1,3-Dipolar Cycloaddition of Nitrile Oxides with Symmetrical Tri- and Polycyclic Strained Olefins

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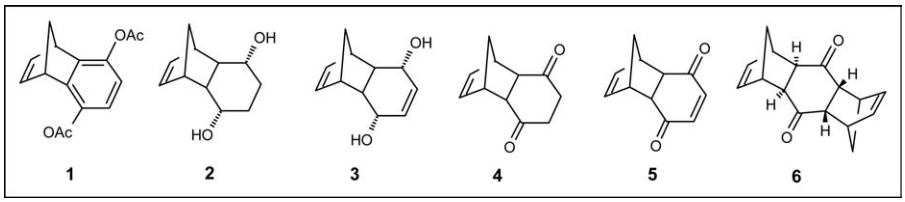

1,3-Dipolar cycloadditions of benzonitrile oxide and carbethoxyformonitrile oxide (CEFNO) with various facially perturbed polycyclic symmetrical dienophiles (**1**–**6**) were investigated. Cycloadditions took place chemoselectively at the norbornyl double bond and were found to be exclusively exo. Cycloadditions of benzonitrile oxide with dienophiles **4** and **5** led to mixture of inseparable products, however, that with CEFNO gave single products. Cycloadduct of dienophile **5** with CEFNO was found to be unstable, and it readily isomerized to more stable aromatic form.

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INTRODUCTION

1,3-Dipolar cycloaddition of nitrile oxides are well documented [1] and provide efficient entries to the synthesis of isoxazolines [2]. Remarkable stereoselectivity has been observed in 1,3-dipolar cycloadditions with bicyclic systems [1a,3,4] and indeed, that with norbornene proceeds exclusively on the exo face [5]. Even unsymmetrically substituted norbornenes are reported to cycloadd completely stereoselectively [6]. The desired exo-isomers are the one in which oxygen of the dipole is attached to the more substituted center of the dipolarophiles (Scheme 1).

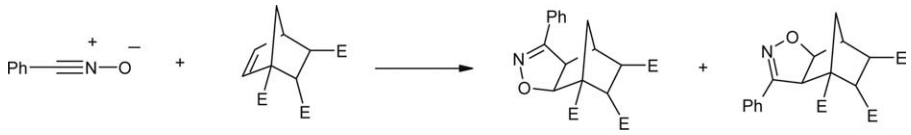
Formation of single regio- and stereoisomers were also noticed in the intramolecular cycloaddition of norbornene tethered nitrile oxides [6c]. Recently, Namboothiri *et al*. [7a] have studied the behavior of multi π-facial dipolarophiles, dicyclopentadiene (DCP), and its analogues toward nitrile oxides. In their study on DCP, the cycloaddition of nitrile oxide was found to be both chemo- and steroselective. However, cycloadducts were reported to be mixture of two regioisomers. In a similar study, Trivedi and coworkers [8] and Tanaka *et al*. [9] have also noticed comparable regio-, chemo-, and stereoselectivity during the cycloaddition of DCP with substituted acetonitrile oxides. As against this, the cycloadducts derived from Thiele's esters were regio-, stereo- and chemoselective [7].

It is interesting to note that the stereochemistry of Diels-Alder additions to norbornene systems, for example, 2,3-norbornenobenzoquinone (NPBQ) [10], 2,3-norbornanobenzoquinone (DNPBQ) have been extensively investigated by Mehata *et al*. [11]. However, complementory investigations involving the cycloaddition of facially perturbed dienophiles to 1,3-dipoles has not received matching attention. This study is, therefore, focused on the 1,3-dipolar cycloaditions of two different types of nitrile oxides *viz*. benzonitrile oxide and carbethoxyformonitrile oxide (CEFNO) toward multi π-facial tricyclic and polycyclic systems incorporating bicyclo-[2.2.1]-heptenyl moity (Figure 1).

RESULTS AND DISCUSSION

Dipolarophile **1** was prepared by treatment of compound **5** with acetic anhydride and pyridine [10]. Compound **5** in turn was obtained by Diels-Alder cycloaddition of cyclopentadiene and *para*-benzoquinone (1:1 eq) [10]. Diels-Alder cycloaddition of cyclopentadiene and *para*-benzoquinone in 2:1 eq gave dipolarophile **6**. Dipolarophile **5** was reduced chemoselectively to dipolarophile **4** by using Zn and acetic acid. Chemoselective reduction of compounds **4** and **5** were carried out using $NaBH_4$ and $CeCl_3.7H_2O$ to get dipolarophiles **2** and **3**, respectively.

Scheme 1



Preference to the symmetrical dipolarophiles was given to negate regiochemistry question. The results presented here deal with both the questions of chemoselectivity and stereoselectivity. As Mayo *et al*. [6c] have noticed dependence of cycloadduct stereochemistry on the methods and conditions of generation of nitrile oxides. Therefore, we have adopted two methods for the generation of nitrile oxides. First one involves *in situ* preparation of benzonitrile oxide by commonly used bleach method in dichloromethane solvent, whereas second one involves *in situ* preparation of carbethoxyformonitrile oxide in ionic liquid medium as described by Taddei *et al* [12].

For initial studies, we have chosen dipolarophiles with only one double bond (**1** and **2**) so as to get rid of chemoselectivity aspect. In these cases, approach of dipole can take place from two faces of dipolarophiles leading to the possibility of two products. However, we observed that dipolarophiles **1** undergo cycloaddition with benzonitrile oxide **7a** giving exclusively exo cycloadduct **1a** (Scheme 2). In ^{1}H-NMR disappearance of signal at δ 5.66 (s, 2 H) and appearance of signal at δ 4.16 (d, 1 H, J = 8.1 Hz) for H^a and 5.08 (d, 1 H, J = 8.1 Hz) for H^b confirmed formation of cycloadduct. The protons H^a and H^b appeared as doublets coupled only to each other but not to bridgehead protons indicating endo orientation [6c,7a]. Diol **2** also underwent cycloaddition with benzonitrile oxide affording exclusively exo-cycloadduct **2a** as indicated by spectral data (Scheme 2). Cycloaddition of **1** and **2** with carbethoxyformonitrile oxide **7b** took place similarly yielding corresponding cycloadducts **1b** and **2b**, respectively.

To further investigate cycloaddition reaction, we have increased the number of π-faces in dipolarophiles to two (two C=C). When dipolarophile **3** was subjected to cycloaddition to benzonitrile oxide, we observed remarkable stereoselectivity along with chemoselectivity. Cycloaddition took place selectively to the olefin of norbornene moity with exclusively exo selectivity giving rise to only one cycloadduct **3a** (Scheme 3). Similar results were obtained in cycloaddition of carbethoxyformonitrile oxide with dipolarophile **3** resulting in formation of cycloadduct **3b**.

Encouraged by these results, we attempted cycloaddition of benzonitrile oxide on more complex systems **4** and **5** containing three (two C=O and one C=C) and four (two C=O and two C=C) π-faces, respectively. In principle, dipolarophile **5** could react with either of the double bonds and/or with the carbonyl groups. In the event, if each of the π-component reacts with the dipole formation of upto three cycloadducts could be envisaged, provided the ''exo addition rule'' prevails [7]. However, the reaction ended up with a complex intractable mixture. To overcome the eventualities arising out of the side reactions due to multiple π-faces, it was decided to reduce the number of reactive sites by saturating the α,β-unsaturated double bond in the dienedione **5**. In such systems, amongst the constituents π-systems, the norbornenyl double bond is expected to deliver the cycloadducts in a chemoselective fashion. However, to our dismay, the cycloaddition reaction with benzonitrile oxide under the chosen condition ended up with the inseparable multiple products (Scheme 4).

However, when dipolarophile **4** was subjected to cycloaddition reaction with carbethoxyformonitrile oxide instead of multiple products as expected from our earlier studies only single product **9** was obtained. Cycloaddition took place chemoselectively to the olefinic double bond of dipolarophile **4**, and it was found to be exclusively exo product. Encouraged by these results, we expected similar chemo- and stereoselectivity in the cycloaddition of CEFNO to the dipolarophile **5**. Although the product of this cycloaddition was found to be pure by thin layer chromatography, the ^{1}H and ^{13}C-

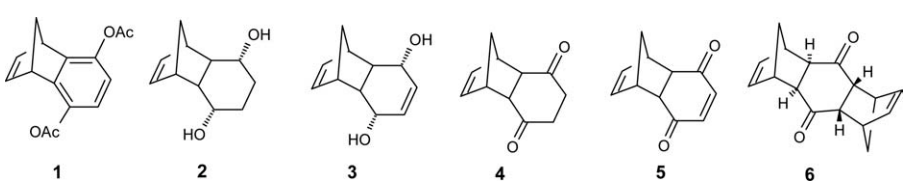
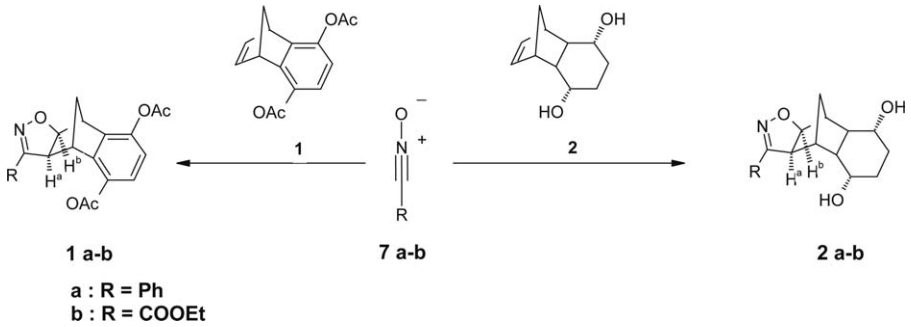


Figure 1. Symmetrically substituted dipolarophiles.

Scheme 2



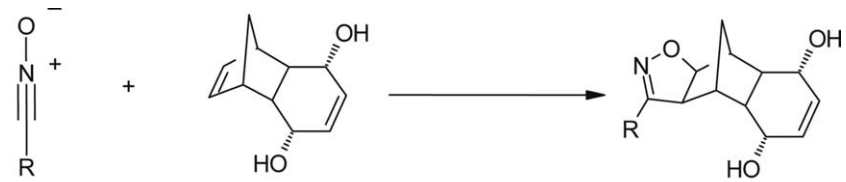
spectral data were little ambiguous and insufficient to confirm the exact structure of cycloadduct. The doublet observed in ^{1}H spectra at δ 8.6 for two protons with J = 8.7 Hz could not be explained. In ^{13}C-spectra also, no signal for carbon of carbonyl was observed indicating absence of C=O group. IR spectrum showed strong absorptions in 3300–3600 cm^{-1} range. To get the more details about the structure, spectral correlation studies were carried out. ^{1}H-^{1}H COSY spectrum (Figure 2) showed only two correlations, one between proton of CH_2 and CH_3 of the ethyl group and another between two protons at δ 3.5 and δ 4.8 ppm. ^{1}H-^{13}C HETCOR spectra (Figure 3) was more informative. It showed absence of correlation for two protons observed at 8.6 in ^{1}H NMR spectrum and absence of protons on four carbon atoms (δ 128.40, 133.05, 143.97, and 144.71). Further, D_2O exchange studies showed that doublet observed at 8.6 is D_2O exchangeable. All these results led us to conclude the structure of adduct as **8** (Scheme 5). The cycloadduct was found to be exclusively exo as indicated by ^{1}H-NMR spectrum.

As compound **5b** could not be obtained directly by cycloaddition of dipolarophile **5** with carbethoxyformonitrile oxide, we thought of preparing it by oxidation of cycloadduct **3b**. When we subjected the cycloadduct **3b** to PCC oxidation, expecting product **5b** as shown in Scheme 6, we ended up with **8** indicating that **5b** is not stable and gets isomerized to more stable form **8**. It further confirms the structure of cycloadduct of **3** with CEFNO as **3b**.

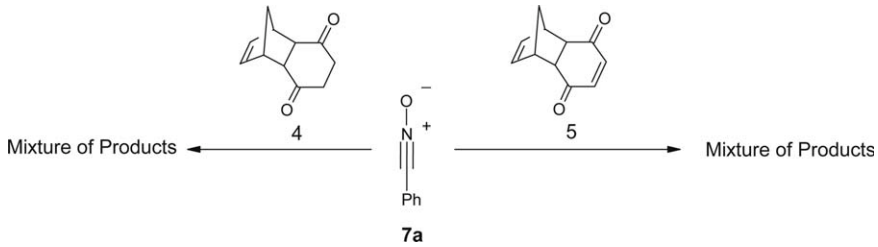
The next dipolarophile used for the study was endo-anti-endo bisadduct **6**. It has four π-faces (two C=C and two C=O). Although we were expecting behaviour of dipolarophile **6** in cycloaddition to benzonitrile oxide similar to that of **4** and **5**, we were surprised to observe exo monoadduct **6a** as the sole product as indicated by ^{1}H and ^{13}C spectral data. Cycloaddition of **6** with carbethoxyformonitrile oxide also resulted in similar results leading to formation of cycloadduct **6b** (Scheme 7).

In conclusion, we have studied the 1,3-dipolar cycloaddition of benzonitrile oxide and carbethoxyformonitrile oxide with various polycyclic dipolarophiles possessing norbornene moiety. Cycloaddition of dipolarophiles **1** and **2** with both the dipoles were found to be stereoselective as only exo cycloadduct was obtained. Dipolarophile **3** reacted with both the dipoles stereoselectively as well as chemoselectively at the norbornene double bond giving corresponding exo cycloadduct. Cycloaddition of dipolarophiles **4** and **5** with benzonitrile oxide led to the formation of mixture of products which could not be characterized; however, cycloaddition of **4** and **5** with carbethoxyformonitrile oxide gave corresponding cycloadducts stereoselectively and chemoselectively. Dipolarophile **6** also reacted with both the dipoles giving corresponding monoadduct stereo and chemoselectively. Hence, from the above study, we can

Scheme 3



Scheme 4



conclude that exo-rule prevails for the norbornene entities present in the polycyclic molecules.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an atmosphere of N_2. Progress of reactions was monitored by TLC (silica gel 60 F254, 0.25 mm, Merck) and purification was effected using silica gel column chromatography. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on Jeol-300 MHz spectrophotometer. Chemical shifts (δ) were reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. IR spectra were recorded on a Nicolet Impact 400 series FTIR spectrophotometer. All commercial grade solvents were distilled before use.

Preparation of dipolarophile 4. To a solution of compound **6** (1.044 g, 6 mmol) in glacial acetic acid (60 mL) was added activated zinc (4.2 g, 64.2 mmol). The reaction mixture was stirred for 3 h at room temperature. The acetic acid was removed under high vacuum *via* dry ice-acetone trap. The residue was dissolved in diethyl ether and filtered through a pad of celite. The filtrate was washed with saturated aq. $NaHCO_3$ (120 mL), brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to furnish the product (0.580 g, 55%). Yellow oil. IR ($CHCl_3$): 3020, 2925, 1705, 1423, 1300 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32–1.51 (m, 2H), 2.30 (m, 2H), 2.65 (m, 2H), 3.22 (s, 2H), 3.46 (s, 2H), 6.18 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.81, 47.31, 48.61, 51.71, 136.51, 209.55.

Preparation of dipolarophile 2. Compound **4** (0.35g, 2 mmol) was dissolved in a solution of cerium (III) chloride heptahydrate (1.5g, 4 mmol) in methanol (6 mL). The resulting solution was cooled to 0°C by external application of an ice bath. Sodium borohydride (0.15 g, 4 mmol) was then added at such a rate that the temperature of the reaction mixture did not rise significantly above 0°C. The reaction mixture was analyzed by TLC 2 h after addition of the sodium borohydride had been completed: The reaction was then quenched via addition of water (2.5 mL) and the resulting mixture was then extracted with chloroform and combined organic layer was concentrated *in vacuo* to yield crude diol. Recrystallization from DCM and petroleum ether afforded pure diol (0.099g, 27.76%). White solid, Mp 127–126°C. IR ($CHCl_3$): 3307, 3224, 2910, 1563, 1527 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (dd, 2 H, J = 7.5 and 8.0 Hz), 1.79 (s, 4 H), 1.86 (bs, 1 H), 2.38 (s, 2 H), 2.77 (bs, 1 H), 2.91 (s, 2 H), 4.12 (s, 2 H), 6.21 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.04, 45.11, 45.83, 52.39, 67.04, 134.56.

Procedure for PCC oxidation of 3b. In a 50-mL round-bottomed flask fitted with a reflux condenser was suspended PCC (0.161 g, 0.75 mmol) in anhydrous dichloromethane (5 mL). Cycloadduct **3a** (0.073 g, 0.25 mmol) was added to it in small portions and stirring was continued till reaction goes to completion. The progress of reaction was monitored on TLC.

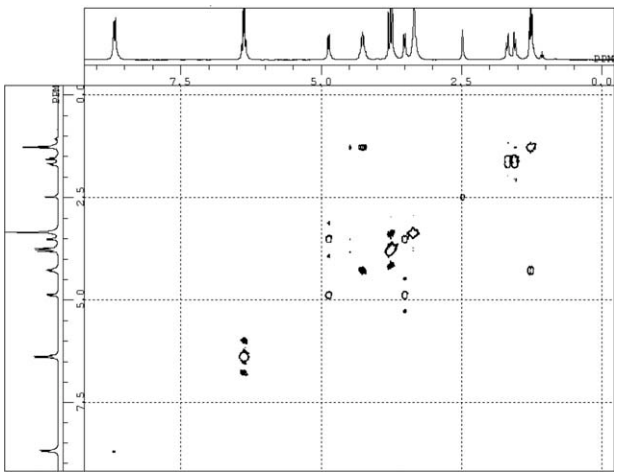


Figure 2. (^{1}H-^{1}H) COSY spectrum of compound **8**.

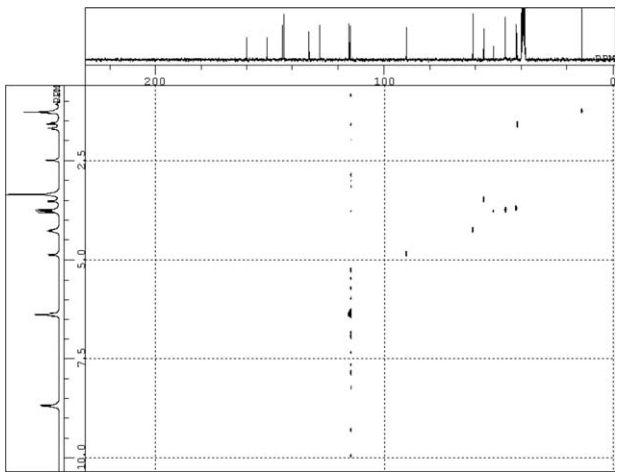
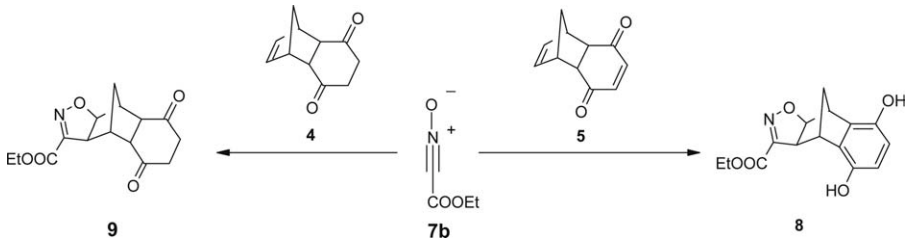


Figure 3. (^{13}C-^{1}H) HETCOR spectrum of compound **8**.

Scheme 5



After completion of the reaction, dichloromethane was removed under vacuum and product was extracted into diethyl ether (4 × 5 mL). All the extracts were dried by using anhydrous sodium sulfate and evaporated under reduced pressure to get the product which was purified by column chromatography, (0.055 g, 76%).

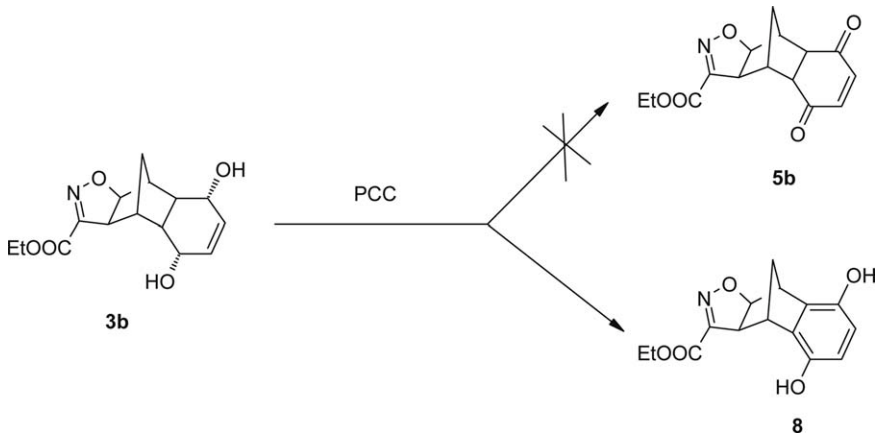
General procedure for cycloaddition of benzonitrile oxides with dipolarophiles. A solution of the benzaldoxime (dipole precursor) (1.2 mmol), dipolarophile (1 mmol) and triethylamine in dichloromethane (10 mL) was cooled to 0°C, sodium hypochlorite (4%, 10 mL) was added dropwise with stirring at 0°C. The reaction mixture was warm to room temperature and kept for 6–8 h with stirring. On disappearance of starting material (TLC), the reaction phases were separated and the aqueous phase was extracted with dichloromethane. The combined layers were washed with brine, dried with sodium sulphate, and the solvent evaporated under reduced pressure to yield crude cycloadduct. The crude product was chromatographed on a silica gel column. Thus, all cycloadducts were prepared following the aforementioned general protocol and characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. The data for cycloadduct obtained from 1,3-dipolar cycloaddition are presented below.

General procedure for cycloaddtion of carbethoxyformonitrile oxide with dipolarophiles. In a typical experimental procedure, dipolarophile (1 mmol) was mixed with $NaHCO_3$ (1 mmol) in [bmim]BF_4 (0.5 g) ionic liquid. Ethyl chloroximidoacetate (1 mmol) was added, and the mixture was stirred at room temperature for 3–4 h when starting material disappeared (TLC); the reaction mixture was treated with diethyl ether to extract the product. Diethyl ether was removed under reduced pressure to get the product. In case of cycloaddition with dipolarophile **3**, due to poor solubility in diethyl ether, cycloadduct **3b** was isolated by dissolving ionic liquid in water followed by filtration. If required, the crude products were chromatographed on silica gel column. Cylcoadducts obtained were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.

Compound 1a. White solid (89%), Mp 168–170°C. IR ($CHCl_3$): 1760, 1593, 1563 1483 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (d, 1 H, J = 9.0 Hz), 2.01 (d, 1 H, J = 9.0 Hz), 2.32 (s, 3 H), 2.37 (s, 3 H), 3.43 (s, 1 H), 3.71 (s, 1 H), 4.16 (d, 1 H, J = 8.1 Hz), 5.08 (d, 1 H, J = 8.1 Hz), 6.83 (s, 2 H), 7.39–7.41 (m, 3 H), 7.77–7.79 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.74, 20.81, 43.16, 44.66, 49.04, 56.99, 87.81, 120.90, 121.08, 126.89, 128.78, 128.93, 129.99, 137.01, 140.76, 142.25, 143.17, 156.16, 169.06, 169.30. HRMS (TOF, ES$^+$): m/z [M + H]$^+$ calcd for $C_{22}H_{20}NO_5$: 378.1341; found: 378.1357.

Compound 1b. White solid (70%), Mp 130–132°C. IR (KBr): 898, 1015, 1194, 1369, 1476, 1579, 1756, 2925, 2983 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, 9.0 Hz), 1.86 (d, 1 H, 9.0 Hz), 1.96 (d, 1 H, 12.0 Hz), 2.33 (s, 3 H), 2.36 (s, 3 H), 3.69 (s, 1 H), 3.71 (s, 1 H), 3.81 (d, 1 H, J = 9.0 Hz), 4.36 (m, 2 H), 5.12 (d, 1 H, J = 9.0 Hz), 6.84 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.14, 20.74, 20.80, 43.03, 44.51, 48.90, 56.00, 62.02, 90.39, 121.17, 121.57,

Scheme 6



Scheme 7

136.50, 140.46, 142.43, 143.06, 151.19, 160.39, 169.84. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{19}H_{20}NO_7$: 374.1240; found: 374.1256.

Compound 2a. Sticky mass (75%). IR ($CHCl_3$): 3351, 1611, 1574 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ = 1.21 (d merged with other peak, 2 H, *J* = 10.5 Hz), 1.61 (d, 2 H, *J* = 10.2 Hz), 1.71 (d, 2 H, *J* = 12 Hz), 1.93 (d, 2 H, *J* = 14.7 Hz), 2.01 (s, 2 H), 2.62 (s, 1 H), 2.80 (s, 1 H), 4.27 (s, 1 H), 4.34 (s, 1 H), 5.01 (d, 1 H, *J* = 8.1 Hz), 5.76 (d, 1 H, *J* = 8.1 Hz), 7.35 (m, 3 H), 7.72 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.73, 28.79, 34.74, 40.87, 41.44, 44.26, 48.73, 51.11, 67.20, 67.80, 84.92, 126.97, 127.41, 128.69, 129.43, 129.66, 158.48. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_3$: 300.1600; found: 300.1614.

Compound 2b. Yellow sticky oil (65%). IR (neat): 757, 829, 940, 1018, 1137, 1173, 1252, 1405, 1449, 1581, 1720, 2962, 3303 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–2.09 (m, 11 H), 2.70 (s, 1 H), 2.80 (s, 1H), 3.47–3.50 (m, 2 H), 4.17–4.34 (m, 4 H), 4.65 (d, 1 H, *J* = 9.0 Hz), 5.87 (d, 1 H, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.97, 28.26, 28.41, 34.58, 40.88, 41.46, 44.06, 48.37, 49.83, 61.75, 66.84, 67.25, 87.90, 162.99, 161.32. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for:$C_{15}H_{22}NO_5$: 296.1498; found: 296.1484.

Compound 3a. White solid (85%), Mp 196–198°C. IR ($CHCl_3$): 3397, 1655, 1460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, 1 H, *J* = 6.9 Hz), 1.30 (d, 1 H, *J* = 11.4 Hz), 1.60 (s, 1 H), 1.67 (d, 1 H, *J* = 10.5 Hz), 2.58 (narrowly splitted triplet, 2 H), 2.68 (s, 1 H), 2.79 (s, 1 H), 3.85 (d, 1 H, *J* = 7.2 Hz), 4.45 (s, 1 H), 4.54 (s, 1 H), 4.72 (d, 1 H, *J* = 8.1 Hz), 5.73 (dd, 2 H, *J* = 10.5 and 10.2 Hz), 7.35–7.37 (m, 3 H), 7.81–7.84 (m, 2 H). ^{13}C NMR (75MHz, $CDCl_3$): δ = 34.23, 39.79, 40.69, 41.41, 45.50, 53.01, 65.84, 65.84, 85.57, 127.01, 128.62, 128.65, 129.32, 129.62, 130.34, 130.57, 157.19. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1446.

Compound 3b. White solid (69%), Mp 108–109°C. IR (KBr): 951, 1071, 1245, 1363, 1576, 1635, 1732, 2957, 3311, 3516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, *J* = 6.6 and 6.9 Hz, one peak merged in it), 1.55 (d, 1 H, *J* = 10.5 Hz), 1.92 (bs, D_2O exch.), 2.58 (s, 2 H), 2.73 (s, 1 H), 2.80(s, 1 H), 3.61 (d, 1 H, *J* = 8.1Hz), 4.32 (m, 2 H), 4.43 (s, 2 H), 4.81 (d, 2 H, *J* = 8.1 Hz), 5.64 (d, 1 H, *J* = 9.9 Hz), 5.74 (d, 1 H, *J* = 9.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.09, 34.29, 39.93, 40.79, 41.06, 45.45, 51.89, 61.95, 65.61, 65.93, 88.47, 130.13, 130.95, 152.04, 160.97. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_5$: 294.1314; found: 294.1344.

Compound 9. Yellow oil (62%). IR (KBr): 927, 1138, 1252, 1705, 2925 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, *J* = 7.2 Hz, signal for 1 H merged in it), 1.57 (d, 1 H, *J* = 11.4 Hz), 2.47 (m, 2 H), 2.89 (m, 2 H), 3.15–3.23 (m, 4 H), 3.44 (d, 1 H, *J* = 9.0 Hz), 3.30–4.38 (m, 2 H), 4.75 (d, 1 H, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 31.85, 38.42, 38.69, 43.48, 47.36, 48.48, 50.54, 51.40, 62.16, 85.82, 151.65, 159.94, 207.60. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_5$: 292.1185; found: 292.1197.

Compound 8. Brown solid (72%), Mp 220–222°C. IR (KBr): 821, 957, 1160, 1339, 1499, 1585, 1724, 2991, 3337, 3653 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 6.9 and 7.2 Hz), 1.56 (d, 1 H, *J* = 9.9 Hz), 1.69 (d, 1 H, *J* = 9.9 Hz), 3.52 (d, 1 H, *J* = 8.4 Hz), 3.74 (s, 1 H), 3.77(s, 1 H), 4.25–4.29 (m, 2 H), 4.87 (d, 1 H, *J* = 8.4 Hz), 6.36 (d, 1 H, *J* = 8.7 Hz), 6.40 (d, 1 H, *J* = 8.7 Hz), 8.67(s, 1 H, D_2O exch.), 8.70(s, 1 H, D_2O exch.). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 42.25, 42.76, 47.34, 56.81, 61.59, 90.53, 115.07, 115.53, 128.46, 133.05, 143.97, 144.71, 151.47, 160.21. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}NO_5$: 290.1028; found: 290.1020.

Compound 6a. White solid (87%), Mp176–178°C. IR ($CHCl_3$): 1690, 1563, 1494, 1444 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, 1 H, *J* = 10.8 Hz), 1.47 (d, 1 H, *J* = 8.7 Hz), 1.58 (m, 2 H), 2.68 (s, 2 H), 2.95 (s, 1 H), 3.13-3.16 (m, 2 H), 3.43 (s, 2 H), 3.56 (d, 1 H, *J* = 8.4 Hz), 4.65 (d, 1 H, *J* = 8.4 Hz), 6.37 (s, 2 H), 7.40 (m, 3 H), 7.78 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.13, 42.81, 46.76, 49.05, 50.66, 50.73, 51.45, 52.32, 54.20, 54.49, 83.27, 126.94, 128.56, 128.85, 129.99, 135.34, 135.51, 56.35, 210.52, 212.39. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{23}H_{26}NO_3$: 360.1600; found: 360.1607 $[M^+ + H]$.

Compound 6b. Off-white solid (50%), Mp 140–141°C. IR (KBr): 932, 1125, 1256, 1690, 1721, 2922, 2983 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.63 (m, 7 H), 2.04 (s, 2 H), 2.66 (m, 2 H), 3.11 (m, 2 H), 3.40 (m, 3 H), 4.33 (m, 2 H), 4.70 (d, 1 H, *J* = 9.0 Hz), 6.35 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 29.69, 31.30, 42.91, 46.70, 48.88, 50.61, 51.07, 51.23, 52.16, 54.05, 54.31, 62.05, 85.93, 135.41, 135.49, 151.71, 160.05, 210.53, 210.77. HRMS (TOF, ES^+): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_5$: 356.1498 ; found: 356.1496.

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