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NEW ACHIEVEMENTS IN THE FIELD OF INTRAMOLECULAR PHENOLIC COUPLING REACTIONS, USING HYPERVALENT (III) IODINE REAGENT: SYNTHESIS OF GALANTHAMINE

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Abstract: Our investigations on the oxidative possibilities of the hypervalent iodine(III) reagent established that phenyliodine(III)bis(trifluoroacetate) (PIFA) can provide one-pot contiguous coupling-cyclization reaction giving a product with narwedine skeleton, when used in a phenolic coupling reaction of p'-bromonorbelladine derivatives. A suitably selected precursor gave up to 60% yield of the coupled product.

The development of the chemistry of hypervalent iodine(III) reagents represents their wide utility in the organic synthesis for halogenation, oxidation, hydroxylation and other reactions[1]. These

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reagents can oxidize some phenols to benzoquinones[2]. Other p-substituted phenols undergo phenol coupling intramolecular transformation to a cross-conjugated cyclodienones[3a-3e].

This fact is used in oxidative intramolecular phenolic coupling reactions for the preparation, starting from some norbelladine derivatives, of para-ortho' cross conjugated coupled products, which can be further transformed into narwedine and galanthamine[4].

(-)-Galanthamine is a natural alkaloid isolated from the Amaryllidaceae family. Early use of (-)-galanthamine pertained the treatment of neuromuscular disorders, due to its action on the central nervous system as an anticholineesterase and anticholinergic agent. Recently, (-)-galanthamine has been evaluated as an active principle for the treatment of Alzheimer's disease[5a,5b], and has entered into clinical trials in Europe and the United States. As a consequence, the interest for finding a suitable and industrially applicable technological scheme for the large scale production of natural galanthamine is rapidly growing[6a]. The crucial step in every approach is the phenolic coupling process leading to a product able to be transformed into galanthamine.

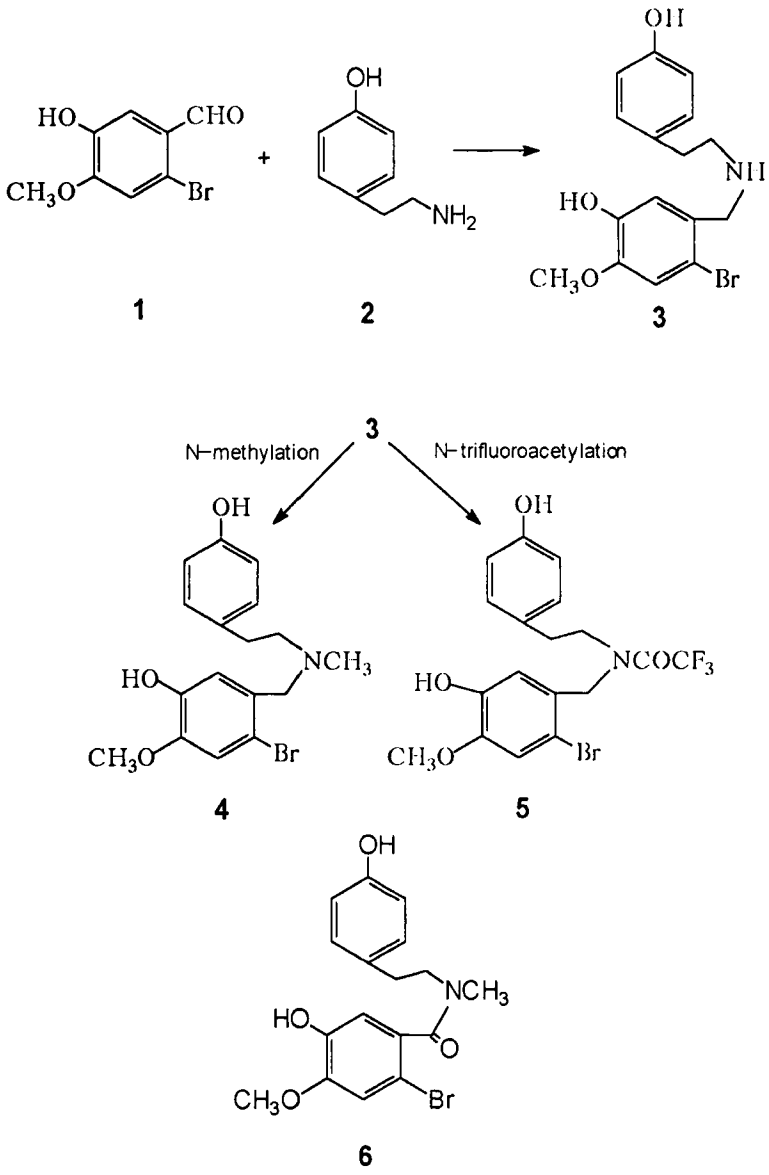
Our long standing investigations on the total synthesis of galanthamine[7a,7b] were developed during the last two years by using the hypervalent iodine(III) in the form of PIFA as an effective reagent in the key phenolic coupling reaction for a direct formation of the basic narwedine skeleton. Further it can be transformed into racemic or optically active galanthamine[4a,6a].

RESULTS AND DISCUSSIONS

It has been shown[3a,4a] that norbelladine precursors, not substituted at para' position, cannot undergo a para-ortho' coupling reaction, because the competing para-para' coupling process is favoured. The same norbelladine derivatives undergo exclusively a para-para' coupling in a phenolic oxidation, independently of the type of the oxidant used. To overcome this phenomenon and aiming at achieving exclusively para-ortho' coupling, authors block the para' position with different substituents[4a,8]. For the same reason in our investigations we ever used products protected at para'-position[7a,7b,9]. As an extension of our work in the field of the para-ortho' phenolic coupling we examined the behaviour of norbelladine derivatives **4**, **5**, **6** when subjected to oxidation with PIFA. The intermediate amine **3** was prepared by reductive alkylation of 2-bromoisovanillin **1** with tyramine **2**[6b]. By subsequent N-methylation[10] or N-trifluoroacetilation[11] , precursors **4** and **5** can be obtained, respectively. Precursor **6** could be prepared in a high yield starting from commercially available isovanillin and 4-hydroxyphenylacetic acid as we have previously reported[7b] (***Scheme 1***).

The presence of both free phenol groups enable phenol coupling reaction and the subsequent Michael vinylogous addition to the conjugated dienone system, leading to the narwedine skeleton. The phenol coupling and cyclization reactions were carried out with PIFA in trifluoroethanol at -40 ^{0}C. The precursors **6** and **4** were transformed in 60% and 30% yield into bromonarwedine derivatives **7** and **8**,

S C H E M E 1



respectively. Precursor **5** gave 20% transformation to **9**, which subsequently cyclized to **10** in 92% yield (***Scheme 2***).

The tetracyclic compound **7** after ethylene glycol ketalization gave the intermediate product **11**, which was transformed into (+/-)-narwedine **12** in a high yield, by $LiAlH_4$ reduction and subsequent deprotection. The L-Selectride reduction of **12** gave racemic galanthamine **13**[12,13] (***Scheme 3***).

Three essential conclusions could be summarized:

1. Hypervalent iodine(III) reagent can be used in a direct preparation of compounds with narwedine skeleton.

2. The use of precursors having free phenol groups enables both reactions of coupling and furan ring formation to proceed as one-pot reaction distinguishing our approach from another work[4a].

3. A suitable precursor **6** is found to give 60 % transformation into a narwedine type enone **7**.

EXPERIMENTAL SECTION

General: Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 or Pye-Unicam SP-200G spectrophotometer. ^1H NMR spectra were recorded on a Bruker WM 250 (250 MHz) in the indicated solvents with TMS as internal standard. MS spectra were recorded on a JEOL-JMS-D300 spectrometer. Amido precursors **5** and **6** proved to be mixtures of two isomers. PIFA and trifluoroethanol

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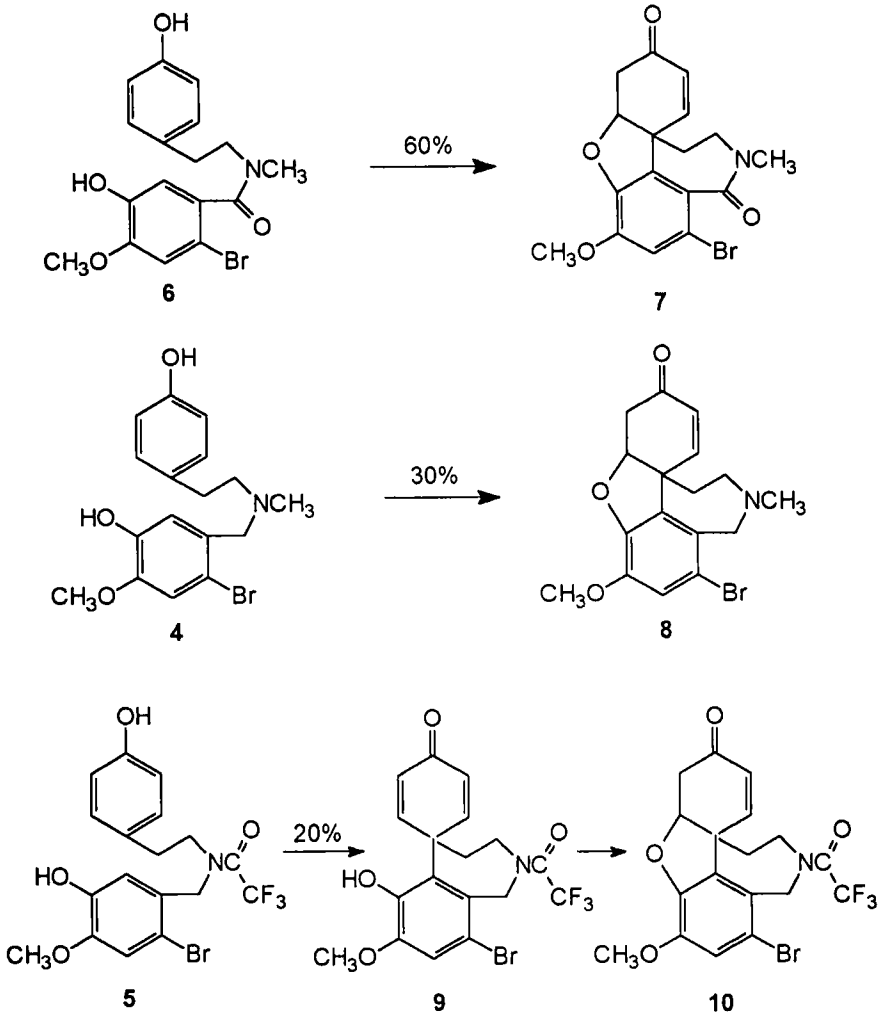
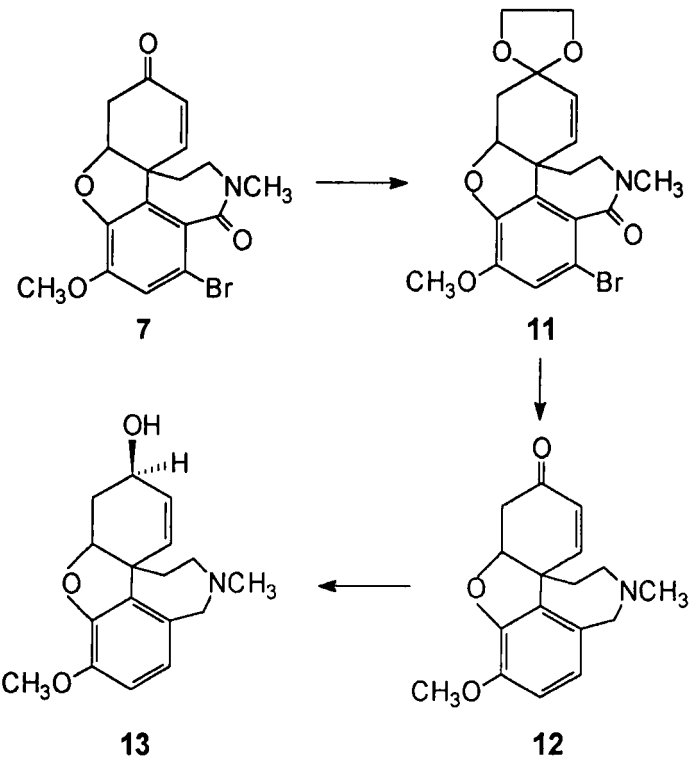


S C H E M E 3



were obtained from commercial supplier and were used without further purification.

A. Synthesis of precursors:

N-(2-bromo-5-hydroxy-4-methoxybenzyl)-4-hydroxy-phenethylamine **3.** To 6.5 g (28 mmol) of 2-bromoisovanilline **1** dissolved in 30 ml of MeOH was added dropwise a solution of 3.8 g

(28 mmole) of tyramine **2** at r.t. The mixture was stirred for 5 hrs, cooled with ice/water and 1.34 g (34 mmol) of $NaBH_4$ were added. Then the reaction mixture was stirred for 5 hrs at r.t. MeOH was evaporated in vacuo and the residual oil was dissolved in EtOAc. This solution was washed with brine, dried over $MgSO_4$ and distilled to dryness. The obtained yellow oil weighted 8.23 g (83.1%). M.p. 229-230 ^{0}C (as HCl salt); IR(film): 3300, 2920, 1030 cm^{-1} ; NMR ($CDCl_3$/DMSO-d_6): δ(ppm): 1.85(1H, brs) 2.72-2.82(4H, m), 3.75(2H, s), 3.83(3H, s), 6.70-7.00(6H, m); MS(70eV), (m/z): 351/353(M^+), 244/246; 215/217 (base peak).

***N-(2-bromo-5-hydroxy-4-methoxybenzyl)-N-(4-hydroxy-phenethyl) methylamine* 4.** 5g (14 mmol) of **3** dissolved in a mixture of 5 ml of 98-100% HCOOH and 5 ml of 36-38% HCHO were stirred at 100 ^{0}C for 8 hrs. The process was controlled by TLC. After completion of the reaction the mixture was cooled to r.t. and 6 ml of 17% HCl were added. The volatiles were distilled under vacuo and 15 ml of water were added. The mixture was alkalized with 10% NH_4OH, extracted with EtOAc (3 x 50 ml), dried over $MgSO_4$ and evaporated to dryness. The residual yellow-brownish oil was refined via HCl salt. The regenerated base of **4** weighted 4.73 g (91.0%); m.p. 176-177 ^{0}C; IR(film): 2980, 2780, 1620 cm^{-1}. NMR($CDCl_3$/DMSO-d_6): δ(ppm) 2.31(3H, s), 2.69-2.71(4H, m), 3.36(1H, brs), 3.56(2H, s), 3.84(3H, s), 6.69(1H, s), 6.73(1H, s), 6.97(2H, s), 7.01(2H, s), 8.80(1H, brs); MS(70eV),(m/z): 365/367(M^+), 258/260, 215/217(base peak).

N-(2-bromo-5-hydroxy-4-methoxybenzy)-N-(4-hydroxy-phenetyl) trifluoroacetamide **5**. 6 g of 3 (17 mmol) are dissolved in 10 ml of anhydrous CH_2Cl_2 , containing 3 ml of Py. The solution is cooled with ice/water and 2.72 ml of trifluoroacetic anhydride are added dropwise. The mixture is stirred for 4 hrs at r.t. and then poured onto 200 ml of ice/water. The organic layer is separated, washed with water, dried over $MgSO_4$ and evaporated to dryness. The isolated yellow-brownish oil is dissolved in hot benzene and precipitated with hexane. The filtered colourless crystals of 7 weights 7,42 g (97,0%); m.p. 133-135 ^{0}C; IR(KBr): 3350, 1680 cm^{-1} ; NMR($CDCl_3$): δ(ppm) 2.77-2.86(2H, m), 3.41-3.47(2H, m), 3.73 and 3.88(3H, two s), 4.48 and 4.75(2H, two s), 5.69(2H, brs), 6.69-7.04(6H, m); MS(70eV),(m/z): 447/449 (M^+), (base peak), 368, 215/217.

B. Synthesis of narwedine type enones 7, 8 and 10:

Compound 7: *4a,5,9,10,11,12-hexahydro-1-bromo-3-methoxy-11-methyl-6H-12-oxo-benzofuro[3a,3,2-ef][2]-benzazepin-6-one*

General procedure: To a stirred and cooled(-40 ^{0}C) solution of 500 mg(1.3 mmol) of 6 in 20 ml of CF_3CH_2OH are added under nitrogen dropwise 620 mg(1,4 mmol) of PIFA dissolved in 5 ml of CF_3CH_2OH. The mixture is stirred for 10 min at -40 ^{0}C. Then the solvent is evaporated in vaccuo, the residue dissolved in 25 ml of EtOAc, washed with 5% NH_4OH, water, dried over $MgSO_4$ and evaporated to dryness. The residual oil is filtered through a short

column with hexane:EtOAc gradient. Thus 300 mg of **7** (59,7%) as white amorphous solid are isolated; m.p. 239-240 ^{0}C from EtOH. IR(KBr): 2920, 2850, 1680, 1640, 1600 cm^{-1} ; *NMR($CDCl_3$), δ (ppm): 1.96(dt, 1H, J=14.7Hz; 2.5Hz), 2.47(ddd, 1H, J=14.7Hz; 13.3 Hz; 3.7Hz), 2.80(dd,1H, J=17.7Hz; 3.9Hz), 3.14(ddd, 1H, J=17.7Hz; 2.5Hz, 0.9 Hz), 3.23(s, 3H), 3.29(ddd, 1H, J=14.9Hz; 3.7Hz; 2.5Hz), 3.88(ddd, 1H, J=14.9Hz; 13.3 Hz; 2.5Hz), 3.90(s, 3H), 4.84(m, 1H), 5.94(dd, 1H, J=10.2Hz; 0.9Hz), 6.34(dd, 1H, J=10.2 Hz; 2.2Hz), 7.13(s, 1H); MS(70eV),(m/z): 377/379 (M^+), 329, 307, 289, 259, 176, 154 (base peak), 136; *(more detailed NMR data are given in reference 7b).

Compound **8**: *4a,5,9,10,11,12-hexahydro-1-bromo-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]-benzazepin-6-one*

Reactants: compound **4** in 250 mg(0.68 mmol), 25 ml CF_3CH_2OH, 324 mg(0.77 mmol) PIFA. Yield 74 mg (29.6%) as colourless oil after short column purification with hexane/EtOAc gradient. IR(film): 3030, 2920, 2850, 1640, 1620 cm^{-1}; NMR($CDCl_3$), δ(ppm): 1.89(1H, dt, J=13.8 Hz; 3.2 Hz), 2.24(1H, m), 2.47(3H, s), 2.74(1H, dd, J=17.9 Hz; 3.7 Hz), 2.97-3.05(1H, m), 3.14(1H, ddd, J=17.9 Hz; 3.7 Hz; 0.9 Hz), 3.14-3.25(1H, m), 3.83(3H, s), 3.92 and 3.98(1H, d, J=17.2 Hz), 4.24 and 4.30(1H,d, J=17.2 Hz), 4.72(1H, m), 6.05(1H, d, J=10.5 Hz), 6.95(1H, s), 7.02(1H, d, J=10.5 Hz); MS(70eV),(m/z): 363/365 (M^+), 320, 294, 284, 254, 149.

Compound **9**.(*dienone preparation*). Reactants: compound **5**, 200 mg(0.45 mmol) in 25 ml CF_3CH_2OH, 211 mg(0.49 mmol) PIFA.

Yield 40 mg(19.5%) as colorless oil after short column purification with hexane/EtOAc gradient. IR(film): 3020, 2930, 1670, 1660, 1600 cm^{-1}; NMR($CDCl_3$),δ(ppm): 2.41-2.46(2H, t, J=12.3 Hz), 3.78 (3H, s), 3.92-3.97 (2H, t, J=12.3 Hz), 5.10 and 5.14(2H, 2s), 6.05(1H, brs), 6.30 and 6.34(2H, d, J=10.2 Hz), 6.49(1H, s), 6.82 and 6.86(1H, d, J=10.2 Hz), 6.96 and 7.01(1H, d, J=10.2 Hz); MS(70eV),(m/z): 445/447 (M^+), 366, 319(base peak), 305/307.

Compound **10** (*vinylogous cyclization*): *4a,5,9,10,11,12-hexahydro-1-bromo-3-methoxy-11-trifluroacetamido-6H-benzofuro[3a,3,2-ef][2]-benzazepin-6-one*

Reactants: compound **9**, 30 mg (0.07mmol) in 3 ml CF_3 COOH. Stirring at r.t. for 1 hr. Yield 27mg (92%). IR(film): 3040, 2920, 1660, 1600, 1510 cm^{-1} ; NMR($CDCl_3$), δ(ppm): 1.98 and 2.05(1H, dt, J=14.4Hz; 2.5Hz), 2.23 and 2.30(1H, dt, J=14.40Hz; 2.5Hz), 273 and 2.80(1H, dd, J=17.5Hz; 3.7Hz), 3.14 and 3.21(1H, ddd, J=17.5Hz; 3.7Hz; 1.0 Hz), 3.28-3.36(1H, m), 3.67-3.75(1H, m), 3.85(3H, s), 4.37 and 4.44(1H, d, J=16.8Hz), 4.71-4.74(1H, m), 5.14 and 5.21(1H, d, J=16.8Hz), 6.07 and 6.11(1H, d, J=13.0 Hz), 6.77 and 6.82(1H, d, J=13.0Hz), 6.97(1H, s); MS(70eV), (m/z): 445/447 (M^+), 305/307.

C. Synthesis of racemic galanthamine 13.

I. 42 mg(0,11 mmol) of the compound **7**, 100 mg of ethylene glycol and few crystals of p-TsOH were heated to reflux in 10 ml of

toluene for 2 hrs, water being separated off. After cooling, the mixture was washed with water, $NaHCO_3$ sol., dried over $MgSO_4$ and evaporated. Yield: 43 mg (91 %) of **11** as an oil. IR(film): 3010, 2920, 2850, 1710, 1650, 1620, 1030 cm^{-1}; NMR($CDCl_3$), δ(ppm): 1.92-2.00 (1H, m), 2.51-2.63(1H, m), 2.71-2.77(1H, m), 3.11-3.13(1H, m), 3.15(3H, s), 3.20-3.23(1H, m) 3.58-3.73(4H, m), 3.73-3.76(1H, m), 3.89(3H, s), 4.45(1H, m), 6.76(1H, d, J=10.9 Hz), 6.98(1H, d, J=10.9 Hz), 7.07(1H, s).

II. In 5 ml of dioxane were introduced 50 mg of $LiAlH_4$ under argon. 100 mg of the compound **11**, dissolved in 5 ml of dioxane, were added dropwise. The mixture was refluxed for 3 hrs. The course of the reaction was monitored by TLC. After cooling, 10 ml of a mixture water:dioxane 1:1 were added dropwise. The pH was brought to 1 with c.HCl and stirred for 15 min at r.t. Then the mixture is alkalized to pH 12 with ammonia sol., diluted with water, and extracted with EtOAc. The organic layer is washed with water and brine, dried over $MgSO_4$ and evaporated under vacuo. Yield: 58 mg (86%) of **12** as pale crystals, which when recrystallized from EtOH had m.p. 188-190 ^0C. IR(KBr): 2950, 2920, 1685, 1670, 1500, 1290 cm^{-1}; NMR($CDCl_3$), δ(ppm): 1.86(1H, d, J=14.5 Hz), 2.28(1H, dt, J=14.5 Hz; 3.9 Hz), 2.45(3H, s), 2.75(1H, dd, J= 17.8 Hz; 3.7 Hz), 3.18(1H, dd, J=17.9 Hz; 3.7 Hz), 3.20(2H, m), 3.76(1H, d, J=15.3 Hz), 3.85(3H, s), 4.11(1H, d, J=15.3 Hz), 4.74(1H, m), 6.05(1H, d, J=10.3 Hz), 6.66(1H, ABq, J=8.2 Hz), 6.71(1H, ABq, J=8.2 Hz), 6.96(1H, d, J=10.3 Hz).

III. To a stirred solution of 50 mg(0.17 mmol) of **12** in 5 ml of THF were added at -78 ^{0}C 0.67 ml of L-Selectride (1 Mol sol. in THF). The mixture was stirred at the same temp. for two hrs. An additional stirring at r.t. for one hr was followed by addition of water, and extraction with EtOAc. The organic solution was dried over $MgSO_4$ and solvent evaporated. Yield: 46 mg (93%) of **13**. PTLC purification gave white crystals with m.p. 121-123 ^{0}C from Et_2O, (lit. 121-123)[14]. IR(KBr): 3370, 3260, 2900, 1600, 1500, 1270, 1080, 1035 cm^{-1}; NMR($CDCl_3$), δ(ppm): 1.58(1H, m), 2.02(1H, dd, J=15.6 Hz; 4.9 Hz), 2.09(1H, m), 2.40(3H, s), 2.50(1H, brs), 2.69(1H, dd, 15.6 Hz, 4.9 Hz), 3.06(1H, d, J=13.6 Hz), 3.28(1H, t, J=13.6 Hz), 3.69(1H, d, J=15.3 Hz), 3.84(3H, s), 4.09(1H, d, J=15.3 Hz), 4.14(1H, t, J=4.9 Hz), 4.62(1H, brs), 6.00(1H, ddd, J=10.5 Hz; 4.6 Hz; 1.0 Hz), 6.06(1H, dd, J=10.5 Hz; 1.0 Hz), 6.64(1H, ABq, J=8.2 Hz), 6.66(1H, ABq, J=8.2 Hz); MS (70 eV),(m/z): 287 (M^+), (base peak), 244, 216, 84, 39. ^{13}C NMR (62,9 MHz, $CDCl_3$), δ(ppm): 29.9, 62.1, 126.9, 127.6, 48.2, 33.8, 53.8, 60.6, 129.3, 122.1, 111.2, 145.8, 144.1, 133.0, 88.7, 42.1, 55.9.

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