TANDEM STEREOSELECTIVE CONJUGATE ADDITIONS TO α,β–UNSATURATED OXAZOLINES †

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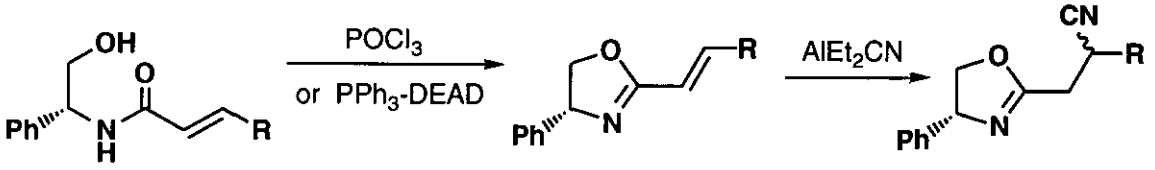
Abstract - Tandem stereoselective conjugate additions to two molecules of activated α,β-unsaturated oxazolines have led to substituted 2,4-bis-(4-phenyl-4,5-dihydrooxazol-2-yl)-cyclopent-1-enylamines. Their general structure was deduced from spectral data and confirmed by X-ray analysis.

α,β-Unsaturated oxazolines can act as efficient acceptors in stereoselective conjugate additions of various nucleophiles, especially organometallic reagents.[1] Asymmetric 1,4-additions of other *C*-nucleophiles as ketone silyl enol ethers[2-3] and ketene silyl acetals[4] have been recently developed in our laboratory. We have also explored the conjugate addition of cyanide in the presence of diethylaluminum cyanide, as an activator of the oxazoline function and as cyanide source. During a preliminary work with the oxazolines (**3**) and (**4**), prepared respectively from *N*-cinnamoyl and *N*-crotonoyl phenylglycinol (**1**) and (**2**), the expected 1,4-additions (Scheme 1) were perturbed by side-reactions which afforded complex compounds (*ca.* 25%), lowering the yield of the adducts (**5**) and (**6**).



1 R = Ph
2 R = Me

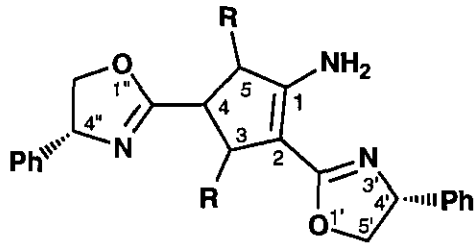
3 R = Ph
4 R = Me

5 R = Ph
6 R = Me

Scheme 1

† Dedicated to the memory of the late Professor Yoshio Ban.

Spectral analysis of the by-products are consistent with the general bis-oxazoline structures (**7**) and (**8**).



7 R = Ph

8 R = Me

Starting from the oxazoline (**3**), two compounds (**7a**) and (**7b**) have been isolated in 25% yield and 2:1 ratio. The mass spectra of both compounds showed a molecular peak at m/z 525 and a peak at m/z 378 which could be attributed to the loss of a 4-phenyloxazoline unit. The molecular formula $C_{35}H_{31}N_3O_2$ was determined by HRms. Their ir spectra are nearly identical between 3600 and 1200 cm^{-1}, with strong absorptions at 3490 (NH), 1650 (C=N) and 1600 (Ar) cm^{-1}. Comparison of their ^1H and ^{13}C nmr data suggested that they are diastereomers (Tables 1 and 2).

Table 1. Relevant ^1H chemical shifts in **7** and **8** ($CDCl_3$, 300 MHz, $\delta = 0$: TMS)

δ	Oxazoline protons				
	OCH_2	NCHPh	C-3-H and C-5-H	C-4-H	NH_2
7a	4.57 (dd, J=10, J'=8) and 4.05 (dd, J=J'=8)	5.16 (2H)	4.54 (d, J~8) 4.51 (d, J~8)	3.00 (dd, J~J'~8)	5.73
	4.34 (dd, J=10, J'=8) and 3.71 (dd, J=J'=8)				
7b	4.43 (dd, J=10, J'=8) and 3.76 (dd, J=J'=8)	5.22 (dd, J=10, J'=8)	4.87 (d, J=6)	3.45 (dd, J=9.5, J'=6)	5.85
	4.12 (dd,J=10, J'=8.5) and 3.63 (dd, J~J'~8.5)	4.77 (dd, J=10, J'=8.5)	4.46 (d, J=9.5)		
8	4.64 (dd, J=10, J'=8) and 4.12 (dd, J=J'=8)	5.19 (dd, J=10, J'=8)	3.24 (2H)	2.35 (dd, J=J'=7.5)	5.77
	4.57 (dd, J=10, J'=8) and 3.96 (dd, J=J'=8)	5.26 (dd, J=10, J'=8)			

In each diastereomer the signals of 20 aromatic protons indicated the presence of four monosubstituted phenyl groups and the broad signal at 5.73 in **7a** (or 5.85 in **7b**) was related to two exchangeable protons. In each spectrum, the chemical shifts and splitting patterns of two sets of three protons, as doublets of doublets, were indicative of the presence of two $OCH_2CH(Ph)N$ units. In addition, three protons of methine were observed at 4.54, 4.51 and 3.00 ppm in **7a** (4.87, 4.46 and 3.45 ppm in **7b**), the most shielded ones being coupled with each other. 2D Nmr studies especially ^1H-^{13}C correlations corroborated these interpretations.

Table 2. Relevant ^{13}C chemical shifts in **7** and **8** (75 MHz, $CDCl_3$)

	Oxazoline carbons			C-1	C-2	C-3 and C-5	C-4
	OCH_2	NCH	OC=N				
7a	75.18	69.38	169.29	156.79	94.38	55.87	55.50
	73.31		165.10			52.85	
7b	74.44	69.36	167.21	156.53	95.64	54.88	52.00
	73.42		165.08			50.92	
8	74.92	69.38	170.00	157.96	94.87	43.65	52.22
	73.28	69.02	165.60			41.55	

Particularly, the chemical shifts of two OCH_2 carbons at 75.18 and 73.31 ppm in **7a** (74.44 and 73.42 ppm in **7b**) as well as the two characteristic quaternary carbons OC=N at 169.29 and 165.10 ppm in **7a** (167.21 and 165.08 ppm in **7b**) attested to the presence of two oxazoline rings in each compound. On the other hand, the signals of two remaining quaternary ethylenic carbons were observed at 156.79 and 94.38 ppm in **7a** (156.53 and 95.64 ppm in **7b**) and these chemical shifts could be attributed to an enamine double bond C-1—C-2.

All spectral data were consistent with the proposed structure (**7**) for these compounds and the same key-arguments are also valuable for the main diastereomer (**8**), obtained from the oxazoline (**4**) (Tables 1 and 2). However, the configurations of the three newly created asymmetric centers are not known and uncertainties remained about the possibility of tautomeric structures. Consequently, recourse was made to X-ray analysis to prove the structure (**7b**) (Figure).

The formation of **7** could be explained by tandem conjugate additions to α,β-unsaturated oxazoline (**3**). It is interesting to note the uncommon intermolecular character of these reactions.[5] The 1,4-addition of cyanide led

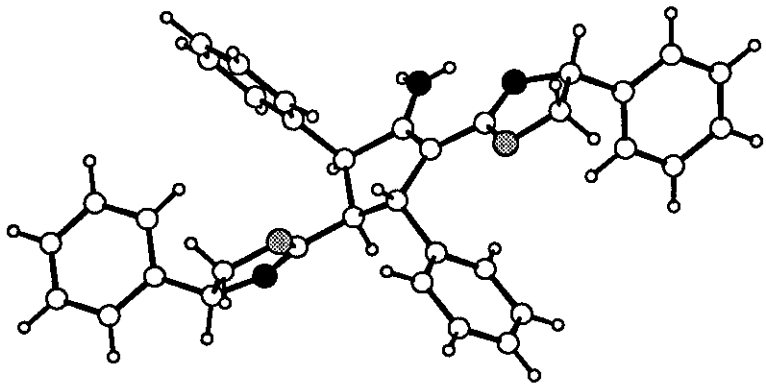
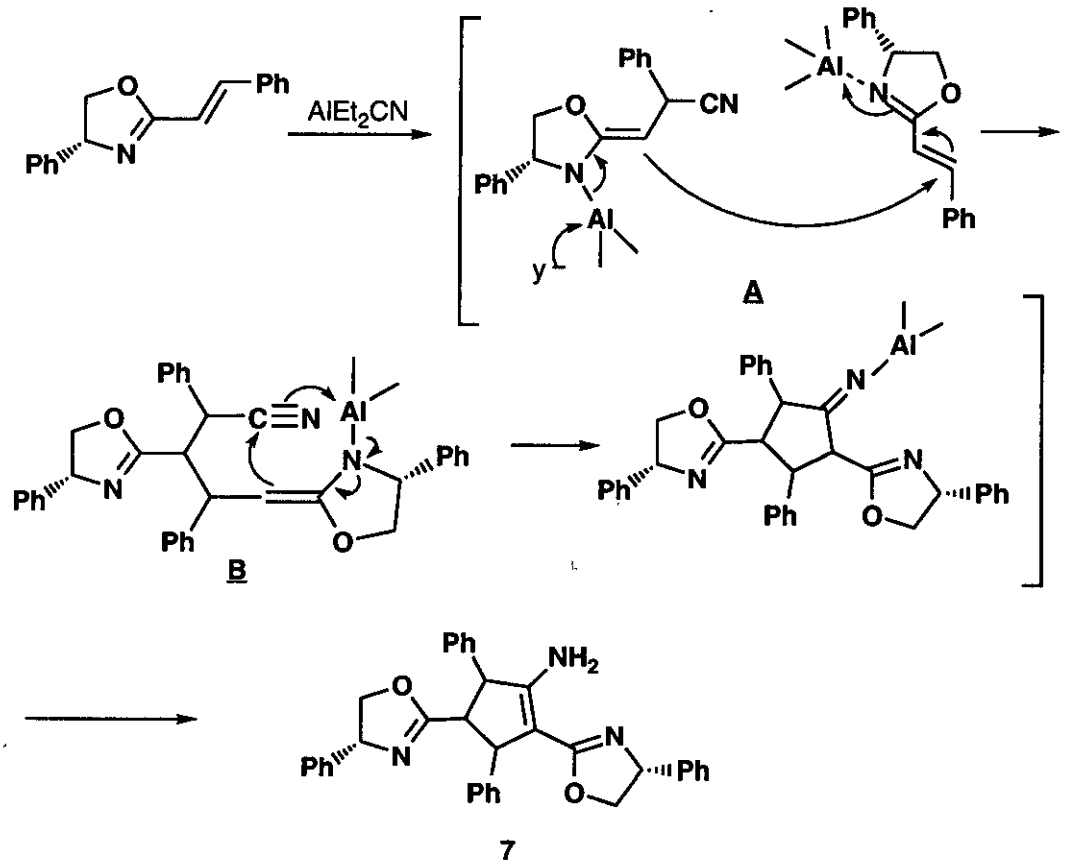


Figure : A perspective view of **7b**



Scheme 2

to the intermediate **A** and was followed by the nucleophilic addition of **A** (at its β enamine position) to the conjugate double bond of a second molecule of oxazoline (**3**) to give **B**. The absence of a nitrile function in **7** and the molecular formula were indicative of a further cyclization of the intermediate **B** (Scheme 2). The formation of the compounds (**7**) (and (**8**)) could be favoured by a transfer of complexation of aluminum species from the nitrogen of the aza-enolate **B** to the introduced cyano group which must be activated to participate. However, the mechanism outlined in Scheme 2 has not been proved.

Taking account the three created asymmetric centers, these reactions were stereoselective, since the formation of two diastereomers (**7**) only, was observed starting from **3**. They could give access to highly functionalized cyclopentenes.

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EXPERIMENTAL

Melting points were taken on a microscope Leitz. Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations were given in g/100 ml. Ir spectra (υ cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H Nmr spectra were obtained ($CHCl_3$, Me_4Si, $\delta = 0$ ppm) from Bruker AC200, AC250 or AM300 spectrometers; coupling constant (J values) are given in Hertz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). ^{13}C Nmr spectra were recorded on AC250 (62.5 MHz) or AM300 (75.0 MHz). Mass spectra and high resolution mass spectra were respectively measured on AEI MS50 and on a Kratos MS80 spectrometers. Flash chromatography was performed on SDS 230-400 mesh silicagel and preparative thin layer chromatography on Merck HF 254 + 366 silicagel. Unless stated otherwise, the experiments were performed under argon atmosphere. Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum.

(2*R*)-*N*-Cinnamoyl-2-amino-2-phenylethanol (1)

To a stirred solution of (*R*)-phenylglycinol (5.0 g, 36.5 mmol) in dichloromethane (182 ml) were successively added a solution of sodium carbonate (4.64 g, 43.8 mmol in water (75 ml) and cinnamoyl chloride (6.7 g, 40.2 mmol). After being stirred at room temperature until completion of the reaction, was added a mixture of 2N

NaOH and methanol (1:1, 100 ml) and the crude amide (**1**) was extracted with dichloromethane. Purification by crystallization (CH_2Cl_2) afforded **1** as white crystals (9.3 g, 95%). mp : 197-198°C. $[\alpha]_D^{23}$ = + 28° (c = 0.55, MeOH). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38 ; H, 6.41 ; N, 5.24. Found : C, 76.28 ; H, 6.44 ; N, 5.04. Ms : 268 $(M + H)^{+\cdot}$, 249, 237, 236 (100%), 131, 106, 104, 103, 77. Ir : 3650, 3440, 2940, 1668, 1631, 1500. ^{1}H Nmr (250 MHz) : 7.67 (d, 1H, J = 15, =C<u>H</u>Ph), 7.52 and 7.36 (2m, 10H, ArH), 6.49 (d, 1H, J = 15, COCH=), 6.29 (m, 1H, NH), 5.22 (m, 1H, H-2), 3.98 (m, 2H, H_2-1), 2.77 (m, 1H, OH). ^{13}C Nmr (62.5 MHz) : 164.5 (CO), 141.1 (qC, Ar), 138.6 (=<u>C</u>HPh), 134.9 (qC, Ar), 129.3, 128.8, 128.0, 127.4, 126.9 and 126.7 (CH, Ar), 122.4 (COCH=), 64.6 (C-1), 55.0 (C-2).

(4*R*)-4-Phenyl-2-(*E*)-2'-phenylethenyl-4,5-dihydrooxazole (<u>3</u>)

$POCl_3$ (32 ml, 348 mmol) was slowly added at room temperature to a stirred mixture of compound (**1**) (9.3 g, 34.8 mmol) and anhydrous toluene (93 ml). The solution was stirred at room temperature for 0.5 h. Solvent and excess of reagent were evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 ml) before addition of an aqueous solution of Na_2CO_3 (10% w/v, 100 ml) and the mixture was stirred for 0.5 h. The crude oxazoline (**3**) was extracted with CH_2Cl_2 and crystallized in Et_2O to give white crystals (6.8 g, 78%). mp 64-66°C, $[\alpha]_D^{20}$ = + 104° (c = 1.5, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90 ; H, 6.06 ; N, 5.62. Found : C, 81.47 ; H, 5.98 ; N, 5.61. Ms : 249 ($M^{+\cdot}$), 218 (100%), 131, 115, 103, 102, 91, 90, 89, 77. Ir : 2975, 1658, 1609, 1499, 1468, 1454, 1363. ^{1}H Nmr (200 MHz) : 7.54 (m, 2H, ArH), 7.47 (d, 1H, J = 16.5, H-2'), 7.30 (m, 8H, ArH), 6.75 (d, 1H, J = 16.5, H-1'), 5.34 (dd, 1H, J = 10, J' ~ 8, H-4), 4.73 (dd, 1H, J = 10, J' ~ 8, H-5), 4.22 (dd, 1H, J ~ J' = 8, H-5). ^{13}C Nmr (62.5 MHz) : 164.3 (C-2), 142.3 (qC, Ar), 140.4 (C-2'), 135.2 (qC, Ar), 129.5, 128.8, 128.7, 127.5 and 126.6 (CH, Ar), 115.0 (C-1'), 74.3 (C-5), 70.0 (C-4).

(4*R*)-4-Phenyl-2-(*E*)-2'-methylethenyl-4,5-dihydrooxazole (<u>4</u>)

Triphenylphosphine (1.41 g, 5.4 mmol) and diethyl azodicarboxylate (0.85 ml, 5.4 mmol) were successively added to a solution of (2*R*)-*N*-crotonoyl-2-amino-2-phenylethanol (**2**) (1.00 g, 4.88 mmol) in anhydrous THF (100 ml). The mixture was stirred for 18 h at room temperature and concentrated under reduced pressure before purification by flash chromatography on silica gel (eluent : heptane-ethyl acetate 7:3). The oxazoline (**4**) was obtained as a pale yellow oil (673 mg, 74%). $[\alpha]_D$ = + 212° (c = 2.15, $CHCl_3$). HRms $C_{12}H_{13}NO$ calcd 187.0997, found 187.0992. Ms : 187 ($M^{+\cdot}$, 100%), 157, 156. Ir : 1673, 1645, 1609. ^{1}H Nmr (300 MHz) : 7.34

and 7.26 (2m, 5H, ArH), 6.70 (m, 1H, H-2'), 6.12 (qd, 1H, J = 16, J'~ 1, H-1'), 5.23 (dd, 1H, J = 10, J' ~ 8, H-4), 4.62 (dd, 1H, J = 10, J' = 8.5, H-5), 4.10 (dd, 1H, J = 8.5, J'~ 8, H-5), 1.89 (dd, 3H, J = 6.5, J'~ 1, CH_3). ^{13}C Nmr (75.0 MHz) : 163.97 (C-2), 142.42 (qC, Ar), 139.76 (C-2'), 128.67, 127.47 and 126.60 (CH, Ar), 118.95 (C-1'), 74.20 (C-5), 69.71 (C-4).

(4'*R*, 4"*R*)-2,4-Bis[4-phenyl-4,5 dihydrooxazol-2-yl]-3,5-diphenylcyclopent-1-enylamines (7)

To a stirred solution of oxazoline (**3**) (874 mg, 3.51 mmol) in dichloromethane (7.0 ml) at -30°C was added Et_2AlCN (1M in toluene, 5.3 ml) under argon atmosphere and the mixture was stirred at 20°C for 24 h. Et_2AlCN (1M, 5.3 ml) was added after being cooled at -30°C and the mixture was stirred for additional 24 h at 20°C. After addition of aqueous 10% w/v Na_2CO_3, the crude product was extracted with CH_2Cl_2. The residue obtained after usual workup was rapidly chromatographied on silica gel (eluent : pentane-ether 1:1) to afford starting oxazoline (**3**) (307 mg, 35%), compounds (**7**) (231 mg, 25%) and 1,4-adducts (**5**) (183 mg, 19%). The diastereomers (**7a**) and (**7b**) (**7a**:**7b** = 2:1) were separated by preparative tlc (eluent : CH_2Cl_2-MeOH 98:2).

Major diastereomer (7a) : $[\alpha]_D^{27}$ = - 13° (c = 1.10, $CHCl_3$). HRms (CI) $C_{35}H_{31}N_3O_2$ calcd 526.2494, found 526.2497. Ms (SI) : 526 $(M + H)^+$, 379, 260, 232, 131, 120, 103. Ir : 3488, 3025, 1650, 1600, 1556, 1500, 1450. ^1H Nmr (300 MHz) : 7.4-7.2 (m, 20H, ArH), 5.73 (m, 2H exch, NH_2), 5.16 (dd, 2H, J = 10, J'~ 8, H-4' and H-4"), 4.57 (dd, 1H, J = 10, $J_{5'a,\ 5'b}$ = 8, Ha-5')[6], 4.54 (d, 1H, J = 8, H-3 or H-5), 4.51 (d, 1H, J = 8, H-5 or H-3), 4.34 (dd, 1H, J = 10, $J_{5"a,\ 5"b}$ = 8, Ha-5"), 4.05 (dd, 1H, J = J'= 8, Hb-5'), 3.71 (dd, 1H, J = J'= 8, Hb-5"), 3.00 (dd, 1H, J = J'= 8, H-4). ^{13}C Nmr (75.0 MHz) : 169.29 and 165.10 (C-2' and C-2"), 156.79 (C-1), 146.05, 143.79, 142.60 and 140.27 (qC, Ar), 129.03-126.47 (CH, Ar), 94.38 (C-2), 75.18 (C-5'), 73.31 (C-5"), 69.38 (C-4' and C-4"), 55.87 and 52.85 (C-3 and C-5), 55.50 (C-4).

Diastereomer (7b) : mp 208-210°C (MeOH), $[\alpha]_D^{22}$ = + 158° (c = 0.24, $CHCl_3$). HRms $C_{35}H_{31}N_3O_2$ calcd 525.2416, found 525.2422 ; $C_{26}H_{22}N_2O$ calcd 378.1732, found 378.1730. Ms : 525 ($M^{+\cdot}$), 378, 91, 77. Ir : 3487, 3026, 1650, 1600, 1560, 1500, 1450. ^1H Nmr (300 MHz) : 7.30 and 6.81 (2m, 20H, ArH), 5.85 (m, 2H, NH_2), 5.22 (dd, 1H, J = 10, J' = 8, H-4'), 4.87 (d, 1H, J = 6, H-3 or H-5), 4.77 (dd, 1H, J = 10, J'= 8.5, H-4"), 4.46 (d, 1H, J = 9.5, H-5 or H-3), 4.43 (dd, 1H, J = 10, $J_{5'a,\ 5'b}$ = 8, Ha-5')[6], 4.12 (dd, 1H, J = 10, $J_{5"a,\ 5"b}$ = 8.5, Ha-5"), 3.76 (dd, 1H, J = J'= 8, Hb-5'), 3.63 (dd, 1H, J ~ J'~ 8.5, Hb-5"), 3.45 (dd, 1H, J = 9.5, J'= 6, H-4). ^{13}C Nmr (75.0 MHz) : 167.21 and 165.08 (C-2' and C-2"), 156.53 (C-1), 145.72, 143.75, 142.15 and 137.33 (qC, Ar), 129.50-126.41 (CH, Ar), 95.64 (C-2), 74.44 (C-5"), 73.42 (C-5'), 69.36 (C-4' and C-4"), 54.88 and 50.92 (C-3 and C-5), 52.00 (C-4).

(4'*R*, 4"*R*)-2,4-Bis[4-phenyl-4,5 dihydrooxazol-2-yl]-3,5-dimethylcyclopent-1-enylamine (8)

The same experimental protocol as above was applied to the oxazoline (**4**) (430 mg, 2.3 mmol), using twice 1.1 equiv. Et_2AlCN. The reaction mixture was stirred at -20°C for 15 h before the second addition of the reagent and then at 0°C for 29 h. The residue obtained after extraction with CH_2Cl_2 and usual workup was chromatographied on silica gel (eluent : CH_2Cl_2-MeOH 98:2) to afford 1,4-adducts (**6**) (134 mg, 27%) and a mixture of more polar compounds (290 mg). This fraction was submitted to preparative tlc (eluent : Et_2O-CH_2Cl_2-MeOH 3:7:0.5) and gave **8** (86 mg, 19%) and diastereomers which could not be obtained pure (61 mg, 13%).

Compound (8) : $[\alpha]_D^{26}$ = - 5° (c = 1.61, $CHCl_3$). HRms $C_{25}H_{27}N_3O_2$ calcd 401.2104, found 401.2128 ; $C_{16}H_{18}N_2O$ calcd 254.1419, found 254.1423. Ms : 401 ($M^{+\bullet}$, 100%), 254, 134, 120, 104, 103, 91, 77. Ir : 3494, 3290, 3000, 1644, 1602, 1553, 1450, 1349. ^1H Nmr (300 MHz) : 7.36 and 7.30 (2m, 10H, ArH), 5.77 (m, NH_2), 5.26 (dd, 1H, J = 10, J'= 8, H-4')[6], 5.19 (dd, 1H, J = 10, J'= 8, H-4"), 4.64 (dd, 1H, J = 10, $J_{5"a,\ 5"b}$ = 8, Ha-5"), 4.57 (dd, 1H, J = 10, $J_{5'a,\ 5'b}$ = 8, Ha-5'), 4.12 (dd, 1H, J = J'= 8, Hb-5"), 3.96 (dd, 1H, J = J' = 8, Hb-5'), 3.24 (m, 2H, H-3 and H-5), 2.35 (dd, 1H, J = J'= 7.5, H-4), 1.41 (d, 3H, J = 6.5, CH_3), 1.31 (d, 3H, J = 7, CH_3). ^{13}C Nmr (75.0 MHz) : 170.00 and 165.60 (C-2' and C-2"), 157.96 (C-1), 143.90 and 142.65 (qC, Ar), 128.75, 128.60, 127.55, 127.55, 126.62 and 126.56 (CH, Ar), 94.87 (C-2), 74.92 (C-5"), 73.28 (C-5'), 69.38 (C-4"), 69.02 (C-4'), 52.22 (C-4), 43.65 and 41.55 (C-3 and C-5), 22.00 (CH_3), 18.37 (CH_3).

X-ray structure analysis for 7b :

Crystal data . $C_{35}H_{31}N_3O_2$, M_W = 525.65, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 10.255 (5), b = 12.325 (7), c = 22.529 (12) Å, V = 2847 (2) $Å^3$, d_c = 1.23 g cm^{-3}, F(000) = 1112, λ (Cu Kα) = 1.5418 Å, μ = 0.57 mm^{-1}; 3724 measured intensities, 2725 unique (Rint = 0.05), 2059 observed with $I > 3.0\sigma(I)$. Intensity data were measured on a Nonius CAD-4 diffractometer using graphite monochromated Cu Ka radiation and the (θ-2θ) scan technique up to θ = 65°. The structure was solved by direct methods using *SHELXS86*[7] and refined by full matrix least-squares with *SHELX76*,[8] minimizing the function $Sw(Fo-|Fcl)^2$. The hydrogen atoms, located in difference Fourier maps, were introduced in theoretical position (d(C-H) = 1.00 Å). The coordinates were refined for HN6a and HN6b. They were assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.061 and R_W = 0.083 (with $R_W = \{Sw(Fo-|Fcl)^2 / SwFo^2\}^{1/2}$ and $w = 1/[s^2(Fo) + 0.0028\ Fo^2]$. No residual was higher than 0.26 e $Å^{-3}$ in the final difference map. The amino group N6 is hydrogen bonded to N3', intramolecularly and to N3" atom of the

neighbourhing molecule: 1/2 +x, 3/2-y,-z (N6...N3' : 2.806(6), H...N3': 2.24 Å, N6-H... N3': 130° ; N6...N3" : 3.013 (7), H..N3": 2.06 Å, N6-H..N3": 171°). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

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