# Stereochemistry of Protonation at C(1) of Nitronate Adducts from 1,6-Conjugate Addition of Grignard Reagents to 2-Methoxy-1-nitronaphthalene

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C(1) protonation of 4-alkyl-2-methoxy-1,4-dihydronaphthalene-1-nitronate anions (7) gives a mixture of *trans*- (9) and *cis*-4-alkyl-2-methoxy-1-nitro-1,4-dihydronaphthalenes (8) with the latter isomer in excess. Isomerization experiments indicate that the *cis* compound is also the more stable isomer. Formation of the more stable isomer under kinetically controlled conditions confirms that the stereochemistry of the reaction is governed by the steric hindrance offered by the axial alkyl group to proton attack in the axial direction in a transition state whose geometry reflects a boat conformation for (7).

When an electrophilic reagent attacks the nucleophilic centre of an exocyclic double bond that has a bulky ring substituent on the vicinal $sp^3$ carbon, preferential formation of the less stable isomer is generally observed.[1]

The most reasonable interpretation [2,3] of this stereochemical phenomenon is that stereoselectivity is induced by the steric control exerted on the electrophile attack by the vicinal axial bulky group in a transition state that closely resembles the reactants.

Only one example has been reported [4] of the formation of the more stable isomer, the *C*-protonation of the anion of 9,10-dihydro-9,10-(*trans*-11-nitro-12-alkylethano)anthracene.

The exclusive formation of the *trans* isomer was explained by assuming that the reaction is controlled by a transition state that closely resembles the final products.

We have recently found [5] that the addition of an $MeCO_2H$–$MeCO_2K$ buffer to 10-alkyl-9,10-dihydroanthracene-9-nitronate anion (2) gives exclusively the more stable *cis* isomer of 9-alkyl-10-nitro-9,10-dihydroanthracene (3).

The hypothesis then formulated, that (3) is the kinetically favoured isomer, was based on the fact that system (2), owing to the *peri*-hydrogens hindrance, must assume a boat geometry with the alkyl group in a pseudoaxial position, and this arrangement forces the proton to approach from the less hindered equatorial direction.

Unfortunately no spectroscopic evidence could be obtained to support this hypothetical conformation.

Since $^1H$ n.m.r. analysis of the 1,4-dihydronaphthalene system could provide stereochemical information more suited to the understanding of the actual geometry of the nitronate anion, the reaction of *C*-protonation at the 1,6-nitronate adduct from 2-methoxy-1-nitronaphthalene (4) was subsequently investigated.

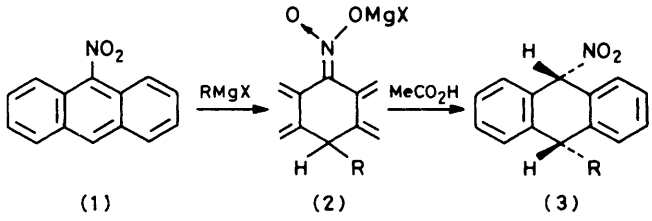
Here we report the results of the n.m.r. studies directed to supply experimental evidences of the factors which govern the stereochemistry of the reaction.

## Results

Tetrahydrofuran solutions of the nitronate adducts (5a—c) were prepared as reported previously [3] by adding an excess of RMgX (a, R = Me; b, R = $PhCH_2CH_2$; c, R = $PhCH_2$) to 2-methoxy-1-nitronaphthalene (4) in THF at room temperature.

Addition of a $MeCO_2H$–$MeCO_2K$ buffer solution gave a mixture of *cis*- (8) and *trans*-4-alkyl-2-methoxy-1-nitro-1,4-dihydronaphthalene (9) (see Scheme). Yields and the relative amounts of the *cis* and *trans* isomers are reported in Table 1.

In order to establish the relative stability of the *cis* compared with the *trans* compound, a mixture of (8a) and (9a) was dissolved in methanol or in dichloromethane in the presence of trace amounts of triethylamine.




(1) (2) (3)

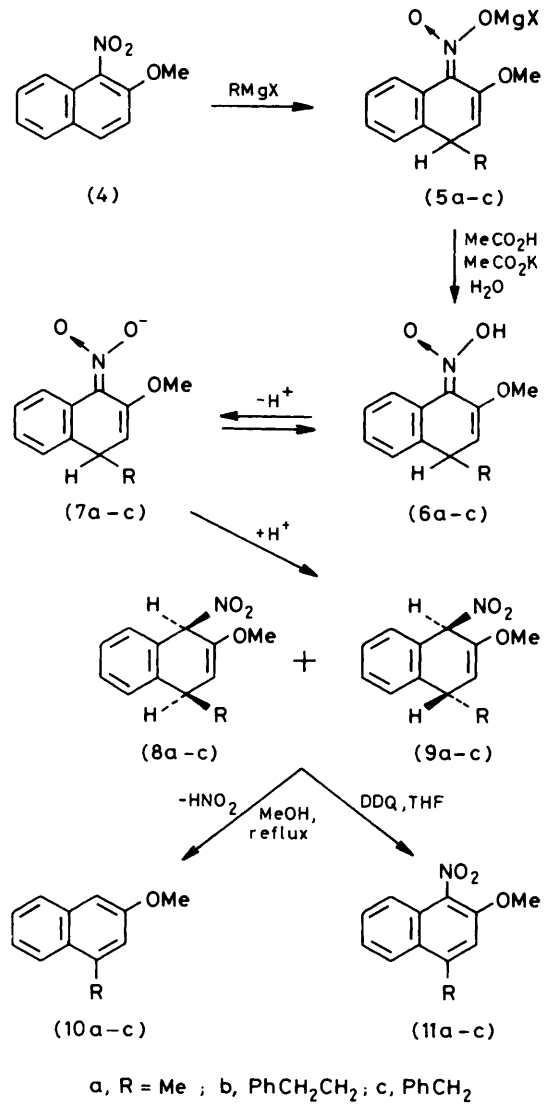
A partial isomerization of (8a) to (9a) was observed at room temperature. In all experiments the relative proportions of the *cis* to the *trans* isomer decreased slightly until a constant ratio of 70 : 30 was reached after 3 days. Analogous experiments carried out on compounds with $PhCH_2$ or $PhCH_2CH_2$ substituents gave the results reported in Table 2. Owing to the high acidity of the 1-H proton, in analogy with closely related systems,[3] we would expect that the isomerization could occur even in the $MeCO_2H$–$MeCO_2K$ buffer medium. Unfortunately, when the reaction mixture was left standing after addition of the buffer, a competitive decomposition of both (8) and (9) to 3-methoxy-1-R-naphthalene (10) was observed. This reaction went to completion after some days. Alternatively, compound (10) can be obtained quantitatively by refluxing a mixture of (8) and (9) in methanol for several hours.

Mixtures of (8) and (9) in varying proportions were converted quantitatively into nitronate anions (7) when treated with an excess of $MeO^-$ in methanol: neutralization of this solution with the acetate buffer produced (8) and (9) again, in the same *cis-trans* proportions as reported in Table 1.

Finally, each of the mixtures of (8a—c) and (9a—c) can quantitatively be converted into 4-alkyl-2-methoxy-1-nitronaphthalenes (11) by refluxing in dry benzene or THF with a slight excess of dichlorodicyanobenzoquinone (DDQ).

*Characterization of Products.*—All compounds were identified by common analytical procedures, including $^1H$ n.m.r. and i.r. analysis. Proton assignments in the $^1H$ n.m.r. spectra of (8) and (9) were made on the basis of their chemical shift values and with the aid of decoupling techniques, with the exception of 1-H and 3-H hydrogens whose determination required a deuterium labelling procedure.

Since 1-H is the only proton that arises from the buffer medium, the nitronate compounds (5) were decomposed with $MeCO_2D$–$MeCO_2K$ in $D_2O$. The $^1H$ n.m.r. analysis of the




a, R = Me ; b, $PhCH_2CH_2$ ; c, $PhCH_2$

**Scheme.**

resulting reaction products showed that the proton at *ca.* 6 p.p.m. in compounds (8) and (9) was replaced by deuterium, thus allowing its assignment as the 1-H proton.

Relevant $^1H$ n.m.r. data for compounds (7), (8), and (9) are reported in Table 3. A precise value for the chemical shift of 4-H cannot be given because of the complexity of the signals, in addition to its being partly hidden by the signal of the methoxy group.

Chemical shifts and coupling constants of compounds (7a—c) were determined from experiments described in the Discussion section.

cis *and* trans *Structure Assignments.*—Homoallylic coupling constants are a useful tool in the structural analysis of the 1,4-dihydronaphthalene system owing to their relatively large magnitude and, mainly, to their sensitivity to conformational changes.

The experimental value (2.0 Hz) of $J_{1,4}$ for compounds (8a—c) is clearly consistent with a *cis* structure, in which 1-H and 4-H occupy the equatorial position almost in a boat conformation. In fact it agrees well with the $J_{1,4}$ value (1.8 Hz) reported by Rabideau [6a] for dipseudoequatorial protons in

**Table 1.** Yields and relative amounts of *cis*- and *trans*-2-methoxy-1-nitro-4-R-1,4-dihydronaphthalenes from decomposition in acetate buffer of the nitronate adducts (5a—c) from reaction of 2-methoxy-1-nitronaphthalene and RMgX

| R | Yield (%) | *cis* (8a—c) (%) | *trans* (9a—c) (%) |
|---|---|---|---|
| Me | 60 | 85 | 15 |
| $PhCH_2CH_2$ | 72 | 95 | 5 |
| $PhCH_2$ | 68 | >99 | traces |

**Table 2.** Percentage amounts of *cis*- and *trans*-2-methoxy-1-nitro-4-R-1,4-dihydronaphthalenes at equilibrium

| R | *cis* (%) | *trans* (%) |
|---|---|---|
| Me | 70 | 30 |
| $PhCH_2CH_2$ | 73 | 27 |
| $PhCH_2$ | 78 | 22 |

**Table 3.** Relevant $^1H$ n.m.r. data of 2-methoxy-4-R-1,4-dihydronaphthalene-1-nitronates (7a—c), *cis*- (8a—c) and *trans*-2-methoxy-1-nitro-4-R-1,4-dihydronaphthalenes (9a—c) in $CD_3OD$–$CD_3O^-$ and $CDCl_3$, respectively at 30 °C

| | Chemical shifts from $Me_4Si$ (p.p.m.) | | | *J*/Hz | |
|---|---|---|---|---|---|
| Compounds | 1-H | 3-H | 4-H | $J_{1,4}$ | $J_{3,4}$ |
| (7a) [a] | | 5.40 | 3.6—3.3 [b] | | 6.5 |
| (7b) [a] | | 5.48 | 3.5—3.3 [b] | | 6.7 |
| (7c) [a] | | 5.26 | 3.7—3.4 [b] | | 6.8 |
| (8a) | 6.02 | 5.34 | 3.7—3.5 [b] | 2.0 | 5.0 |
| (8b) | 6.06 | 5.42 | 3.7—3.5 [b] | 2.0 | 5.0 |
| (8c) | 6.04 | 5.10 | 3.9—3.6 | 2.0 | 5.0 |
| (9a) | 6.12 | 5.22 | 4.0—3.7 [b] | 3.5 | 3.3 |
| (9b) | 6.20 | 5.30 | 4.0—3.8 | 3.5 | 3.5 |
| (9c) | 5.92 | 5.06 | 4.1—3.9 | 3.5 | 3.5 [b] |

[a] In $CD_3OD$–$CD_3O^-$. [b] Approximate.

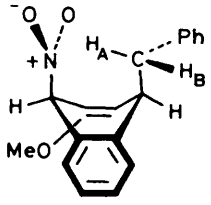
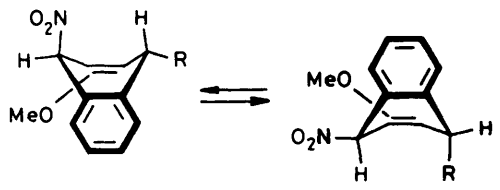



**Figure 1.** Preferred rotational conformation of (8c)

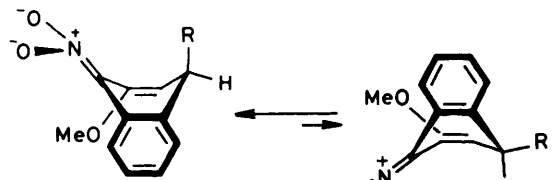
true boat-shaped systems. This statement is also confirmed by the $J_{3,4}$ value, its magnitude (5.0 Hz) being identical with the 5.0—5.2 Hz value reported for the vicinal coupling constant between a vinylic and an equatorial proton in boat-shaped systems.[6b] The present results are somewhat surprising, considering that large *cis* substituents are expected [7] to cause some flattening of the dihydro ring. The axial nitro and alkyl groups can probably minimize their mutual steric interactions by assuming a preferred rotational conformation as shown in Figure 1.

However, the validity of this assumption is supported by some $^1H$ n.m.r. results: the magnitude of $J_{A,4}$ (10.5 Hz) and $J_{B,4}$ (6.5 Hz) indicates that the two dihedral angles between the benzylic $CH_2$ protons and the 4-H are close to 180 and 60°, respectively.

A *trans* structure can reasonably be assigned to compounds (9a—c), the value of $J_{1,4}$ (3.5 Hz) being very close to the 3.1 Hz



(9A) (9B)



(7A) (7B)

value reported for a *trans* pseudoaxial/pseudoequatorial relationship [6a] in boat-shaped systems. In addition, from the observed magnitude of $J_{3,4}$, the suggestion arises that these compounds exist in $CDCl_3$ solution at room temperature as a mixture of two conformational isomers [(9A) and (9B)], which rapidly interconvert, its value (3.3—3.5 Hz) lying between the 1.2—1.6 and 5.0—5.2 Hz values reported for the coupling constants of 3-H with an axial and equatorial vicinal hydrogen, respectively.

## Discussion

The mechanism of formation of nitroderivatives (8) and (9) is well recognized; treatment of a tetrahydrofuran solution of (5) with an $MeCO_2H$–$MeCO_2K$ buffer solution gives nitronic acid (6). In such a weak acidic medium, (6) is largely ionized. Thus, a rapid and complete *C*-protonation of the nitronate anion (7) can occur, leading to nitro-isomers (8) and (9).

Isomerization experiments demonstrated that the *cis* compound is the more stable isomer and formation of the more stable isomer is also observed under kinetically controlled conditions.

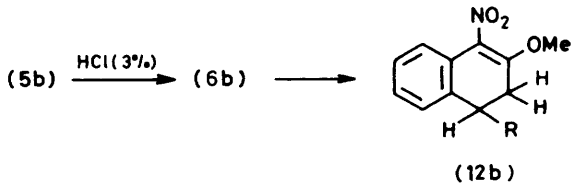
However, a comparison of the data of Table 1 with those of Table 2 shows that for all three alkyl substituents the relative proportions of the *cis* to the *trans* compound are larger than those expected from differences in thermodynamic stability. These findings strongly support our hypothesis that the observed stereoselectivity arises from the steric hindrance exerted by the axial alkyl group towards the prototropic attack in an axial direction at C(1), the reaction being controlled by a transition state whose geometry reflects a boat conformation of (7), *i.e.* (7A) and (7B).

Further support for this interpretation is given by inspection of the *cis* to *trans* ratios for different alkyl substituents.

An increase in the size of the R group causes a drastic increase in kinetic preference for the *cis* compound, while its effect on *cis versus trans* stability is less marked.

If the stereochemistry were induced by steric strain between the nitro-group and the *peri* 8-H when the former begins to become equatorial under an axial approach of the proton in a transition state that closely resembles the final products, it would be rather insensitive to the size of the alkyl substituents at position 4, and certainly less sensitive than predicted from the relative stability of the two isomers.

In order to obtain direct evidence for the conformation of (7a—c), mixtures of (8) and (9), the compositions of which are



(12b)

indicated in Table 2, were quantitatively converted into (7) by treatment with a large excess of $CD_3O^-$ in $CD_3OD$. $^1H$ N.m.r. analysis showed that in all compounds 3-H resonates at 5.26—5.40 p.p.m. with the following $J_{3,4}$ values: (7a) 6.5 Hz, (7b) 6.7 Hz, and (7c) 6.8 Hz. This represents a very high value for a vicinal coupling constant in a 1,4-dihydronaphthalene system and indicates a preferential axial arrangement of the alkyl group associated with a high degree of puckering of the dihydrobenzene skeleton.

In a previous work [8] we reported that decomposition of a THF solution of (5b) with HCl gives 2-methoxy-1-nitro-4-phenylethyl-3,4-dihydronaphthalene (12b) instead of the expected 2-methoxy-1-nitroso-4-phenylethylnaphthalene. At that time we interpreted this unusual reactivity in terms of a preferred *aci*-nitro tautomerization due to the high stability of the final compound.

Present results afford a more detailed evaluation of the mechanistic aspect of the reaction. In spite of its high stability there was no evidence for the formation of (12b), even for prolonged times of reaction during the isomerization of (8b) into (9b). This indicates that the delocalization of a negative charge on C(3) is negligible. However, the amount of negative charge on C(3) induced by the mesomeric effect of the methoxy substituent at C(2) is too small to allow an attack at this position to compete with protonation at C(1) in (7b) when the concentrations of the protonating species are low.

In strongly acidic medium, protonation at C(1) is prevented by the very low dissociation of (6b). At the same time *C*-protonation at position 3 is allowed by the presence of an electron-donating substituent such as the methoxy group at position 2 with consequent irreversible formation of (12b). Substantial proof of this interpretation is that compound (12b) is quantitatively isomerized into a mixture of (8b) and (9b) by treatment with trace amounts of triethylamine in dichloromethane [equation (i)]. In addition the (8b) : (9b) ratio reflects

$$\text{(12b)} \xrightarrow{CH_2Cl_2,Et_3N\ (1\%)} \underset{(95\%)}{\text{(8b)}} + \underset{(5\%)}{\text{(9b)}} \qquad \text{(i)}$$

what is to be expected from the relative stability of the two isomers. It is clear that in the absence of strong electron-donor substituents at position 2, preferential *O*-protonation occurs in strongly acidic medium and the usual decomposition pathway to the corresponding nitroso compound is observed.[8]

## Experimental

I.r. spectra were recorded with a Perkin-Elmer 257 instrument. $^1H$ N.m.r. spectra were recorded on a Varian 100 MHz spectrophotometer; all spectra were on solutions in $CDCl_3$ with $Me_4Si$ as the internal standard, with the exception of spectra of compounds (7a—c), which were run on solutions in $CD_3OD$.

THF was purified as reported previously.[9]

2-Methoxy-1-nitronaphthalene was prepared according to the cited literature procedure.[10]

*Preparation of THF Nitronate Solution.*—A sample (6.6 ml) of a 3M solution of RMgX in THF was added dropwise to a

solution in the same solvent (30 ml) of 2 g of (4) ($9.8 \times 10^{-3}$ mol) at 20 °C under nitrogen. After a few minutes the reaction goes to completion. This solution must be used immediately.

*Preparation of* cis- (8a—c) *and* trans-4-*Alkyl*-2-*methoxy*-1-*nitro*-1,4-*dihydronaphthalenes* (9a—c).—The THF solution of the nitronate was poured into the buffer, prepared by dissolving potassium acetate (20 g) and glacial acetic acid (5 ml) in water (50 ml) at room temperature and under nitrogen. The mixture was stirred for 5 min and then extracted with $CH_2Cl_2$. The organic layer was washed once with a saturated aqueous solution of $NaHCO_3$ and several times with water, dried, and evaporated under reduced pressure. The residue, dissolved in the minimum amount of ethyl acetate, was submitted to a rapid chromatographic purification on a silica gel column [light petroleum (b.p. 40—60 °C)–ethyl acetate, 9 : 1 as eluant] to give a mixture of (8) and (9) in which the relative amounts of the two isomers were determined by quantitative $^1H$ n.m.r. analysis. Yields and percentages are reported in Table 1.

By comparison with data from the $^1H$ n.m.r. analysis of the crude reaction product it was confirmed that the *cis* to *trans* ratio did not change during the chromatographic purification. Attempts to separate (8) and (9) by chromatographic methods were unsuccessful because long residence times in the column brought about the decomposition of dihydronaphthalenes to give alkylmethoxynaphthalenes through an $HNO_2$ elimination.

*Reactions of Mixtures of* (8) *and* (9) *with DDQ.*—In order to obtain chemical confirmation of the dihydronaphthalene structure, any mixture of (8a—c) and (9a—c) was quantitatively converted into the corresponding aromatic nitrocompounds (11a—c), by treatment with a slight excess of DDQ whilst refluxing in dry THF for 8 h. The mixture was washed with a solution of NaOH, then with water, dried and evaporated under reduced pressure. The residue was chromatographed on a short silica gel column using the appropriate mixture of cyclohexane–ethyl acetate as eluant, yielding (11c): m.p. 133—135 °C (from ethanol); $\nu_{NO_2}$ (KBr) 1 520—1 360 $cm^{-1}$; $^1H$ n.m.r. ($CDCl_3$), δ 3.86 (s, 3 H, OMe), 4.4 (s, 2 H, $CH_2$), 7.0—8.0 (m, 10 H, ArH) (Found: C, 73.78; H, 5.15; N, 4.75. $C_{18}H_{15}NO_3$ requires C, 73.73; H, 5.11; N, 4.77%).

Data for compounds (11a) and (11b) have been reported previously.[11,8]

*Isomerization of* cis *and* trans *Mixtures with Triethylamine.*—The mixtures of (8a—c) and (9a—c) from chromatographic purification were dissolved at room temperature in $CDCl_3$ containing trace amounts of triethylamine (1%). A direct $^1H$ n.m.r. analysis of the reaction mixture indicated that isomerization, to the equilibrium values of Table 2, was complete after *ca.* 4 days and that no by-products were formed.

*Decomposition of* cis- *and* trans-4-*Alkyl*-2-*methoxy*-1,4-*dihydronaphthalenes to* 1-*Alkyl*-3-*methoxynaphthalenes* (10a—c).—When the reaction mixture of the nitronate adducts and acetate–acetic acid buffer was kept, under stirring, at room temperature for longer reaction times, a slow decomposition of *cis*- and *trans*-4-alkyl-2-methoxy-1-nitro-1,4-dihydronaphthalenes to 1-alkyl-3-methoxynaphthalenes occurred. The decomposition went to completion in 3—4 days. The reaction mixture was then poured into water, extracted with $CH_2Cl_2$, washed with a saturated aqueous solution of $NaHCO_3$, then with water, dried, and evaporated under reduced pressure. The residue was submitted to chromatographic separation on a silica gel column (hexane–ethyl acetate, 95 : 5 as eluant) to give the title products.

Alternatively a quantitative conversion of (8) and (9) into (10a—c) was obtained by refluxing any mixture of the *cis* and *trans* isomers, in methanol for 8 h. Concentration of the solution and recrystallization of the crude residue gave the pure products (10a—c): (10a), m.p. 48—49 °C (from ethanol); $^1H$ n.m.r. ($CDCl_3$), δ 2.66 (s, 3 H, Me), 3.93 (s, 3 H, Me), 7.06—8.2 (m, 6 H, ArH) (Found: C, 83.79; H, 6.93. $C_{12}H_{12}O$ requires C, 83.73; H, 6.97%). (10b), m.p. 57—58 °C (from ethanol); $^1H$ n.m.r. ($CDCl_3$), δ 2.94—3.48 (m, 4 H, $CH_2$–$CH_2$), 3.9 (s, 3 H, OMe), 7—8.10 (m, 6 H, ArH) (Found: C, 86.35; H, 7.23. $C_{18}H_{18}O$ requires C, 86.40; H, 7.19%). (10c), m.p. 100—102 °C (from ethanol); $^1H$ n.m.r. ($CDCl_3$), δ 3.9 (s, 3 H, OMe), 4.4 (s, 2 H, $CH_2$), 6.94—8.04 (m, 6 H, ArH) (Found: 86.52; H, 6.79. $C_{17}H_{16}O$ requires 86.45; H, 6.77%).

I.r. spectra (KBr discs) of all compounds lacked the nitro-group characteristic stretching bands.

*Reconversion of* cis *and* trans *Dihydronaphthalenes into Nitronate Anions.*—A mixture of (8) and (9) was treated with $CD_3O^-$ (*ca.* 1M) in $CD_3OD$ for 30 min and then subjected to n.m.r. analysis, which indicated the nitronate anions formation. The 3-H and 4-H chemical shifts and the $J_{3,4}$ values are reported in Table 3.

Other relevant n.m.r. data are as follows: (7a), δ 1.32 (d, 3 H, Me), 3.72 (s, 3 H, OMe), 7.10—7.34 (m, ArH) 8.42—8.62 (m, 1 H, 8-H). (7b), δ 1.70—2.00 (m, 2 H, $CH_2$), 2.50—2.78 (m, 2 H, $CH_2$), 3.74 (s, 3 H, OMe), 7.00—7.38 (m, ArH), 8.40—8.60 (m, 1 H, 8-H). (7c), δ 2.70—2.88 (d, 2 H, $CH_2$), 3.64 (s, 3 H, OMe), 6.74—7.50 (m, ArH), 8.46—8.60 (m, 1 H, 8-H).

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