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NMR-Spectroscopic, computational and mass-spectrometric investigations on the *cis/trans* analogues of 2,3,4-trihydronaphthalene-1-one

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This paper is dedicated to the memory of Professor Dr Marina Attinà

Abstract—NMR-Spectroscopic, computational and mass-spectrometric studies of the *cis/trans* isomers of *N*-[8-(acetylamino)-4-(2,2-dimethyl-1,1-diphenyl-silapropoxy)-6-fluoro-5-methyl-1-one-2,3,4-trihydronaphthyl]acetamide (**1a** and **1b**), obtained as intermediates in the synthesis of an important class of alkaloid molecules, are reported. ^{1}H and ^{13}C NMR analyses show an unusual axial preference of the TBDPSi– (*tert*-butyldiphenylsilyl) group in position 4 in both the isomers. Mass spectrometric evidence demonstrates that *trans* isomer has a higher affinity for ammonium ions than the *cis* isomer and that only the ammonium adduct $[\mathbf{1b}+NH_4]^+$ and the protonated molecule $[\mathbf{1b}+H]^+$ show the fragmentation in which loss of benzene is observed. Moreover, molecular mechanics and semi-empirical calculations indicate that a group of *trans* conformers tend to place one of the phenyl rings of the TBDPSiO– group in a offset π-stacked geometry with the compound's aromatic ring. The combination and the detailed analyses of these experimental and theoretical results could support the π–π interaction obtained as a conformational preference in the *trans* isomer.

1. Introduction

Non-covalent bonding interactions and their influence in molecular organisation, recognition and fragmentation have been the subject of many studies.[1] These interactions define and rule the spatial arrangements adopted by different important molecules and biomolecules and in particular aromatic interactions have been shown to play an important role in many cases.[2]

In this paper we report the preparation and structural characterisation of the *cis/trans* isomers of **1** obtained as intermediates in the synthesis of an important class of alkaloid molecules (Fig. 1B).[3] A conformational analysis of **1** has been performed using ^{1}H and ^{13}C NMR spectroscopy, molecular mechanics and semi-empirical calculations. Electrospray ionisation mass spectrometry (ESI-MS) and low-energy collision-induced dissociation (CID) experiments complete the structural investigation of **1**. The influence of different interactions has been analysed to account for the conformational preferences of isomers **1a** and **1b**.

It is important to emphasize that the characterization of a large molecule such as **1**, via a combination of different techniques, while not always easy, is fundamental since a detailed understanding of the non-covalent interactions that rule the conformational preferences of the *cis/trans* isomers of **1** could lead to a model compound for the rational design of new molecules with specific conformations.

The present study can be seen as a particular example of the importance of π–π and cation–π interactions in defining the spatial arrangements adopted by the molecules.

2. Results

2.1. Synthesis

The *cis/trans* isomers of *N*-[8-(acetylamino)-4-(2,2-dimethyl-1,1-diphenyl-silapropoxy)-6-fluoro-5-methyl-1-one-2,3,4-trihydronaphthyl]acetamide (**1a** and **1b**) were synthesised from methyl 4-(4-fluoro-3-methyl-6-nitrophenyl)butanoate (**2**) by a multistep sequence and each

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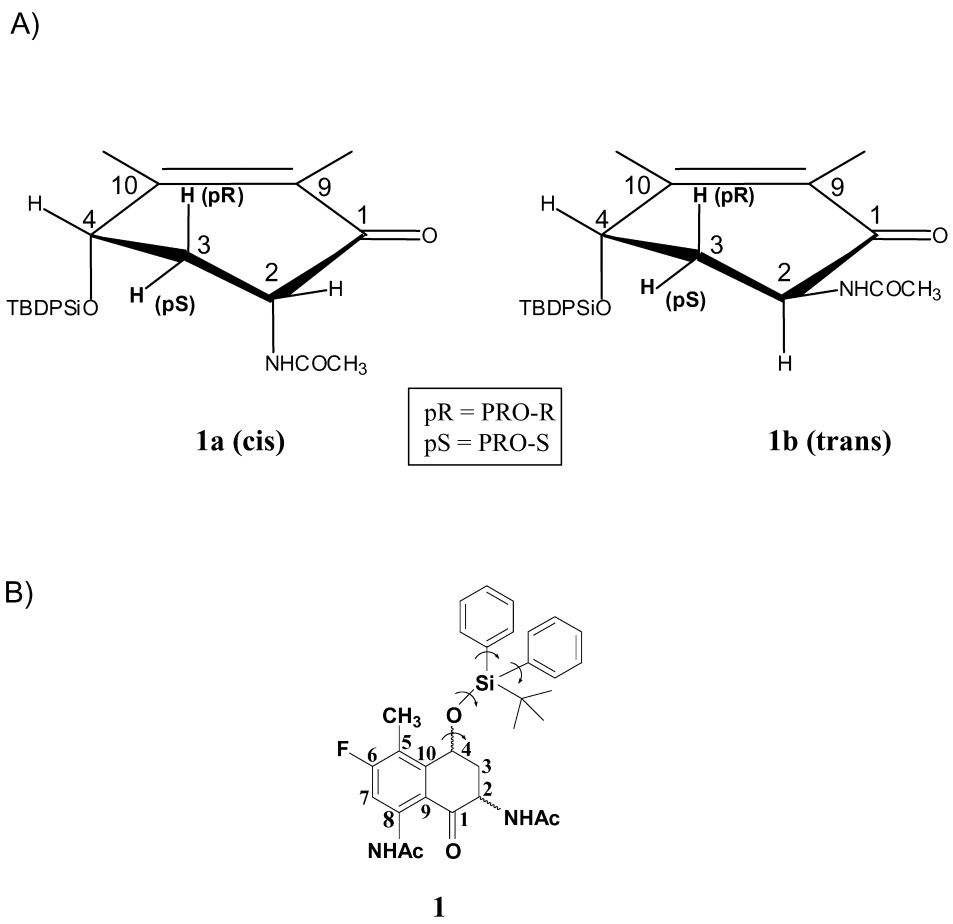


Figure 1. (A) Details of the atoms of **1a** and **1b** used for NMR experiments. (B) Numbering of **1** and bonds (indicated with arrows) used for the conformational studies.

step was repeated several times (Scheme 1).[4] Compound **2** was easily synthesised from 2-fluorotoluene as already described in literature.[5]

2.2. NMR results

The *cis* and *trans* geometries of compounds **1a** and **1b** were established using $^{1}H-^{1}H$ and $^{1}H-^{13}C$ coupling constant data, considering a simple conformational model. An envelope with carbons 1, 2, 9, 10 and 4 in the same plane and C3 out of the plane was obtained as displayed in Figure 1A.

The small value for $^{3}J_{C4H2}$ (2.0–2.5 Hz) and the large value for $^{3}J_{C2H4}$ (9.5–10.0 Hz) defined the *trans* geometry for compound **1b** (Table 1) and indicated the axial position of H2 and the equatorial position of H4 (Fig. 1A). This information was further confirmed by the large axial–axial coupling between H2 and H3pR ($^{3}J_{H2H3}$(pR)=12.5 Hz) and the two small couplings between H4 and H3 ($^{3}J_{H4H3}$(pS)=$^{3}J_{H4H3}$(pR)=2.2 Hz).

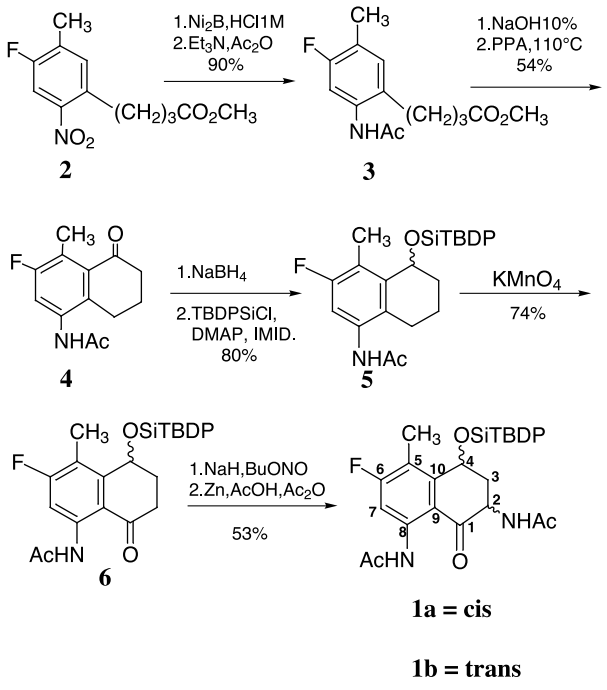
Two similar coupling constants ($^{3}J_{C4H2}$=6.0 Hz and $^{3}J_{C2H4}$=6.5–7.0 Hz) for C4H2 and C2H4 were in agreement with a *cis* configuration for compound **1a**. Also the $^{1}H-^{1}H$ coupling constants confirmed this assignment (Table 1).

2.3. Theoretical results

The conformational analysis of **1a** and **1b** gives two groups of conformers A and B for both isomers. The values of the torsions ϕ ($C_4-C_3-C_2-H_2$, $C_2-C_3-C_4-H_4$, $H_4-C_4-C_3-H_3$(pR), $H_4-C_4-C_3-H_3$(pS), $H_2-C_2-C_3-H_3$(pR), $H_2-C_2-C_3-H_3$(pS), see Fig. 1A) obtained as the average of the values for the structures belonging to the same group, are reported in Tables 2 and 3. The dihedral angles ϕ of each conformer present in groups A and B were used as inputs in the specific Karplus-type equations[6,7] and average values of $^{3}J_{CH}$ and $^{3}J_{HH}$ coupling constants were calculated and are reported in Tables 2 and 3. As shown in bold characters in Tables 2 and 3, experimental $^{3}J_{CH}$ and $^{3}J_{HH}$ obtained in the NMR studies (Table 1) could be satisfactorily explained considering only the conformers of group B for both the *cis* and the *trans* isomers (Fig. 2).

2.4. Mass spectrometric results

The structural characterisation of organic molecules is an important application of mass spectrometry. In many cases mass spectrometry is able to elucidate the stereochemistry of a compound under investigation since the sterically controlled ionic fragmentations involve a transition state easily accessible to one of the stereoisomers.[8] To enhance the stereochemical effects it is important to control the



Scheme 1.

internal energy excess of the precursor ion. Consequently soft-ionisation techniques and low-energy CID experiments have to be used.[9] Furthermore, in the last few years, ESI-MS has become another convenient tool to perform low-energy CID experiments (in source CID)[10] aimed at structural elucidation and compares favourably with other established methods.[10–12]

The ESI-MS spectra of the isomers **1a** and **1b** are strongly affected by the cone voltage differences (C.V.) between the sample cone and the skimmer of the ion source. In Figure 3 the compared ESI-MS spectra of the *cis* (a) and *trans* (b) isomers at 45 V potential difference are shown. The loss of benzene, giving the ion at *m/z* 469 $[M+H-78]^+$, is observed exclusively in the *trans* isomer at any value of the C.V. used, while the ions at *m/z* 291 and 273 are always present in both spectra. The same results were obtained performing the ESI-MS experiments with the VG Quattro mass spectrometer, changing the C.V. up to 60 V [spectra not reported], and in the low-energy CID measurements of the mass selected *m/z* 547 $[\mathbf{1}+H]^+$ and *m/z* 564 $[\mathbf{1}+NH_4]^+$ obtained using VG Quattro mass spectrometer as Triple Quadrupole (Fig. 4).

The MS experiments show clearly that the loss of benzene from the protonated $[\mathbf{1b}+H]^+$ and the ammonium adduct $[\mathbf{1b}+NH_4]^+$ of *trans* isomer is a stereospecific fragmentation process. Moreover, the *trans* isomers apparently have a higher affinity for the ammonium ion than *cis* isomers (Fig. 3 and data not shown). The ions at *m/z* 569 and *m/z* 585 are referred to the adducts between **1** and Na^+ and K^+, respectively.

Relative to the precursor ion $[\mathbf{1}+H]^+$ at *m/z* 547, the ions of *m/z* 291 and 273 from both isomers **1a** and **1b**, have been examined with the energy resolved mass spectrometry (ERMS) curve obtained with in source CID experiments (data not shown)[10] and with low-energy CID measurements. As expected, the ions at *m/z* 273 are generated from the ions of *m/z* 291 in both isomers.

Table 1. $^1H-^1H$ (±0.1 Hz) and $^1H-^{13}C$ (±0.5 Hz) coupling constants (in Hz) of compounds **1a** and **1b** in $CDCl_3$ at 298 K

Isomers	$^3J_{C4H2}$	$^3J_{C2H4}$	$^3J_{H4H3}$(pR)	$^3J_{H4H3}$(pS)	$^3J_{H2H3}$(pR)	$^3J_{H2H3}$(pS)
cis **1a**	6.0	6.5–7.0	2.4	4.1	7.2	3.0
trans **1b**	2.0–2.5	9.5–10.0	2.2	2.2	12.5	5.1

Table 2. *trans* Isomer. Torsions ϕ (°) for the conformers in groups A and B. $^3J_{CH}$ (Hz) and $^3J_{HH}$ (Hz) calculated from the values of ϕ using specific Karplus equations.[6,7] Only the data obtained for group B conformers are in agreement with NMR ($CDCl_3$) experimental results (values in bold)

	$C_4-C_3-C_2-H_2$		$C_2-C_3-C_4-H_4$		$H_4-C_4-C_3-H_3$(pR)		$H_4-C_4-C_3-H_3$(pS)		$H_2-C_2-C_3-H_3$(pR)		$H_2-C_2-C_3-H_3$(pS)	
	ϕ (°)	$^3J_{C4H2}$	ϕ (°)	$^3J_{C2H4}$	ϕ (°)	$^3J_{H4H3}$	ϕ (°)	$^3J_{H4H3}$	ϕ (°)	$^3J_{H2H3}$	ϕ (°)	$^3J_{H2H3}$
Group A	−178	9.4	−85	0.5	37	5.5	155	8.8	60	2.8	−57	3.1
Group B	**−59**	**2.2**	**171**	**9.2**	**−56**	**3.2**	**63**	**2.5**	**−174**	**10.2**	**62**	**2.6**
NMR ($CDCl_3$)		**2.0–2.5**		**9.5–10.0**		**2.2**		**2.2**		**12.5**		**5.1**

Table 3. *cis* Isomer. Torsions ϕ (°) for the conformers in groups A and B. $^3J_{CH}$ (Hz) and $^3J_{HH}$ (Hz) calculated from the values of torsion using specific Karplus equations.[6,7] Only the data obtained for group B conformers are in agreement with NMR ($CDCl_3$) experimental results (values in bold)

	$C_4-C_3-C_2-H_2$		$C_2-C_3-C_4-H_4$		$H_4-C_4-C_3-H_3$(pR)		$H_4-C_4-C_3-H_3$(pS)		$H_2-C_2-C_3-H_3$(pR)		$H_2-C_2-C_3-H_3$(pS)	
	ϕ (°)	$^3J_{C4H2}$	ϕ (°)	$^3J_{C2H4}$	ϕ (°)	$^3J_{H4H3}$	ϕ (°)	$^3J_{H4H3}$	ϕ (°)	$^3J_{H2H3}$	ϕ (°)	$^3J_{H2H3}$
Group A	−50	3.2	82	0.5	−39	5.2	−156	8.9	70	1.9	−172	10.1
Group B	**−154**	**7.8**	**−172**	**9.2**	**59**	**2.9**	**−59**	**2.9**	**−34**	**5.8**	**84**	**1.4**
NMR ($CDCl_3$)		**6**		**6.5–7.0**		**2.4**		**4.1**		**7.2**		**3.0**

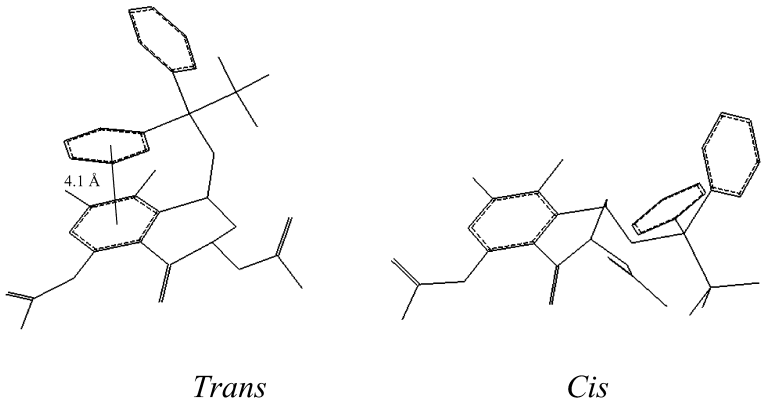


Figure 2. Conformers of group B for *cis* and *trans* isomers of **1**. *trans* Conformers show a preference to place one of the phenyl rings of the TBDPSiO– group in an offset π-stacked geometry with the compound's aromatic ring. The distance between the centroids of aromatic rings is 4.1 Å.

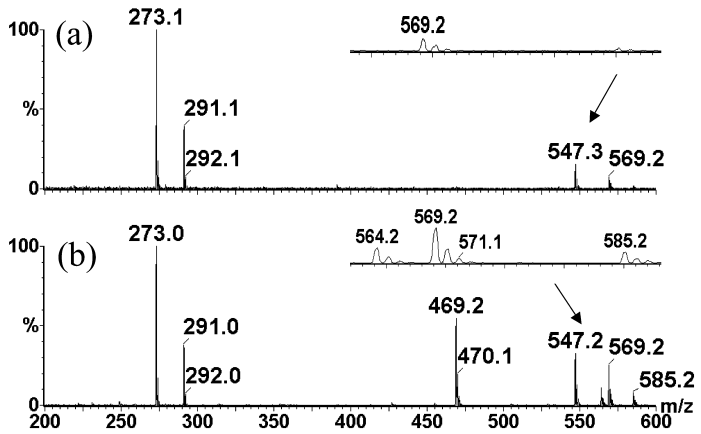


Figure 3. ESI mass spectra of *cis* (a) and *trans* (b) isomers of compound **1** recorded at C.V. 45 V.

3. Discussion

A combination of different techniques (ESI-MS/MS, $^{1}H-^{13}C$ NMR and theoretical methods) have been used to investigate the structure of compounds **1a** and **1b**. The *cis* and *trans* isomers were characterised via ^{1}H and ^{13}C NMR spectroscopy. NMR data (Table 1) indicated the axial preference of the bulky TBDPSiO– group in position 4 in both isomers (Fig. 1A). This axial preference for the most sterically demanding group of compound **1** can be rationalised by the unfavourable interaction between TBDPSiO– group in the equatorial position 4 and the methyl group in position 5 (Fig. 1B).[13,14]

The conformational analysis of **1a** and **1b** performed using molecular mechanics and semi-empirical methods rendered

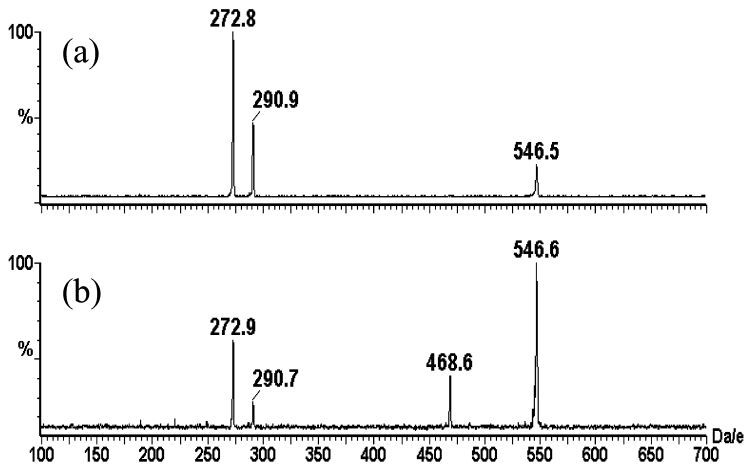
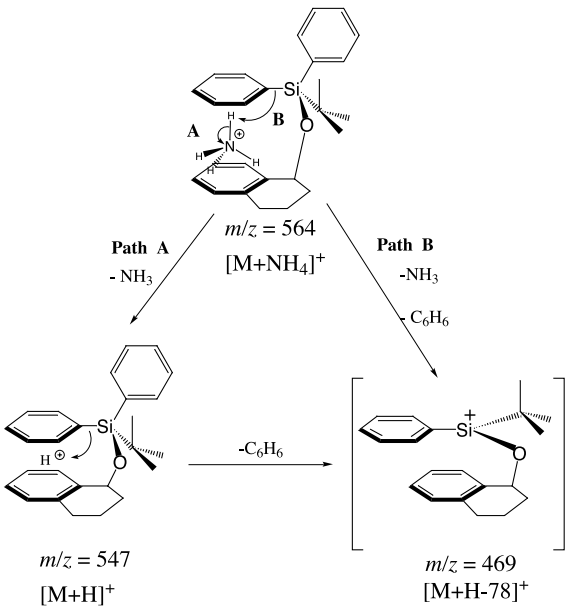


Figure 4. Typical low-energy CID spectrum of the mass selected $[\mathbf{1}+H]^{+}$ ions from *cis* (a) and *trans* (b) isomers recorded in Argon at C.V.=20 V and C.E. (collision energy)=40 V.



Scheme 2. Schematic representation of the possible fragmentation pathways for ions $[\mathbf{1b}+NH_4]^+$ to give fragments at *m/z*=469 $[M+H-78]^+$.

two groups of conformers A and B. The experimental NMR data obtained for these compounds suggested the preference for group B conformers in $CDCl_3$ (Tables 2 and 3). The results indicated that a group of *trans* conformers have a tendency to place one of the phenyl rings of the TBDPSiO– group in an offset π-stacked geometry with the compound's aromatic ring (Fig. 2).[15] On the other hand, ESI-MS and low-energy CID experiments showed that the loss of benzene from the ammonium adduct $[\mathbf{1}+NH_4]^+$ and the protonated molecule $[\mathbf{1}+H]^+$ was a peculiar feature of the *trans* isomer (Figs. 3 and 4). This observation pointed out there must be reacting conformations for ions at *m/z* 547 $[\mathbf{1b}+H]^+$ and 564 $[\mathbf{1b}+NH_4]^+$, but not for *cis* adduct ions, that favour the characteristic fragmentation pathway.

In other mass spectrometric experiments carried out under electron ionisation (EI) conditions (data not shown), where a [1b] radical cation was generated, ions at *m/z* 469 were not observed. These mass spectrometric results suggest a $(NH_4^+/H^+)-\pi$ interaction (Scheme 2) in the *trans* isomer that favours the loss of benzene to form a silylium ion stabilised by a cation–π interaction with the compound's aromatic ring.[16] Moreover, the observed higher affinity for the NH_4^+ cation of **1b** (*m/z*=564) rather than that of the **1a** isomers[17] (Fig. 3 and data not shown) and semi-empirical results for **1b** are consistent with the π–π interaction obtained as a conformational preference in the *trans* isomer (Fig. 2). NMR data, although fundamental in defining the spatial arrangement of the bulky TBDPSiO– group and in theoretical study, were not useful in studying the π–π interaction in *trans* isomer. ^{1}H NMR chemical shifts of H7 (δ 1.80) and of CH_3 (δ 8.40) in C5 have the same values in both *trans* and *cis* isomers. However it is well known[25] that the NMR study of weak attractive intramolecular interactions in relatively flexible organic molecules such as **1** are most valid at low temperature since these interactions are entropically disfavoured in solution at room temperature. For this reason and to eliminate the inevitable limitations of each technique a combination of different methods were used for the structural investigation of **1**. Only mass spectrometric results, supported by semi-empirical study, show clearly that **1b** isomer must have conformations in solution, not present in **1a**, that favour the interactions with cations. These conformations allow easy formation of $[\mathbf{1b}+H]^+$ and $[\mathbf{1b}+NH_4]^+$ ion adducts in solution, which are able to lose benzene in the fragmentation process. We think that these conformations could be those obtained by theoretical calculations where one of the phenyl rings of the TBDPSiO– group is in an offset π-stacked geometry with the compound's aromatic ring.

4. Conclusions

In conclusion, the axial preference of the bulky TBDPSiO– group in **1a** and **1b** observed by NMR studies can be explained by the unfavourable steric interaction between the methyl and the TBDPSiO– group in the equatorial position. Mass spectrometric evidence suggests a π–π interaction between one of the phenyl rings of TBDPSiO– group and the compound's aromatic ring in the *trans* isomer pointing to a higher affinity for the ammonium ion and a characteristic fragmentation pathway in **1b** (Scheme 2). Theoretical results support this view showing that a group of *trans* conformers could tend to place one of the phenyl rings of the TBDPSiO– group in a offset π-stacked geometry with the compound's aromatic ring.

5. Experimental

5.1. General information (for preparation of compounds 3–6)

All reactions involving air- or moisture-sensitive reagents and intermediates were carried out under a nitrogen atmosphere. Dry solvents were from Fluka, and triethylamine (Et_3N) was distilled from CaH_2 and stored under argon over KOH pellets. All the other reagents and solvents were used as received from Aldrich and Fluka. All reactions were monitored by thin layer chromatography, which was carried out on Merck 60 PF_{254} silica gel-coated aluminium sheets.

Proton NMR spectra of the reaction intermediates (**3**–**6**) and carbon NMR spectra of **1b** were obtained on a 300 MHz Varian Gemini (BB) instrument at 298 K using the solvent resonance ($CDCl_3$ or Me_2SO-d_6) as internal standard. ^{1}H NMR of **1a** and **1b** and ^{13}C NMR of **1a** were recorded on a 400 MHz Avance Bruker spectrometer. Chemical shifts are reported in ppm (δ). ESI+/MS spectra of intermediates (**3**–**6**) were carried out using a Single (ZMD, Micromass, UK) Quadrupole at low C.V. Elemental analyses were carried out by REDOX snc (Milan, Italy).

Matrix assisted laser desorption ionization (MALDI) mass spectra of **1a** and **1b** were obtained on a Reflex IV time of flight (TOF) mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with a SCOUT source. Data were acquired in the positive reflectron delayed extraction mode of operation. High-resolution mass spectra of **1a** and **1b** were recorded on a Micromass Analytical Autospec

spectrometer in EI+ condition and the *m/z* of the fragment ion at 273 is reported.

5.1.1. Preparation of methyl 4-(6-acetylamino-4-fluoro-3-methyl)butanoate (3). To a solution of compound **2** (1.1 g, 4.3 mmol) in CH_3OH (75 mL) and HCl 1 M (19 mL) was added Ni_2B (1.3 g, 10.3 mmol), freshly prepared as described in literature.[18] After stirring for 30 min at 60°C, the reaction mixture was diluted with water and the pH was approximately adjusted to a value of 8 with 15% NH_3 solution. The mixture was extracted with Et_2O, dried with Na_2SO_4 and evaporated in vacuo. The residue, a yellow oil (0.88 g, 3.9 mmol) was dissolved in CH_2Cl_2 (150 mL) and Et_3N (0.67 mL) and Ac_2O (0.46 mL) were added under stirring. After 1 h, the solution was diluted with $CHCl_3$, washed with 0.1 M HCl, saturated $NaHCO_3$ and saturated NaCl. The mixture was dried (Na_2SO_4) and concentrated in vacuo to give **3** as yellow oil (0.94 g, 3.5 mmol, yield 90%). The latter was used without purification in the successive reaction. ^{1}H NMR ($CDCl_3$); 1.78 (2H, m, $-CH_2-CH_2-CH_2-$) 2.21 (3H, s, CH_3CON), 2.34 (3H, s, $ArCH_3$), 2.36 (2H, m, $-CH_2CO_2-$), 2.60 (2H, m, $ArCH_2-$), 3.81 (3H, s, $-CO_2CH_3$), 6.95 (1H, d, ^3J=9 Hz), 7.87 (1H, d, ^3J=12 Hz), 8.38 (1H, bs, NH); ESI-MS: *m/z* 268.0 $[M+H]^+$ (100%) 285.0 $[M+NH_4]^+$ (55%). Anal. calcd (%) for $C_{14}H_{18}NO_3F$: C 61.47; H, 6.58 N 5.12; F 6.94. Found: C 61.95; H 6.85; N 4.98; F 6.77.

5.1.2. Preparation of 5-acetylamino-7-fluoro-8-methyl-1-tetralone (4). To a solution of compound **3** (1.2 g, 4.5 mmol) in CH_3OH (10 mL) was added 10% NaOH (3.5 mL). The mixture was stirred for 20 h at room temperature, concentrated and acidified with 37% HCl solution to give a white precipitate that was filtered, washed with water and dried. The residue (1.0 g, 3.9 mmol) was slowly added to preheated (110°C) polyphosphoric acid (PPA, 16 mL) and the mixture stirred for 2 h at 100°C. The reaction was cooled at room temperature and carefully quenched by the slow addition of ice–water and the mixture extracted with ethyl acetate, washed with saturated $NaHCO_3$ and saturated NaCl. The organic phase was dried (Na_2SO_4), evaporated in vacuo and the residue was triturated with CCl_4, filtered and dried to give a pale yellow solid (0.5 g, 2.1 mmol, yield 54%). The latter was used without purification in the successive reaction. ^{1}H NMR ($CDCl_3$); 2.12 (2H, m, $-CH_2-CH_2-CH_2-$), 2.32 (3H, s, CH_3CON), 2.48 (3H, s, $ArCH_3$), 2.59 (2H, m, $-CH_2CO$), 2.83 (2H, m, $ArCH_2-$), 7.01 (1H, bs, NH), 7.57 (1H, d, ^3J=12 Hz, ArH);); ESI-MS: *m/z* 235.8 $[M+H]^+$ (100%) 252.9 $[M+NH_4]^+$ (20%). Anal. calcd for $C_{13}H_{14}NO_2F$: C, 66.31; H, 5.95; N, 5.95; F, 8.08. Found: C, 66.93: H, 6.10; N, 5.27; F, 7.99.

5.1.3. Preparation of 5-acetylamino-1-(2,2-dimethyl-1,1-diphenyl-silapropoxy)-7-fluoro-8-methyl-1,2,3,4-tetrahydronaphthalene (5). To a stirred solution of compound **4** (0.6 g, 2.6 mmol) in absolute EtOH (12 mL) and THF (1 mL) at room temperature was added $NaBH_4$ (97 mg, 2.6 mmol). After 2 h the reaction mixture was diluted with $CHCl_3$, shaken for 20 min with 10% citric acid and washed with saturated NaCl. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The residue was triturated with CCl_4, filtered and dried to give a white solid (0.46 g, 1.9 mmol). This was dissolved in anhydrous CH_2Cl_2 (15 mL) and a mixture of imidazole (IMID., 0.48 g, 7 mmol), 4-(dimethylamino)pyridine (DMAP., 23 mg, 0.19 mmol) and *tert*-butyldiphenylsilyl chloride[19] (1.2 mL, 4.5 mmol) was added at room temperature. After 20 h the solution was diluted with CH_2Cl_2, washed with 1 M HCl solution and saturated NaCl. The organic extracts were dried (Na_2SO_4), evaporated in vacuo and the residue triturated with diethyl ether/acetone (2:1), filtered and dried to give a white solid (0.72 g, 1.6 mmol, yield 80%). The latter was used without purification in the successive reaction. ^{1}H NMR (Me_2SO-d_6); 1.04 (9H, m, $(CH_3)_3CSi$), 1.46 (2H, m, $-CH_2-CH_2-CH_2-$), 1.69 (3H, s, $ArCH_3$), 1.80 (2H, m, $-CH_2CHO$), 2.15 (3H, s, CH_3CON), 2.78 (2H, m, $ArCH_2-$), 4.64 (1H, t, ^3J=3 Hz, $-CHO$), 7.34 (1H, d, ^3J=12 Hz, ArH), 7.40–7.77 (10H, m, $(Ar)_2Si$), 9.21 (1H, bs, NH). ESI-MS: *m/z* 493 $[M+NH_4]^+$ (100%). Anal. calcd (%) for $C_{29}H_{34}NO_2FSi$: C 72.22; H 7.05; N 2.90; F 3.94. Found: C 72.49; H 7.19: N 2.91; F 3.67.

5.1.4. Preparation of 8-acetylamino-4-(2,2-dimethyl-1,1-diphenyl-silapropoxy)-6-fluoro-5-methyl-1-one-2,3,4-tetrahydronaphthalene (6). To a solution of **5** (0.13 g, 0.27 mmol) in acetone (6.4 mL) and 15% aqueous $MgSO_4$ (0.64 mL) was added $KMnO_4$ (210 mg, 1.4 mmol) in portions at 0°C. After stirring for 2 h at room temperature the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with saturated $NaHCO_3$ and saturated NaCl, dried (Na_2SO_4) and evaporated. The crude material was purified by flash chromatography (Merck silica gel 60, 230–400 mesh) using petroleum ether–ethyl acetate (1:4) as eluent to give compound **6** (93 mg, 0.2 mmol, yield 74%). The latter was used without further purification in the successive reaction. ^{1}H NMR (Me_2SO-d_6); 1.03 (9H, m, $(CH_3)_3CSi$), 1.62 (3H, s, $ArCH_3$), 2.08 (2H, m, $-CH_2CHO$), 2.19 (3H, s, CH_3CON), 3.11 (2H, m, $-CH_2CO$), 5.25 (1H, bs, -CHO), 7.34–7.67 (10H, m, $(Ar)_2Si$), 8.29 (1H, d, ^3J=12 Hz, ArH), 11.86 (1H, bs, NH). ESI-MS: *m/z* 507 $[M+NH_4]^+$ (100%). Anal. calcd (%) for $C_{29}H_{32}NO_3FSi$: C, 71.22; H 6.55; N 2.87; F 3.89. Found: C 71.49; H 6.68: N 2.84; F 3.77.

5.1.5. Preparation of *N*-[8-(acetylamino)-4-(2,2-dimethyl-1,1-diphenyl-silapropoxy)-6-fluoro-5-methyl-1-one-2,3,4-trihydronaphthyl]-acetamide (1a and 1b). To a solution of compound **6** (480 mg, 0.98 mmol) in anhydrous THF (10 mL) was added a suspension of NaH (35 mg, 1.5 mmol) in anhydrous THF (5 mL). After stirring under a nitrogen atmosphere for 1 h, *n*-butyl nitrite (*n*-BuONO, 0.25 mL) was added. After 2 h the yellow–orange reaction mixture was acidified with 1 M HCl solution and diluted with $CHCl_3$. The organic phase was washed with saturated NaCl, dried (Na_2SO_4) and evaporated in vacuo. The residue (415 mg, 0.80 mmol) was dissolved in AcOH/Ac_2O (1:1; 18 mL) and zinc powder (630 mg, 9.6 mmol) was added. After stirring for 40 h the reaction mixture was carefully filtered and the grey solid was successively washed with AcOH and $CHCl_3$. The combined filtrate was evaporated to dryness and the residue was dissolved in $CHCl_3$, washed with saturated NaCl, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue on silica gel using petroleum ether–ethyl acetate (from 1:1 to 1:4) as eluent gave the mixture of the diasteroisomers **1a**, **1b**

(232 mg, 0.42 mmol, yield 53%). Further purification by semi-preparative HPLC [Merck column, LiChrosphere 100 RP-18 (10 μm), 250×10 mm, CH_3CN+0.1% TFA: H_2O+0.1% TFA, 80:20 at the flow rate of 3.5 mL/min] gave the separate stereoisomers **1a** and **1b** (Fig. 1 and Scheme 1).

cis **1a**. ^{1}H NMR ($CDCl_3$); 0.90 (9H, m, $(CH_3)_3CSi$), 1.80 (3H, s, CH_3Ar), 2.10 (3H, s, C*H*$_3$CONHCH), 2.15 (1H, m, ^3J=15.0, 2.4, 7.2 Hz, H3pR), 2.20 (3H, s, C*H*$_3$CONHAr), 2.80 (1H, dt, ^3J=15.0, 3.0, 4.1 Hz, H3pS), 4.85 (1H, m, ^3J=8.2, 7.2, 3.0 Hz, H2), 5.30 (1H, dd, ^3J=4.1, 2.4 Hz, H4), 6.60 (1H, d, ^3J=8.2 Hz, CHN*H*COCH$_3$), 7.29–7.76 (10H, m, $(Ar)_2Si$), 8.40 (1H, d, ^3J=12 Hz, H7), 11.10 (1H, s, ArN*H*COCH$_3$). ^{13}C NMR (Me_2SO-d_6): 10.0 (CH_3Ar), 19.0 ($(CH_3)_3CSi$), 22.3 (–CHNHCO*C*H$_3$), 25.0 (ArNHCO*C*H$_3$), 26.3 ((*C*H$_3$)$_3$CSi), 35.8 (C3), 51.3 (C2), 65.7 (C4), 106.0 (C7), 117.0 (C9); 127.5, 127.8, 134.0, 134.8, 135.0 ($(Ar)_2Si$); 139.0 (C8), 147.0 (C5), 149.0 (C10), 163.0 (C6), 169.0 (CONH), 197.0 (C1). MALDI MS: *m*/*z*: found 569.24 [M+Na$^+$]. HR-MS: *m*/*z*: found 273.1030, calcd for $C_{15}H_{14}FN_2O_2^+$: 273.1039.

trans **1b**. ^{1}H NMR ($CDCl_3$); 1.00 (9H, m, $(CH_3)_3CSi$), 1.80 (3H, s, CH_3Ar), 2.10 (3H, s, C*H*$_3$CONHCH), 2.20 (3H, s, C*H*$_3$CONHAr), 2.45 (2H, m, H3pS and H3pR), 5.15 (1H, t, ^3J=2.2 Hz, H4), 5.55 (1H, m, ^3J=12.5, 6.5, 5.1 Hz, H2), 6.15 (1H, d, ^3J=6.5 Hz, CHN*H*COCH$_3$), 7.30–7.78 (10H, m, $(Ar)_2Si$), 8.50 (1H, d, ^3J=12 Hz, H7), 11.10 (1H, s, ArN*H*COCH$_3$). ^{13}C NMR (Me_2SO-d_6): 10.2 (CH_3Ar), 19.7 ($(CH_3)_3CSi$), 23.3 (–CHNHCO*C*H$_3$), 26.0 (ArNHCO*C*H$_3$), 27.1 ((*C*H$_3$)$_3$CSi), 37.0 (C3), 50.7 (C2), 66.0 (C4), 106.5 (C7), 117.0 (C9); 128.3, 130.9, 132.9, 135.1, 135.9, ($(Ar)_2Si$); 142.0 (C8), 146.0 (C5), 151.0 (C10), 164.5 (C6); 170.5, 171.0 (CONH), 200.0 (C1). MALDI MS: *m*/*z*: found 569.20 [M+Na$^+$]. HR-MS: found 273.1043, calcd for $C_{15}H_{14}FN_2O_2^+$: 273.1039.

5.2. NMR spectroscopy

^{1}H NMR spectra of **1a** and **1b** were recorded in $CDCl_3$ (Aldrich), on a 400 MHz Avance Bruker spectrometer, equipped with *z*-shielded gradient inverse detection probe, using tetramethylsilane (0.00 ppm, ^{1}H NMR) as internal standard. Chemical shifts (δ, ppm) in the case of multiplets are measured from the approximated centre.

^{1}H–^{13}C coupling constants were measured applying the phase-sensitive HMBC experiment described in Ref. 20 on a 5 mM sample of **1a** and **1b** in $CDCl_3$, at 298 K. The acquisition times t_2 and t_1 were 1.3 s (spectral width 6410 Hz, 8 K complex data points) and 3 ms (spectral width 20, 100 Hz, 64 real data points), respectively. The relaxation delay was 2 s; 80 scans were accumulated per t_1 increment.

5.3. Computational methods

The conformational preferences of *cis* **1a** and *trans* **1b** molecules were investigated using a combination of molecular mechanics and semi-empirical methods. For both **1a** and **1b** two structures were built with C3 out of plane by +55° and −55°, respectively. The four structures were employed as starting points to perform a systematic search, in steps of 30°, for the four bonds indicated in Figure 1B. The conformers' energy was then minimised with molecular mechanics and after removing duplicate minima, 39 conformers for **1a** and 32 for **1b** were obtained. Molecular mechanics calculations were performed in Sybyl[21] with the Tripos force field[22] using the vacuum dielectric constant and without non-bonded cut off. Geometries of the molecular mechanics minima were then optimised with the semi-empirical AM1[23] method using PC Spartan Pro[24] software. For parameters affecting SCF and geometry optimisation Spartan default values were used except for the application of mmok and hess=unit options. Removing duplicate structures after semi-empirical geometry optimisation 27 conformers for **1a** and 26 for **1b** were obtained. Final structures were grouped considering the similarity of the dihedral angles (ϕ) C_4–C_3–C_2–H_2 and C_2–C_3–C_4–H_4 (Fig. 1). Two groups of conformers (named A and B) were obtained for both isomers **1a** (15 conformers for A and 12 conformers for B) and **1b** (11 conformers for A and 15 conformers for B).

5.4. Mass spectrometry

ESI/MS and low-energy CID measurements in the positive ion-mode were carried out using a Single (ZMD, Micromass, UK) and a Triple (TQ, VG Quattro, Micromass, UK) Quadrupole mass spectrometers, respectively.

The *cis* and *trans* isomers of **1** were separately dissolved in CH_3CN or CH_3OH (0.5 μg/μL) and 50 μL of this solution was added to a mixture of CH_3CN/H_2O (1:1) containing CH_3COONH_4 (2 mM). The sample was introduced into the source in the infusion mode (syringe pump Harvard Apparatus, Model 11) at a flow rate of 7 μL/min. The ESI-MS spectra of both isomers were recorded under the same experimental conditions (source temperature and desolvation temperature=100°C, cone N_2 flow=98 L/h, desolvation N_2 flow=488 L/h and capillary voltage=3.67 kV) changing only the sampling cone voltage from 10 to 90 V.

In the low-energy CID experiments the ions generated in the ESI source (source temperature=85°C, desolvation N_2 flow=150 L/h, nebulizing N_2=10 L/h and capillary voltage=3.80 kV) were mass selected in the first quadrupole (Q1) and allowed to collide with Argon in the RF-only Hexapolar Cell (Q2) at a collision energy (C.E.) of up to 90 V (lab Frame). The charged products were analysed at the frequency of 400 amu/s in MCA (Multi Channel Analysis) mode.

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