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Conformational analysis of *N*-aryl-*N*-(2-azulenyl)acetamides

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ABSTRACT

Aromatic amides bearing 2-azulenyl group on the amide nitrogen were synthesized and their structures were investigated. The π-electron density of the *N*-aryl group was found to influence the *cis-trans* conformational preferences of these compounds in solution. X-ray crystallography revealed that the plane of the 2-azulenyl ring has a strong tendency to lie coplanar with the amide plane when the azulene group is located on the same side as the amide oxygen atom.

Although amides exist as *cis* and *trans* isomers because of the partial double bond character of the C—N amide bond, the rotation barrier of the C—N bond is low, and the isomers are usually in rapid equilibrium at ambient temperature. Nevertheless, the conformational preference of amide compounds plays a key role in protein folding [1–3], the bioactivities of pharmaceutical drugs, peptides and proteins [4–6], and the catalytic activity of enzymes [7–9]. For example, the *cis-trans* isomerization of pSer/Thr-Pro motifs catalyzed by Pin1 [protein interacting with NIMA (never in mitosis A)-1] is involved in regulating a wide range of cellular processes [9]. We have previously shown that the conformational preference of *N*,*N*-diaryl amides bearing six-membered aromatic rings, such as benzene and pyridine, is dependent on the relative π-electron density of the *N*-aromatic moieties; i.e., the more π-electron-rich *N*-aryl group favors the *trans* position with respect to the amide oxygen atom [10–13]. We also showed that some aromatic *cis*-amides switch their conformation in response to external stimuli, such as pH [14–17]. Further, in aromatic amides bearing *N*-thienyl group [18], although the π-electron density influences the conformational preference, the size of the aromatic ring is also important. Many kinds of aromatic groups can be used to build new functional compounds incorporating amide structure [19,20], and here we focused on azulene as a new type of *N*-aryl group for amides.

Azulene ($C_{10}H_8$) is a nonbenzenoid aromatic compound possessing 10 π-electrons, and its unique characteristics are well documented (Fig. 1) [21–23]. It is an isomer of naphthalene, but has significantly different properties; e.g., naphthalene is colorless, while azulene has a deep blue color [23]. In addition, the molecule of azulene has a zwitterionic character with a negatively charged 5-membered ring and a positively charged 7-membered ring that enable Hückel aromatic stabilization of the structure. This means that azulene has a relatively large dipole moment of μ = 1.08 D [22], whereas naphthalene has zero dipole moment. Azulene and its derivatives have been widely applied in developing novel advanced materials [24], such as conducting polymers [25,26], optical materials [27,28], fluorescence switches [29,30], organic field-effect transistors (OFETs) [31] and organic solar-cell materials [32,33]. Furthermore, natural products and synthetic derivatives bearing an azulene moiety, such as guaiazulene, possess interesting bioactivities; e.g., anti-inflammatory [34], anti-ulcer [35,36], anti-cancer [37] and other activities [38,39]. However, little information is available about the conformational preferences of azulenyl amides.

Therefore, in this study, we aimed to explore the properties of azulene-containing amide derivatives by synthesizing various *N*-(2-azulenyl)acetamides and investigating their conformational preferences in solution and in the solid state by means of NMR and X-ray analysis. Our results indicate that the conformational preference of *N*-(2-azulenyl)acetamides is dependent on the π-electron density of the *N*-aromatic moieties. Interestingly, *N*-(2-azulenyl)acetamides tend to exist predominantly in the *B-form*, in which the 2-azulenyl group is located on the same side as the amide oxygen atom, in contrast to *N*,*N*-diaryl acetamides bearing *N*-thienyl group [18].

2-Bromoazulene **4** was prepared *via* three steps from azulene **1** according to the reported procedures (Scheme 1) [40–42]. First, a mixture of azulene **1**, pin_2B_2, $[IrCl(cod)]_2$ and 2,2′-bipyridine was refluxed in dry cyclohexane to give **2** (65% yield) together with a small quantity of **2′** (15%). Compound **2** was converted into

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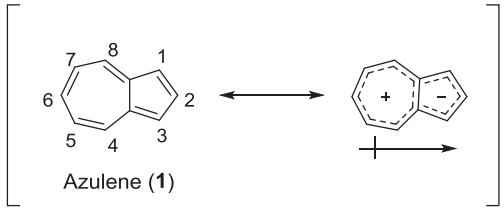
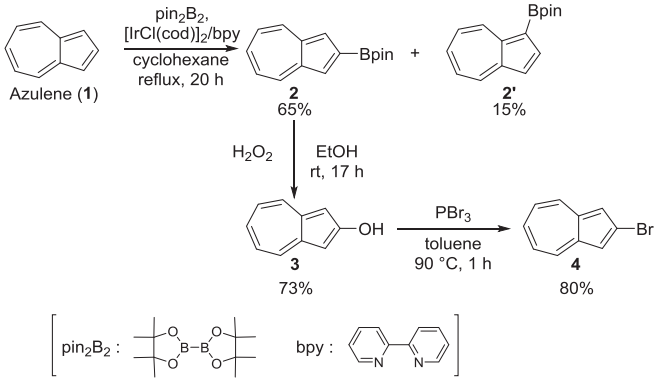


Fig. 1. Properties of azulene.



Scheme 1. Synthesis of 2-bromoazulene (**4**).

2-hydroxyazulene **3** using hydrogen peroxide. Bromination of **3** using PBr_3 gave 2-bromoazulene **4** (80% yield).

We synthesized *N*-(2-azulenyl)acetamides **7a**–**7g** using 2-bromoazulene **4** as summarized in Scheme 2. First, compound **5** was prepared from **4** and aniline in the presence of $Pd_2(dba)_3$ catalyst and (±)-BINAP in 78% [43]. When compound **5** was reacted with acetic anhydride, compound **8** was obtained in 75% yield as the major product instead of **7a** (Route A). Therefore, **7a**–**7g** were prepared from the corresponding amides **6a**–**6g** with 2-bromoazulene (**4**) by means of Cu-catalyzed coupling reaction [44] (Route B).

In order to investigate the conformational preference of *N*-(2-azuleny)acetamides **7** in solution, we first examined the temperature dependence of the ^{1}H NMR spectra of **7a** bearing a phenyl group. The ^{1}H NMR spectra of **7a** in CD_2Cl_2 showed one set of signals at 303 K, but at lower temperature these peaks were broadened and separated into two sets of signals, due to the *A-form* and *B-form* amide conformers (Fig. S1). Here, *A-form* and *B-form* refer to the conformers in which the 2-azulenyl group is located

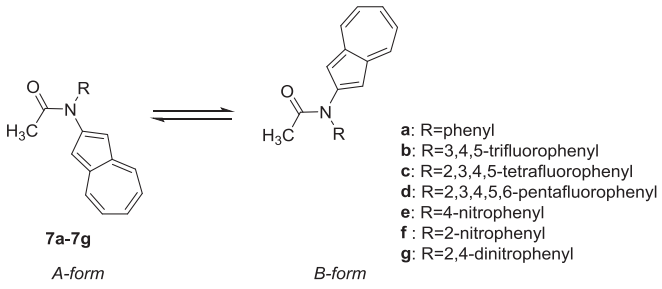


Fig. 2. Conformational preference of *N*-(2-azulenyl)acetamide **7a**–**7g**.

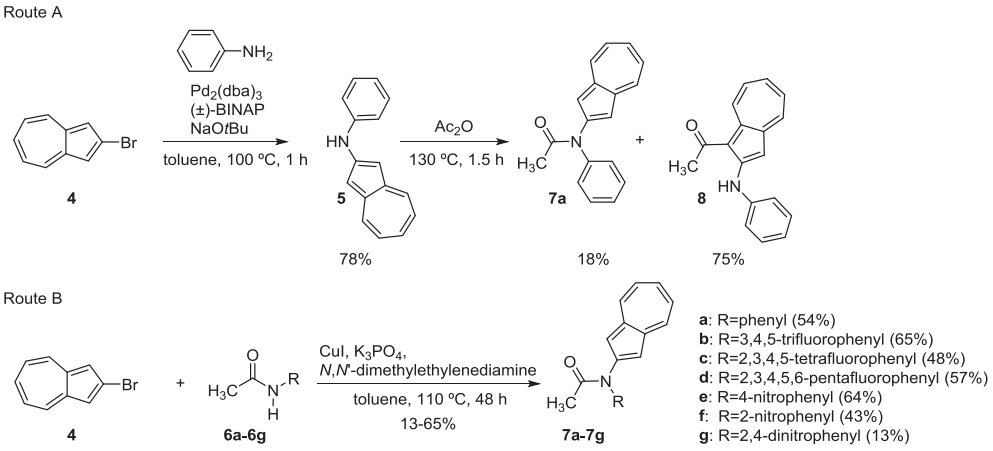
on the opposite side and the same side as the amide oxygen atom, respectively (Fig. 2).

The major conformer was assigned by means of NOE measurements at low temperature. In the case of **7a**, the major acetyl proton signal was correlated with only *N*-phenyl protons (Ph-2 and Ph-6, 3.1%, Fig. 3 and Fig. S2), indicating that the major conformer of **7a** is the *B-form* in which the azulenyl group is located on the same side as the amide oxygen atom (99% at 183 K, Table 1, entry 1).

Next, we investigated the conformational preferences of *N*-(2-azulenyl)acetamides bearing an electron-withdrawing group on the benzene ring, **7b**–**7d** (fluoro series) and **7e**–**7g** (nitro series) (see Fig. 2). The temperature dependence of the ^{1}H NMR spectra and the NOE correlations of **7b**–**7g** at 183 K are shown in the supplementary data.

Major conformers and NOE correlations of **7a**–**7g** are shown in Fig. 3. In the cases of **7b**–**7d**, the major acetyl proton signal was correlated with the *N*-phenyl protons (**7b**, 3.3%; **7c**, 2.5%), and the minor acetyl proton signal was correlated with azulenyl protons (**7b**, 7.7%; **7c**, 7.1%; **7d**, 8.6%), respectively (Figs. S4, S6, S8). These results indicated that the major conformers of **7b**–**7d** are in *B-form*.

In the cases of **7e** and **7f** bearing a mono-nitrophenyl group, the major acetyl proton signal was correlated with *N*-phenyl protons (**7e**, 3.4%; **7f**, 3.7%) and the minor signal was correlated with azulenyl protons (**7e**, 4.8%; **7f**, 8.0%) (Figs. S10 and S12). But, in the case of **7g** bearing a dinitrophenyl group (*para* and *ortho* positions), the major acetyl proton signal was correlated with the 1,3-position azulene protons (**7g**, 1.7%) and the minor signal was correlated with the 6-position *N*-phenyl proton (**7g**, 2.8%) (Fig. S14). These results indicated that the major conformers of **7e** and **7f** are the *B-form*, but the major conformer of **7g** is the *A-form*.



Scheme 2. Synthesis of *N*-(2-azulenyl)acetamides **7a**–**7g**.

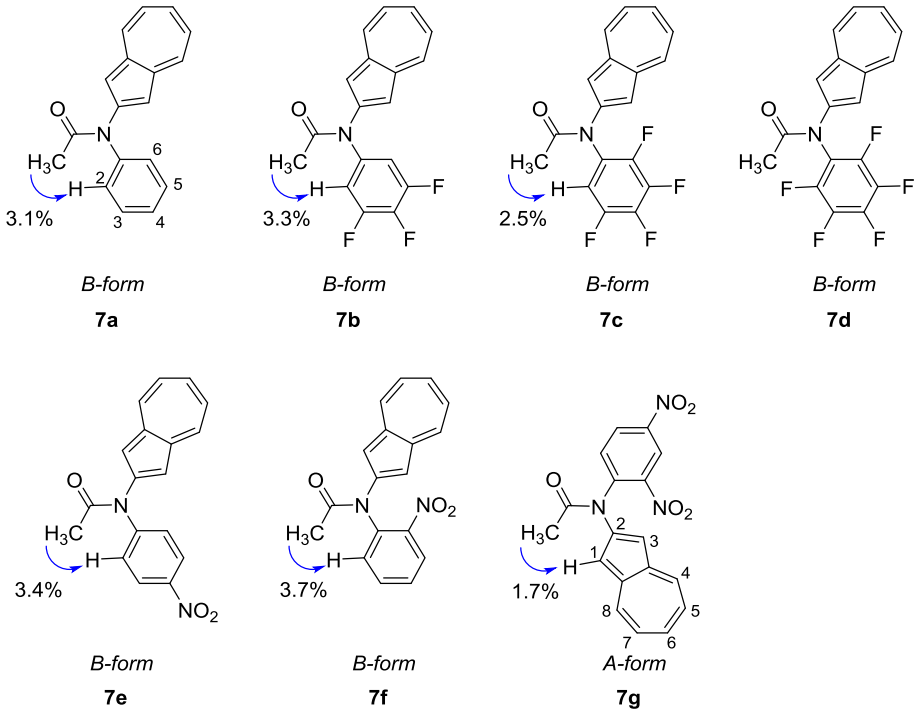


Fig. 3. Major conformers and NOE correlations of **7a**–**7g**.

Table 1
Conformational preference of *N*-(2-azulenyl)acetamides **7a**–**7g** in CD_2Cl_2 at 183 K.

Entry	Amide[a]	R	Major form	Ratio (%)[b]	ΔG° (kcal/mol)[c]
1	**7a**	phenyl	*B*	99	−1.67
2	**7b**	3,4,5-trifluorophenyl	*B*	93	−0.94
3	**7c**	2,3,4,5-tetrafluorophenyl	*B*	85	−0.63
4	**7d**	2,3,4,5,6-pentafluorophenyl	*B*	67	−0.26
5	**7e**	4-nitrophenyl	*B*	80	−0.50
6	**7f**	2-nitrophenyl	*B*	82	−0.55
7	**7 g**	2,4-dinitrophenyl	*A*	89	+0.76

[a] See Fig. 2.
[b] The ratio at 183 K was determined by ^{1}H NMR measurement.
[c] $\Delta G^\circ = -RT \ln ([B\text{-}form]/[A\text{-}form])$.

These assignments were supported by the observed anisotropic effects (Fig. S15). For example, the Az-4 and Az-8 proton peaks of the major conformers of **7a**–**7f** were shifted to higher field than those of the minor conformers owing to the carbonyl group, whereas the Az-4 and Az-8 proton peaks of the major conformer of **7g** were shifted to lower field than those of the minor conformer. In addition, the acetyl signals of the major conformers of **7a**–**7f** appeared at higher field than those of the corresponding minor conformers. On the other hand, the acetyl signal of the major conformer of **7g** appeared at lower field than that of the corresponding minor conformer. This is reasonable, because benzene and azulene should have different effects on the acetyl signals. A similar phenomenon was reported for *N*-aryl-*N*-(2-thienyl)acetamides [18].

Conformation ratios of **7b**–**7g** are summarized in Table 1. In the cases of **7b**-**7d** bearing tri-, tetra- and penta-fluoro benzene derivatives, the ratios of the *B-form* conformers at 183 K are 93% (**7b**, 3,4,5-triFPh), 85% (**7c**, 2,3,4,5-tetraFPh) and 67% (**7d**, 2,3,4,5,6-pentaFPh), respectively (Table 1, entries 2–4). In the cases of **7e** (4-NO_2Ph) and **7f** (2-NO_2Ph), the major conformers are also *B-form*, and the ratios of *B-form* conformers at 183 K are almost the same; 80% (**7e**) and 82% (**7f**) (Table 1, entries 5 and 6). On the other hand, in the case of **7g** (2,4-diNO_2Ph), the ratio of the *A-form* conformer at 183 K is 89% (Table 1, entry 7). These results suggest that the conformational preferences of these amides are dependent on the π-electron density of the *N*-phenyl group. In the case of **7b**–**7d**, as the number of fluoro groups on the benzene ring increases, the ratio of major *B-form* conformer decreases. Likewise, in the case of **7e**–**7g** containing nitrobenzene, the ratio of *A-form* increases as the π-electron density of the *N*-phenyl group decreases.

Next, we conducted X-ray crystallographic analysis of **7a** and **7e**–**7g** (see Supplementary data). The crystal structures are illustrated in Fig 4. The three conformers of **7a** and **7e** all exist in the *B-form*. In addition, the two conformers of **7f** both take the *B-form* in the crystal. Thus, the conformational preferences of **7a**, **7e** and **7f** in the crystal were the same as those in solution. On the other hand, **7g** bearing a 2,4-dinitrophenyl group exists in *B-form* in the crystal; that is, its conformational preference in the crystal is different from that in solution. This may be because intermolecular aromatic interaction stabilizes the *B-form* in the crystal, that is, the 2,4-dinitrophenyl group is placed with its edge close to the face of the azulene moiety, and this edge-to-face interaction affects the structure in the crystal (see Supplementary data).

The amide torsion angle and dihedral angle between the amide plane and the *N*-(2-azulenyl) and *N*-phenyl groups in **7a** and **7e**–**g**

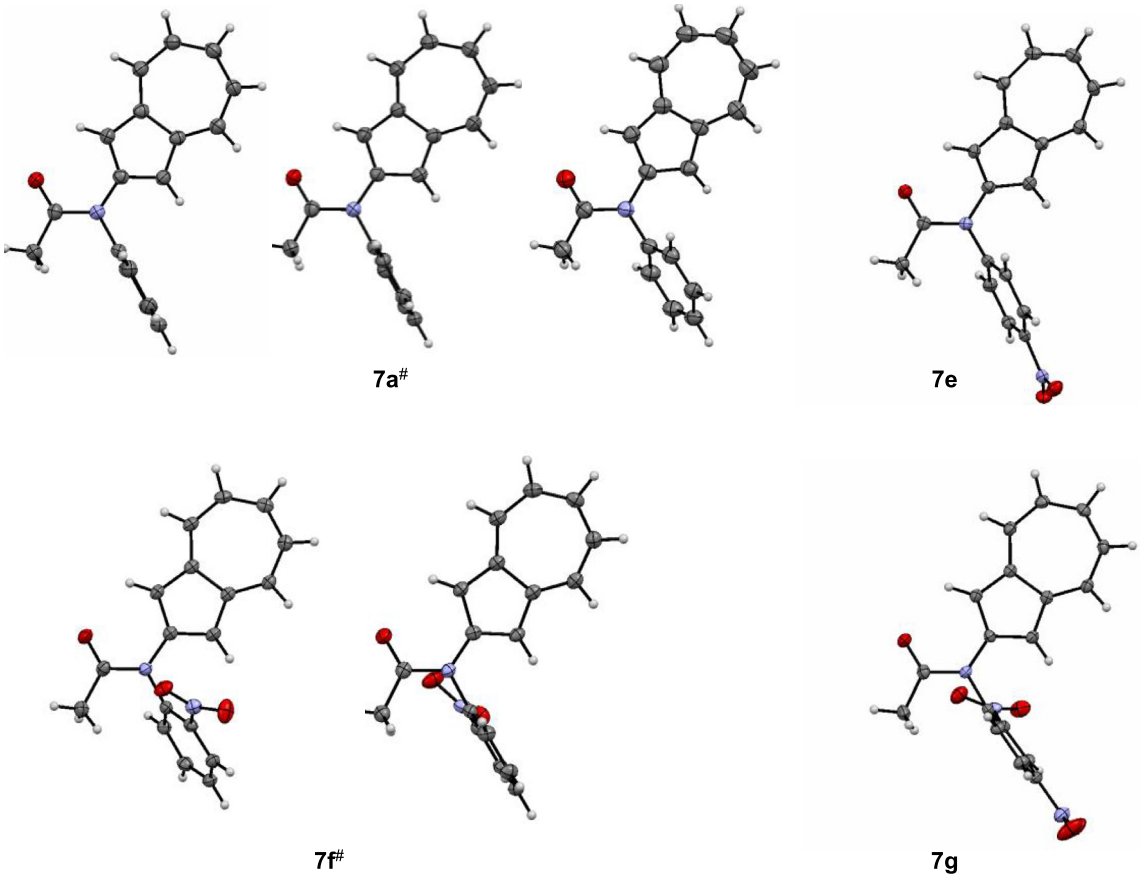


Fig. 4. Crystal structures of **7a** and **7e**–**7g**. #The crystal contains several conformers: **7a** (three types); **7f** (two types).

Table 2
Torsion and dihedral angles (°) around amide bonds of *N*-(2-azulenyl)acetamides **7a** and **7e**–**7g**.

Amide	Amide-form	Torsion angle[a] (°)		Dihedral angle (°)	
		R—N—C=O		R-amide	
7a	*B*	4.43 (Az[b])	4.64 (Ph)	5.61 (Az[b])	87.69 (Ph)
	B	6.43 (Az)	2.08 (Ph)	17.57 (Az)	86.79 (Ph)
	B	9.59 (Az)	14.39 (Ph)	35.77 (Az)	66.59 (Ph)
7e	*B*	8.47 (Az)	7.57 (4-NO_2Ph)	32.77 (Az)	72.04 (4-NO_2Ph)
7f	*B*	0.78 (Az)	3.12 (2-NO_2Ph)	8.24 (Az)	76.70 (2-NO_2Ph)
	B	7.15 (Az)	3.21 (2-NO_2Ph)	8.40 (Az)	82.07 (2-NO_2Ph)
7 g	*B*	0.02 (Az)	1.84 (2,4-diNO_2Ph)	1.22 (Az)	83.62 (2,4-diNO_2Ph)

[a] The absolute values (0–90°) of the torsion angles are indicated.
[b] Az is the 2-azulenyl group.

are shown in Table 2. The torsion angles are less than 15°, and each amide bond is planar in the crystal. In the cases of **7a**, **7e**–**g**, the azulene ring, which is located on the same side as the amide oxygen atom, is coplanar with the amide plane: the dihedral angles between the amide plane and *N*-azulenyl ring are 5.6°, 17.6° and 35.8° (**7a**), 33° (**7e**), 8.2° and 8.4° (**7f**), and 1.2° (**7g**). On the other hand, the *N*-phenyl ring, which is located on the opposite side to the amide oxygen atom, is nearly perpendicular to the amide plane with dihedral angles of 66-88°. Recently, we reported that in *N*-aryl-*N*-(3-thienyl)acetamides, the thiophene ring tends to lie at a smaller dihedral angle from the amide plane than the benzene ring, when it is cis to oxygen. For example, in the case of *N*,*N*-diphenylacetamides, the dihedral angles between the amide plane and the phenyl ring are ca. 60–89° in the crystal [12]. On the other hand, in *N*-phenyl-*N*-(3-thienyl)acetamide, the dihedral angle between the amide plane and *N*-thienyl ring is 24.1° in the crystal [18]. Therefore, the azulene ring in *N*-aryl-*N*-(2-azulenyl)acetamides shows a similar tendency to the thiophene ring in *N*-aryl-*N*-(3-thienyl)acetamides, as described above. In addition, the azulene ring tends to be more nearly coplanar with the amide plane than does the thiophene ring in the solid state. Thus, the 2-azulenyl group on amide nitrogen tends to favor the amide plane, and the conformational preference of these amides in solution can be regarded as a result of this steric feature of the *N*-azulenyl group. That is, although the π-electron density of the five-membered ring of azulene may be greater than that of benzene, the electronic repulsion between carbonyl oxygen and *N*-2-azulene part is less severe than that between carbonyl oxygen and the *N*-phenyl moiety (Fig. 5).

In conclusion, we synthesized **7a**–**7g** and investigated their conformations in solution and in the solid state by means of NMR and X-ray crystallographic analysis. Our results are essentially consistent with previous findings showing that the conformational pref-

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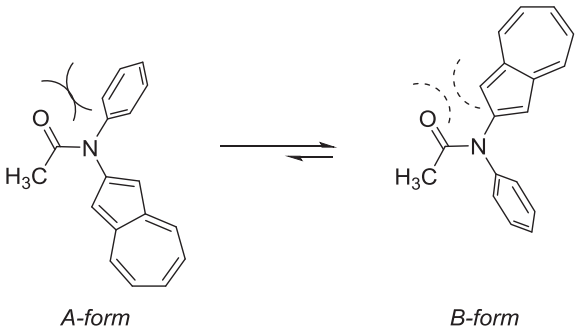

Fig. 5. Electronic repulsion and conformational preference of *N*-(2-azulenyl) acetamides **7**.

erences of these amides are dependent on the relative π-electron density of the *N*-phenyl group [10–13]. However, the electronic repulsion between carbonyl oxygen and the *N*-2-azulene group is less than that between carbonyl oxygen and the *N*-phenyl group, and the 2-azulenyl group on amide nitrogen has a strong tendency to be located coplanar with the amide plane.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.09.053.

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