br s, 3 H (*trans* $CH_3C{=}C$); 1·81 br s, 1 H (NH); 3·60 dd, 1 H (H-6, J_1 = 10·5; J_2 = 2·5); 5·18 m, 1 H ($HC{=}C$); 6·44 m, 1 H H-4, furan); 7·41 m, 2 H (H-2 and H-5, furan) ppm. ^{13}C NMR data are in accordance within ±0·1 ppm with the cited ones for the natural alkaloid[15].

(−)-Nupharamine (*I*)

Hydration of the isolated double bond in (−)-*IX* was accomplished by a method of Forrest and Ray[9] reported for transformation of (−)-nuphenine to (−)-3-epinupharamine. An oil (94 mg) was obtained starting from *IX* (93 mg, 0·4 mmol), which was chromatographed on alumina using benzene and benzene–ether mixtures as eluents. It gave 49 mg of a mixture of (−)-*VIII* and (−)-*IX*, and 37 mg (yield 37%) of *I*, $[\alpha]_D$ −33·6. A sample of natural (−)-nupharamine had $[\alpha]_D$ −32·0. Ref.[8] $[\alpha]_D^{22}$ −35·04 ($CHCl_3$). IR, ^1H NMR and MS data were identical for both compounds. ^{13}C NMR spectrum was in accordance within ±0·1 ppm with the reported one[15].

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