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The Organometallic Route to Benzylamine Type Monoamine Oxidase Inhibitors

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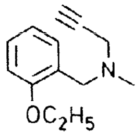
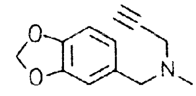
Abstract: *N*-Methyl-*N*-(2-propynyl)piperonylamine can be simultaneously lithiated at the terminal acetylenic and at that aromatic position which is flanked by both the side chain and an oxygen atom. Under carefully established conditions, the metal occupying the latter *ortho* position can be selectively replaced by an electrophile. In general, it is however more convenient and also more efficacious to protect the acetylenic site by silylation. Then lithium may be introduced into the double-*ortho* position either by hydrogen/metal or by halogen/metal exchange, using 2-bromo-*N*-methyl-*N*-[(3-trimethylsilyl)-2-propynyl]piperonylamine as the starting material in the latter case. One of the new products (**1b**) proved to be a strong monoamine oxidase (MAO) inhibitor. © 1998 Elsevier Science Ltd. All rights reserved.

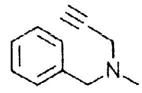
Despite its structural simplicity, the well-known drug Pargyline or, chemically speaking, *N*-methyl-*N*-(2-propenyl)benzylamine, is a powerful inhibitor of monoamine oxidase (MAO) [1]. It is prescribed as both an antidepressant and a hypotensor. The antagonistic activity (expressed as the negative logarithm of the molar concentration which causes MAO inhibition with 50% probability, pI_{50}) can be amplified by changes in the vicinity of the heteroatom, for example, hundredfold to thousandfold when the methyl is replaced by an ethyl, propyl or 2-propynyl group. In contrast, substituents at aromatic positions generally exhibit only modest effects. Thus, the parent compound and its 3,4-dimethoxy or 3,4-methylenedioxy analogs do not behave very differently. However, *ortho* substituents such as ethoxy, methoxy, fluoro, chloro and methyl invariably enhance the activity [2-4].



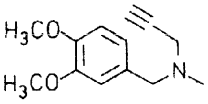
pI_{50} 7.5



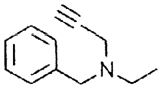
pI_{50} 6.8



pI_{50} 6.0



pI_{50} 5.3



pI_{50} 3.1

In the light of these results, some improvement of the MAO-inhibitory potency was to be expected upon introduction of further substituents into the 2-position of the piperonylamine (or, synonymously, 4-position of the 1,3-benzodioxolanyl) part. However, if we did synthesize such substances, our prime objective was not the search for better drugs, the more so as in the meantime *N*-methyl-*N*-2-propargyl-2-arylpropylamines (*e.g.*, deprenyl) have been recognized to be particularly powerful and selective MAO inhibitors [5-6]. We rather wanted to explore the ability of the (*N*-methyl-*N*-propargylamino)methyl entity to act as an *ortho*-lithiation promoting neighboring group. Previously we have successfully applied a similar reaction sequence to the synthesis of cotarnine related isoquinolines : selective *ortho* lithiation of an acetal derivative of piperonylamine, electrophilic substitution and ring-closure under Pomeranz-Fritsch-Bobbitt conditions [5].

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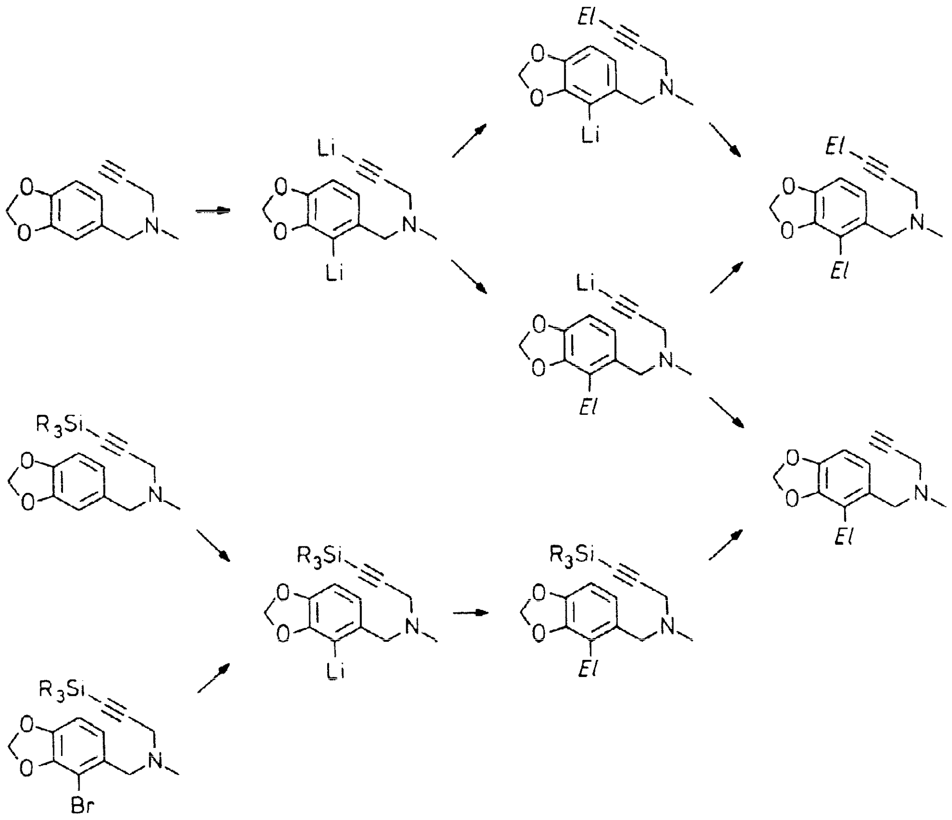
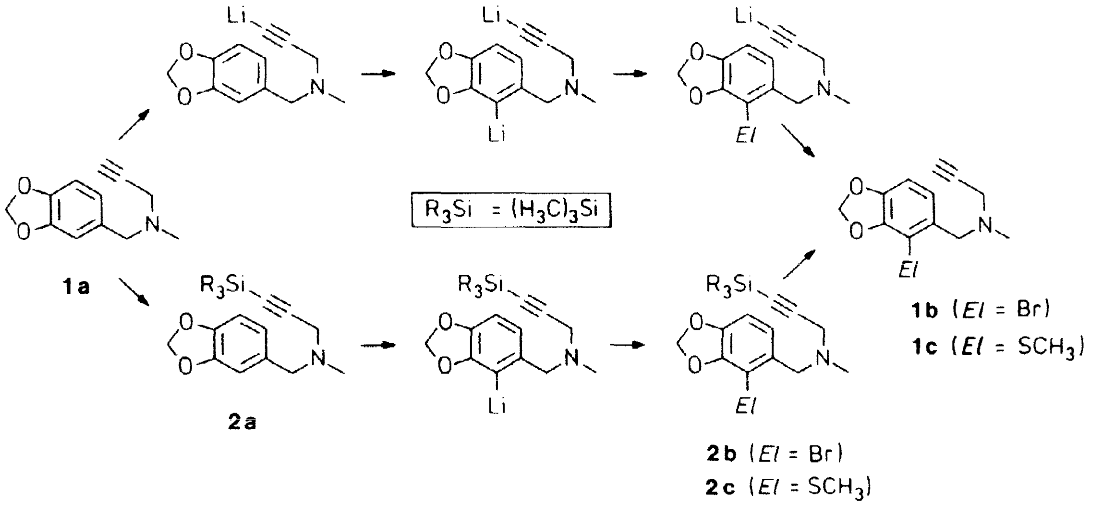
The new challenge was to cope with the complications possibly caused by the presence of the propargyl side chain. Without doubt the acetylenic terminus will perform an instantaneous hydrogen/metal exchange when treated with an organolithium reagent. Would, however, the resulting acetylide still undergo a second deprotonation, this time at the far less acidic *ortho* position ? If this is to happen, would the dilithio species thus generated react with electrophiles (*El*-X) randomly, ultimately affording mixtures of zero-, mono- and disubstituted products, or could it be induced to attach the electrophile exclusively at the aromatic position ? In case of unsatisfactory results one could next envisage to protect the terminal acetylene by trialkylsilylation. But would the modified propargyl side chain not withdraw electrons from the nitrogen atom and thus impart the capacity of the latter element to coordinate lithium, a prerequisite for effective *ortho* metalation ? If all else fails one could finally resort to an halogen/metal exchange which constitutes the easiest and most reliable route, provided the required halogenated precursor is readily accessible.

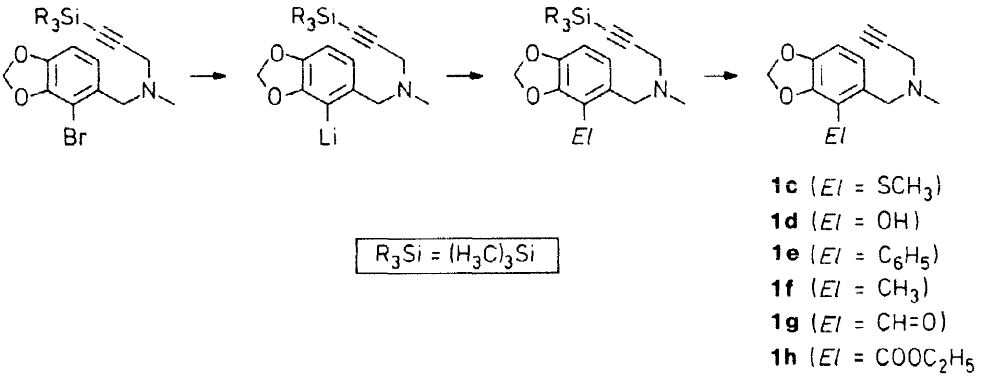


The best protective group is the one which can be omitted. Therefore, we have paid much attention to the ω,*o*-dilithiation of the unprotected *N*-methyl-*N*-(prop-2-ynyl)piperonylamine (**1a**). As shown by deuterolysis, it was indeed possible to accomplish a two-fold deprotonation when *tert*-butyllithium was used in diethyl ether as the metalating reagent. The dilithio species thus generated was found to react selectively at the aromatic position as long as "soft" electrophiles like 1,1,2,2-tetrabromoethane or dimethyl disulfide were employed. The derivatives **1b** (57%) and **1c** (68%), respectively, were the sole products identified. However, other reagents such as methyl iodide proved to be less discriminating, attacking both metal bearing sites concomitantly. Finally, as already demonstrated in model studies [8] tetrahydrofuran activates the reactivity of lithium acetylide in a singular way. Therefore, when this solvent was employed, substitution affected preferentially or exclusively the terminal position of the propargyl side chain.

To avoid all such uncertainties, we have resigned ourselves to protect the terminal acetylene function by a trimethylsilyl moiety. Metalation and electrophilic substitution were now unequivocally directed to the *ortho* position, as evidenced by the clean formation of **2b** (76%) and **2c** (83%). The fluoride promoted desilylation proceeded quantitatively (96 - 97%) to afford the *N*-propargylamines **1b** and **1c**.



There remained, however, a drawback. The metalation of *N*-methyl-*N*-(3-trimethylsilyl-2-propynyl)-piperonylamine (**2a**) progressed sluggishly and required long exposure times (*e.g.*, 6 h) to give satisfactory yields (about 80%). On the other hand, the bromo compound **2b**, made in this way, exchanges its halogen against metal instantaneously when in the presence of an alkyllithium reagent. On this basis we have elaborated a protocol using 2-bromo-*N*-methyl-*N*-(3-trimethylsilyl-2-propynyl)piperonylamine (**2b**) as an universal relay compound. It was consecutively treated with butyllithium, the electrophile and finally tetrabutylammonium fluoride to remove the trimethylsilyl group. This very convenient multi-step one-pot reaction sequence was applied to the preparation of piperonylamine derivatives having as 2-substituents methylthio (**1c**, 96%), hydroxy (**1d**, 67%), phenyl (**1e**, 87%), methyl (**1f**, 91%), formyl (**1g**, 78%) and ethoxycarbonyl (**1h**, 85%).



Assays [9, 10] performed with a few compounds **1** have revealed a remarkably high inhibitory activity of the brominated derivative **1b** (pI_{50} 7.9 after 5 min). Moreover, there was no discrimination at all between MAO-A and MAO-B whereas pargyline is some 20 times more potent toward the latter subtype [8].

EXPERIMENTAL PART

Generalities : The ^{1}H-NMR spectra were recorded at 400 MHz of samples dissolved in deuterochloroform. Chemical shifts (δ) are given relative to the signal of tetramethylsilane, which was used as an internal standard. - For working routine and abbreviations see recent publications [11] from this laboratory.

1. Starting Materials

N-*Methyl*-N-*(2-propynyl)piperonylamine* (N-*methyl*-N-*2-prop-ynyl-1,3-benzodioxolane-5-methaneamine*, N-*methyl*-N-*2-propynyl-3,4-methylenedioxybenzylamine*, **1a**) : Piperonal (15 g, 0.10 mol) in methanol (60 mL) was added to a 40% aqueous solution of methylamine (20 mL, 18 g, 0.23 mol). The mixture was stirred at 25 °C until, after some 15 min, it became clear. Then sodium borohydride (3.8 g, 0.10 mol) was dissolved. After 20 h at 25 °C, the volatiles were evaporated under reduced pressure. At -25 °C, the dry residue was taken up in tetrahydrofuran (0.10 L) and consecutively treated with butyllithium (0.10 mol) in hexane (70 mL) and propargyl bromide (7.5 mL, 12 g, 0.10 mol). After 30 min at +25 °C, the mixture was concentrated and the product, a colorless liquid, isolated by distillation; mp -30 to -28 °C; bp 112 - 115 °C /1 mmHg (lit. [12] : bp 112 °C/0.8 mmHg); n_D^{20} 1.5418; 4.5 g (89%). - ^{1}H-NMR : δ 6.86 (1 H, d, *J* 1.3), 6.79 (1 H, dd, *J* 7.7, 1.3), 6.75 (1 H, d, *J* 7.7), 5.93 (2 H, s), 3.49 (2 H, s), 3.30 (2 H, d, *J* 2.2), 2.33 (3 H, s), 2.25 (1 H, t, *J* 2.2). - MS : 204 (37%, M^+ + 1), 135 (100%).

N-*Methyl*-N-*(3-trimethylsilyl-2-propynyl)piperonylamine* (**2a**) : At -75 °C, *N*-methyl-*N*-2-propynylpiperonylamine (**1a**, 10.2 g, 50 mmol) in tetrahydrofuran (50 mL) was consecutively treated with butyllithium (50 mmol) in hexane (35 mL) and chlorotrimethylsilane (7.0 mL, 6.0 g, 55 mmol). Evaporation and distillation afforded a colorless oil; mp -33 to -30 °C; bp 118 - 120 °C /1 mmHg; n_D^{20} 1.5298; 6.7 g (98%). ^{1}H-NMR : δ 6.85 (1 H, s, broad), 6.8 (2 H, m), 5.94 (2 H, s), 3.46 (2 H, s), 3.28 (2 H, s), 2.31 (3 H, s), 0.20 (9 H, s). MS : 276 (100%, M^+ + 1), 135 (77%). - Analysis : calc. for $C_{15}H_{21}NO_2Si$ (275.42) C 65.41, H 7.68; found C 65.28, H 7.87%.

2. Hydrogen/Lithium Exchange Reactions Followed by Electrophilic Trapping

2-Bromo-N-*methyl*-N-*(2-propynyl)piperonylamine* (**1b**) : At -50 °C, *N*-methyl-*N*-(2-propynyl)-piperonylamine (**1a**, 5.1 g, 25 mmol) was added to *tert*-butyllithium (50 mmol) in pentane (20 mL) and diethyl ether (30 mL). After 6 h at -25 °C, the mixture was treated with 1,1,2,2-tetrabromoethane (2.9 mL, 8.6 g, 25 mmol) and absorbed on silica gel (25 mL). Once dry, the powder was poured on top of a column filled with more silica (0.15 L). Elution with a 1 : 3 (v/v) mixture of diethyl ether and hexane gave a colorless oil which solidified upon standing; mp 37 - 39 °C (from hexane); 4.0 g (57%). - ^{1}H-NMR : δ 6.89 (1 H, d, *J* 8.1), 6.70 (1 H, d, *J* 8.1), 6.01 (2 H, s), 3.59 (2 H, s), 3.36 (2 H, d, *J* 2.3), 2.35 (3 H, s), 2.25 (1 H, t, *J* 2.3). - MS : 282 (25%, M^+) 215 (100%). - Analysis : calc. for $C_{12}H_{12}BrNO_2$ (282.14) C 51.09, H 4.29; found C 51.02, H 4.32%.

N-*Methyl-2-methylthio*-N-*(2-propynyl)piperonylamine* (**1c**) : In a strictly analogous reaction, dimethyl disulfide (2.5 mL, 2.6 g, 28 mmol) was used instead of 1,1,2,2-tetrabromoethane. Upon distillation, a colorless oil was obtained; mp -12 to -11 °C; bp 51 - 53 °C /0.5 mmHg; 4.2 g (68%). - ^{1}H-NMR : δ 6.84 (1 H, d, *J* 7.9), 6.67 (1 H, d, *J* 7.9), 6.01 (2 H, s), 3.62 (2 H, s), 3.31 (2 H, d, *J* 2.4), 2.43 (3 H, s), 2.32 (3 H, s), 2.26 (1 H, t, *J* 2.4). - MS : 250 (100%, M^+ + 1), 181 (30%). - Analysis : calc. for $C_{13}H_{15}NO_2S$ (249.33) C 62.62, H 6.06; found C 62.60, H 6.13%.

2-Bromo-N-*methyl*-N-*(3-trimethylsilyl-2-propynyl)piperonylamine* (**2b**) : At -50 °C, *tert*-butyllithium (25 mmol) in pentane (20 mL) and, 6 h later, 1,1,2,2-tetrabromoethane (2.9 mL, 8.6 g, 25 mmol) were added to *N*-methyl-*N*-(3-trimethylsilyl-2-propynyl)piperonylamine (**2a**, 6.9 g, 25 mmol) in diethyl ether (30 mL). The mixture was absorbed on silica gel (25 mL). Elution with a 3 : 7 (v/v) mixture of diethyl ether and pentane from a column filled with more silica gel (125 mL) afforded a colorless oil; mp -17 to -15 °C, bp 124 - 125 °C/0.4 mmHg; n_D^{20} 1.5385; 6.7 g (76%). - ^{1}H-NMR : δ 6.88 (1 H, d, *J* 7.8), 6.70 (1 H, d, *J* 7.8), 6.03 (2 H, s), 3.58 (2 H, s), 3.35 (2 H, s), 2.33 (3 H, s), 0.32 (9 H, s). - MS : 355 (31%, M^+ + 1), 215 (100%). - Analysis : calc. for $C_{15}H_{20}BrNO_2Si$ (354.32) C 50.85, H 5.69; found C 50.90, H 5.65%.

N-*Methyl-2-methylthio*-N-*(3-trimethylsilyl-2-propynyl)piperonylamine* (**2c**) : A reaction mixture was prepared in the same way as described above (see product **2b**) and treated with dimethyl disulfide (2.5 mL, 2.6 g, 28 mmol). After chromatography (elution with a 1 : 1 mixture of diethyl ether and hexanes) a colorless oil was collected; mp -21 to -20 °C; bp 136 - 138 °C/0.4 mmHg; n_D^{20} 1.5032; 6.7 g (83%). - ^{1}H-NMR : δ 6.84 (1

H, d, *J* 7.9), 6.68 (1 H, d, *J* 7.9), 6.01 (2 H, s), 3.62 (2 H, s), 3.31 (2 H, s), 2.43 (3 H, s), 2.31 (3 H, s), 0.20 (9 H, s). - MS : 311 (40% M^+ + 1), 140 (100%). - Analysis : calc. for $C_{16}H_{23}NO_2SSi$ (321.51) C 59.77, C 7.21; found C 60.10, H 6.93%.

The deprotected acetylenes **1b** (mp 37 - 39 °C) and **1c** (mp -12 to -11 °C) were recovered in 96 and 97% yield when solutions of the silanes **2b** and **2c** (25 mmol) and tetrabutylammonium fluoride trihydrate (12 g, 38 mmol) in tetrahydrofuran (25 mL) were kept 2 h at 50 °C before the product was isolated by extraction and distillation.

3. Bromine/Lithium Exchange Followed by Electrophilic Trapping and Desilylation

N-*Methyl-2-methylthio*-N-*(2-propynyl)piperonylamine* (**1c**) : At 0 °C, 2-bromo-*N*-methyl-*N*-(3-trimethylsilyl-2-propynyl)piperonylamine (**2b**, 8.9 g, 25 mmol) in diethyl ether (25 mL) was treated with butyllithium (25 mmol) in hexane (17 mL) and, 5 min later, with dimethyl disulfide (2.5 mL, 2.6 g, 28 mmol). After 45 min at 25 °C, water (25 mL) was added, the organic phase was separated and the aqueous one extracted with diethyl ether (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried and evaporated. Tetrabutylammonium fluoride trihydrate (12 g, 38 mmol) in tetrahydrofuran (25 mmol) was added to the residue and the mixture was warmed for 2 h to 50 °C. The solvent was evaporated and the residue partitioned between water (25 mL) and diethyl ether (3 × 25 mL). The combined organic layers were washed, dried and evaporated to give product **1c** (see Section 2); 96%.

N-*Hydroxy*-N-*methyl*-N-*(2-propynyl)piperonylamine* (**1d**) : At 0 °C, 2-bromo-*N*-methyl-*N*-(3-trimethylsilyl-2-propynyl)piperonylamine (**2b**, 8.9 g, 25 mmol) in diethyl ether (25 mL) was treated with butyllithium (25 mmol) in hexane (17 mL) and, 5 min later, with fluorodimethoxyborane diethyl etherate (5.0 mL, 4.5 g, 27 mmol). At 0 °C, 35% aqueous hydrogen peroxide (2.6 mL, 3.0 g, 30 mmol) and, after 1 h of vigorous stirring, water (20 mL) were added. The mixture was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 10 mL) and evaporated. The residue was dissolved in tetrahydrofuran (25 mL) containing tetrabutylammonium fluoride trihydrate (12 g, 38 mmol). After 2 h at 50 °C, the solution was absorbed on silica gel (20 mL) and eluted with a 3 : 7 (v/v) mixture of diethyl ether and hexanes from a column filled with more silica (80 mL); mp 54 - 57 °C (from methanol); 3.6 g (66%). - ^{1}H-NMR : δ 6.50 (1 H, d, *J* 7.9), 6.34 (1 H, d, *J* 7.9), 5.95 (2 H, s), 3.76 (2 H, s), 3.41 (2 H, d, *J* 2.4), 2.41 (3 H, s), 2.32 (1 H, t, *J* 2.4). - MS : 219 (28%, M^+), 150 (100%), 135 (39%).- Analysis : calc. for $C_{12}H_{13}NO_3$ (219.24) C 65.74, H 5.98; found C 65.64, H 6.03%.

N-*Methyl-2-phenyl*-N-*(2-propynyl)piperonylamine* (**1e**) : At the beginning, it was proceeded as described in the foregoing paragraph. After the addition of fluorodimethoxyborane, the volatiles were stripped off. Ethanol (15 mL), bromobenzene (2.8 mL, 4.0 g, 25 mmol) in monoethyleneglycol dimethyl ether (0.25 L), tetrakis(triphenylphosphine)palladium (0.9 g, 0.8 mmol) and a 2 M aqueous solution (28 mL) of sodium carbonate (56 mmol) were added. The suspension was heated to reflux for 6 h under stirring, before being filtered and evaporated. A solution of the residue in dichloromethane (0.10 L) was washed with brine (2 × 25 mL), dried and evaporated. After the treatment with tetrabutylammonium fluoride and extraction as described above, product **1e** was collected upon distillation as a colorless viscous oil; mp -11 to - 10 °C; bp 77 - 79 °C /0.4 mmHg; n_D^{20} 1.5805; 6.1 g (87%). - ^{1}H-NMR : δ 7.5 (4 H, m), 7.37 (1 H, tt, *J* 6.7, 2.0), 7.02 (1 H, d, *J* 8.0), 6.81 (1 H, d, *J* 8.0), 5.93 (2 H, s), 3.37 (2 H, s), 3.24 (2 H, d, *J* 2.4), 2.22 (3 H, s), 2.16 (1 H, t, *J* 2.4). - MS : 280 (64%, M^+ + 1), 240 (100%, 211 (56%). - Analysis : calc. for $C_{18}H_{17}NO_2$ (279.34) C 77.40, H 6.13; found C 77.24, H 6.46%.

*2,*N-*Dimethyl*-N-*(2-propynyl)piperonylamine* (**1f**) : The same protocol was applied as described above (see first paragraph of this Section) except that methyl iodide (1.7 mL, 3.9 g, 28 mmol) was allowed to react with the lithiated intermediate. The colorless product was purified by distillation; mp -26 to -25 °C; bp 102 - 103 °C /0.4 mmHg; n_D^{20} 1.5378; 4.9 g (91%). - ^{1}H-NMR : δ 6.76 (1 H, d, *J* 7.8), 6.61 (1 H, d, *J* 7.8), 5.93 (2 H, s), 3.48 (2 H, s), 3.30 (2 H, s, broad), 2.33 (3 H, s), 2.28 (1 H, s, broad), 2.24 (3 H, s). - MS : 218 (24%, M^+ + 1), 149 (100%). - Analysis : calc. for $C_{13}H_{15}NO_2$ (217.27) C 71.87, H 6.96; found C 71.84, H 6.85%.

*5-*N-*Methyl*-N-*2-propynyl-1,3-benzodioxolane-4-carbaldehyde* (**1g**) : The same protocol was applied as described above (see first paragraph of this Section) except that *N,N*-dimethylformamide (2.2 mL, 2.0 g, 28 mmol) was employed to intercept the *ortho*-lithiated intermediate. After the final extraction, the colorless product was isolated by evaporation of the solvent and crystallization of the residue from hexane; mp 131 - 133 °C; 4.5 g (78%). - ^{1}H-NMR : δ 10.36 (1 H, s), 6.89 (1 H, d, *J* 7.8), 6.82 (1 H, d, *J* 7.8), 6.12 (2 H, s), 3.77 (2 H, s), 3.29 (2 H, d, *J* 2.0), 2.31 (3 H, s), 2.28 (1 H, t, broad). - MS : 232 (100%, M^+ + 1). - Analysis : calc. for $C_{13}H_{13}NO_3$ (231.25) C 67.52, H 5.67; found C 67.47, H 5.70%.

*Ethyl 5-*N*-Methyl-*N*-2-propynyl-1,3-benzodioxolane-4-carboxylate* (**1h**) : After the treatment of bromoarene **2b** with butyllithium (see the first paragraph of this Section), the reaction mixture was cooled to -75 °C and slowly poured into a vigorously stirred solution of ethyl chloroformate (2.7 mL, 3.0 g, 28 mmol), equally kept at -75 °C. The residue obtained after filtration and evaporation was dissolved in tetrahydrofuran (25 mL) containing tetrabutylammonium fluoride trihydrate (12 g, 38 mmol). After 2 h at 50 °C, water (50 mL) was added and the product extracted with diethyl ether (3 × 25 mL) before being purified by chromatography (elution with a 3 : 7 mixture of diethyl ether and hexanes) and distillation; bp 84 - 86 °C/0.6 mmHg; n_D^{20} 1.5143; 5.9 g (85%). - ^{1}H-NMR : δ 6.76 (2 H, s), 6.02 (2 H, s), 4.36 (2 H, q, *J* 7.2), 3.66 (2 H, s), 3.23 (2 H, d, *J* 2.4), 2.25 (3 H, s), 2.22 (1 H, t, *J* 2.4), 1.38 (3 H, t, *J* 7.2). - MS : 276 (100%, M^+ + 1), 236 (52%), 190 (21%). - Analysis : calc. for $C_{15}H_{17}NO_4$ (275.30) C 65.44, H 6.22; found C 65.23, H 6.17%.

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