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Synthesis and NMR configurational study of Imidazo[2,1-b]thiazoles from 1*H*-1,4-Diazepine-7(6*H*)-thiones

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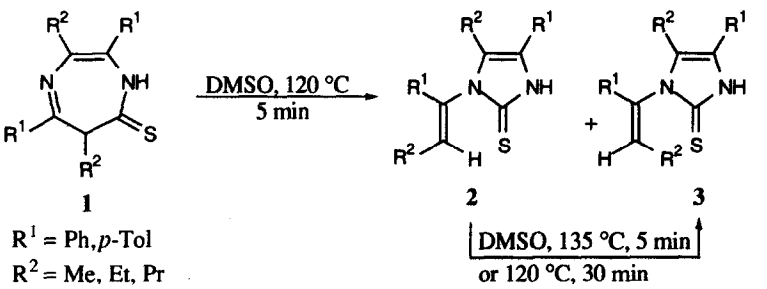
Key Words: 1*H*-1,4-diazepine-7(6*H*)thiones; imidazo[2,1-b]thiazoles; HMQC; HMBC

Abstract: A thermal intramolecular cyclization of 1-vinyl-2,3-dihydro-3*H*-imidazole-2-thiones to imidazo[2,1-b]thiazoles is reported. A heteronuclear correlation study of these systems was made in order to establish the configuration of the products.

One important characteristic of unsaturated seven-membered heterocyclic compounds is their ability to rearrange to smaller cyclic systems [1]. In this way a great variety of five [2] and/or six [3] membered rings containing one or several heteroatoms can be obtained.

We have recently applied this feature to the synthesis of 1-vinyl-2,3-dihydro-3*H*-imidazole-2-thiones by a thermal contraction of 1*H*-1,4-diazepine-7(6*H*)-thiones **1** [4]. Thus, on heating of compounds **1** at 120°C a mixture of two imidazole derivatives **2** and **3** isomeric around the vinyl moiety is detected, which upon increasing the temperature to 135°C rapidly interconvert to yield the more stable *Z* form **3** (Scheme 1). This procedure affords a regioselective way of access to *N*-vinylimidazole-2-thiones avoiding the problems encountered in the direct vinylation process (*i.e.* low yields and lack of regioselectivity) carried out on the imidazole ring itself [5].

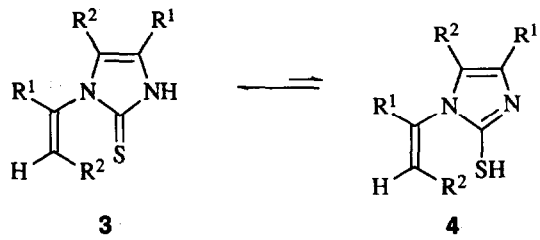


1
R^1 = Ph, *p*-Tol
R^2 = Me, Et, Pr

2 **3**

Scheme 1

Imidazoles **3** can adopt two tautomeric structures (Scheme 2), but variable temperature ^{1}H-NMR experiments carried out in chloroform-*d* and toluene-d_8 showed the presence of a single tautomer in solution. This is easily assigned to the thioamide form based on the long range correlations observed by 2D proton-carbon correlation spectroscopy [4].



3 **4**

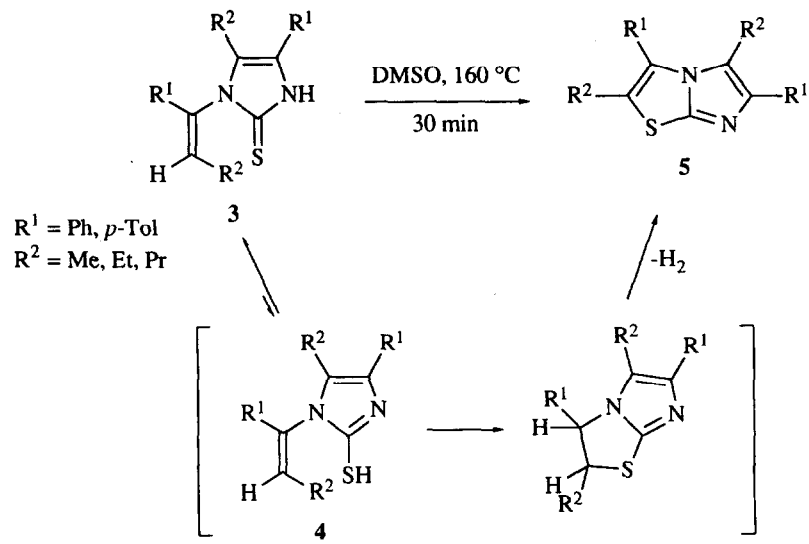
Scheme 2

Compounds **3** contain two nucleophilic centers, i.e. the sulphur atom and the β-carbon of the *N*-vinyl substituent, placed in a 1,5 arrangement, so that no further reaction between them should be expected.

However, the aromatic imidazole ring present in tautomer **4** could reverse the charge density distribution on the vinyl moiety and promote an umpolung intramolecular cyclization. In this way, imidazo[2,1-b]thiazole derivatives could be obtained, a class of compounds well known by their biological and pharmacological activity [6].

In fact, the reverse reaction has been reported by Spicer [7] and more recently by Isomura *et al.* [8] for tetrahydroimidazo[2,1-b]thiazoles. Their ring fission by treatment with ^{t}BuOK in DMSO affords the corresponding *N*-vinylimidazole-2-thiones. Moreover, hydrogen bond interaction between the sulphur and the C_α carbon of vinyl substituents in 1,3-divinylimidazoline-2-thione has been spectroscopically established [9].

In principle, two strategies can be envisaged for favoring the structure **4** over **3**: a) by addition of a base, or b) thermally, with the concomitant help of high polar solvents. Taking into account the synthetic process affording the *N*-vinylimidazoles **3** we choose the second option as the most appropriate. Effectively, heating of **3** in DMSO at 160°C for 5 minutes affords imidazo[2,1-b]thiazol **5** which is isolated in quantitative yield after column chromatography purification. The reaction can be easily carried out (and monitored step by step by ^{1}H-NMR) starting from the diazepines **1**, thus allowing the conversion of **1** into **5** to be accomplished in a clean one-pot reaction.



3 **5** **4**

Scheme 3

A plausible reaction pathway assumes that at the working temperature, the thioamide functionality of **3** tautomerizes to the thiolimide **4**, which in an intramolecular fashion adds to the *N*-vinyl substituent. The intermediate compound thus obtained would dehydrogenate to the more stable bicyclic system **5**, which is eventually isolated (see Scheme 3, Table).

Table. Imidazo[2,1-b]thiazoles **5** and imidazo[2,1-b]-2,6-dihydro-3*H*-1,3-thiazine **6d**.

Compound	R^1	R^2	Yield (%)
5a	C_6H_5	CH_3	97
5b	*p*-CH_3-C_6H_4	CH_3	96
5c	C_6H_5	C_2H_5	96
5d + 6d	C_6H_5	C_3H_7	92

The structural identification of **5** was based on their mass and spectroscopic data. The EI mass spectra of **5** indicates the loss of a molecule of hydrogen in relation to the molecular weight of imidazoles **3**.

On the ^{1}H-NMR spectra, the most remarkable changes are the disappearance of the signals corresponding to the NH and the vinylic protons present in the parent imidazoles **3**. On the other hand, a marked upfield shift of the former thiocarbonyl carbon in **3** is observed in the ^{13}C-NMR spectra of imidazothiazoles **5**. This shift is consistent with a decrease in the bond order of the carbon-sulphur bond [10].

The structural assignment can be accomplished by considering compound **5** as constituted by two main blocks of proton and carbon signals, linked together through heteroatoms to an isolated quaternary carbon atom.

The connectivity within each block is established in the usual way by means of two dimensional proton to carbon correlations through one and several bonds. For this porpouse we used the indirect detection pulse sequences HMQC [11] and HMBC [12] (see experimental section) and the results for **5b** are depicted in Figure 1.

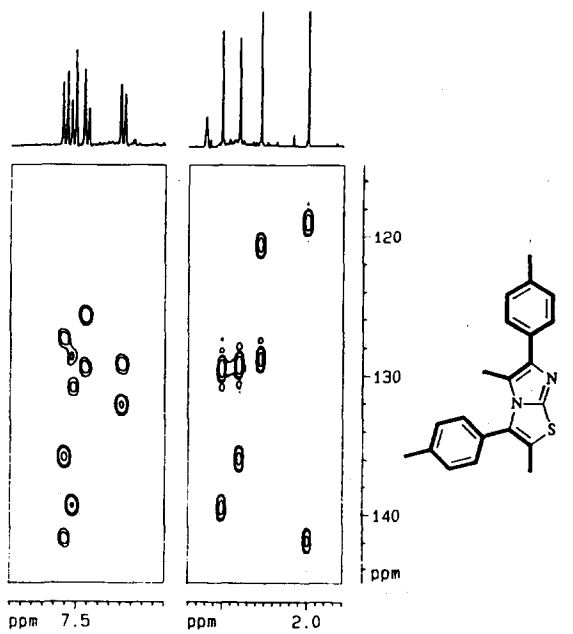


Figure 1. Part of the 2D HMBC spectrum of 5b showing the connections in bold face on the adjacent formula.

Even though each block of signals contain the same group of protons and carbons, they can be easily assigned as belonging to the thiazoles or imidazole ring by comparing their ^{13}C chemical shifts with those of the parent *N*-vinylimidazoles **3**.

This assignment was further confirmed by NOE-difference spectroscopy. From the two alkyl groups bonded to the bicyclic system of **5** only one should exhibit NOE enhancement over two different types of aromatic proton signals. This is illustrated on Figure 2 again for **5b**. Moreover, the methyl group sandwiched by the two aromatic rings appears at the lowest chemical shift probably due to the diamagnetic shielding anisotropy effect of these rings, thus suggesting that the aryl substituents are not fully coplanar with the heteroaromatic system due to steric interactions.

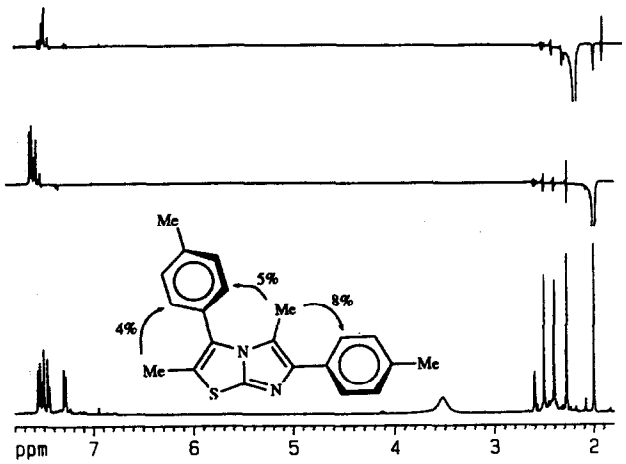


Figure 2. Steady-state NOE enhancements observed by selective presaturation of the methyl groups bonded to the heteroaromatic system in **5b**.

Finally, the only carbon atom which lacks any correlation with protons, can be safely assigned to the bridge between both heterocyclic substructures.

The reaction described here represents a regioselective synthesis of imidazo[2,1-b]thiazoles starting from 1*H*-1,4-diazepine-7(6*H*)-thiones and provides an alternative to other synthetic approaches of this kind of systems [13].

Only when **1d** was heated at 160°C a second product **6d** was formed together with **5d**, their relative ratio being 1:1. All attemps to separate the mixture failed. Even in the EI mass spectrum is observed a single ionization curve for the mixture, *i.e.* both compounds are isomers.

Fortunately, all the aliphatic signals in the ^{1}H- and ^{13}C-NMR spectra are resolved enough at a field of 9.4 T to identify each compound by applying the same procedure outlined above.

The 2D HMQC and HMBC spectra of **6d** show again two different blocks of signals. The one proceeding from the imidazol ring remains practically unchanged except for the disappearance of the NH signal, whereas the parent *N*-vinyl moiety is markedly transformed.

In the ^{1}H-NMR spectrum of **6d** a doublet is observed at 5.68 ppm ($^{3}J_{HH}$=6.3 Hz) coupled to a double triplet at 3.70 ppm ($^{3}J_{HH}$=6.3 Hz and 7.9 Hz). This two signals can be used as the key entries in the HMBC spectrum for the elucidation of the second structure present in **6d**.

Their long range connections to carbons are plotted on Figure 3 together with the structural assignment derived from them. The quaternary carbons at 138.68 and 135.39 ppm are further correlated with aromatic protons (not shown in the Figure).

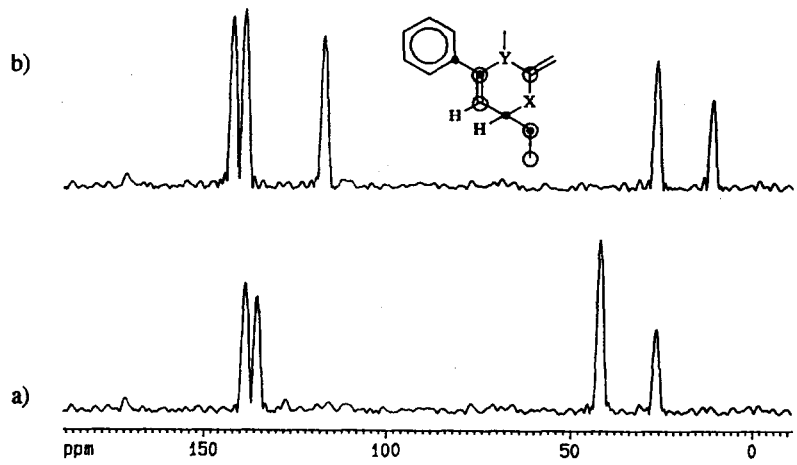
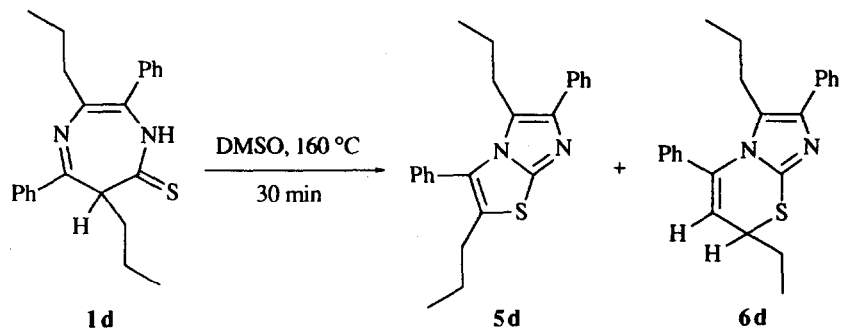


Figure 3. Columns extracted from the 2D HMBC spectrum of **6d** at the ^{1}H chemical shift of: a) 5.69 ppm (correlations indicated by filled circles) and b) 3.70 ppm (correlations indicated by empty circles).

The whole information is compatible with a structure of imidazo[2,1-b]dihydrothiazine for **6d** (Scheme 4) which as for **5** is also supported by the NOE-enhancement observed in the 2D NOESY spectrum. The formation of **6d** could be explained through the same mechanism depicted in Scheme 3 assuming an additional step involving the isomerization of **4** to its allylic derivative, which would evolve in a similar way to **6d**.



1d **5d** **6d**

Scheme 4

In conclusion, the intramolecular cyclization of 1-vinylimidazole-2-thiones to imidazo[2,1-b]thiazoles is reported for the first time. The imidazo[2,1-b]thiazoles thus obtained are the final step of the thermal rearrangement process experienced by 1*H*-1,4-diazepine-7(6*H*)-thiones which involves their intermediate transformation into 1-vinyl-2,3-dihydro-3*H*-imidazole-2-thiones. Analogous bicyclic compounds are known to have biological and pharmacological activity.

EXPERIMENTAL

Materials and General Methods.

All organic chemicals were reagent grade and were used without further purification. The solvents used were destilled and/or dried prior to use following the standard procedures [14]. Melting points were measured in a Buchi-Tottoli apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 B instrument. Infrared spectra were recorded on a Phillips PU 9716 and/or Perkin-Elmer 1720 X instrument. Mass spectra were obtained on a Hewlett-Packard 5987 A.

NMR spectra were acquired on a Brucker AMX-400 spectrometer working at 400.13 MHz for the proton and at 100.61 MHz for the carbon-13 nucleus. A 5 mm reverse BB probehead was used. The 90° pulse was calibrated to 9.6 μs and 10.5 μs for the proton and carbon-13 respectively. The total power output was attenuated in 3 dB in both channels. ^{1}H- and ^{13}C-chemical shifts are reported downfield to the TMS, using $CDCl_3$ or DMSO-d_6 as solvents.

NOE-difference spectra were acquired over degassed samples by the selective presaturation of each line within a given multiplet method [15]. The saturation period was set to 7 s with a power attenuation of 80 dB.

NOESY parameters. Spectral width = 4000 Hz; F_2 size = 2k; F_1 size = 1k after zero filling. Number of increments: 256. Phase sensitive adquisition mode (TPPI). Shifted sinus bell weighting of $\pi/2$.

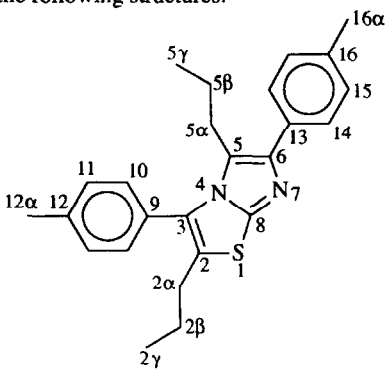
HMQC/HMBC. The same set of parameters was used in both experiments except for the delays necessary to develop heteronuclear antiphase magnetization: 3.45 ms for the observation of direct coupling and 60 ms to detect the long-range couplings. Spectral width 4000 Hz (F_2) and 16000 Hz (F_1). Number of increments: 256. Size in F_2 = 1k. Size in F_1 after zero filling = 1k. Sine bell apodization of factor 80 in both dimensions.

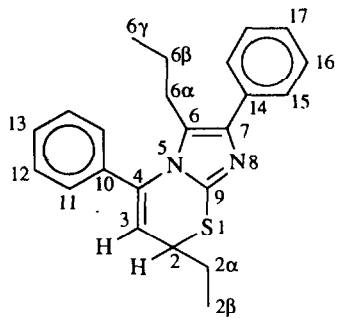
The HMQC spectra were adquired in the phase sensitive mode (TPPI) [16] using GARP decoupling of the heteronucleus. HMBC spectra are presented in the magnitude mode.

General preparative procedure for imidazo[2,1-b]thiazoles **5**.

A solution of 0.5 mmol of **3** in DMSO (10 mL) is heated at 160 °C during 30 minutes. After cooling down to room temperature, this solution was diluted with 150 mL of CH_2Cl_2 or $CHCl_3$ and washed for at least 6 times with 100 mL of water. The organic layer was dried, concentrated and purified by silica gel column chromatography eluted with a mixture of *n*-hexane/ether (or ethyl acetate were indicated) to give the corresponding imidazo[2,1-b]thiazoles **5** in very good yields (see Table).

In the following, the spectral assignements for each compound are described in accordance to the numbering in the following structures:





2,5-dimethyl-3,6-diphenylimidazo[2,1-b]thiazol **5a**.

m.p. 148-150 °C. IR (KBr) n 1429, 1411 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400.13 MHz) d 1.75 (s, 3H, $H_{5\alpha}$), 2.28 (s, 3H, $H_{2\alpha}$), 7.12-7.55 (m, 10H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 100.61 MHz) d 11.40 ($C_{5\alpha}$), 13.20 ($C_{2\alpha}$), 119.07 (C_5), 121.38 (C_2), 126.62 (C_{16}), 127.75 (C_{14}), 128.32 (C_{15}), 128.46 (C_9), 128.57 (C_{11}), 129.18 (C_3), 129.55 (C_{12}), 130.73 (C_{10}), 135.00 (C_{13}), 142.71 (C_6), 146.16 (C_8) ppm. MS (EI) m/z 304 (M^+). Anal. Calcd. for $C_{19}H_{16}N_2S$: C, 74.97; H, 5.30; N, 9.21. Found: C, 74.89; H, 5.35; N, 9.23. R_f (*n*-hexane/ether, 2:1): 0.14.

2,5-dimethyl-3,6-di-*p*-tolylimidazo[2,1-b]thiazol **5b**.

m.p. 127-129 °C. ^{1}H-NMR (DMSO-d_6, 400.13 MHz) d 2.00 (s, 3H, $H_{5\alpha}$), 2.27 (s, 3H, $H_{2\alpha}$), 2.40 (s, 3H, $H_{16\alpha}$), 2.50 (s, 3H, $H_{12\alpha}$), 7.29 (d, 2H, $^3J_{HH}$=7.9 Hz, H_{15}), 7.45 (d, 2H, $^3J_{HH}$=7.9 Hz, H_{11}), 7.51 (d, 2H, $^3J_{HH}$=7.9 Hz, H_{10}), 7.55 (d, 2H, $^3J_{HH}$=7.9 Hz, H_{14}) ppm. ^{13}C-NMR (DMSO-d_6), 100.61 MHz) d 11.10 ($C_{5\alpha}$), 12.88 ($C_{2\alpha}$), 20.74 ($C_{16\alpha}$), 20.98 ($C_{12\alpha}$), 118.66 (C_5), 120.32 (C_2), 125.50 (C_9), 127.18 (C_{14}), 128.51 (C_3), 128.94 (C_{15}), 129.20 (C_{11}), 130.62 (C_{10}), 131.90 (C_{13}), 135.70 (C_{16}), 139.25 (C_{12}), 141.64 (C_6), 144.60 (C_8) ppm. MS (EI) m/z 332 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2S$: C, 75.87; H, 6.07; N, 8.43. Found: C, 75.92; H, 6.01; N, 8.45. R_f (*n*-hexane/ethyl acetate, 8:1): 0.21.

2,5-diethyl-3,6-diphenylimidazo[2,1-b]thiazol **5c**.

m.p. 135-137 °C. IR (KBr) n 1493, 1476, 1456, 1445 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400.13 MHz) d 0.69 (t, 3H, $^3J_{HH}$=7.4 Hz, $H_{5\beta}$), 1.20 (t, 3H, $^3J_{HH}$=7.4 Hz, $H_{2\beta}$), 2.47 (q, 2H, $^3J_{HH}$=7,4 Hz, $H_{5\alpha}$), 2.54 (q, 2H, $^3J_{HH}$=7.4 Hz, $H_{2\alpha}$), 7.25-7.63 (10H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 100.61 MHz) d 14.51 ($C_{5\beta}$), 15.72 ($C_{2\beta}$), 17.57 ($C_{5\alpha}$), 21.27 ($C_{2\alpha}$), 125.57 (C_5), 126.68 (C_{16}), 127.62 (C_{14}), 127.71 (C_3), 128.33 (C_{15}), 128.54 (C_{11}), 129.23 (C_2), 129.51 (C_9), 129.68 (C_{12}), 130.80 (C_{10}), 135.22 (C_{13}), 142.22 (C_6), 146.33 (C_8) ppm. MS (EI) m/z 332 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2S$: C, 75.87; H, 6.07; N, 8.43. Found: C, 75.81; H, 6.05; N, 8.39. R_f (*n*-hexane/ether, 2:1): 0.23.

3,6-diphenyl-2,5-dipropylimidazo[2,1-b]thiazol **5d** and 2-ethyl-4,7-diphenyl-6-propylimidazo[2,1-b]-2,6-dihydro-3*H*-1,3-thiazine **6d**.

No attempts were made to assign the aromatic carbon atoms of **5d** and **6d** from the mixture.

5d. ^{1}H-NMR ($CDCl_3$, 400.13 MHz) d 0.39 (t, 3H, $^3J_{HH}$=7.3 Hz, $H_{5\gamma}$), 0.89 (t, 3H, $^3J_{HH}$=7.3 Hz, $H_{2\gamma}$), 1.11 (m, 2H, $H_{5\beta}$), 1.60 (tq, 2H, $^3J_{HH}$=7.3 Hz and 7.4 Hz, $H_{2\beta}$), 2.37 (m, 2H, $H_{5\alpha}$), 2.48 (dd, 2H, $^3J_{HH}$=7.4 and 7.3 Hz, $H_{2\alpha}$), 7.18-7.62 (m, 10H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 100.61 MHz) d 13.38 ($C_{2\gamma}$), 13.50 ($C_{5\gamma}$), 23.60 ($C_{5\beta}$), 24.00 ($C_{2\beta}$), 26.25 ($C_{5\alpha}$), 29.45 ($C_{2\alpha}$), 124.07 (C_5), 126.30-130.87 (12C, Ar), 127.53 (C_2), 142.34 (C_6), 146.37 (C_8) ppm.

6d. ^{1}H-NMR ($CDCl_3$, 400.13 MHz) d 0.48 (t, 3H, $^3J_{HH}$=7.3 Hz, $H_{6\gamma}$), 1.08 (t, 3H, $^3J_{HH}$=7.2 Hz, $H_{2\beta}$), 1.19 (tq, 2H, $^3J_{HH}$=7.3 and 7.4 Hz, $H_{6\beta}$), 1.76 (m, 2H, $H_{2\alpha}$), 2.16 (m, 2H, $H_{6\alpha}$), 3.70 (dt, 1H, $^3J_{HH}$=6.2 and 7.8 Hz, H_2), 5.68 (d, 1H, $^3J_{HH}$=6.2 Hz, H_3), 7.18-7.62 (m, 10H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 100.61 MHz) d 11.51 ($C_{2\beta}$), 13.12 ($C_{6\gamma}$), 22.30 ($C_{6\beta}$), 26.70 ($C_{2\alpha}$), 27.26 ($C_{6\alpha}$), 41.91 (C_2), 117.02 (C_3), 127.53 (C_6), 126.30-130.87 (11C, Ar), 135.39 (C_{10}), 138.68 (C_4), 139.02 (C_7), 142.05 (C_9).

5d + **6d**. MS (EI) m/z 360 (M^+).

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