1,3-Dipolar Cycloaddition Reactions of 4-Silacyclohex(hept)-2-en-1-one Derivatives: Synthesis of Novel Azasilabicyclic Compounds

D. Damour, M. Barreau, V. Fardin, F. Dhaleine, M. Vuilhorgne and S. Mignani*

Rhône-Poulenc Rorer S.A. Centre de Recherche de Vitry-Alfortville, 13 Quai Jules Guesde-BP 14, 94403, Vitry-sur-Seine Cedex, France, Fax 33 1 55 71 81 29

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Abstract : [3+2] Cycloaddition reactions of *N*-benzyl-azomethine ylide with 4-silacyclohex(hept)-2-en-1-ones provides novel 3-aza-1-silabicyclo[3.4.0]hexanes and 3-aza-1-silabicyclo[3.5.0] heptanes.

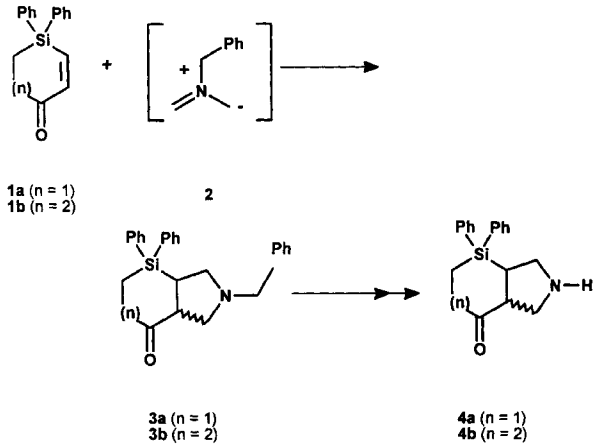
The [3+2] cycloaddition reaction of azomethine ylides with ethylenic compounds represents an outstanding tool in organic synthesis to provide various five-membered nitrogen heterocycles[1], generally with high regio- and stereoselectivities.[2]

To the best of our knowledge, only two [3+2] cycloaddition reactions of azomethine ylide with a carbon-carbon multiple bond bearing a silicon substituent have been described. In both cases, the azomethine ylide used was C-unsubstituted and was generated from trimethylamine-*N*-oxide in presence of a large excess of LDA. Thus, Roussi *et al.* described the preparation of 3-trimethylsilyl-4-phenyl-2,5-dihydro-pyrrole starting from 1-phenyl-2-(trimethylsilyl)acetylene[3], and recently we described the preparation of 5-aza-1,1-diphenyl-1-silabicyclo[3.3.0]-octane derivatives from the corresponding 4-substituted-1-silacyclopent-2-enes.[4] These findings prompted us to study the additions of various azomethine ylides with cyclic β-silyl-substituted α,β-unsaturated ketones. Herein, we wish to report the construction of the novel fused sililano-pyrrole derivative **3a** and the silepano-pyrrole derivative **3b** *via* [3+2] cycloaddition reaction of the azomethine ylide 1,3-dipole **2** with 4-silacyclohex- and 4-silacyclohept-2-enones **1a** and **1b**. The cycloadducts **3a,b** were then *N*-debenzylated to give the corresponding *NH* derivatives **4a,b** as outlined in Scheme 1.[5]

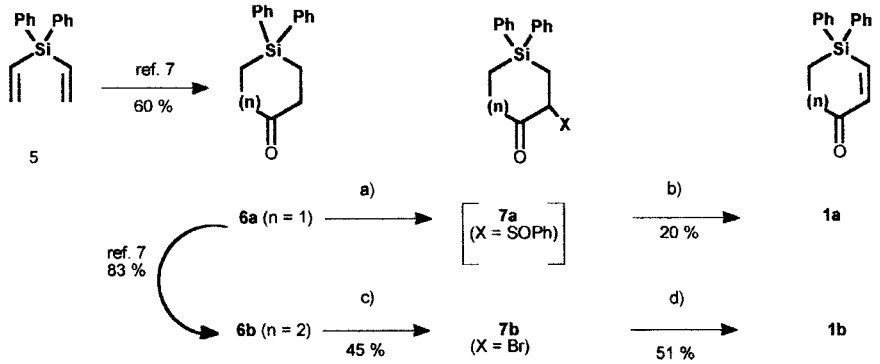
The silacycloalkenones **1a** and **1b** were prepared *via* three- and five-step syntheses, respectively, in ~12% yield, both starting from commercially available divinyldiphenylsilane as shown in Scheme 2.

Thus, 4,4-diphenyl-4-silacyclohexan-1-one[6] **6a** was prepared in a one-step synthesis *via* hydroboration reaction in 60% yield from **5** as described previously[7], whereas 4,4-diphenyl-4-silacycloheptane-1-one **6b** was prepared from **6a** in a two-step synthesis through a one-carbon homologation reaction in 83% overall yield.[7] Silacyclohexanone **6a** was directly transformed to the silacyclohexenone **1a** by the condensation of methyl benzenesulfinate in the presence of NaH affording **7a** which was transformed to **1a**[8] by an elimination of sulfenic acid at room temperature in 20% yield.

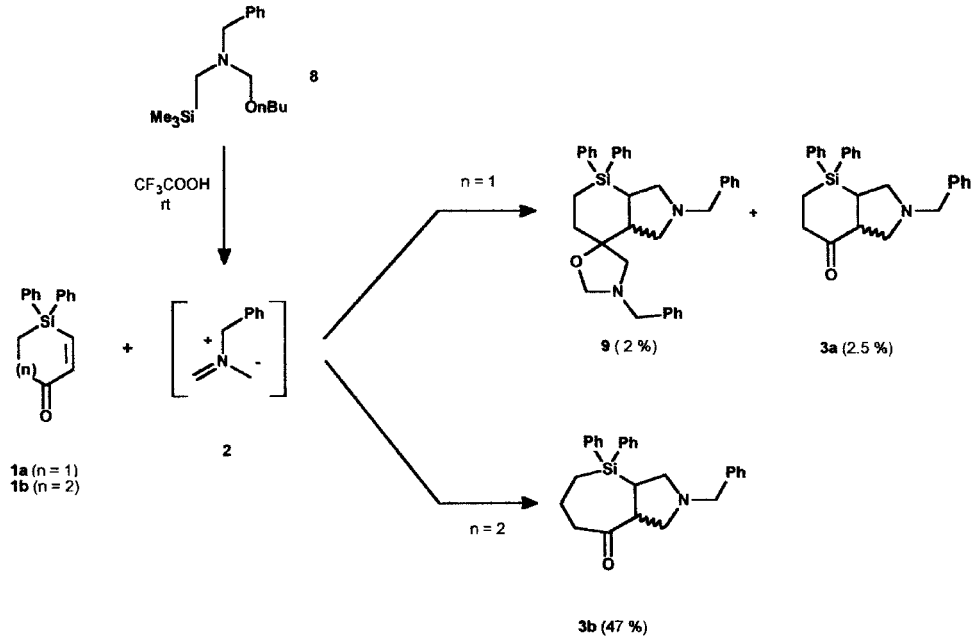
Silacycloheptenone **1b** was synthesized in a two-step synthesis from **6b** which was first converted to the corresponding 2-bromo derivative **7b** in 45% yield under standard radical conditions. β-Elimination in refluxing 2,4,6-collidine generated then the required silacycloheptenone **1b** in 51% yield.



Scheme 1



Scheme 2 . a) preparation of **7a** (not isolated) : **6a**, PhS(O)OMe (for preparation see ref. 9), NaH, diethyl ether, rt, 12 h then 1N HCl at -10°C to rt ; **b) 7a**, CH_2Cl_2, rt, 12 h, 20% ; **c) 6b**, NBS, cat. benzoyl peroxide, CCl_4, reflux, 12 h, 45% ; **d) 7b**, 2,4,6-collidine, reflux, 0.5 h, 51%



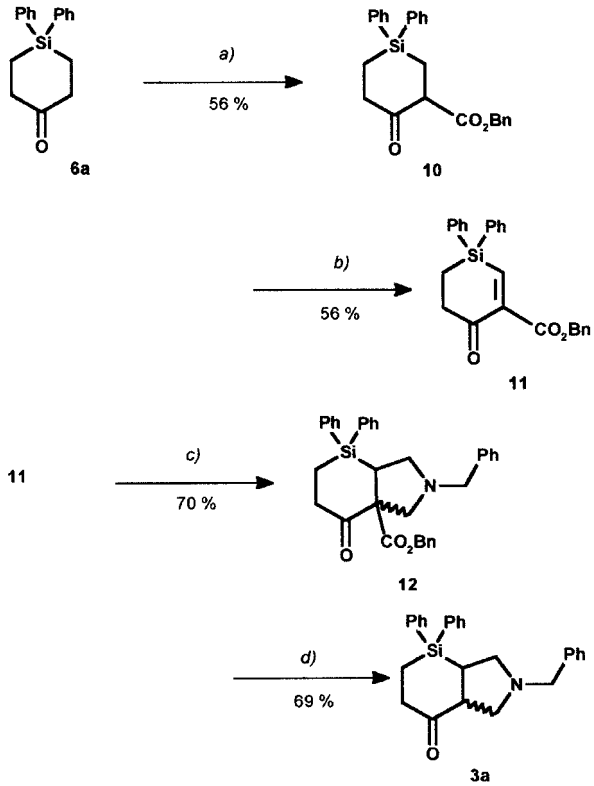
Scheme 3

Once the olefinic dipolarophiles **1a** and **1b** had been prepared, they were subjected to [3+2] cycloaddition reaction with the azomethine ylide **2** generated *in situ* from *N*-*n*-butoxymethyl-*N*-trimethylsilylmethyl benzylamine **8** in the presence of a catalytic amounts of trifluoroacetic acid through an alkoxy elimination and subsequent desilylation process[10] (Scheme 3).

Thus, starting from **1a**, condensation of **8** afforded the desired tetrahydropyrrole derivative **3a** in very low yield (2.5%), besides the oxazolidine-dicycloadduct **9** (2% yield) derived from cycloaddition reactions of two equivalents of ylide **2** with both the carbonyl group and the double bond moieties of **1a**. Surprisingly, cycloaddition of **8** with the seven-membered silacycloheptenone **1b** afforded exclusively cycloadduct **3b**[11] in 47% yield. These studies demonstrate the crucial influence of the size of the β-silyl-substituted α,β-unsaturated ketone dipolarophile on the regioselectivity of the [3+2] cycloaddition. This different behaviour of **1a** and **1b** is probably due to either varied polarization of the conjugated β-silyl α,β-unsaturated ketone system or to steric effects (during the dipole approach) or both.

Investigating alternative routes to **3a**, we found that the [3+2] cycloaddition of **2** with silacyclohexenone **11** afforded cycloadduct **12** in an epimeric ratio of ~4/1[11,12] in 70% yield[13], which was then transformed to **3a**[11] by a tandem hydrogenolysis-decarboxylation reaction in 69% yield (Scheme 4). Introduction of an electron-withdrawing group such as benzyloxycarbonyl in position 2 of **1a** enhanced the reactivity of the carbon-carbon double bond and produced exclusively the mono-adduct **12**.

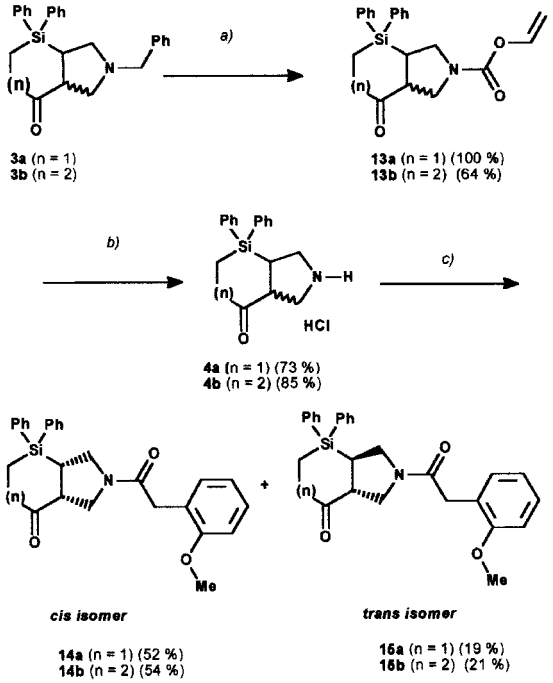
The synthesis of **11** started from **6a**, which was converted to the corresponding 2-benzyloxycarbonyl-4-silacyclohexanone derivative **10** using dibenzylcarbonate as electrophile in the presence of KH in 56% yield. Then, regioselective oxidation of **10** with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in acetic acid/dioxane mixture afforded **11** in 56%. Note that introduction of an electron-withdrawing substituent such as a benzyloxycarbonyl group in position 2 of the carbonyl moiety regioselectively produced the mono-oxidation product **11**, while the same reaction conditions applied to **6a** generated 4,4-diphenyl-4-silacyclohexadien-1-one in 40% yield.[6]



Scheme 4 . a) *1.* **6a**, KH (2.5 eq.), $BnOCO_2Bn$ (1.5 eq.), dioxane, 80°C, 4 h *2.* 10% HCl, 56% ; **b) 10**, DDQ (2 eq.), acetic acid (2.5 eq.), dioxane, 48 h, rt, 56% ; **c) 11** (1 eq.), **8** (2 eq.), CH_2Cl_2, CF_3CO_2H (1.3 eq.), rt, 1 h, 70% ; **d) 12**, MeOH, conc. HCl, Pd/C, H_2 (22 psi), 1 h, 40°C, 69%

With **3a** and **3b** in hand, we turned our attention to the synthesis of *N*-debenzylated derivatives **4a**[11] and **4b**[11] which were crucial starting materials for the preparation of tetrahydropyrrole derivatives **14a,b** and **15a,b** as shown in Scheme 5. The synthesis of these sila-derivatives was

initiated pursuing our goals to prepare either biologically active silicon compounds which do not possess any known carbon counterpart[14] or to study silyl analogues of known bioactive carbon compounds in order to determine the sila-substitution effects.[15]



Scheme 5 . a) **3a** or **3b** (1 eq.), $ClCO_2CH{=}CH_2$ (2 eq.), Et_3N (2 eq.), 1,2-dichloroethane, rt, 2.5 h, **13a** : 100%, **13b** : 64% ; **b)** *1.* **13a** or **13b**, conc. HCl, dioxane, rt, 3 h *2.* EtOH, reflux, 1 h, **4a**: 73.5%, **4b**: 85% ; **c)** preparation of **14a** and **15a** : *1.* preparation of (2-methoxyphenyl)acetyl chloride : (2-methoxyphenyl)acetic acid, ClCOCOCl, cat. DMF, CH_2Cl_2, rt, 1h *2.* **4a**, conc. NaOH, pH = 14 then Et_3N (2 eq.), (2-methoxyphenyl)acetyl chloride, CH_2Cl_2, 0°C to rt, 12 h, **14a** : 52.5%, **15a** : 19.5% ; preparation of **14b** and **15b** : *1.* **4b**, iPr_2NH, CH_2Cl_2, 5°C then (2-methoxyphenyl)acetic acid (1.1 eq.), HOBT (0.15 eq.), EDCI, CH_2Cl_2, 0°C to rt, 3 h, **14b** : 54%, **15b** : 21%

Facile *N*-debenzylation of **3a** and **3b** was achieved using vinyl chloroformate[16] affording **13a**[11] and **13b**[11] in good yields which were then hydrolyzed with a conc. HCl/dioxane mixture to give **4a**[11] and **4b**[11] in 73% and 85% yield, respectively. Pure amide derivatives **14a** and **15a** were obtained by condensation of (2-methoxyphenyl)acetyl chloride under standard conditions giving *cis*-adduct **14a** and *trans*-adduct **15a** in 52% and 19% yield, respectively, after purification by chromatography on silica gel.[17] The condensation of (2-methoxyphenyl)acetic acid in presence of 1-hydroxy-benzotriazole (HOBT) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDCI) with **4b** under standard conditions afforded pure **14b** and **15b** in 54% and 21% yield, respectively.[18]

In summary, we have developed a methodology for the preparation of novel perhydrosilolano[2,3-c]pyrrole derivatives **3a,b** ; **4a,b** ; **14a,b** and **15a,b** based on a 1,3-cycloaddition reaction with 4-silacyclo- hex(hept)-2-enones.

Acknowledgements : We wish to thank A. Renaudon, the analytical team for technical and analytical assistance respectively, J. F. Peyronel and coll. and Prof. G. Manuel (Université Paul Sabatier, Toulouse, France) for interesting and valuable discussions.

References and Notes

(1) For reviews, see : Tsuge, O ; Kanemasa, S. *Advances in Heterocyclic Chemistry*, **1989**, *45*, 231 ; Carruthers, W. *'Cycloaddition Reactions in Organic Synthesis'*, Vol. 8, ed. by Baldwin, J. E. ; Magnus, F. R. S. ; Magnus, P. D. Pergamon Press, **1990**, pp. 269-331 ; Dell, C. P. *Contemporary Organic Synthesis*, **1997**, *4*, 87 and references cited therein.

(2) McDouall, J. J. W. ; Robb, M. A. ; Niazi, U. ; Bernardi, F. ; Schlegel, H. B. *J. Am. Chem. Soc*. **1987**, *109*, 4642 and references cited therein.

(3) Beugelmans, R. ; Chastanet, J. ; Roussi, G. *Heterocycles* **1987**, *26*, 3197.

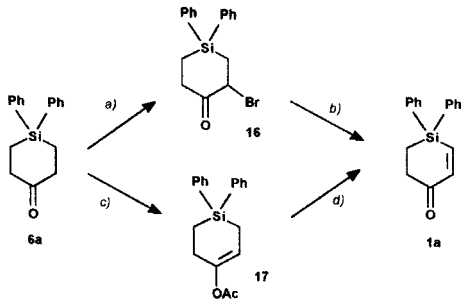
(4) Damour, D. ; Doerflinger, G. ; Mignani, S. *Heterocycles* **1997**, accepted for publication.

(5) All new compounds gave satisfactory analytical and spectroscopic data (^{1}H-NMR, IR, MS); in addition correct elemental analyses has been determined for **14a, b** and **15a, b**.

(6) To the best of our knowledge only 4,4-dimethyl-4-silacyclohex-2-enone has been described: Felix, R. A. ; Weber, W. P. *J. Org. Chem.* **1972**, *37*, 2323.

(7) Damour, D. ; Renaudon, A. ; Mignani, S. *Synlett* **1995**, 111.

(8) Silacyclohexenone **1a** was also prepared in low yield (1-15%) either *via* dehalogenation reaction through the syntheses of compound **16** or *via* decarboxylation-dehydrogenation reaction of **17** using $Pd(OAc)_2$ (see, Minani, I.; Takahashi, K.; Shimizu, I.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971) as depicted in Scheme 6.



Scheme 6 . a) *1.* **6a** (1 eq.), NBS (2 eq.), cat. benzoyl peroxide, CCl_4, relux, 12 h, *2.* flash chromatography on silica gel (CH_2Cl_2), 29% ; **b)** *1.* **16** (1 eq.), DBU (3.5 eq.), THF, -30°C to rt, 5 min. *2.* flash chromatography on silica gel (CH_2Cl_2/cyclohexane, 8/2), 4% ; **c)** *1.* **6a** (1 eq.), PTSA (0.1 eq.), CH_2=C(Me)OAc (0.024 eq.), neat phase, reflux, 12 h *2.* flash chromatography on silica gel (CH_2Cl_2/cyclohexane, 1/1), 73% ; **d)** *1.* **17** (1 eq.), $CH{=}CHCH_2OCO_2Me$ (2 eq.), $Pd(OAc)_2$ (0.1 eq.), $MeOSn(Bu)_3$ (0.2 eq.), MeCN, 80°C, 10 h *2.* flash chromatography on silica gel (CH_2Cl_2), 20%

(9) Field, L.; Locke, J. M. *Org. Syntheses* **1966**, *46*, 62.

(10) Terao, Y. ; Kotaki, H. ; Imai, N. ; Achiwa, K. *Chem. Lett.* **1984**, 1117.

(11) The epimeric ratios for compounds **3a**, **12** and **13a** were ~3/2, ~4/1 and ~3/1 respectively, and were determined by ^{1}H-NMR, whereas for the compound **4b**, the ratio (~1/1) was determined by ^{13}C-NMR. The *cis*-isomers **14a** and **14b** and the *trans*-isomers **15a** and **15b** were isolated in pure form by flash chromatography on silica gel (see Scheme 5). The formation of *cis*- and *trans*-cycloadduct mixture could result from either a non-stereospecific 1,3-cycloaddition reaction (*vs* the cycloaddition of **2** with 4,4-diphenyl-cyclohex-2-en-1-one, see ref. 12) or a subsequent stereo-isomerisation reaction (see for example, Huisgen, R.; Weinberger, R. *Tetrahedron Lett.* **1985**, *26*, 5119 and references cited therein).

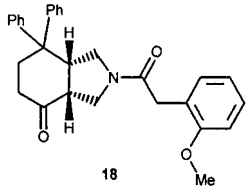
(12) a) Under the same reaction conditions, condensation of *N*-methoxymethyl-*N*-trimethylsilylmethylbenzylamine with 4,4-

diphenyl-cyclohex-2-en-1-one gave only the corresponding *cis*-2-benzyl-7,7-diphenyl-2-perhydroisoindol-4-one in 80% yield (Peyronel, J. F. ; Truchon, A. ; Moutonnier, C. ; Garret, C., *Bioorg. & Med. Chem. Lett.* **1992**, *2*, 37) b) Other examples of stereoselective condensations of azomethine ylides (generated from oxazolidinone or *N*-substituted-*N*-alkoxymethyl-*N*-trimethylsilylmethylamine derivatives) giving only *cis* cycloadducts from the corresponding cyclic enones: see, Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117; Ogata, M. ; Matsumoto, H.; Shimizu, S. ; Nakai, H. ; Motokawa, K. ; Miwa, H. ; Matsuura, S. ; Yoshida, T. *Eur. J. Med. Chem.* **1991**, *26*, 889; Ogata, M. ; Matsumoto, H., Shimizu, S. ; Kida, S. EP 0359172 (*C.A. 114*: 6288); Carmosin, R. J.; Carson, J. R.; Pitis, M. US 5523412 (*C.A. 125*: 142548).

(13) The [3+2] cycloaddition reaction of **11** affording **12** is given hereafter as a representative experimental procedure :
To a stirred solution of **11** (9.4g, 23.6 mmol), *N*-*n*-butoxymethyl-*N*-trimethylsilylmethylbenzylamine (13.1g, 47.2 mmol), CH_2Cl_2 (190 ml) under nitrogen, was added dropwise CF_3CO_2H (2.3 ml, 30 mmol). An exothermic reaction was observed, and the resulting mixture was stirred for 1 h at room temperature. This solution was then neutralized with Na_2CO_3 and the reaction mixture was stirred for an additional 15 min at room temperature. The insoluble precipitate was filtered, and CH_2Cl_2 (20 ml) was then added. The organic phase was concentrated *in vacuo*, and the resulting orange oil was purified by flash chromatography on silica gel (eluant : CH_2Cl_2) to give 8.7g of **12** (70%) as a yellow oil.

(14) For previous work in this field, see : Damour, D., Barreau, M., Dutruc-Rosset, G., Doble, A., Piot, O. Mignani, S. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 415 ; Mignani, S., Damour, D. *Synth. Commun.* **1994**, 2017 ; Boukkerroud, R., Manuel, G., Mignani, S., Damour, D. *J. Organomet. Chem.* **1994**, *484*, 119 ; Mignani, S., Damour, D. *French Patent Applications*, FR 2689892 (*C.A. 120:* 323854) ; FR 2689893 (*C.A. 121:* 9696) ; FR 2689894 (*C.A. 120:* 323853).

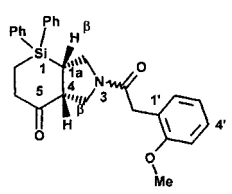
(15) The 7,7-diphenylperhydroisoindol-4-one **18** which is a close C-analogue of **14a**, revealed interesting activity in [3H]-Substance P (SP) binding assay in rat membranes with IC_{50} of 60 nM. (for previous work, see: Fardin, V.; Garret, C. *Eur. J. Pharmacol.* **1991**, *201*, 231; Peyronel, J-F.; Truchon, A.; Moutonnier, C.; Garret, C. *Bioorg. & Med. Chem. Lett.* **1992**, *2*, 37; Peyronel, J-F. ; Tabart, M.; Achard, D.; Malleron, J-L.; Grisoni, S.; Carruette, A.; Montier, F.; Moussaoui, S.; Fardin, V.; Garret, C. *Eur. J. Med. Chem.* **1995**, 30, 576s).



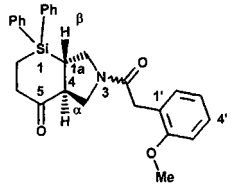
18

(16) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, *18*, 1567.

(17)

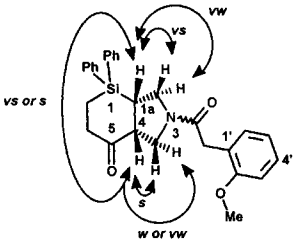


14a



15a

14a: white solid, m.p. 155°C, R_f=0.4 (cyclohexane/AcOEt mixture, 25/75). IR (KBr pellets) ν cm^{-1} : 3425, 3070, 3040, 3005, 2930, 2840, 1705, 1630, 1600, 1585, 1565, 1495, 1460, 1440, 1425, 1250, 1110, 1030, 750 , 700. ^{1}H NMR (DMSO(d6), 600 MHz) (the amide function gives way to an equilibrated mixture of two rotamers A and B in a 6/4 ratio, coalescence occurred at 433 K) δ : 1.55-1.80 (m, 2x2H, H7, A and B), 2.55-2.65 (m, 2x2H, H6, A and B), 2.68 (m, 1H, H1aβ, A), 2.77 (m, 1H, H1aβ, B), 2.85 (d, J=16Hz, 1H, H2α, A), 3.45 (m, 1H, H2β, A), 3.10 (d, J=16Hz, 1H, H2α, B), 3.58 (m, 1H, H2β, B), 3.30 (m, 1H, H4β, A), 4.16 (d, J=9Hz, 1H, H4α, A), 3.08 (m, 1H, H4β, B), 4.08 (d, J=9Hz, 1H, H4α, B), 3.56 (m, 1H, H4aβ, A), 3.40 (m, 1H, H4aβ, B), 3.40 (AB, J=12Hz, 2H, N-COC$\underline{H}_2$-, B), 3.55 (AB, J=12Hz, 2H, N-COC$\underline{H}_2$-, A), 3.60 and 3.88 (two s, 2X3H, -OC$\underline{H}_3$, A and B), 6.85 (t, J=7Hz, H5', 2x1H, A and B), 6.92 (d, J=7Hz, 1H, H3') and 6.97 (d, J=7Hz, 1H, H3') A and B, 7.82 (m, 2x1H, H6', A and B), 7.1-7.6 (m, 2x11H, other phenyl groups, A and B).
^{13}C NMR (DMSO(d6), 100.6 MHz) δ : 7.8 (C7), 25.9 (C6), 27.6 (C1a), 45.8 and 46.6 (C4), 46.6 or 46.9 (C2), 47.0 (N-CO-$\underline{C}H_2$-), 49.8 and 51.5 (C4a), 55.2 (-CH_3), 110.0 (C3'), 120 (C5'), 124.0 (C1'), 136.0 (C4'), 136.0 (C6'), 157.0 (C2'), 168.2 and 168.3 (N-$\underline{C}O$-CH_2-), 210.0 (C5), 133.0 (*ipso*C), 128.0-134.0 (Phenyl groups). NOESY connectivities (400 MHz):



vs: very strong, ***s***: strong, ***m***: medium, ***w***: weak, ***vw***: very weak

MS (EI, 70eV) : m/z 455 ($M^{+\cdot}$), 334, 199, 181, 121, 105, 91 (100%). Anal. Calc. for $C_{28}H_{29}NO_3Si$: C, 73.82 ; H, 6.42 ; N, 3.07 ; Si, 6.16. Found : C, 74.2 ; H, 6.7 ; N, 3.0 ; Si, 6.2.

15a: white solid, m.p. 60°C, R_f=0.6 (cyclohexane/AcOEt mixture, 25/75). IR (KBr pellets) ν cm^{-1} : 3425, 3070, 3040, 3000, 2925, 2850, 1710, 1640, 1600, 1585, 565, 1495, 1465, 1440, 1425, 1245, 1110, 1030, 755, 740, 700, 710.
The relative stereochemistry of **15a** was conferred from **14a**.
^{1}H NMR (DMSO(d6), 250 MHz, the amide function gives way to an equilibrated mixture of two conformers in a 1/1 ratio) δ : 1.40 and 1.80 (m, 2x2H, H7), 2.5-2.9 (m, 2x2H, H6), 2.0-2.1 (m, 2x1H, H1a), 3.0-3.4 (m, 2x2H, H4), 2.95 (t,1H, J=11Hz, H2), 3.3 (m, 1H, H2), 3.90 (dd, 1H, J=7.5 and 11.0Hz, H2), 4.15 (dd, 1H, J=7.5 and 9 Hz, H2), 3.75 (s, 3H, -OC$\underline{H}_3$), 3.80 (s, 3H, -OC$\underline{H}_3$), 3.5 (m, 2x1H, H4a), 3.5 (m, 2x2H, N-COC$\underline{H}_2$-), 6.8-7.2 (m, 2x1H, H6'), 7.3-7.6 (m, 2x11H, other phenyl groups). MS (EI, 70eV) : m/z 455 ($M^{+\cdot}$), 334, 199, 181, 121, 105 (100%). Anal. Calc. for $C_{28}H_{29}NO_3Si$: C, 73.82 ; H, 6.42 ; N, 3.07 ; Si, 6.16. Found : C, 73.7 ; H, 6.9 ; N, 3.0 ; Si, 5.4.

(18) Only the *cis*-adducts **14a** and **14b** inhibited the binding of [^{3}H]-SP to membrane preparations of rat brain with IC_{50} of 136 and 356 nM, respectively, *vs* 60 nM for the carbon analogue **18** (see ref. 15), whereas the *trans*-adducts **15a** and **15b** exhibited very weak binding activities (IC_{50} (3μM).