A NEW SYNTHESIS OF RIZATRIPTAN BASED ON RADICAL CYCLIZATION

Stanislav RÁDL[1,*], Ondřej KLECÁN[2], Robert KLVAŇA[3] and Jaroslav HAVLÍČEK[4]

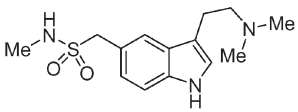
Zentiva, U kabelovny 130, 102 37 Prague 10, Czech Republic;
e-mail: [1] stanislav.radl@zentiva.cz, [2] ondrej.klecan@zentiva.cz, [3] robert.klvana@zentiva.cz, [4] jaroslav.havlicek@zentiva.cz

Received December 6, 2007
Accepted January 23, 2008

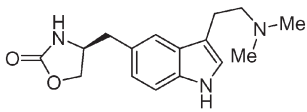
A new methodology useful for preparation of indole derivatives bearing a 2-(dialkylamino)-ethyl substituent at the 3-position has been developed. Application of this methodology to the synthesis of *N*,*N*-dimethyl-2-{5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-3-yl}ethan-1-amine (rizatriptan; **3**) is described. The key reaction step is based on the radical cyclization of *N*-[4-(dimethylamino)but-2-yn-1-yl]-*N*-{2-iodo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]phenyl}-acetamide (**21**), easily available by the Mannich reaction, and subsequent isomerization of the primarily formed methylidene derivative **22**.

Keywords: Rizatriptan; Triptans; Migraine treatment drugs; Serotonin agonists; Radical cyclizations; Indoles; Mannich reaction.

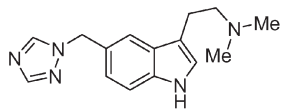
A class of potent serotonin 5-$HT_{1B/1D}$ receptor agonists collectively termed triptans brought a substantial improvement in the migraine treatment. Sumatriptan[1] (**1**; Imitrex®, Imigran®) was the first of these compounds on the market. This drug was quickly followed by a number of second generation triptans, e.g. zolmitriptan[2] (**2**; Zomig®), and rizatriptan[3] (**3**; Maxalt®), characterized by improved pharmacokinetic properties and/or tolerability profiles.



1



2

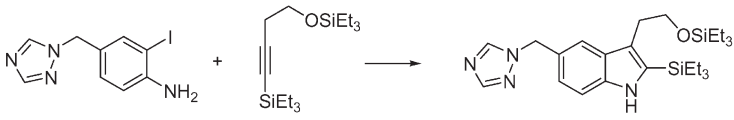


3

There are several methods of synthesis of these drugs, mostly based on the Fischer indole synthesis[4]. However, many side-reactions have been observed during the synthesis, very often providing 2-substituted analogs or dimers linked at the 2-position[5]. The Japp–Klingemann reaction was

doi:10.1135/cccc20080116

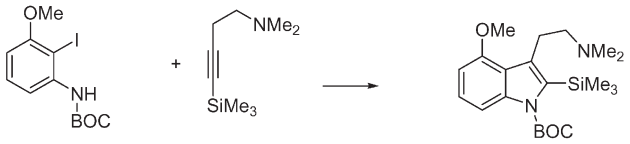
used to overcome the dimer formation[6], but high temperatures insuitable for industrial production are necessary for the decarboxylation step. Various modifications of the Fischer indolization were found useful in the synthesis of some triptans[7] but all of them, with the exception of the Japp–Klingemann reaction[8], were found ineffective in the synthesis of rizatriptan. A different approach to the synthesis of rizatriptan based on the Larock[9] palladium-catalyzed ring closure has been also described[10]. Application of this methodology in the synthesis of rizatriptan using disilylated compound **5** led to the formation of intermediate **6**, which was then transformed into rizatriptan **3** in three steps (Scheme 1).



4 **5** **6**

SCHEME 1

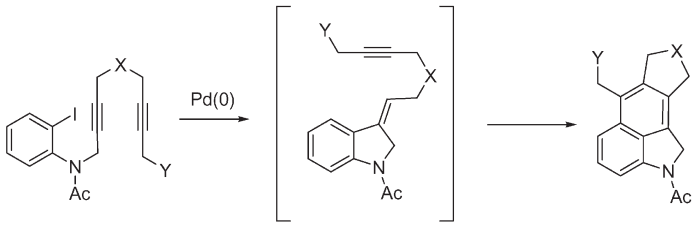
The same approach was useful also in the preparation of avitriptan[7b] and zolmitriptan[7c], and also in the synthesis of compound **9**, which was then transferred into hallucinogenic mushroom alkaloid psilocin[11] (Scheme 2).



7 **8** **9**

SCHEME 2

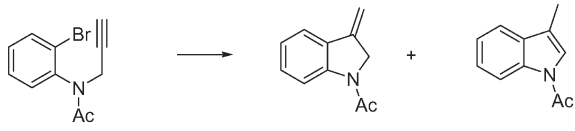
Grigg and co-workers described palladium-catalyzed cascade reactions[12] starting from 2′-iodo-*N*-propargylacetanilides **10**, where the intermediate formation of **11** can be expected (Scheme 3).



10 **11** **12**

SCHEME 3 X = $C(CO_2Et)_2$, NSO_2Ph; Y = NR_2

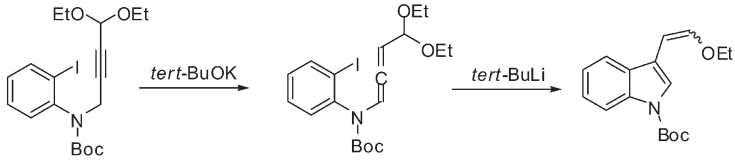
Formally similar radical cyclization of several 2′-bromo-*N*-propargylacetanilides with terminal acetylenic bond has also been described[13]. The use of Bu_3SnH and AIBN provided high yields of a mixture of exo- and endocyclic products **14** and **15** (ref.[13a]) (Scheme 4) while the SmI_2-promoted cyclization[13b] of compound **13** yielded only the deacetylated 3-methyl derivative corresponding to compound **15**. An efficient synthesis of pineal hormone melatonin based on radical cyclization of the corresponding *N*-(2-iodophenyl)methanesulfonamide initiated by 1-ethylpiperidine hypophosphite (EPHP) or tris(trimethylsilyl)silane (TTMSS) has been reported[14].



13 **14** **15**

SCHEME 4

A different approach based on the carbanion addition leading to indoles has been recently reported[15]. Allene **17**, obtained from the corresponding acetylenic compound **16** by treatment with potassium *tert*-butoxide, when treated with 2.4 equivalents of *tert*-butyllithium gave a good yield of **18** as a mixture of the *E* and *Z* isomers (Scheme 5). On the other hand, the same treatment of **16** provided only a complex mixture.



16 **17** **18**

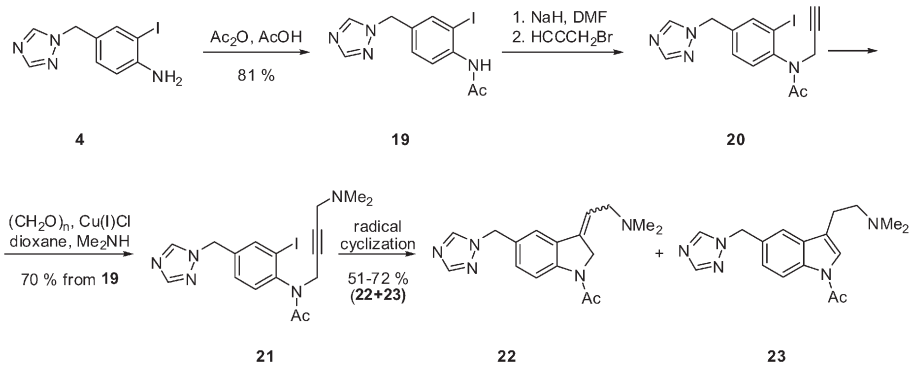
SCHEME 5

The expected easy availability of *N*-[4-(dimethylamino)but-2-yn-1-yl]-*N*-(2-iodophenyl)acetamides via the Mannich reaction of the corresponding propargylic intermediates inspired us to develop a new way useful for preparation of indole derivatives bearing the 2-(dimethylamino)ethyl substituent at position 3. We have considered all the above mentioned variations, i.e. palladium-catalyzed cyclization, carbanion cyclization, and radical cyclization. In this paper we report application of this approach to the synthesis of rizatriptan.

The starting iodo derivative **4** was prepared by iodination of the corresponding aniline with iodine monochloride in the presence of calcium carbonate according to the literature[8a,10]. Acetylation of **4** with acetic anhydride in acetic acid provided anilide **19**. Its sodium salt generated in situ with sodium hydride in DMF was then alkylated with propargyl bromide to give **20** as an oil. Initially we tried to isolate the compound by chromatography and identified it by NMR spectroscopy but the compound was found rather unstable. Therefore, it was used without purification and its treatment with paraformaldehyde in a dioxane solution of dimethylamine gave **21**. This compound obtained as yellow oil was characterized as hydrochloride. In the reactions, however, it was used as the oily base.

For the cyclization we tried first the palladium-catalyzed cyclization under different conditions. The reaction using palladium acetate–sodium carbonate as well as combinations of palladium acetate and triphenylphosphine with both sodium carbonate and silver carbonate gave complex mixtures with only traces of compound **23** (TLC).

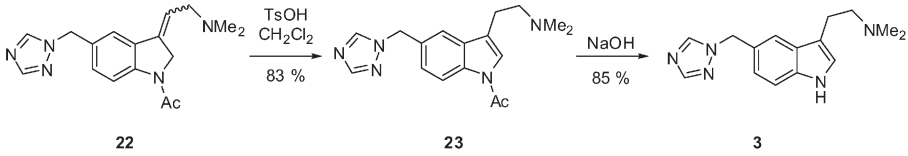
Better results were obtained when the cyclization was done under conditions of radical cyclization. Our initial experiments using tributyltin hydride led to a mixture of two compounds with very similar R_F in several used solvent mixtures. Relatively good resolution with R_F ca. 0.4 and 0.45 was obtained using the system toluene–ethanol–dioxane–concentrated aqueous ammonia 5:2:4:1. After workup and chromatographic separation, low yields of both compounds, which were identified as the corresponding exocyclic derivative **22** (R_F = 0.40) and endocyclic derivative **23** (R_F = 0.45), were obtained. In attempts to alleviate problems associated with toxic tin residues and to improve the yields, we applied conditions described by Thompson et al.[14], using EPHP or TTMSS. Again, mixtures of exocyclic and



SCHEME 6

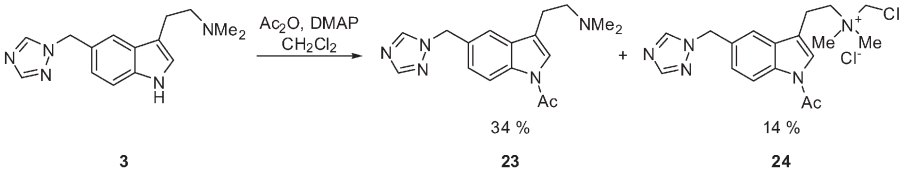
endocyclic derivatives **22** and **23**, respectively, were formed. The overall yields obtained in repeated runs with 1-ethylpiperidine hypophosphite or tris(trimethylsilyl)silane reactions were comparable or higher than with tributyltin hydride, but the ratio of compound **22** and **23** varied, probably due to the easy isomerization of **22** to **23** (Scheme 6). The exocyclic compound **22** is not quite stable and its partial isomerization occurs even during attempts of crystallization of the corresponding crude chromatographic fraction from ethyl acetate. Therefore, no elemental analysis results are reported and the compound was characterized only by MS and NMR of the corresponding chromatographic fraction after evaporation.

Indoline derivatives similar to **22** are known to isomerize under acid conditions to the corresponding indole derivatives[14,16]. In our case, treatment of **22** or mixture of **22** and **23** with 4-methylbenzene-1-sulfonic acid was used to get pure indole **23** in a high yield. Its alkaline hydrolysis with sodium hydroxide in aqueous methanol at room temperature provided the target product – rizatriptan base (Scheme 7).



SCHEME 7

Since the yields in our initial experiments of deacetylation of **23** were low and our supply of **23** was limited, we decided to prepare **23** by acetylation of rizatriptan (**3**) prepared by the Fischer indole synthesis. Finally, the acetylation with acetic anhydride in acetonitrile was successful. However, our first attempt done in dichloromethane provided surprisingly a mixture of the required acetyl derivative **23** and its quaternary salt **24** (Scheme 8). Formation of **24** under such mild conditions is, in our opinion, interesting and quotable.



SCHEME 8

All the prepared compounds were duly characterized by elemental analysis, IR, UV and MS/MS spectra as well as by the ^{1}H and ^{13}C NMR spectra. For the assignment of signals in proton and carbon NMR spectra, 2D NMR techniques (COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC) were used.

In conclusion, a novel method of preparation of rizatriptan based on a radical cyclization of easily available intermediates was developed. This methodology could be also used in the synthesis of similar 3-(2-aminoethyl)indole derivatives. Unlike the Fischer indole synthesis, which provides only low yields of rizatriptan, our approach does not use potentially carcinogenic aryl hydrazine intermediates. Compared to similar approach based on the Pd-catalyzed Larock methodology, our approach is simpler and more straightforward.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Perkin–Elmer Spectrum BX FT-IR machine by the diffuse reflectance method (KBr); wavenumbers are given in cm^{-1}. The UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument (Bruker Biospin GmbH) at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C). At 500 MHz, standard 5 mm TXO (triple-nucleus X-observe) and TBI (triple-broadband inverse) probeheads equipped with z-gradient coils were employed for all measurements. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The mass spectra (MS/MS; ionization mode APCI(+)) were measured on an API 3000 PE device (Sciex Instruments, Applied Biosystems). The purity of the substances prepared was evaluated by TLC on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm.

2-Iodo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]aniline (**4**) was prepared according to the published procedure[8a,10]. ^{1}H NMR ($CDCl_3$): 4.22 bs, 2 H (NH_2); 5.16 s, 2 H (CH_2); 6.70 d, 2 H, *J* = 10.0 (H-6); 7.06 dd, 2 H, *J* = 10.0, 2.5 (H-5); 7.58 d, 2 H, *J* = 2.5 (H-3); 7.95 s, 1 H (H-5 of triazole); 8.01 s, 1 H (H-3 of triazole). ^{13}C NMR ($CDCl_3$): 52.3 (CH_2), 83.6 (C-2), 114.6 (C-6), 125.4 (C-4), 129.5 (C-5), 138.8 (C-3), 142.7 (C-1), 147.2 (C-5 of triazole), 152.1 (C-3 of triazole). UV, λ_{max} (log ε): 216 (4.54), 248 (4.11), 302 (3.52).

N-{2-Iodo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]phenyl}acetamide (**19**)

Acetic anhydride (51 g, 0.5 mol) was added dropwise to a solution of **4** (30 g, 0.1 mol) in acetic acid (100 ml) and the mixture was stirred at ambient temperature for 2 h. The mixture was poured onto ice and the mixture was neutralized with concentrated sodium hydroxide. The formed solid was filtered off, washed with water and dried. Crystallization from ethanol provided 27.6 g (81%) of off-white solid, m.p. 170–171 °C. For $C_{11}H_{11}IN_4O$ (342.1) calculated: 38.62% C, 3.24% H, 37.09% I, 16.38% N; found: 38.33% C, 3.27% H, 37.41% I, 16.07% N. ^{1}H NMR (DMSO-d_6): 2.04 s, 3 H (CH_3CO); 5.38 s, 2 H (CH_2); 7.27dd, 2 H, *J* = 6.6, 1.5 (H-5); 7.37 d, 2 H, *J* = 7.1 (H-6); 7.80 d, 2 H, *J* = 1.3 (H-3); 7.98 s, 1 H (H-5 of triazole); 8.66 s, 1 H (H-3 of triazole); 9.38 bs, 1 H (NH). ^{13}C NMR (DMSO-d_6): 23.1 (CH_3),

50.6 (CH_2), 96.3 (C-2), 127.2 (C-6), 128.1 (C-5), 135.4 (C-4), 138.1 (C-3), 139.4 (C-1), 144.2 (C-5 of triazole), 151.8 (C-3 of triazole), 168.3 (C=O). IR: 1516, 1573 (arom.), 1685 (CO), 3326 (NH). UV, λ_{max} (log ε): 208 (4.36), 222 (4.40), λ_{infl} = 245 nm.

N-[4-(Dimethylamino)but-2-yn-1-yl]-*N*-{4-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-iodophenyl}-acetamide (**21**)

Sodium hydride (50% dispersion in mineral oil, 4.8 g, 0.1 mol) was added to a solution of **19** (27 g, 80 mmol) in dry DMF (200 ml) and the mixture was stirred at ambient temperature under nitrogen for 1 h. A solution of propargyl bromide (80% in toluene, 15 g, 0.1 mol) was added and the mixture was stirred at 50 °C under nitrogen for 2 h. The mixture was cooled and poured into water (750 ml), the formed precipitate was filtered off on Celite. The pH of the filtrate was adjusted to 8–9 with acetic acid, the mixture was extracted with ethyl acetate and the combined extracts were dried with anhydrous magnesium sulfate. The solution containing only one major product (TLC, toluene–ethanol–dioxane–concentrated aqueous ammonia 5:2:4:1) was evaporated to give 35 g of a brown oily residue. The residue was dissolved in dry dioxane (250 ml), and paraformaldehyde (9 g, 0.3 mol), copper(I) chloride (3 g, 30 mmol) and a 20% solution of dimethylamine in dioxane (50 ml) were added. The mixture was then stirred at 50 °C for 2 h and filtered through a Celite pad while hot. The filtrate was evaporated, the residue was dissolved in 5% aqueous hydrochloric acid (500 ml), the turbid solution was washed with ether (2 × 25 ml). The aqueous solution was then alkalinized with saturated aqueous sodium carbonate and the formed greasy precipitate was filtered off with Celite. The Celite pad was washed with water (500 ml) and dichloromethane (1000 ml). The combined aqueous fractions were extracted with dichloromethane washings (5 × 200 ml) and the organic solution was dried with anhydrous magnesium sulfate. The desiccant was filtered through a pad of silica and the residue after evaporation (24.4 g, 69.7%) was used without isolation in the following step. A small sample (1 g) was transformed into hydrochloride, m.p. 135–142 °C (dec.) and repeatedly recrystallized from ethyl acetate–ethanol 2:1. For $C_{17}H_{21}ClIN_5O$ (473.7) calculated: 43.10% C, 4.47% H, 7.48% Cl, 26.79% I, 14.78% N; found: 42.79% C, 4.21% H, 7.48% Cl, 26.93% I, 14.55% N. ^{1}H NMR (DMSO-d_6): 1.69 s, 3 H (CH_3); 2.69 s, 6 H (CH_3N); 4.00 s, 2 H ($Me_2NC\mathbf{H}_2$); 4.04 d, 1 H, *J* = 12.6 (AcNC**H**$_2$); 4.84 d, 1 H, *J* = 12.4 (AcNC**H**$_2$); 5.49 s, 2 H (CH_2); 7.42 dd, 2 H, *J* = 7.6, 1.3 (H-5); 7.60 _, 1 H, *J* = 8.0 (H-6); 7.96 d, 2 H, *J* = 1.3 (H-3); 8.20 s, 1 H (H-5 of triazole); 8.98 s, 1 H (H-3 of triazole); 11.40 bs, 1 H (HCl). ^{13}C NMR (DMSO-d_6): 22.2 ($\mathbf{C}H_3CO$), 36.7 (AcN$\mathbf{C}H_2$), 41.1 (CH_3N), 45.4 ($Me_2N\mathbf{C}H_2$), 50.6 (CH_2), 73.6 ($Me_2NCH_2\mathbf{C}$), 84.9 (AcN$CH_2\mathbf{C}$), 101.3 (C-2), 129.3 (C-6), 130.6 (C-5), 138.5 (C-4), 138.8 (C-3), 143.1 (C-1), 144.7 (C-5 of triazole), 150.8 (C-3 of triazole), 168.5 (C=O). IR: 1487, 1653 (CO). UV, λ_{max} (log ε): 206 (4.42), λ_{infl} = 227 nm. MS/MS (*m/z*, %): 438 (100, M + 1), 393 (87), 351 (8), 325 (10), 282 (38).

1-{(*Z*)-3-[2-(Dimethylamino)ethylidene]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-2,3-dihydro-1*H*- indol-1-yl}ethan-1-one (**22**) and
1-{3-[2-(Dimethylamino)ethyl]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-1-yl}ethan-1-one (**23**)

A) EPHP (17.9 g, 0.1 mol) and AIBN (0.25 g, 1.5 mmol) were added to a solution of **21** (4.4 g, 10 mmol) in toluene (500 ml) and the solution was refluxed under nitrogen for 2 h. The mixture was evaporated, the residue was dissolved in dichloromethane (150 ml) and the solution was successively washed with saturated sodium carbonate (25 ml) and brine, and

dried with anhydrous magnesium sulfate. The residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) to give 2.1 g of **22** (67%) as white crystals, m.p. 150–159 °C (dec.) and 0.16 g of **23** (5%) as white crystals, m.p. 135–137 °C.

Compound **22**: ^{1}H NMR ($CDCl_3$): 2.33 s, 3 H (CH_3CO); 2.68 s, 6 H (CH_3N); 3.51 m, 2 H (Me_2NCH_2); 4.92 s, 2 H (H-2); 5.35 s (CH_2); 6.04 m, 1 H (Me_2NCH_2CH); 7.27 dd, 1 H, *J* = 8.2, 1.5 (H-6); 7.41 d, 1 H, *J* = 8.2, 1.5 (H-4); 8.00 s, 1 H (H-3 of triazole); 8.10 s, 1 H (H-5 of triazole); 8.34 d, 1 H, *J* = 8.5 (H-7). MS/MS (*m/z*, %): 312 (48, M + 1), 267 (100), 243 (14), 225 (33), 198 (39), 158 (11), 156 (90).

Compound **23**: For $C_{17}H_{21}N_5O$ (311.4) calculated: 65.57% C, 6.80% H, 22.49% N; found: 65.43% C, 6.41% H, 22.72% N. ^{1}H NMR (DMSO-d_6): 2.32 s, 6 H (CH_3N); 2.60 s, 3 H (CH_3CO); 2.62 t, 2 H, *J* = 7.5 ($Me_2NCH_2CH_2$); 2.84 t, 2 H, *J* = 7.5 (Me_2NCH_2); 5.44 s (CH_2); 7.26 d, 1 H, *J* = 10.0 (H-6); 7.30 s, 1 H (H-2); 7.45 s, 1 H (H-4); 7.97 s, 1 H (H-3 of triazole); 8.05 s, 1 H (H-5 of triazole); 8.40 d, 1 H, *J* = 10.0 (H-7). ^{13}C NMR (DMSO-d_6): 22.3 ($Me_2NCH_2CH_2$), 23.8 (CH_3CO), 45.4 (Me_2N), 53.8 (CH_2), 59.0 (Me_2NCH_2), 117.2 (C-7), 118.6 (C-6), 120.8 (C-3), 123.0 (C-4), 125.2 (C-2), 129.5 (C-3a), 131.2 (C-5), 135.7 (C-7a), 142.9 (C-5 of triazole), 152.0 (C-3 of triazole), 168.2 (C=O). IR: 1 386, 1 693 (CO). UV, λ_{max} (log ε): 206 (4.42), 242 (4.44), 294 (3.87), 304 (3,88). MS/MS (*m/z*, %): 312 (100, M + 1), 243 (82), 201 (18), 200 (11), 158 (48), 58 (32).

B) Tributyltin hydride (1.5 g, 5 mmol) and AIBN (0.05 g, 0.3 mmol) were added to a solution of **21** (0.87 g, 2 mmol) in toluene (150 ml) and the solution was refluxed under nitrogen for 2 h. The solution was evaporated under reduced pressure, the residue was dissolved in dichloromethane (50 ml) and the solution was successively washed with saturated sodium carbonate (10 ml) and brine, and dried with anhydrous magnesium sulfate. The residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) to give 0.27 g of **22** (43%) as white crystals, m.p. 152–160 °C (dec.) and 0.05 g of **23** (8%) as white crystals, m.p. 135–137 °C.

C) A solution of AIBN (0.2 g) and TTMSS (2 ml, 1.5 g, 6 mmol) in toluene (20 ml) was added via a syringe pump during 5 h to a refluxing solution of **21** (3 g, 6.8 mmol) in toluene (400 ml) under argon and the solution was refluxed for additional 1 h. The cold solution was washed with saturated sodium carbonate and brine, dried with anhydrous magnesium sulfate and the residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) to give 1.1 g of **22** (52%) as white crystals, m.p. 152–159 °C (dec.) and 0.25 g of **23** (12%) as white crystals, m.p. 135–137 °C.

D) A solution of 1,1′-azodi(cyclohexane-1-carbonitrile) (0.05 g) and TTMSS (0.5 ml, 0.75 g, 3 mmol) in toluene (8 ml) was added via a syringe pump during 5 h to a refluxing solution of **21** (0.75 g, 1.7 mmol) in toluene (100 ml) under argon. The solution was washed with saturated sodium carbonate and brine, dried with anhydrous magnesium sulfate and the residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) to give 0.21 g of **22** (40%) as white crystals, m.p. 152–159 °C (dec.) and 0.17 g of **23** (32%) as white crystals, m.p. 135–137 °C.

1-{3-[2-(Dimethylamino)ethyl]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-1-yl}-ethan-1-one (**23**)

A) EPHP (12.5 g, 70 mmol) and AIBN (0.2 g, 1.2 mmol) were added to a solution of **21** (3 g, 67 mmol) in toluene (400 ml) and the solution was refluxed under nitrogen for 2 h.

The mixture was evaporated, the residue was dissolved in dichloromethane (100 ml) and the solution was succesively washed with saturated sodium carbonate and brine. Solid 4-methylbenzenesulfonic acid monohydrate (1.9 g, 100 mmol) was added and the mixture was refluxed for 24 h. Then another portion of the acid (1.9 g, 100 mmol) was added and the reflux continued for additional 24 h. The cold mixture was washed with saturated sodium carbonate and brine, the residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) followed by crystallization from ethyl acetate–ethanol 1:1 to give 1.1 g (53%) of white crystals, m.p. 135–137 °C.

B) A mixture of **22** (0.3 g, 1 mmol), dichloromethane (25 ml) and 4-methylbenzenesulfonic acid monohydrate (0.2 g) was refluxed for 24 h. After cooling, it was washed with saturated sodium carbonate and brine, the residue after evaporation was purified by flash chromatography (dichloromethane–methanol–triethylamine 40:1:1) followed by crystallization from ethyl acetate–ethanol 1:1 to give 0.25 g (83%) of white crystals, m.p. 135–137 °C.

3-[2-(Dimethylamino)ethyl]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]indole (**3**)

Aqueous sodium hydroxide (10%, 25 ml) was added to a solution of compound **23** (1.55 g, 5 mmol) in methanol (25 ml) and the solution was stirred at room temperature for l h. Then it was evaporated, diluted with water (25 ml), extracted with ethyl acetate and the extract was dried with anhydrous magnesium sulfate. The residue after evaporation was dissolved in boiling isopropyl acetate, then heptane was added until the solution became turbid. The solution was seeded and left standing overnight at –20 °C. The formed crystalline solid was filtered off to give 1.15 g (85%) of rizatriptan base; m.p. 119–122 °C. ^{1}H NMR ($CDCl_3$): 2.34 s, 6 H (CH_3N); 2.65 t, 2 H, *J* = 7.5 ($Me_2NC\mathbf{H}_2$); 2.92 t, 2 H, *J* = 7.5 ($Me_2NCH_2C\mathbf{H}_2$); 5.39 s (CH_2); 7.03 m, 2 H (H-4, H-6); 7.24 d, *J* = 7.5, 1 H (H-7); 7.53 s, 1 H (H-2); 7.97 s, 1 H (H-3 of triazole); 7.98 s, 1 H (H-5 of triazole); 9.20 bs (NH). ^{13}C NMR ($CDCl_3$): 23.4 ($Me_2NCH_2\mathbf{C}H_2$), 45.2 (Me_2N), 54.5 (CH_2), 60.1 ($Me_2N\mathbf{C}H_2$), 111.8 (C-7), 114.1 (C-3), 119.0 (C-2), 122.0 (C-6), 122.8 (C-4), 124.6 (C-5), 127.6 (C-3a), 136.2 (C-7a), 142.7 (C-5 of triazole), 151.7 (C-3 of triazole). IR: 1364, 1440, 1505, 3181. UV, λ_{max} (log ε): 204 (4.31), 228 (4.62), 284 (3.74). MS/MS (*m/z*, %): 270 (65, M + 1), 201 (100), 158 (58), 58 (17).

1-{3-[2-(Dimethylamino)ethyl]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-1-yl}ethan-1-one (**23**) and
2-{1-Acetyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-3-yl}ethyl-(chloromethyl)dimethylamminium Chloride (**24**)

DMAP (68 mg, 0.56 mmol), triethylamine (0.93 ml, 6.7 mmol) and acetic anhydride (0.63 ml, 6.7 mmol) were added to rizatriptan (1.5 g, 5.6 mmol) in dichloromethane (15 ml). The reaction mixture was stirred at room temperature for 65 h. The formed solid was filtered off to give 0.3 g (14%) of quaternary ammonium salt **24**, m.p. 168–170 °C. ^{1}H NMR (DMSO-d_6): 2.63 s, 3 H (CH_3CO); 3.23 m, 2 H ($Me_2NCH_2C\mathbf{H}_2$); 3.33 s, 6 H (CH_3N); 3.85 m, 2 H ($Me_2NC\mathbf{H}_2$); 5.52 s (CH_2); 5.66 s, 2 H (CH_2Cl); 7.32 dd, 1 H, *J* = 7.5, 1.2 (H-6); 7.75 d, 1 H, *J* = 1.2 (H-4); 7.93 s, 1 H (H-2); 7.97 s, 1 H (H-3 of triazole); 8.28 d, 1 H, *J* = 7.5 (H-7); 8.75 s, 1 H (H-5 of triazole). ^{13}C NMR (DMSO-d_6): 18.1 ($Me_2NCH_2\mathbf{C}H_2$), 24.0 ($\mathbf{C}H_3CO$), 49.1 (Me_2N), 52.5 (CH_2), 60.1 ($Me_2N\mathbf{C}H_2$), 68.4 (CH_2Cl), 116.7 (C-3), 116.2 (C-7), 119.1 (C-4), 125.3 (C-6), 125.9 (C-2), 129.9 (C-3a), 131.4 (C-5), 134.8 (C-7a), 144.3 (C-5 of triazole), 151.7 (C-3 of triazole), 169.3 (C=O). IR: 1700 (CO). UV, λ_{max} (log ε): 204 (4.39), 240 (4.37), 264 (3.94), 292 (3.77), 302 (3.80). MS/MS (*m/z*, %): 362 (32), 360 (100), 267 (37), 225 (10).

The filtrate was washed with water and the organic layer was dried with anhydrous sodium sulfate. The residue after evaporation was crystallized from ethyl acetate to give 585 mg (34%) of **23**, m.p. 138–139 °C.

1-{3-[2-(Dimethylamino)ethyl]-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-1-yl}-ethan-1-one (**23**)

DMAP (136 mg, 1.2 mmol), triethylamine (1.9 ml, 13.4 mmol) and acetic anhydride (1.3 ml, 13.4 mmol) were added to rizatriptan (3 g, 11.1 mmol) in acetonitrile (15 ml). The reaction mixture was stirred at room temperature for 24 h. The precipitated product was filtered off and washed with cold acetonitrile to give 2.7 g (78%) of **23** as white crystals; m.p. 138–139 °C. Spectral characteristics of this compound were identical with the compound prepared by isomerization of compound **22**.

Financial support provided by Zentiva Praha is greatly appreciated. The authors' thanks are due to Ms. L. Tisovská for measuring the IR and UV spectra and Mr. L. Plaček for MS spectra.

REFERENCES

1. *The Merck Index*, 13th ed., p. 1605. Merck & Co, Whitehouse Station (U.S.A.) 2001 (ref. 9088).
2. a) *The Merck Index*, 13th ed., p. 1816. Merck & Co, Whitehouse Station (U.S.A.) 2001 (ref. 10241); b) Ngo J., Mealy N., Castaner J.: *Drugs Future* **1997**, *22*, 260.
3. a) *The Merck Index*, 13th ed., p. 1480. Merck & Co, Whitehouse Station (U.S.A.) 2001 (ref. 8324); b) Rabasseda X., Mealy N., Castaner J.: *Drugs Future* **1995**, *20*, 676.
4. Downing R. S., Kunkeler P. J. in: *Fine Chemicals Through Heterogeneous Catalysis* (R. A. Sheldon and H. Bekkum, Eds), pp. 173–178. Wiley–VCH, New York 2001.
5. a) Chen D., Yu L., Wang P. G.: *Tetrahedron Lett.* **1996**, *37*, 4467; b) Pete B., Bitter I., Szantay C., Schön I., Töke L.: *Heterocycles* **1998**, *48*, 1139.
6. a) Pete B., Bitter I., Harsanyi K., Töke L.: *Heterocycles* **2000**, *53*, 665; b) Pete B., Töke L.: *Tetrahedron Lett.* **2001**, *42*, 3373.
7. a) Chen C., Senanayake C. H., Bill T. J., Larsen R. D., Verhoeven T. R., Reider P. J.: *J. Org. Chem.* **1994**, *59*, 3738; b) Brodfuehrer P. R., Chen B.-C., Sattelberg T. R., Smith P. R., Reddy J. P., Stark D. R., Quinlan S. L., Reid J. G.: *J. Org. Chem.* **1997**, *62*, 9192; c) Sternfeld F., Guiblin A. R., Jelley R. A., Matassa V. G., Reeve A. J., Hunt P. A., Beer M. S., Heald A., Stanton J. A., Sohal B., Watt A. P., Street L. J.: *J. Med. Chem.* **1999**, *42*, 677; d) Kamiya S., Shirahase H., Nakamura S., Kanda M., Matsui H., Yoshimi A., Kasai M., Takahashi K., Kurahashi K.: *Chem. Pharm. Bull.* **2001**, *49*, 563.
8. Barjoan D. P., Asparo A. K. (Laboratorios Vita): WO 2004/014877 A1; *Chem. Abstr.* **2004**, *140*, 181454.
9. a) Larock R. C., Yum E. K.: *J. Am. Chem. Soc.* **1991**, *113*, 6689; b) Gribble G. W.: *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
10. Chen C.-Y., Lieberman D. R., Larsen R. D., Reamer R. A., Verhoeven T. R., Reider P. J., Cottrell I. F., Houghton P. G.: *Tetrahedron Lett.* **1994**, *35*, 6981.
11. Gathergood N., Scammells P. J.: *Org. Lett.* **2003**, *5*, 921.

12. a) Grigg R., Loganathan V., Sridharan V.: *Tetrahedron Lett.* **1996**, *37*, 3399; b) Brown D., Grigg R., Sridharan V., Tambyrajah V., Thornton-Pett M.: *Tetrahedron* **1998**, *54*, 2595.
13. a) Dittami J. P., Ramanathan H.: *Tetrahedron Lett.* **1988**, *29*, 45; b) Inanaga J., Ujikawa O., Yamaguchi M.: *Tetrahedron Lett.* **1991**, *32*, 1737.
14. Thomson D. W., Commeureuc A. G. J., Berlin S., Murphy J. A.: *Synth. Commun.* **2003**, *33*, 3631.
15. Le Strat F., Maddaluno J.: *Org. Lett.* **2002**, *4*, 2791.
16. Tietze L. F., Grote T.: *J. Org. Chem.* **1994**, *59*, 192.