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CONVERGENT APPROACH TO TETRACYCLIC [ABCE] INTERMEDIATES IN *ASPIDOSPERMA* ALKALOIDS SYNTHESIS

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Abstract : An efficient convergent synthesis of tetracyclic amidoalcohol **5**, key intermediate in the synthesis of *Aspidosperma* alkaloids framework, starting from *trans*-hexahydrocarbazol-4-one **1** and substituted iodoacetamides **6** was achieved.

We have previously reported a new approach to type **3**[1] pentacyclic *Aspidosperma* alkaloid framework using tetracyclic enamide **2**[2] easily obtained from hexahydrocarbazol-4-one **1**, as the key intermediate. This strategy was applied to the synthesis of (±) aspidofractinine **4**[3], which required an N(b) protection/deprotection sequence at the end of the synthesis for the introduction of the three carbon atom appendage precursor of ring D.

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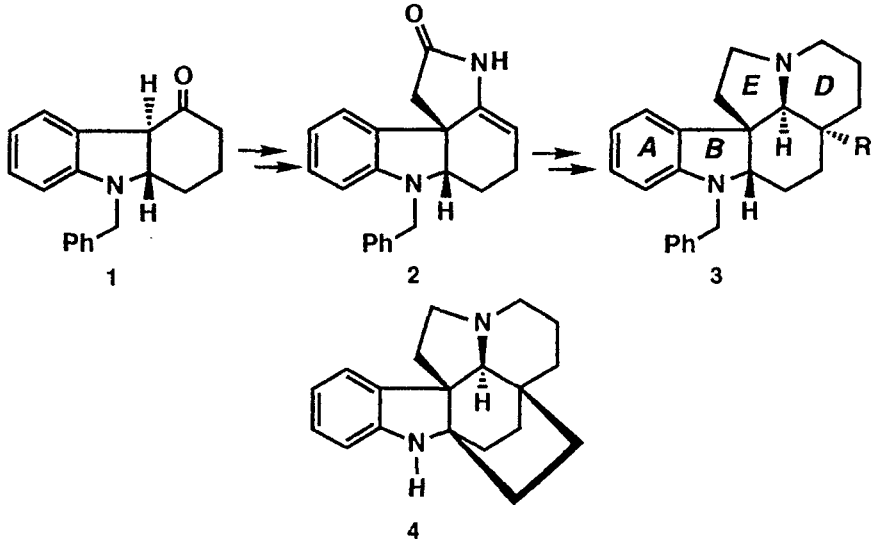


We wish to report a convergent synthesis of tetracyclic amidoalcohols **5** bearing the three carbon atom side chain which will constitute the D ring, instead of a protective group.

The amidoalcohols **5** were prepared by alkylation of the hexahydrocarbazol-4-one **1** with a *N*-substituted iodoacetamide **6**. Its three carbon atom side chain bears a protected primary alcohol function which will be transformed into a leaving group in order to allow the cyclization step (FIG. 1).

Thus, the two iodoacetamide derivatives **6a** and **6b** in which the alcohol functions were protected as TBDMS and allyl ethers respectively were synthesized (FIG. 2 and FIG. 3).

Compound **6a** was prepared in five steps with 70% overall yield from 3-bromopropanol as follows : preparation of the TBDMS ether was carried out easily in CH_2Cl_2 using *tert*-butyldimethylsilyl chloride, NEt_3 and a catalytic amount of DMAP[4] to give compound **7**[5] in 95% yield. Treatment of **7** with sodium azide either in DMSO under argon during 48h[6] or at reflux in a mixture of $EtOH/H_2O$ for 24h[7] furnished the azide **8** in 89% yield. Reduction of the azido function[8] was performed using Ph_3P in THF (Staudinger reaction)[9] and gave 3-(*tert*-butyldimethylsilyloxy)propylamine **9**[10] in nearly quantitative yield. Acylation of the amino

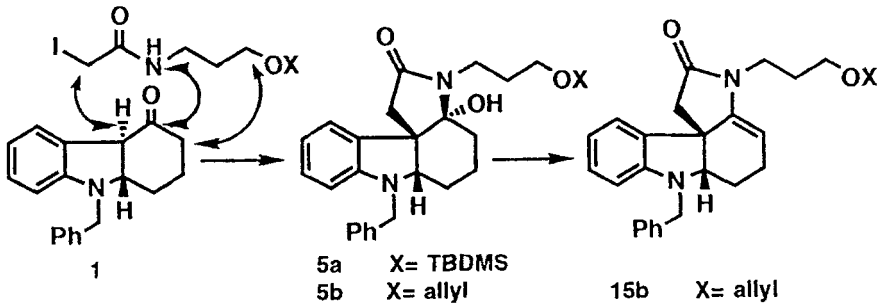
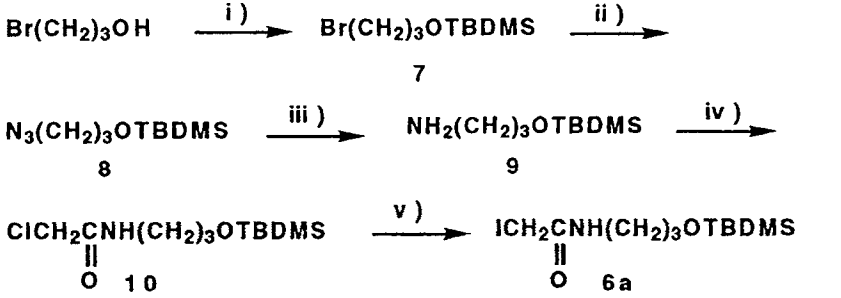


FIG. 1

group of **9** by chloroacetyl chloride (CH_2Cl_2, NEt_3, 0°C, argon) led to the expected chloroacetamide **10** in 83% yield which was converted quantitatively into the iodo derivative **6a** by the Finkelstein method[12] (FIG. 2).

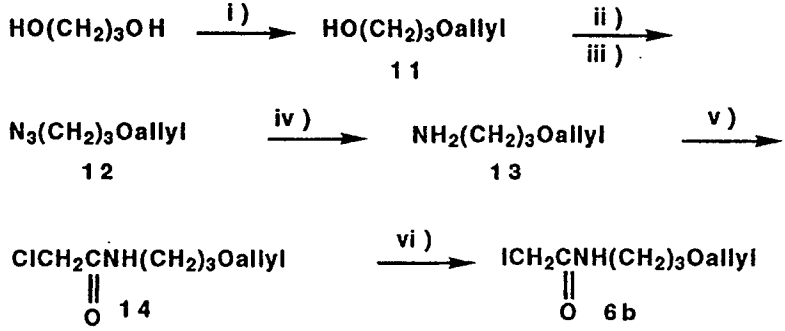
Iodoacetamide derivative **6b** was synthesized in six steps with 66% overall yield starting from 1,3-propanediol (FIG. 3) as follows : the monosubstituted alcohol **11**[12] was prepared conveniently by monoalkylation[13] of 1,3-propanediol with allylbromide (86% yield). Compound **11** was then converted by tosylation followed by treatment with sodium azide in DMSO[6] into the corresponding azide **12** (85% yield for the two steps). Reduction of the azido function using $LiAlH_4$[9] gave the amine **13**[14] which was immediately acylated with chloroacetyl chloride (CH_2Cl_2, NEt_3, DMAP) to give the chloroacetamide **14** (89% in two steps). Halogen exchange as described above furnished quantitatively the iodoacetamide derivative **6b**.

With the two expected iodoacetamide derivatives **6a** and **6b** now in hand, the synthesis of tetracyclic amidoalcools **5a** and **5b** was achieved. *trans*-Hexahydrocarbazol-4-one **1**[15], the corner stone in our synthesis, was obtained as usual by non-oxidative photocyclization of the corresponding tertiary enaminone. Alkylation [2,15] of **1** with the *N*-substituted iodoacetamide **6a** gave the expected tetracyclic amidoalcohol **5a** in a 80 % yield. Compound **5a** was obtained as a single diastereoisomer with a *cis* B/C and C/E ring junction, and showed spectroscopic data in accord with the proposed structure. In the same way,



reagents : i) TBDMSCl, CH_2Cl_2, NEt_3, DMAP ; ii) NaN_3, DMSO, argon or EtOH/H_2O, Δ; iii) Ph_3P THF ; iv) CH_2Cl_2, NEt_3, 0°C, argon, $ClCH_2COCl$; v) NaI, acetone, Δ

FIG.2



reagents : i) NaH/THF, $BrCH_2CH{=}CH_2$; ii) TsCl, pyridine, argon ; iii) NaN_3, DMSO, argon ; iv) $LiAlH_4$, Et_2O ; v) CH_2Cl_2, NEt_3, 0°C, argon, $ClCH_2COCl$; v) NaI, acetone, Δ

FIG. 3

tetracyclic amidoalcohol **5b** was obtained in 95% yield starting from hexahydrocarbazol-4-one 1 and iodoacetamide derivative **6b**. Spectroscopic data obtained from **5b** were quite similar to those of **5a**. The instable carbinol amide **5b** was immediately dehydrated[2] and gave tetracyclic enamide **15b** in nearly quantitatively yield. This compound has already been used for the total synthesis of (±) aspidofractinine[3].

This convergent synthesis is shorter and more efficient than the previous approach involving N(b) protection/deprotection sequence.

Moreover, the use of variously substituted iodoacetamides should allow modification of the size and substitution of D ring.

EXPERIMENTAL :

Infrared spectra (IR) were recorded in CCl_4 solution on a PERKIN-ELMER 377 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimetres with polystyrene calibration. Peaks yielding structural information are reported. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, $\delta = 0$) on a JEOL C60H, a BRUKER WM 250 or a BRUKER MSL 300. Chemical shift data are reported in parts per million downfield from tetramethyl-silane, where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quadruplet and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS, $\delta = 0$) on a JEOL FX 60, or a BRUKER MSL 300 instrument. Low-resolution (70 ev) and high-resolution mass spectrometry was performed on a VARIAN CH5 instrument. In usual workup procedures, the organic extracts were invariably dried over anhydrous Na_2SO_4 and solvents were evaporated *in vacuo*. Column and flash chromatography were done with 70-230 and 230-400 mesh silica gel (E. Merck) respectively.

Preparation of bromide 7

To a solution of 3-bromopropanol (2.26 ml ; 25 mmol) in CH_2Cl_2 (20 ml) under argon at 0°C was added NEt_3 (4.18 ml ; 30mmol) and DMAP (0.122 g ; 1 mmol)

followed 5 min. later by a solution of *tert*-butyldimethylsilyl chloride (4.15 g ; 27.5 mmol) in CH_2Cl_2 (25 ml). The mixture was stirred for 2 h, then water (15 ml) was added.Usual workup gave a crude product that was purified by flash chromatography (elution with AcOEt-hexane, 1:4) to give 6.0 g of *tert*-butyldimethyl (3-bromopropoxy) silane **6** (95 % yield).^{1}H NMR ($CDCl_3$, 60 MHz) : 0.2 (s, 6H), 0.98 (s, 6H), 1.5-1.9 (m, 2H), 3.0-3.3 (m, 2H), 3.3-3.6 (m, 2H).

Preparation of azide **8**

a) To a solution of **7** (4.00 g ; 15.81 mmol) in EtOH/H_2O (105 ml/15.6 ml) was added sodium azide (1.43 g ; 21.9 mmol). The resultant mixture was heated at reflux under an argon atmosphere for 48h. After cooling the majority of the solvent was carefully evaporated and CH_2Cl_2 was added. Work up gave 3.02 g of the nearly pure azide in 89 % yield.

b) A solution of **7** (1.0 g ; 3.95 mmol) and sodium azide (0.39 g ; 5.93 mmol) in freshly distilled DMSO (4 ml) was stirred under argon . After 48h, 4ml of ice-water was added and the resulting solution was extracted several times with 3ml of Et_2O. Usual workup afforded 0.76 g of compound **8** (89 %). IR : 2100. ^{1}H NMR ($CDCl_3$, 60 MHz) : 0.2 (s, 6H), 0.98 (s, 6H), 1.5-2.0(m, 2H), 3.1-3.5 (m, 2H), 3.6-3.9 (m, 2H).^{13}C NMR ($CDCl_3$, 60 MHz) : 59.6, 48.2, 31.9, 25.8, 18.2, -5.6.

Preparation of amine **9**

To compound **8** (1.49 g ; 6.93 mmol) in THF (7 ml) was added H_2O (0.16 g ; 9.01 mmol) and Ph_3P (1.82 g ; 6.93 ml). The resulting mixture was stirred under an argon atmosphere for 24h. The majority of the solvent was then evaporated and a solution of ether/petroleum ether (1:1) was added. The precipitate was filtered off, and this operation was repeated until Ph_3PO was completely removed. The solvent was then evaporated without heating to give 1.28 g of compound **9** (98 %). IR : 3500, 3600. ^{1}H NMR ($CDCl_3$, 60 MHz) : 0.2 (s, 6H), 0.98 (s, 6H), 1.2 (s, 2H),

1.5-1.9 (m, 2H), 2.7-3.0 (m, 2H), 3.5-3.9 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) : 61.0, 39.2, 36.3, 25.7, 18.0, -5.6.

2-chloroacetamide **10**

To a solution of **9** (0.70 g ; 3.70 mmol) in ether (20 ml) under argon was added NEt_3 (0.62 ml ; 4.44 mmol) and chloroacetyl chloride (0.33 ml ; 4.07 mmol). After 1h the precipitate was filtered off, the filtrate was washed with water (20 ml) and dried over sodium sulfate. The crude product was purified by flash chromatography (elution with AcOEt-hexane, 1:1) to give 0.82 g of compound **10** (83 %). IR : 3435, 1745, 1675. ^1H NMR ($CDCl_3$, 60 MHz) : 0.2 (s, 6H), 0.98 (s, 6H), 1.5-2.0 (m, 2H), 3.2-3.5 (m, 2H), 3.6-3.9 (m, 2H), 4.0 (s, 2H). ^{13}C NMR ($CDCl_3$, 60 MHz) : 62.1, 42.5, 38.4, 31.3, 25.9, 18.3, -5.5.

2-iodoacetamide **6a**

A solution of **10** (0.82 g ; 3.08 mmol) in acetone (50 ml) was added to a solution of sodium iodide (2.32 g ; 15.40 mmol) in acetone (20 ml). The resulting mixture was heated at reflux for 12 h. After cooling the bulk of acetone was evaporated. Water (30 ml) was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with a 5% sodium thiosulfate solution, dried over sodium sulfate and concentrated to give 1.09 g of compound **6a** (quantitative yield).

Preparation of alcohol **11**

Sodium hydride (2.20 g ; 54.93 mmol) was suspended in THF (150 ml) after being washed with hexane. 1,3-Propanediol (3.80 g ; 49.93 mmol) was added to this mixture at room temperature and stirred for 45 min. by which time a large amount of an opaque white precipitate had formed. Allylbromide (4.80 ml ; 54.93 mmol)) was then added and vigorous stirring was continued for 45 min. The mixture was poured into ether (200 ml) washed with 10% aqueous K_2CO_3 (3 x 40 ml) and brine (3 x 50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was

purified by flash chromatography (elution with AcOEt-hexane , 1:1) to give 0.29 g (86 % yield) of the monoprotected alcohol **11**. IR : 3640, 3540. ^{1}H NMR ($CDCl_3$, 300 MHz) : 1.7-1.9 (m, 2H), 2.9 (s, 1H), 3.5-3.65 (m, 2H), 3.65-3.8 (m, 2H), 3.9-4.0 (m, 2H), 5.1-5.4 (m, 2H), 5.8-6.0 (m, 1H). ^{13}C NMR ($CDCl_3$, 60 MHz) : 134.8, 116.9, 71.9, 68.0, 60.0, 32.4.

Preparation of azide **12**

To a solution of 3-(2-propenyloxy) propanol **11** (3.60 g ; 31.03 mmol) in anhydrous pyridine (2 ml) was added tosyl chloride (7.1 g ; 37.24 mmol). After 48 h at 0°C under an atmosphere of argon, the reaction mixture was poured into ice-water and extracted three times with Et_2O (20 ml) and then worked up. Purification by filtration on silica gel (elution with AcOEt-hexane, 1:1) gave 7.80 g of the expected tosylate (93 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz) : 1.6-2.0 (m, 2H), 2.3 (s, 3H), 3.2-3.5 (m, 2H), 3.6-3.9 (m, 2H), 3.95-4.1 (m, 2H), 4.9-5.2 (m, 2H), 5.5-6.0 (m, 1H), 7.2-7.9 (AA'BB', 4H). ^{13}C NMR ($CDCl_3$, 60 MHz) : 142.0, 132.0, 130.0, 127.2, 125.1, 113.7, 68.8, 65.1, 62.6, 26.5, 18.6.
To a solution of the tosylate (1.00 g ; 3.70 mmol) in freshly distilled DMSO (4 ml) under argon was added sodium azide (0.36 g ; 5.54 mmol). After 48 h at room temperature 4 ml of water was added. The reaction mixture was then extracted six times with 2 ml of Et_2O. After usual work up, 0.48 g of the desired azide **12** was obtained pure as a volatile oil (92 % yield). IR : 2100. ^{1}H NMR ($CDCl_3$, 300 MHz) : 1.7-1.9 (m, 2H), 3.25-3.4 (m, 2H), 3.4-3.5 (m, 2H), 3.8-4.0 (m, 2H), 5.0-5.3 (m, 2H), 5.8-6.0 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) : 135.1, 116.8, 71.7, 66.6, 48.3, 29.1. MS m/z (relative intensity) : 141 (15), 127 (10), 114 (10), 110 (10), 97 (20), 94 (15), 71 (12), 58 (10), 44 (100), 40 (40), 29 (18).

2-chloroacetamide **14**

A solution of the azide **12** (0.23 g ; 1.63 ml) in Et_2O (2 ml) was added dropwise under argon to a suspension of lithium aluminium hydride (0.12 g ; 3.26 mmol) in Et_2O (3 ml). After 10 h, 0.2 ml of water was added followed by 0.2 ml of a 15% solution of NaOH and 0.6 ml of water. Usual workup afforded 0.18 g of

compound **13** which was used in the next step without further purification. A solution of the crude product **13** inEt_2O (10 ml) was cooled to 0°C and NEt_3 (0.26 ml ; 1.89 mmol) was added followed by chloroacetyl chloride (0.15 ml ; 1.89 mmol). The reaction mixture was stirred for 1 h. Water was then added to dissolve the precipitate which had formed. Workup using Et_2O to extract gave a crude mixture that was purified by flash chromatography (elution with AcOEt-hexane, 1:1) to give 0.28 g of *N*-(3-allyloxypropyl)chloroacetamide **14** in 89 % yield from **12**. IR : 3380, 3440, 1760. ^1H NMR ($CDCl_3$, 300 MHz) : 1.7-1.9 (m, 2H), 3.3-3.4 (m, 2H), 3.45-3.55 (m, 2H), 3.9-3.95 (m, 2H), 5.1-5.3 (m, 2H), 5.8-6.0 (m, 1H), 7.45 (s, 1H).^{13}C NMR ($CDCl_3$, 300 MHz) : 165.7, 134.2, 116.7, 71.7, 66.7, 42.3, 38.2, 28.4. MS m/z (relative intensity) : 266 (2), 250 (30), 221 (32), 208 (32), 150 (25), 134 (42), 106 (30), 98 (22), 94 (26), 75 (28), 58 (50), 49 (20), 41 (95), 30 (100).

2-iodoacetamide **6b**

Treatment of **14** (0.14 g ; 0.73 mmol) in acetone (20 ml) with sodium iodide (0.55 g ; 3.65 mmol) in acetone (10 ml) according to the same procedure as **6a** gave 0.21 g of **6b** (quantitative yield).

Compound **5a**

A solution of **1** (0.66 g ; 2.38 mmol) in THF (10 ml) was added to a suspension of potassium hydride (35 % in oil ; 0.30 g, 2.62 mmol) in THF (10 ml) and stirred at room temperature for 5 min. under an atmosphere of argon. The resulting medium was then added to a solution of *N*-(3-*tert*-butylsilyloxypropyl)iodoacetamide **5a** (1.02 g ; 2.86 mmol) in THF (20 ml). After the mixture has been stirred for an additional 10 min., water was added to the reaction mixture in order to solubilize the precipitate. Most of the THF was distilled, and the mixture was worked up to give after filtration through a column of silica gel (elution with AcOEt-hexane, 1:1) 0.96 g of the pure compound **5a** (80 % yield) as an oil : IR : 3520, 1700. 1H NMR ($CDCl_3$, 60 MHz) : 0.02 (s, 6H), 0.9 (s, 9H) ; 1.1-2.0 (m, 8H) ; 2.65 (s, 2H) ; 3.0 (s, 1H, exchangeable with D_2O) ; 3.1-4.3 (m, 8H) ; 6.3-7.4 (m, 9H).

^{13}C NMR ($CDCl_3$, 60 MHz) : 172.3, 152.9, 138.4, 129.5, 129.2, 124.0, 118.8, 108.6, 90.9, 68.3, 61.5, 52.2, 50.5, 40.9, 36.2, 33.5, 32.2, 25.9, 23.5, 18.3, 16.9, -3.44. Exact mass m/z 506.2963 (calc for $C_{30}H_{42}N_2O_3Si$ m/z 506.2940).

Compound **5b**

Compound **5b** was prepared in a similar manner to **5a**, from **1** (0.55 g ; 1.98 mmol) in THF (10 ml), potassium hydride (35% in oil ; 0.25 g, 2.18 mmol) in THF (5 ml), and *N*-(3-allyloxypropyl)iodoacetamide **6b** (0.62 g ; 2.12 mmol) in THF (5 ml). After filtration through a column of silica gel (elution with AcOEt-hexane, 1:1), 0.82 g of the pure compound **5b** (95 % yield) was obtained as an oil and was immediately dehydrated because of its instability . IR : 3520, 1700. ^1H NMR ($CDCl_3$, 300 MHz) : 1.4-2.0 (m, 4H) , 2.1-2.3 (m, 2H) , 2.7 (2H, J_{AB} = 16 Hz, $\Delta\nu$ = 28 Hz), 3.0 (s, 1H) , 3.85-3.95 (m, 2H), 3.95-4.05 (m, 1H), 4.3 (2H, J_{AB} = 16 Hz, $\Delta\nu$ = 94 Hz), 5.1-5.4 (m, 2H), 5.8-6.0 (m, 1H), 6.5 (d, 1H, J = 8 Hz), 6.75 (t, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.2 (d, 1H, J = 8Hz), 7.2-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$, 300 MHz) : 172.1, 152.9, 138.3, 134.5, 129.5, 129.1, 128.6, 127.1, 123.9, 121.3, 118.7, 117.3, 108.6, 90.8, 71.9, 68.6, 67.9, 50.5, 47.0, 40.7, 36.5, 33.6, 29.4, 23.4, 16.8.

Compound **15b**

(±)-10-Camphorsulfonic acid (0.015 g) was added to a solution of **5b** (0.50 g ; 1.02 mmol) in CH_2Cl_2 (50 ml). The resultant solution was refluxed in the presence of molecular sieves (4 Å) for 12 h. The reaction mixture was then neutralized at room temperature with anhydrous K_2CO_3. After filtration and concentration of the organic phase 0.46 g of compound **15b** was obtained as an oil in nearly quantitative yield. IR : 1710, 1680. ^1H NMR ($CDCl_3$, 300 MHz) : 1.4-2.2 (m, 6H), 2.6 (2H, J_{AB} = 15 Hz, $\Delta\nu$ = 33 Hz), 3.3-3.4 (m, 2H), 3.4-3.5 (m, 1H), 3.8-4.0 (m, 4H), 4.4 (2H, J_{AB} = 15 Hz, $\Delta\nu$ = 49 Hz), 5.1-5.4 (m, 3H), 5.8-6.0 (m, 1H), 6.35 (d, 1H, J = 7.5 Hz), 6.55 (t, 1H, J = 7.5 Hz), 6.9 (d, 1H, J = 7.5 Hz), 7.0 (t, 1H, J = 7,5 Hz), 7.2-7.4 (m, 5H). ^{13}C NMR ($CDCl_3$, 300 MHz) : 172.7, 150.6, 143.2, 138.7, 134.9, 128.7, 127.2, 121.4, 117.6, 116.8, 106.5, 100.7,

71.9, 67.8, 67.5, 50.4, 48.3, 47.2, 36.9, 24.5, 24.1, 16.2. MS m/z (relative intensity) : 414 (19), 373 (2), 323 (11), 265 (13), 130 (11), 91 (100) ; exact mass m/z 414.2299 (calc. for $C_{27}H_{30}N_2O_2$ m/z 414.2306).

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