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A Simple Route to Optically Active, Functionalized Five-, Six- and Seven-Membered Carbocyclic Derivatives

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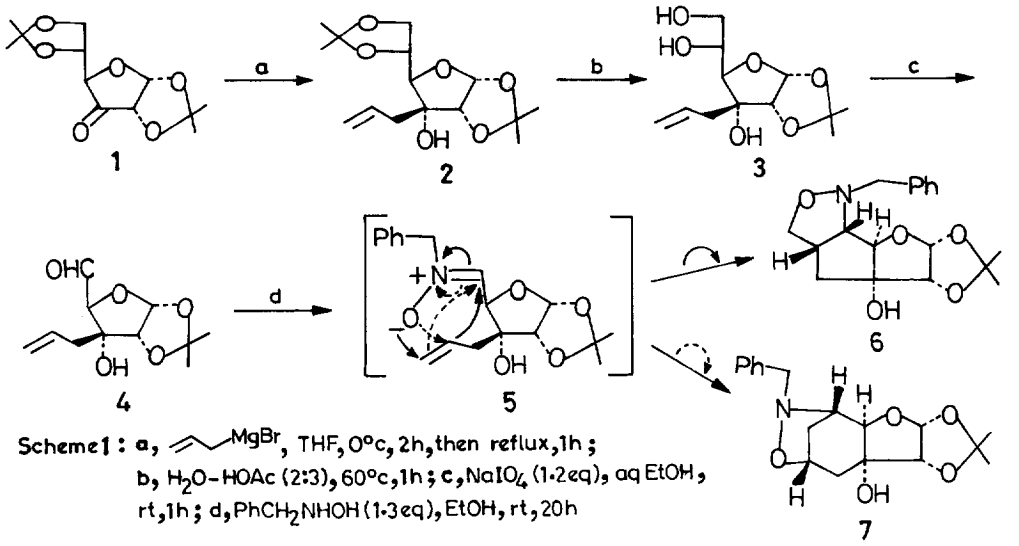
Abstract : The isoxazolidinocarbocyclic derivatives **6**, **7** and **13**, useful as precursors for unnatural bioactive chiral carbocyclic nucleosides and for glycosidase inhibitors have been synthesized from D-glucose through intramolecular 1,3-dipolar cycloaddition. Copyright © 1996 Elsevier Science Ltd

There is considerable interest in the application of carbohydrates as chiral building blocks for the generation of optically active compounds. Pioneering work by Vasella[1] and subsequently by others[2-4] on intramolecular addition with enose nitrone or olefinic nitrile oxide has proved their enormous potential for stereocontrolled access to enantiomerically pure carbocyclic compounds of different ring-sizes. Some of them are used as enzyme inhibitors[5,6] or antibiotics[7] and some are present in bioactive nucleosides.[8] In this route the nitrone or nitrile oxide derived from a carbohydrate nucleus has been commonly used as diene, the olefinic part acting as dienophile. Herein we report the efficacy of the intramolecular nitrone cycloaddition (INC) on glucose derived substrates **4** and **11** in the synthesis of optically active five-, six- and seven-membered isoxazolidinocarbocycle derivatives **6**, **7** and **13** following simple and short reaction sequences. The cycloaddition methodology thus allows access to enantiomerically pure aminocarbocycles of different ring-sizes containing stereochemically defined quaternary carbon centre present in some glycosidase inhibitors, e.g. aminocyclitol[9] and AO-128.[9] To our knowledge, this approach to synthesize chiral polyhydroxylated aminocarbocycles, useful intermediates for various classes of bioactive compounds of current research interest, is both novel as well simple and flexible.

The key reaction in this synthesis involved the intramolecular cycloaddition of nitrones **5** and **12** derived from C-allyl or homoallyl carbohydrate derivatives (scheme 1 and 2). Thus, 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexafuranos-3-ulose (**1**) readily prepared from D-glucose in two steps was reacted with allyl magnesiumbromide to obtain **2**. The β-orientation of the allyl group in **2** is based on literature report[10] on the Grignard reaction of the compound **1**. The 5,6-isopropylidene ring in **2** was selectively opened with aqueous HOAc to furnish the trihydroxy compound **3**.

Oxidative cleavage of **3** with sodium metaperiodate in aqueous EtOH led to the aldehyde **4**[11] which was directly treated with N-benzyl hydroxylamine.[12] The in situ generated nitrone **5** then cyclized in dry EtOH/C_6H_6 at rt in two different modes (Scheme 1) to furnish a mixture of the isoxazolidine derivatives **6** and **7** in different



Scheme 1: a, $CH_2=CH-CH_2MgBr$, THF, 0°c, 2h, then reflux, 1h; b, H_2O-HOAc (2:3), 60°c, 1h; c, $NaIO_4$ (1·2eq), aq EtOH, rt, 1h; d, $PhCH_2NHOH$ (1·3eq), EtOH, rt, 20h

Table 1 : Yields and product ratio of **6**, **7** and **13** in different solvents

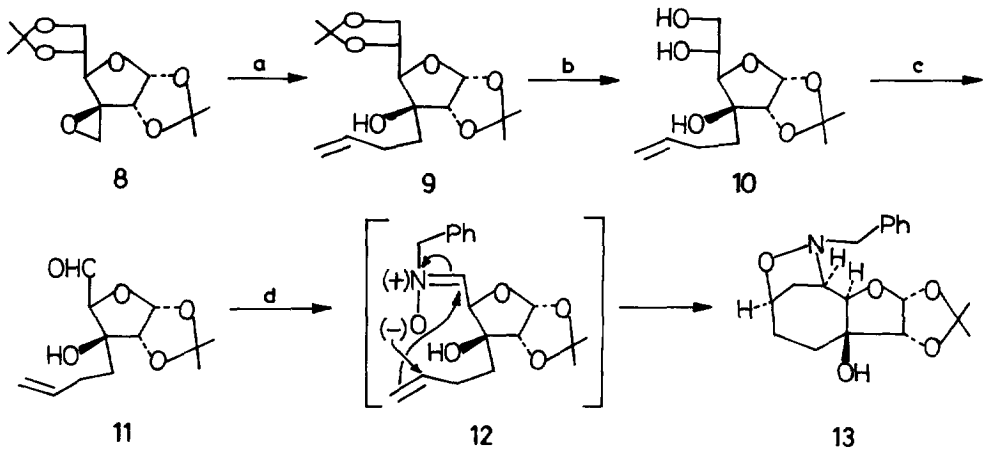
Solvent	Benzene	Toluene	DMF	DMSO	MeCN	EtOH	MeOH	^tBuOH
Ratio, **6:7**	1.6:1	1.7:1	4:1	4:1	3.5:1	1:1.6	1:1	1:1.2
Yield (%) **6+7**	85	83	80	82	84	86	82	88
Yield (%) **13**	82	80	80	85	81	98	95	93

ratio (Table 1). On the other hand, opening of the epoxide[13] ring in **8** with allyl magnesiumbromide afforded **9** in good yield. Deprotection of the 5,6-isopropylidene group of **9** to furnish **10**, followed by vicinal diol cleavage with sodium metaperiodate led to the aldehyde **11**.[11] Treatment with N-benzyl hydroxylamine thereafter in ethanol afforded the compound **13** through intramolecular cycloaddition of the nitrone **12** where only one mode of attack was observed.

Regarding the product ratio in the cyclization step, it was noted that the use of non-polar aprotic solvents like benzene and toluene afforded **6** and **7** in ~1.6:1 ratio, but in polar aprotic solvents, e.g. DMF, DMSO or CH_3CN the ratio changed to 4:1. Surprisingly, when EtOH, MeOH or ^tBuOH were employed as solvents the product ratio was reversed, as **7** was obtained in higher yield than **6**. However, in all the solvents used the total yields of product(s) was ≥80%.

Structure elucidation of **6**, **7** and **13**

That the compound **7** was a bridged isoxazolidine was clearly evident from the appearance of two upfield triplets at δ 29.6 and 39.5 in its ^{13}C NMR spectrum due to the methylene groups at the bridgehead and in the cyclohexane ring. On the other hand, the isoxazolidine derivative **6** showed a downfield triplet at δ 72.5 in the ^{13}C NMR spectrum which clearly indicated the presence of $-CH_2O-$ linkage. Similarly, three upfield triplets at δ 25.1, 29.0, 31.7 in the ^{13}C NMR spectrum indicated the presence of the bridged ring structure in **13**.



Scheme 2 : a, $\sim\!\!\sim$MgBr, THF, 0°c, 12h ; b, H_2O–HOAc (1:3), 60°c, 1.5h ; c, $NaIO_4$ (1.2eq), aq EtOH, rt, 1h ; d, $PhCH_2NHOH$, EtOH, rt, 12h

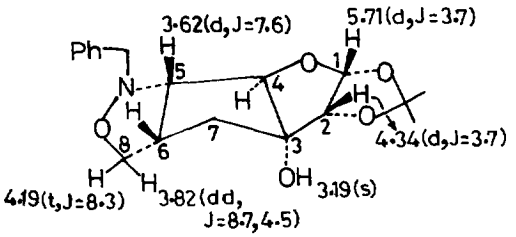
Table 2 : Comparison of experimental and calculated J values of **6**, **7** and **13**

	6		**7**		**13***	
	Found	Calcd	Found	Calcd	Found	Calcd
$J_{1,2}$	3.7	5.1	3.4	4.2	3.7	4.1
$J_{4,5}$	0	0	4.5	4.8	2.4	1.1
$J_{5,6}$	7.6	8.1	-	-	-	-
$J_{5,6a}$	-	-	0	1.5	-	-
$J_{5,6b}$	-	-	5.0	4.8	-	-
$J_{6,8a}$	4.5	3.6	-	-	-	-
$J_{6,8b}$	8.3	8.7	-	-	-	-
$J_{6a,7}$	-	-	0	0.9	-	-
$J_{6b,7}$	-	-	5.2	6.5	-	-
$J_{7,8a}$	-	-	0	1.4	-	-
$J_{7,8b}$	-	-	5.2	5.3	-	-

*H-7 shows two J values of 8.8 and 4.1 against calculated values 7.9, 7.9, 1.0 and 0.9.

Since the structure and the stereochemistry of the carbohydrate ring derived olefinoaldehyde intermediates **4** and **11** are based on literature report [10,13], only the relative configuration

of the newly formed stereocentres needed to be established. For this, recourse was taken to computer assisted molecular modelling coupled with $^3J_{HH}$ calculations. Some of the plausible conformations were created in a Desk Top Molecular Modeller (Version 1.2, Oxford University Press), the energy allowed to minimize to a large extent, the resulting structure transferred for full energy minimization in the MMPMI programme of QCPE (Indiana University) and the $^3J_{HH}$ values calculated using the 3JHHPC programme (of QCPE). The agreement with the experimental J values (in Hz) which could be unambiguously determined (from high-field NMR spectral analysis) was best (Table 2) for the indicated structures of **6**, **7** and **13** (Scheme 3).



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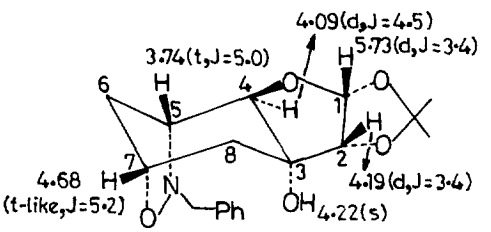

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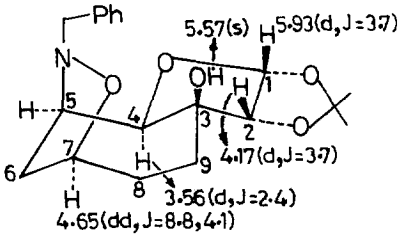

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Scheme 3: Conformations of **6**, **7** and **13** with characteristic nmr data

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were measured on a JASCO 700 spectrophotometer. ^1H NMR spectra were measured on a JEOL FX-100 FT spectrometer using TMS as internal standard. All high-field NMR spectra were recorded on a Bruker AM 300L spectrometer. Mass spectra were run on a JEOL AX-500 spectrometer at 70 eV.

1,2: 5,6-Di-O-isopropylidene-3-C-prop-1-enyl-α-D-allofuranose (2)

To a solution of allyl magnesiumbromide [prepared from allylbromide (6.54g), Mg-turnings (1.22g) and a catalytic amount of iodine] in dry THF (70 ml) at 0°C

was added dropwise a solution (40 ml) of 1,2 : 5,6—di-O-isopropylidene-α-D-ribo-hexafuranos-3-ulose (**1**) (7.74g, 30 mmol) in the same solvent. After stirring (2h at 0°C, then reflux for 1h) the reaction mixture was decomposed (cold water) and then filtered (celite). The solvent was evaporated and the residue extracted with $CHCl_3$ (3x50 ml). The combined extracts were dried (Na_2SO_4), solvent evaporated in vacuo to furnish a material which was purified by column chromatography over silica gel. Petroleum ether-$CHCl_3$ (1:4) eluents gave a solid which was recrystallized from petroleum ether-ether to furnish **2** as colourless crystals (7.20g, 80%) : mp 125-126°C; $[\alpha]_D^{25}$ + 42.3° (c 0.104, $CHCl_3$); IR (KBr) : 3482, 1637, 1504, 1456, 1376, 1261, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.30 (s, 6H), 1.40 (s, 3H), 1.56 (s,3H), 4.20 (d, 1H, J=4.0 Hz), 4.85-5.30 (m, 2H), 5.56 (d, 1H, J = 4.0 Hz), 5.66-6.23 (m, 1H); EIMS, m/z (%) : 300 (M^+,5), 284 (22), 167 (18), 100 (100), 85 (47), 69 (75); Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.99; H, 8.05. Found : C, 60.01; H, 8.07.

1,2-O-Isopropylidene-3-C-prop-1-enyl-α-D-allofuranose (3)

Compound **2** (1.00g, 3.33 mmol) in a mixture of H_2O-HOAc (2:3) (25 ml) and MeOH (5 drops) was stirred and heated at 60°C for 1h when TLC showed complete disappearance of the starting material. The solvent was evaporated in rotary evaporator and the last traces of HOAc by toluene co-evaporation (3x20 ml). The residue was then chromatographed over silica gel. Elution with $CHCl_3$-MeOH (49:1) mixture gave the trihydroxy compound **3** (823 mg, 95%) : mp 101-103°C; $[\alpha]_D^{25}$ + 41.5° (c 0.15, $CHCl_3$); IR (KBr) : 3424, 1642, 1376, 1217, 1170, 875 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.59 (s, 3H), 2.00-3.00 (m, 3H), 3.23-4.00 (m, 7H), 4.33 (d, 1H, J=4.0 Hz), 4.84-5.47 (m, 2H), 5.66 (d, 1H, J=4.0 Hz), 5.84-6.36 (m, 1H); EIMS (m/z, %) : 260 (M^+,8), 259 (33), 244 (21), 100 (44), 71 (100).

1-β-Formyl-3-α-hydroxy-3-β-allyl-4α, 5α-O-isopropylidene-tetrahydrofuran (4)

To a solution of trihydroxy compound **3** (520 mg, 2 mmol) in aq. EtOH (50%, 20 ml) was added dropwise a solution (5 ml) of $NaIO_4$ (513 mg, 2.4 mmol) in water. After stirring at rt for 1h it was filtered, solvent evaporated and the product was extracted with $CHCl_3$ (3x30 ml). The $CHCl_3$ solution was dried (Na_2SO_4), evaporated and the crude product **4** dried under vacuum : IR (neat) : 3540, 1734, 1640, 1379, 1215, 1080, 1004, 746 cm^{-1}. Compound **4** was used without further purification for the next step.

Dioxolofurocyclohexanoisoxazolidine derivative 7; Dioxolofurocyclopentanoisoxazolidine derivative 6

To a solution of crude aldehyde **4** (1.59g, 7.0 mmol) in dry EtOH (25 ml) was added N-benzyl hydroxylamine (1.12g, 9.1 mmol) and stirred for 20h at rt. The solvent was evaporated and the product extracted with $CHCl_3$ (3x25 ml). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated to a solid compound. TLC showed two spots when developed in $CHCl_3$. The crude material

was chromatographed over silica gel. Elution with petroleum ether - $CHCl_3$ (3:7) afforded two crystalline compounds **6** (701 mg, 30%) and **7** (1.12g, 56%). **6**: mp 151-152°C (Pet. ether - Et_2O); $[\alpha]_D^{25}$ - 10.3°(c 0.097, $CHCl_3$); IR (KBr) : 3474, 1602, 1448, 1371, 1295, 1165, 1077, 990, 879, 728 cm^{-1}; ^1H NMR ($CDCl_3$) (300 MHz) : δ 1.33 (s, 3H), 1.53 (s, 3H), 1.91 (m, 2H), 3.19 (s,1H), 3.33 (m, 1H), 3.62 (d, 1H, J=7.6 Hz), 3.82 (dd, 1H, J=4.5, 8.7 Hz), 3.87 (d, 1H, J=13.1 Hz), 4.05 (d, 1H, J=13.1 Hz), 4.11 (s, 1H), 4.19 (t, 1H, J=8.3 Hz), 4.34 (d, 1H, J=3.7 Hz), 5.71 (d, 1H, J=3.7 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) (75 MHz) : δ 26.7,27.1 (2xq), 40.5, 61.2, 72.5 (3xt), 48.2, 75.1, 82.3, 89.4, 105.1, 127.5 (6xd), 128.4 (2xd), 129.2 (2xd), 88.3, 112.9, 136.9 (3xs); EIMS (m/z, %) : 333 (M^+, 100), 318 (14), 230 (8), 174 (28), 160 (43), 91 (85); Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found : C, 64.90; H, 6.89; N, 4.50. **7**: mp 133-134°C (Pet. ether - Et_2O); $[\alpha]_D^{25}$ - 90.4° (c 0.094, $CHCl_3$); IR (KBr) : 3490, 1585, 1409, 1370, 1253, 1166, 1016, 891, 869, 754, 700 cm^{-1}; ^1H NMR ($CDCl_3$) (300 MHz) : δ 1.32 (s, 3H), 1.57 (s, 3H), 2.10 (m, 2H), 2.28 (d, 1H, J=11.6 Hz), 3.74 (t, 1H, J=5.0 Hz), 3.76 (d, 1H, J=12.6 Hz), 4.09 (d, 1H, J=4.5 Hz), 4.12 (d, 1H, J=12.6 Hz), 4.19 (d, 1H, J=3.4 Hz), 4.22 (s, 1H), 4.68 (t-like, 1H, J=5.2 Hz), 5.73 (d, 1H, J=3.4 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) (75 MHz) : δ 26.2, 26.7 (2xq), 29.6, 39.5, 63.0 (3xt), 61.1, 75.4, 78.0, 84.1, 104.0, 127.4 (6xd), 128.3 (2xd), 128.8 (2xd), 112.9, 136.7 (2xs), one signal merged with $CDCl_3$ signals; EIMS (m/z, %) : 333 (M^+, 87), 318 (22), 160 (82), 132 (18), 91 (100); Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found : C, 64.99; H, 6.88; N, 4.51.

1,2 : 5,6-Di-O-isopropylidene-3-C-but-1-enyl-α-D-glucofuranose (9)

To a solution of allyl magnesiumbromide [prepared from allyl bromide (3.14g), Mg-turnings (0.60 g) and a catalytic amount of iodine] in dry THF (60 ml) at 0°C was added dropwise a solution (25 ml) of the epoxide, 1,2 : 5,6-Di-O-isopropylidene -3-C-hydroxymethyl-3,3'-anhydro-α-D-glucofuranose (**8**) (3.68g, 14.4 mmol) in the same solvent and the mixture was stirred overnight (12h) at 0-10°C. The reaction mixture was decomposed by dropwise addition of cold water and then filtered through celite. The solvent was evaporated and the residue extracted with $CHCl_3$ (3x50 ml). The combined extracts were dried, solvent evaporated and the residue was chromatographed over silica gel. Elution with $CHCl_3$ afforded pure compound **9** as an oil (3.24g, 72%) : $[\alpha]_D^{25}$ + 38.1° (c 0.105, $CHCl_3$); IR (neat) : 3476, 1641, 1455, 1376, 1215, 1165, 847 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 4.32 (d, 1H, J=4.0 Hz), 4.92-5.36 (m, 2H), 5.72-6.20 (m, 1H), 5.86 (d, 1H, J=4.0 Hz); EIMS, m/z : 299 (M^+-15), 256, 129, 97, 83, 69; Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.12; H, 8.34. Found : C, 61.11; H, 8.33.

1,2-O-Isopropylidene-3-C-but-1-enyl-α-D-glucofuranose (10)

Compound **9** (628 mg, 2 mmol) was converted to **10** (433 mg, 79%) using aqueous HOAc (1:3) and following the procedure described for **3**.

10 : mp 95-97°C; $[\alpha]_D^{25}$ + 35.4° (c 0.11, $CHCl_3$); IR (KBr) : 3522, 1641, 1378, 1318, 1216, 1166, 877, 751 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.32 (s, 3H), 1.52 (s, 3H), 1.86 (brt, 2H, J=8.0 Hz), 2.14-2.50 (m, 2H), 2.68 (brs, 3H), 3.66-4.18 (m, 4H), 4.34 (d, 1H, J=4.0 Hz), 4.86-5.30 (m, 2H), 5.70-6.14 (m, 1H), 5.80 (d, 1H, J=4.0 Hz); EIMS, m/z : 259 (M^+-15), 183, 155, 139, 127, 109, 85.

2-β-Formyl-3-β-hydroxy-3-α-(but-1-enyl)-4α,5α-O-isopropylidene tetrahydrofuran (11)

Compound **10** (822 mg, 3 mmol) was converted to **11** (700 mg crude) following the procedure described for **4**. TLC showed single spot. **11** : IR (neat): 3442, 1735, 1643, 1378, 1217, 1166, 876, 749 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.36 (s, 3H), 1.52 (s, 3H), 4.20 (d, 1H, J=2.0 Hz), 4.36 (d, 1H, J=4.0 Hz), 4.90-5.30 (m, 2H), 5.88 (m, 1H), 6.12 (d, 1H, J=4.0 Hz), 9.68 (d, 1H, J=2.0 Hz).

Dioxolofurocycloheptanoisoxazolidine derivative 13

To a solution of crude aldehyde **11** (600 mg, 2.48 mmol) in dry EtOH (10 ml) was added N-benzyl hydroxylamine (397 mg, 3.23 mmol) and stirred for 12h at rt. The solvent was removed, residue extracted with $CHCl_3$ (2x50 ml), $CHCl_3$ extracts washed with water, dried (Na_2SO_4) and evaporated to give a solid white material. The crude material was chromatographed over silica gel. Elution with $CHCl_3$ solvent afforded the crystalline product **13** (846 mg, 98%) : mp 180-181°C (Pet. ether - $CHCl_3$); $[\alpha]_D^{25}$ + 120° (c 0.113, $CHCl_3$); IR (KBr) : 3372, 1583, 1456, 1378, 1210, 1162, 1058, 870, 683 cm^{-1}; ^1H NMR ($CDCl_3$) (300 MHz) : δ 1.27 (s, 3H), 1.45 (s, 3H), 1.63 (m, 2H), 1.85 (m, 2H), 2.04 (m, 1H), 2.32 (m, 1H), 3.56 (d, 1H, J=2.4 Hz), 3.83 (d, 1H, J=13.4 Hz), 3.85 (m, 1H), 3.96 (d, 1H, J=13.5 Hz), 4.17 (d, 1H, J=3.7 Hz), 4.65 (dd, 1H, J=4.1, 8.8 Hz), 5.57 (s,1H), 5.93 (d, 1H, J=3.7 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) (75 MHz) : δ 26.0, 26.6 (2xq), 25.1, 29.0, 31.7 (3xt), 62.7 (t+d), 77.1, 80.7, 86.4, 105.3, 127.3 (5xd), 128.1 (2xd), 128.7 (2xd), 79.8, 111.8, 136.5 (3xs); EIMS (m/z, %) : 347 (M^+, 30), 332 (8), 247 (14), 160 (37), 91 (100); Anal. Calcd for $C_{19}H_{25}NO_5$; C, 65.69; H, 7.25; N, 4.03. Found : C, 65.70; H, 7.30; N, 4.72.

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