Investigation of arene–arene interaction in stereoselective MCPBA epoxidation

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Effect of arene–arene interaction in stereoselective MCPBA epoxidation was investigated using 5,6-dimethyl-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-diones **1**. From the good correlation between the stereoselectivity of the products and Hammett's coefficients of *para*-substituents (σ_P) on the phenyl group, it was found that polar/π interaction between the phenyl group and MCPBA is the main interaction for controlling the stereoselectivity in the reaction. Other arene–arene interactions, charge-transfer complexation and edge-to-face interaction, were assumed to be much weaker than polar/π interaction in this reaction.

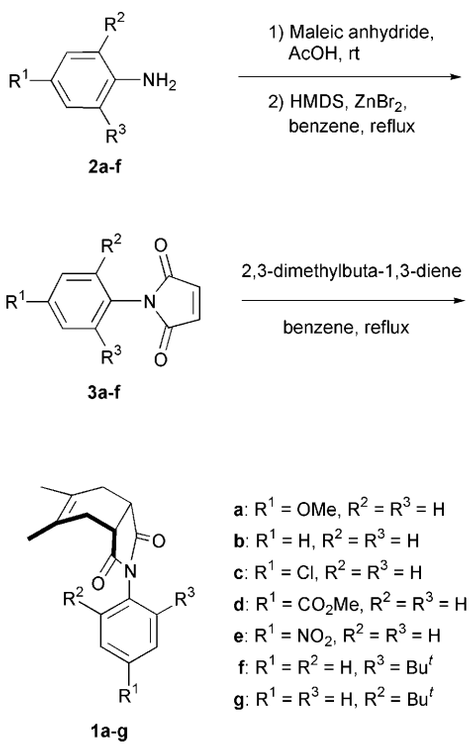
Epoxidation of alkenes with commercially available *m*-chloroperbenzoic acid (MCPBA) is one of the most important reactions in organic synthesis and is useful for laboratory-scale experiments.[1] Moreover, the excellent face-selectivity was reported in the epoxidation of dienes,[2] sterically hindered alkenes (steroidal olefins[3]), cyclic alkenones,[4] and alkenes possessing hydrogen-bond acceptors (allyl alcohols,[5] allylamides,[6] allyl carbamates,[7] allyl ethers,[8] bicylic diketones (α-diones),[9] and unsaturated carboxylic acids[10]). Recently, it has been said that arene–arene interaction[11] is important in self-assembly of molecules to superstructures.[12] Further, arene–arene interaction has attracted synthetic scientists as an important control element for stereoselective synthesis.[13] Though MCPBA is a unique oxidizing reagent which has a large π-system in its molecule, arene–arene interaction has not been utilised for stereoselective oxidation yet. In this paper we investigate the effect of arene–arene interaction in this stereoselective reaction, using tailor-made molecules, 5,6-dimethyl-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-diones **1**. To the best of our knowledge, this is the first example of stereoselective MCPBA epoxidation directed by arene–arene interaction.

Compounds **1** have the following significant features to allow investigation of the arene–arene interaction in the transition state; 1) the tetraalkyl-substituted double bond, which is highly reactive in MCPBA epoxidation,[14] 2) the arrangement of a benzene ring at the suitable position for arene–arene interaction with MCPBA in the reaction transition state, 3) adjustable π-electron density of the benzene ring by introduction of the *para*-substituent group, and 4) the bicyclic structure which makes determination of *exo*/*endo* ratios of the products easier in NMR and HPLC analyses.

Results and discussion

Bicyclic *N*-phenylimides **1a–e**, possessing a substituent R^1 (OMe, H, Cl, CO_2Me, NO_2), and **1f**, possessing R^3(Bu^t) were synthesized by Diels–Alder reaction of 2,3-dimethylbuta-1,3-diene and *N*-phenylmaleimides **3a–f**, which were in turn prepared by condensation of anilines **2a–f** and maleic anhydride. Compound **1g** was derived from **1f** (Scheme 1).[15]

The results of the epoxidation of alkenes **1a–e** are shown in Table 1. A single crystal of tricyclic compound **4f** was obtained by recrystallization from chloroform–hexane, and its stereochemistry was determined by X-ray crystallography to be the *anti*-form for the relationship between the imide ring and the oxirane ring (Fig. 1). Accordingly, the other stereoisomer **5f** was determined to be the *syn*-form. The stereochemistry of epoxides **4a–e** and **5a–e** was estimated from the ^{1}H NMR chemical shifts of H^a–H^d shown in Table 2, based on the differences between **4f** and **5f**. Conformers (I and II) of **4f** and **5f** are shown in Scheme 2 and the 'flapping' between them is so rapid because of the small barrier (about 5 kcal mol^{-1}† by AM1 calculations).



Scheme 1 Synthesis of **1**.

† 1 cal = 4.184 J.

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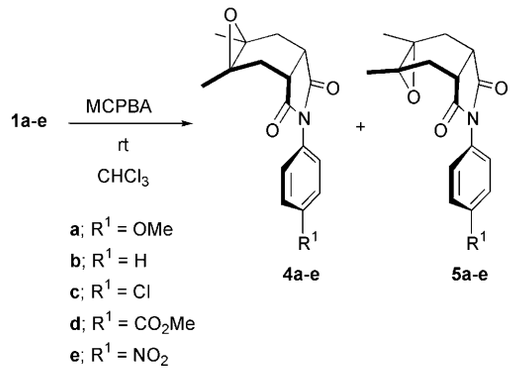
Table 1 Epoxidation of **1a–e** with MCPBA[a]



Entry	Starting material	R^1	Yield (%)[b]	Ratio[c] **4**:**5**
1	**1a**	OMe	69	42:58
2	**1b**	H	79	37:63
3	**1c**	Cl	81	26:74
4	**1d**	CO_2Me	79	26:74
5	**1e**	NO_2	79	16:84

[a] The reaction was carried out at room temperature for 3 h in chloroform. [b] Isolated yields for a mixture of **4** and **5**. [c] The ratios were determined by ^{1}H NMR spectroscopy (400 MHz).

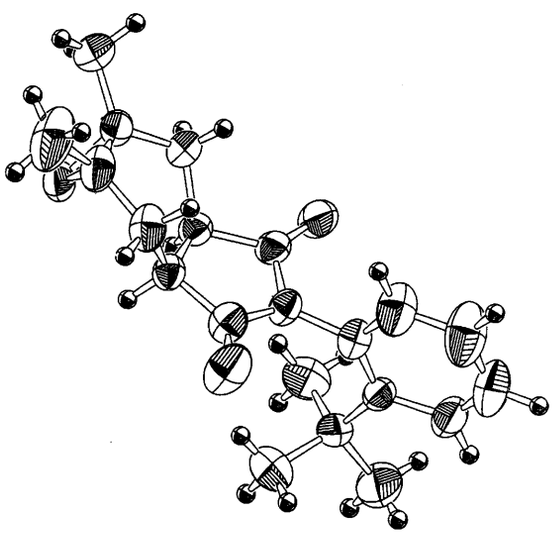
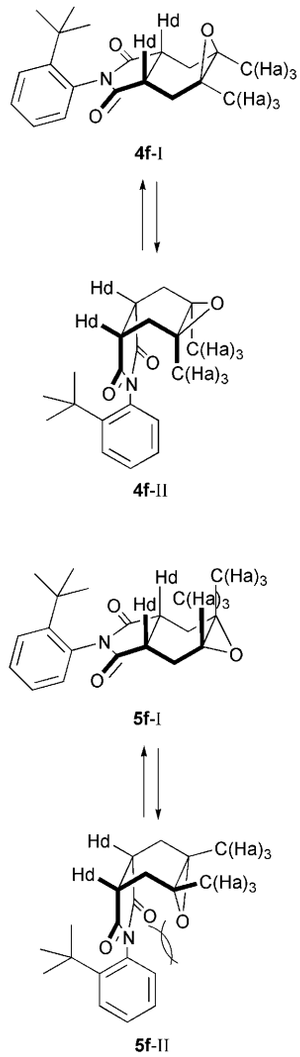


Fig. 1 ORTEP diagram of compound **4f**.

In **4f**-I H^d protons are in the diamagnetic deshielding zone of the oxirane oxygen atom, and in **4f**-II H^a protons of the methyl groups are in the deshielding zone of the benzene ring. On the other hand, in **5f**-I and **5f**-II, protons H^b and H^c are within the deshielding zone of the O–C bonds of the oxirane ring. As a result, chemical shifts of H^a and H^d of **4f** are at lower field than those of **5f**, and H^b and H^c of **5f** are at lower field than those of **4f**.[16] In all cases, the chemical shifts of H^a and H^d of isomers **4** are at lower field than those of isomers **5**, and shifts of H^b and H^c of isomers **5** appear at lower field than those of isomers **4**, and the coupling patterns of **4a**–**e** and **5a**–**e** are similar to those of **4f** and **5f**, respectively.

An electron-withdrawing group increased the *exo*/*endo* ratio of products [**5**/(**4** + **5**)], while an electron-donating group decreased the ratio. This selectivity seems to be related to the arene–arene interaction between the *N*-phenyl group and MCPBA. In the case of **1e** ($R^1 = NO_2$), which has the most electron-deficient benzene ring in this series, the epoxidation mainly proceeded from the *endo*-side of **1**, to give the highest **5**/(**4** + **5**) ratio. Relative rates of the epoxidation in 10% conversion were measured in a solution of **1a** (R^1 = OMe) and **1e** ($R^1 = NO_2$) in chloroform at 21 °C to give the relative proportions of k_{rel}(**4a**):k_{rel}(**5a**):k_{rel}(**4e**):k_{rel}(**5e**) = 1.0:1.8:1.1:4.6. Generation of **5e** is about 2.6-times faster than that of **5a**, though generation of **4e** is only 1.1-times faster than that of **4a**. This means that the epoxidation of the double bond from its down side is accelerated more than that from its upper side. In attack of an MCPBA molecule from the down side of **1**, the activation energy in the reaction of **1e** ($R^1 = NO_2$) is 0.56 kcal mol^{-1} smaller than that in the reaction of **1a** (R^1 = OMe). In other words, the transition state of **1e** and MCPBA is more stabilized than that of **1a** and MCPBA by a certain interaction between MCPBA and **1**.

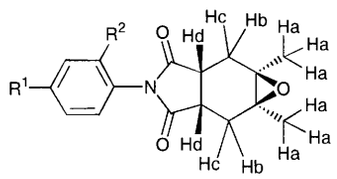


Scheme 2 Flapping of **4f** and **5f**.

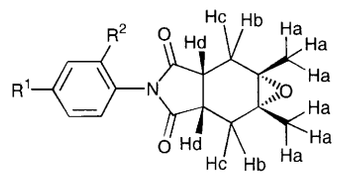
The arene–arene interaction seems to consist chiefly of the following three types of interactions: 1) charge-transfer complexation,[17] 2) edge-to-face interaction,[18] 3) polar/π interaction.[19] From PM3 calculations,[20] rotational barriers of the N–Ar bonds are only 2–3 kcal mol^{-1} for **1a–e**, which means that the bond freely rotates under the reaction conditions. It was found that the cyclohexene ring also 'flapped' freely at room temperature (the barrier 19.6 kcal mol^{-1} was obtained from the coalescence temperature of the 5- and 6-methyl peaks of 2,5,6-trimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione **6**). From the flexibility of its molecular structure, both the face-to-face and face-to-edge arrangements are possible between MCPBA and **1a–e**. The three above mentioned arene–arene interactions were investigated by calculations and experiments.

From PM3 calculations,[20] both HOMO and LUMO energy levels of MCPBA and *N*-(4-nitrophenyl)succinimide **1e**′ (a model compound of **1e**) were obtained as follows: MCPBA:

Table 2 ^{1}H NMR spectra[a] of epoxides **4** and **5**



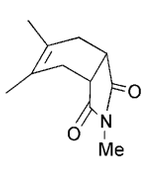
4a-g



5a-g

Products[b]	H[a]	H[b]	H[c]	H[d]
4a (R^1 = OMe)	1.39 (s, 6H)	2.02 (m, 2H)	2.51 (m, 2H)	3.13 (m, 2H)
5a (R^1 = OMe)[c]	1.44 (s, 6H)	2.20 (A) (dd, *J* 7.2, 15.2 Hz, 1H) 2.20 (B) (dd, *J* 2.5, 15.2 Hz, 1H)	2.59 (d, *J* 15.2 Hz, 2H)	2.90 (A) (d, *J* 7.2 Hz, 1H) 2.90 (B) (dd, *J* 1.0, 2.5 Hz, 1H)
4b (R^1 = H)	1.40 (s, 6H)	1.99–2.08 (m, 2H)	2.47–2.56 (m, 2H)	3.11–3.20 (m, 2H)
5b (R^1 = H)[c]	1.34 (s, 6H)	2.22 (A) (dd, *J* 7.3, 15.3 Hz, 1H) 2.22 (B) (dd, *J* 2.7, 15.3 Hz, 1H)	2.61 (d, *J* 15.3 Hz, 2H)	2.93 (A) (d, *J* 7.3 Hz, 1H) 2.93 (B) (dd, *J* 1.0, 2.7 Hz, 1H)
4c (R^1 = Cl)	1.40 (s, 6H)	2.02 (m, 2H)	2.51 (m, 2H)	3.15 (m, 2H)
5c (R^1 = Cl)[c]	1.33 (s, 6H)	2.19 (A) (dd, *J* 7.2, 15.4 Hz, 1H) 2.19 (B) (dd, *J* 2.5, 15.4 Hz, 1H)	2.59 (d, *J* 15.4 Hz, 2H)	2.92 (A) (d, *J* 7.2 Hz, 1H) 2.92 (B) (dd, *J* 1.0, 2.5 Hz, 1H)
4d (R^1 = CO_2Me)	1.40 (s, 6H)	2.04 (m, 2H)	2.52 (m, 2H)	3.17 (m, 2H)
5d (R^1 = CO_2Me)[c]	1.34 (s, 6H)	2.22 (A) (dd, *J* 7.0, 15.2 Hz, 1H) 2.22 (B) (dd, *J* 2.5, 15.2 Hz, 1H)	2.60 (d, *J* 15.2 Hz, 2H)	2.93 (A) (d, *J* 7.0 Hz, 1H) 2.93 (B) (dd, *J* 1.0, 2.5 Hz, 1H)
4e (R^1 = NO_2)	1.40 (s, 6H)	2.04 (m, 2H)	2.53 (m, 2H)	3.20 (m, 2H)
5c (R^1 = NO_2)[c]	1.35 (s, 6H)	2.25 (A) (dd, *J* 7.1, 15.4 Hz, 1H) 2.25 (B) (dd, *J* 2.7, 15.4 Hz, 1H)	2.60 (d, *J* 15.4 Hz, 2H)	2.97 (A) (d, *J* 7.1 Hz, 1H) 2.97 (B) (dd, *J* 1.0, 2.7 Hz, 1H)
4f (R^1 = H, R^2 = *exo*-Bu^t)	1.38 (s, 6H)	2.03 (m, 2H)	2.48 (m, 2H)	3.13 (m, 2H)
5f (R^1 = H, R^2 = *exo*-Bu^t)[c]	1.34 (s, 6H)	2.18 (A) (dd, *J* 7.0, 15.1 Hz, 1H) 2.18 (B) (dd, *J* 2.7, 15.1 Hz, 1H)	2.60 (br d, *J* 15.1 Hz, 2H)	2.90 (A) (d, *J* 7.0 Hz, 1H) 2.90 (B) (dd, *J* 1.0, 2.7 Hz, 1H)
4g (R^1 = H, R^2 = *endo*-Bu^t)	1.40 (s, 6H)	2.01 (m, 2H)	2.53 (m, 2H)	3.15 (m, 2H)

[a] ^{1}H NMR samples were prepared as dilute solutions in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei. [b] R^2 = H unless otherwise stated. [c] Two conformers (A and B, 1:1) were observed in the ^{1}H NMR spectrum.



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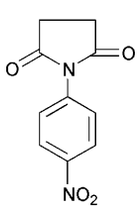


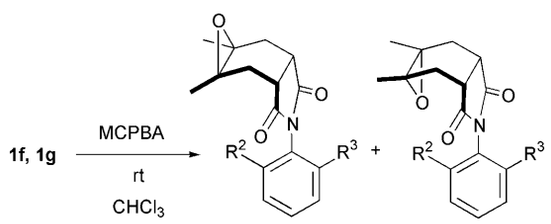
1e'

HOMO −10.10, LUMO −1.07 eV, **1e**′: HOMO −10.32, LUMO −1.33 eV, respectively. Those values indicated that the charge transfer between MCPBA and **1e** would be difficult.

A known value for edge-to-face interaction is about 0.5 kcal mol^{-1} for one hydrogen.[18] From PM3 calculations,[20] net atomic charges of hydrogen atoms on the *N*-phenyl group change from +0.63 to +0.67 (**1b**) to +0.82 to +0.97 (**1e**) in this series, and hydrogen atoms of **1a** (+0.66 to +0.78) are more positive than those of **1b**. The orders of the net atomic charges do not agree with that of the product ratios. To investigate the edge-to-face interaction, compound **1f** (R^1 = R^2 = H, R^3 = Bu^t) was synthesized stereoselectively by Diels–Alder reaction of **3f** with 2,3-dimethylbuta-1,3-diene. Rotation around the N–Ar single bond is fixed by steric repulsion between the two carbonyl and 2-*tert*-butyl groups at room temperature.[21] The π-face of MCPBA interacts with the hydrogen atoms of the *N*-phenyl group of **1f** in the transition state. In the reaction of **1f**, the ratio of **4f**:**5f** was 69:31 (Table 3), which is larger than that of **4b**:**5b** (=37:63, in Table 1). This indicates that the edge-to-face arrangement does not accelerate the generation of products **5** and weakens the arene–arene interaction. Further, the rotational isomer (**1g**) also reacted with MCPBA to give **4g** in perfect stereoselectivity (>99:1). Accordingly, the steric effect is much more dominant than the arene–arene effect in this case.

In order to investigate the polar/π interaction, the ratios [**5**/(**4** + **5**)] were plotted against the Hammett's coefficient

Table 3 Epoxidation of **1f**–**g** with MCPBA[a]



4f, 4g **5f, 5g**

f; R^2 = H, R^3 = Bu^t
g; R^2 = Bu^t, R^3 = H

Entry	Starting material	R^2	R^3	Time (*t*/h)	Yield (%)[b]	Ratio[c] **4**:**5**
1	**1f**	H	Bu^t	20	64	69:31
2	**1g**	Bu^t	H	29	61	>99:1

[a] The reaction was carried out at room temperature in chloroform. [b] Isolated yields for a mixture of **4** and **5**. [c] The ratios were determined by ^{1}H NMR spectroscopy (400 MHz).

σ_P (Fig. 2).[22] The ratios were clearly correlated with σ_P of R^1. The results are in good accord with the precedent reports on polar/π interaction in rotational isomerization of 1,8-biphenylnaphthalene which interacts as a repulsive force between two aromatic rings.[19] The stabilization energy by polar/π interaction was 1.0–1.3 kcal mol^{-1} which was measured as the difference in rotational barriers between 8-(4-methoxyphenyl)- and 8-(4-nitrophenyl)-1-(2-methylphenyl)naphthalene. The difference in stabilization energy between **1a** and **1e** (0.56 kcal mol^{-1}) is smaller than above value in the naphthalenes. This difference may originate in the difference between the inter- and intramolecular relations, or between their molecular structures. The

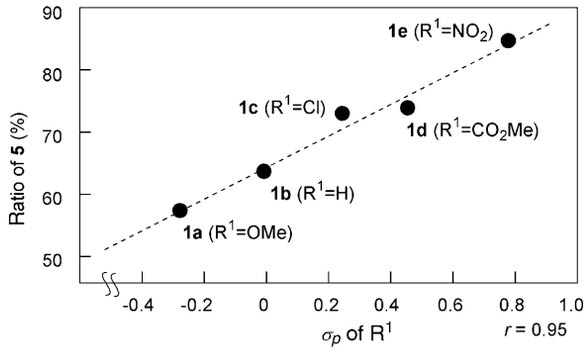


Fig. 2 Plots of ratio of **5** against Hammett's coefficient σ_P.

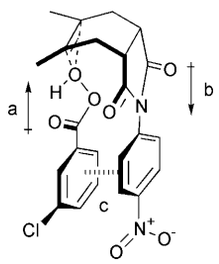


Fig. 3 Interaction between MCPBA and 4-nitrophenyl group of **1e** in the transition state. a) Dipole moment of the peracid part [-C(O)OOH], b) dipole moment of the imide part (O=C–N–C=O), and c) polar/π interaction (⁞⁞⁞⁞) between the arenes.

repulsive Cl/π interaction between the chlorine atom of MCPBA and the benzene ring may be suggested as one of the reasons.

The following mechanism is postulated for this stereoselective MCPBA epoxidation on the basis of 'butterfly' models[1a,13d,23,24] (Fig. 3). The dipole moments of model compounds, *viz*. peracetic acid and *N*-methylsuccinimide, were calculated by PM3 as 2.5 and 2.1 debyes, respectively. Therefore, the dipole–dipole interaction between the peracid moiety [-C(O)OOH)] of MCPBA and the imide part (O=C–N=C=O) of compounds **1** acts as an attractive force which is almost constant [net atomic charges of the imide oxygen atoms are from −0.33 (**1a**) to −0.31 (**1e**) in PM3 calculations)[20]] in the series of compounds **1a–e**. The polar/π interaction is known to act as a repulsive force which correlates the product ratios with the σ_P values.[19] Repulsive (polar/π) interaction of **1a** with MCPBA is larger than that of **1e**, and the attractive (dipole–dipole) interactions are almost constant and stronger than the polar/π interactions. Accordingly, epoxidation of **1e** is faster than that of **1a**. Thus, stereoselectivity in this epoxidation can be explained from the balance of these two interactions. The edge-to-face arrangement of the arenes seems to prevent the approach of the MCPBA molecule because of the steric repulsion.

Conclusions

We conclude that epoxidation of alkenes **1a–g** with MCPBA has the following features; 1) the stereoselectivity in MCPBA epoxidation of alkenes can be explained from a balance of the arene–arene and dipole–dipole interactions, 2) an edge-to-face interaction was not observed in the reaction of substrates **1**, and 3) a polar/π interaction is the main arene–arene interaction for controlling the stereoselectivity. In this paper, we demonstrate that arene–arene interaction of MCPBA with a substrate can be utilised as a control element of the stereoselective epoxidation.

Experimental

General methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) samples were prepared as dilute solutions in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and $\delta_C = 0.00$) for ^{1}H and ^{13}C nuclei. Compounds **3b** and **3f** were prepared by our previous method.[21b] IR spectra were measured with the KBr method on a Hitachi I-2000 spectrometer.

Synthesis of *N*-phenylmaleimides 3a and 3c–e

A *para*-substituted aniline **2a**,**c–e** (1.02 mmol) was added to a stirred solution of maleic anhydride (1.02 mmol) in acetic acid (10 cm^3) in a 100 cm^3 round-bottom flask. After being stirred for 1 h at room temperature, the solution was concentrated and 10 cm^3 of benzene was added. The solution was refluxed, and then zinc bromide (1.02 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (2.04 mmol) were added and the mixture was refluxed for 3 h with stirring. Ice–water (50 cm^3) and ethyl acetate (50 cm^3) were added. The organic phase was washed successively with 1 M hydrochloric acid (5 cm^3) and brine (50 cm^3), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was purified with silica gel column chromatography and elution with ethyl acetate–hexane (1 : 1) and recrystallized from chloroform–hexane.

***N*-(4-Methoxyphenyl)maleimide 3a.** Yield 83%; yellow crystals (Found: C, 64.78; H, 4.32; N, 6.81. Calc. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%); mp 148–151 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1715 (C=O), 1515, 1400; δ_H 3.83 (s, 3H), 6.84 (s, 2H), 6.98 (d, *J* 9.0 Hz, 2H), 7.23 (d, *J* 9.0 Hz, 2H); δ_C 55.47, 114.46, 123.73, 127.58, 134.11, 159.13, 169.82.

***N*-(4-Chlorophenyl)maleimide (3c).** Yield 83%; yellow solid (Found: C, 57.87; H, 2.73; N, 6.61. Calc. for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.91; N, 6.75%); mp 116–117 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1720 (C=O), 1505, 1390; δ_H 6.84 (s, 2H), 7.30 (d, *J* 8.9 Hz, 2H), 7.42 (d, *J* 8.9 Hz, 2H); δ_C 127.09, 129.32, 129.73, 133.64, 134.29, 169.14.

***N*-[4-(Methoxycarbonyl)phenyl]maleimide 3d.** Yield 86%; yellow crystals (Found: C, 62.47; H, 3.82; N, 5.95. Calc. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06%); mp 170–171 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 3100, 1715 (C=O), 1605, 1515, 1445, 1395; δ_H 3.94 (s, 3H), 6.89 (s, 2H), 7.51 (d, *J* 8.9 Hz, 2H), 8.14 (d, *J* 8.9 Hz, 2H); δ_C 52.24, 125.15, 129.06, 130.39, 134.34, 135.34, 166.17, 168.90.

***N*-(4-Nitrophenyl)maleimide 3e.** Yield 88%; yellow crystals (Found: C, 54.95; H, 2.61; N, 12.73. Calc. for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84%); mp 168–169 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 3080, 1720 (C=O), 1605, 1525, 1390, 1355; δ_H 6.91 (s, 2H), 7.66 (d, *J* 8.9 Hz, 2H), 8.31 (d, *J* 8.9 Hz, 2H); δ_C 124.48, 125.47, 134.60, 137.07, 147.23, 168.48.

Synthesis of bicyclic imides 1a–f

In a two-necked 100 cm^3-flask equipped with a reflux condenser capped with a calcium chloride drying tube and a rubber septum was stirred a solution of an imide **3** (0.493 mmol) in toluene (10 cm^3). Then, 2,3-dimethylbuta-1,3-diene (1.48 mmol) was added and the mixture was heated at 70 °C for 2 h with stirring. After cooling, the solution was concentrated *in vacuo* and the products were separated by column chromatography on silica gel and elution with ethyl acetate to give the corresponding bicycle **1**. Further, crystals were obtained by recrystallization from chloroform–hexane.

2-(4-Methoxyphenyl)-5,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1a. Yield 88%; yellow crystals (Found: C, 71.56; H, 6.67; N, 4.82. Calc. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91%); mp 143–144 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2930, 1710 (C=O), 1515, 1440, 1390, 1310; δ_H 1.70 (d, *J* 1.0 Hz,

6H), 2.29 (br d, *J* 15.2 Hz, 2H), 2.52 (d, *J* 15.2 Hz, 2H), 3.17 (br d, *J* 2.4 Hz, 2H), 3.79 (s, 3H), 6.93 (d, *J* 9.0 Hz, 2H), 7.07 (d, *J* 9.0 Hz, 2H); δ_C 19.21, 30.96, 40.01, 55.46, 114.43, 124.77, 127.02, 127.58, 159.41, 179.58.

5,6-Dimethyl-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1b. Yield 74%; white crystals (Found: C, 75.16; H, 6.71; N, 5.49. Calc. for $C_{16}H_{17}NO_2$: C, 75.28; H, 6.71; N, 5.49%); mp 86–87 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 3070, 2930, 2840, 1700 (C=O), 1600, 1440; δ_H 1.73 (d, *J* 0.9 Hz, 6H), 2.33 (dm, *J* 15.4 Hz, 2H), 2.55 (d, *J* 15.4 Hz, 2H), 3.21 (m, 2H), 7.18 (d, *J* 7.7 Hz, 2H), 7.43 (m, 3H); δ_C 19.12, 30.88, 40.01, 126.32, 126.94, 128.97, 129.69, 132.08, 179.22.

2-(4-Chlorophenyl)-5,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1c. Yield 96%; colorless crystals (Found: C, 66.41; H, 5.49; N, 4.72. Calc. for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83%); mp 123–125 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2850, 1715 (C=O), 1630, 1495, 1385; δ_H 1.695 [s, 3H (conformer A)], 1.697 [s, 3H (conformer B)], 2.25 (br d, *J* 14.6 Hz, 2H), 2.52 (d, *J* 14.6 Hz, 2H), 3.18 (br t, *J* 2.4 Hz, 2H), 7.14 (d, *J* 9.1 Hz, 2H), 7.40 (d, *J* 9.1 Hz, 2H); δ_C 19.14, 30.81, 39.98, 126.94, 127.00, 127.52, 129.17, 130.49, 134.10, 134.18, 178.95.

Methyl 4-(5,6-dimethyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl) benzoate 1d. Yield 97%; colorless crystals (Found: C, 69.11; H, 6.05; N, 4.40. Calc. for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47%); mp 152–153 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1715 (C=O), 1635; δ_H 1.703 [s, 3H (conformer A)], 1.705 [s, 3H (conformer B)], 2.31(br d, *J* 14.9 Hz, 2H), 2.53 (d, *J* 14.9 Hz, 2H), 3.20 (br t, *J* 2.5 Hz, 2H), 3.91 (s, 3H), 7.31 (d, *J* 8.5 Hz, 2H), 8.10 (d, *J* 8.5 Hz, 2H); δ_C 19.25, 30.93, 40.12, 52.29, 126.09, 127.05, 129.87, 130.37, 136.01, 166.08, 178.89.

5,6-Dimethyl-2-(4-nitrophenyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1e. Yield 90%; yellow crystals (Found: C, 63.46; H, 5.28; N, 9.27. Calc. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33%); mp 117–118 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1710 (C=O), 1630, 1350; δ_H 1.726 [s, 3H (conformer A)], 1.729 [s, 3H (conformer B)], 2.35 (br d, *J* 14.8 Hz, 2H), 2.56 (d, *J* 14.8 Hz, 2H), 3.26 (br t, *J* 2.1 Hz, 2H), 7.51 (d, *J* 8.9 Hz, 2H), 8.32 (d, *J* 8.9 Hz, 2H); δ_C 19.25, 30.87, 40.16, 124.32, 126.77, 127.10, 137.54, 146.88, 178.56.

***exo*-2-(2-*tert*-Butylphenyl)-5,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1f.** Yield 72%; white crystals (Found: C, 77.19; H, 8.20; N, 4.43. Calc. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50%); mp 124–125 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2966, 2912, 1715 (C=O), 1495, 1380, 1315; δ_H 1.29 (s, 9H), 1.76 (d, *J* 1.1 Hz, 6H), 2.39 (dm, *J* 15.0 Hz, 2H), 2.59 (d, *J* 15.0 Hz, 2H), 3.21 (m, 2H), 6.51 (dd, *J* 7.7, 1.5 Hz, 1H), 7.25 (td, J = 7.7, 1.5 Hz, 1H), 7.36 (td, J = 7.7, 1.5 Hz, 1H), 7.54 (dd, *J* 7.7, 1.5 Hz, 1H); δ_C 18.91, 30.28, 31.20, 35.14, 40.06, 127.09, 128.11, 128.44, 129.24, 130.38, 130.91, 147.56, 180.17.

Synthesis of bicyclic imide 1g

Imide **1f** (2.22 g, 7.13 mmol) was dissolved in toluene (50 cm^3) and the solution was refluxed for 29 h. After cooling, the solution was concentrated *in vacuo*. The residue was separated by column chromatography on silica gel and elution with hexane–ethyl acetate (9 : 1) to give **1f** (1.09 g, 49% recovery; R_f 0.25) and **1g** (1.13 g, 51%; R_f 0.1).

***exo*-2-(2-*tert*-Butylphenyl)-5,6-dimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 1g.** Yield 51%; white crystals (Found: C, 76.81; H, 7.89; N, 4.44%); mp 178–179 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2938, 1710 (C=O), 1445, 1379; δ_H 1.22 (s, 9H), 1.70 (d, *J* 1.1 Hz, 6H), 2.36 (dm, *J* 15.0 Hz, 2H), 2.56 (d, *J* 15.0 Hz, 2H), 3.22 (m, 2H), 6.79 (dd, *J* 7.7, 1.5 Hz, 1H), 7.26 (td, *J* 7.7, 1.5 Hz, 1H), 7.36 (td, *J* 7.7, 1.5 Hz, 1H), 7.53 (dd, *J* 7.7, 1.5 Hz, 1H); δ_C 19.36, 30.46, 31.08, 35.05, 40.05, 127.36, 127.42, 128.17, 129.54, 130.85, 131.90, 148.63, 180.74.

MCPBA epoxidation of 1a–g

In a 100 cm^3 round-bottom flask equipped with a dropping funnel capped with a calcium chloride drying tube was slowly added a solution of MCPBA (0.588 mmol) in chloroform (5 cm^3) to a solution of **1** (0.392 mmol) in chloroform (10 cm^3) *via* the dropping funnel within 20 min. The solution was stirred at room temperature for 3 h, washed successively with 20% aq. $NaHSO_3$ (100 cm^3), saturated aq. $NaHCO_3$ (100 cm^3), and water (50 cm^3), and dried over anhydrous $MgSO_4$. The products were separated by column chromatography on silica gel and elution with ethyl acetate–hexane (1 : 1) to give a mixture of diastereoisomers **4** and **5**. The ratio **4**:**5** was obtained by ^{1}H NMR (400 MHz) spectroscopy. The products were separated by HPLC [Merck, Lichrosorb Si 60; ethyl acetate–hexane (1 : 1)] to give pure **4** and **5**.

9-(4-Methoxyphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 4a. Yield 29%; colorless crystals (Found: C, 67.81; H, 6.42; N, 4.51. Calc. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65%); mp 144–145 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1715 (C=O), 1520, 1400; δ_H 1.39 (s, 6H), 2.02 (m, 2H), 2.51 (m, 2H), 3.13 (m, 2H), 3.82 (s, 3H), 6.97 (d, *J* 9.0 Hz, 2H), 7.17 (d, *J* 9.3 Hz, 2H); δ_C 18.49, 30.23, 36.81, 55.48, 59.19, 114.48, 124.36, 127.58, 159.41, 179.06.

9-(4-Methoxyphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 5a. Yield 40%; colorless crystals (Found: C, 67.51; H, 6.32; N, 4.51%); mp 179–181 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2920, 1710 (C=O), 1630, 1520; δ_H 1.33 (s, 6H), 2.20 [dd, *J* 7.2, 15.2 Hz, 1H (conformer A)], 2.20 [dd, *J* 2.5, 15.2 Hz, 1H (conformer B)], 2.59 (d, *J* 15.2 Hz, 2H), 2.90 [d, *J* 7.2 Hz, 1H (conformer A)], 2.90 [dd, *J* 1.0, 2.5 Hz, 1H (conformer B)], 3.82 (s, 3H), 6.97 (d, *J* 9.0 Hz, 2H), 7.22 (d, *J* 9.0 Hz, 2H); δ_C 18.48, 29.55, 36.75, 55.46, 61.06, 114.43, 125.38, 127.93, 159.40, 180.09.

3,5-Dimethyl-9-phenyl-4-oxa-9-azatricyclo[5.3.0.0^{3,5}]decane-8,10-dione 4b. Yield 29%; colorless crystals (Found: C, 70.63; H, 6.40; N, 5.18. Calc. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%); mp 169–171 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2950, 1710 (C=O), 1505, 1450, 1390; δ_H 1.40 (s, 6H), 1.99–2.08 (m, 2H), 2.47–2.56 (m, 2H), 3.11–3.20 (m, 2H), 7.25–7.27 (m, 2H), 7.39 (dd, *J* 7.4, 7.4 Hz, 1H), 7.45–7.49 (m, 2H); δ_C 18.43, 30.19, 36.84, 59.13, 126.32, 128.53, 129.09, 178.71.

3,5-Dimethyl-9-phenyl-4-oxa-9-azatricyclo[5.3.0.0^{3,5}]decane-8,10-dione 5b. Yield 50%; colorless crystals (Found: C; 71.02, H; 6.32, N; 5.24%); mp 180–183 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2920, 1706 (C=O), 1598, 1504, 1402; δ_H 1.34 (s, 6H), 2.22 [dd, *J* 7.3, 15.3 Hz, 1H (conformer A)], 2.22 [dd, *J* 2.7, 15.3 Hz, 1H (conformer B)], 2.61 (d, *J* 15.3 Hz, 2H), 2.93 [d, *J* 7.3 Hz, 1H (conformer A)], 2.93 [dd, *J* 1.0, 2.7 Hz, 1H (conformer B)], 7.30–7.33 (m, 2H), 7.38 (dd, *J* 7.5, 7.5 Hz, 1H), 7.44–7.48 (m, 2H); δ_C 18.40, 29.50, 36.75, 61.01, 126.68, 128.32, 128.97, 128.97, 132.70, 179.72.

9-(4-Chlorophenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 4c. Yield 24%; colorless crystals (Found: C; 62.82, H; 5.26, N; 4.43. Calc. for $C_{16}H_{16}ClNO_3$: C; 62.85, H; 5.27, N; 4.58%); mp 214–215 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1710 (C=O), 1635; δ_H 1.40 (s, 6H), 2.02 (m, 2H), 2.51 (m, 2H), 3.15 (m, 2H), 7.24 (d, *J* 8.8 Hz, 2H) , 7.44 (d, *J* 8.8 Hz, 2H); δ_C 18.46, 30.17, 36.84, 59.12, 127.53, 129.32, 130.14, 134.33, 178.47.

9-(4-Chlorophenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 5c. Yield 57%; colorless crystals; high-resolution FAB MS (Found: *m*/*z*, 306.0872. Calc. for $C_{16}H_{16}ClNO_3$: *M*H$^+$, 306.7682); mp 205–207 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1710 (C=O), 1500, 1405; δ_H 1.33 (s, 6H), 2.19 [dd, *J* 7.2, 15.4 Hz, 1H (conformer A)], 2.19 [dd, *J* 2.5, 15.4 Hz, 1H (conformer B)], 2.59 (d, *J* 15.4 Hz, 2H), 2.92 [d, *J* 7.2 Hz, 1H (conformer A)], 2.92 [dd, *J* 1.0, 2.5 Hz, 1H (conformer B)], 7.27 (d, *J* 8.8 Hz, 2H), 7.43 (d, *J* 8.5 Hz, 2H); δ_C 18.42, 29.55, 36.82, 61.11, 128.02, 129.23, 131.18, 134.17, 179.53.

Methyl 4-(3,5-dimethyl-8,10-dioxo-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decan-9-yl)benzoate 4d. Yield 19%; colorless crystals; high-resolution FAB MS (Found: *m*/*z*, 330.1337. Calc. for $C_{18}H_{19}NO_5$ *M*H$^+$, 330.1342); mp 184–186 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1720 (C=O), 1445, 1380; δ_H 1.40 (s, 6H), 2.04 (m, 2H), 2.52 (m, 2H), 3.17 (m, 2H), 3.93 (s, 3H), 7.40 (d, *J* 8.8 Hz, 2H), 8.13 (d, *J* 8.7 Hz, 2H); δ_C 18.44, 30.16, 36.90, 59.11, 126.05, 129.93, 130.39, 135.72, 166.14, 178.31.

Methyl 4-(3,5-dimethyl-8,10-dioxo-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decan-9-yl)benzoate 5d. Yield 60%; colorless crystals (Found: C, 65.66; H, 5.82; N, 4.13. Calc. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25%); mp 173–175 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2930, 1715 (C=O), 1605, 1445, 1385; δ_H 1.34 (s, 6H), 2.22 [dd, *J* 7.0, 15.2 Hz, 1H (conformer A)], 2.22 [dd, *J* 2.5, 15.2 Hz, 1H, (conformer B)], 2.60 (d, *J* 15.2 Hz, 2H), 2.93 [d, *J* 7.0 Hz, 1H (conformer A)], 2.93 [dd, *J* 1.0, 2.5 Hz, 1H (conformer B)], 3.92 (s, 3H), 7.44 (d, *J* 8.7 Hz, 2H), 8.13 (d, *J* 8.8 Hz, 2H); δ_C 18.42, 29.57, 36.88, 52.24, 61.12, 126.49, 129.79, 130.35, 136.75, 166.32, 179.31.

3,5-Dimethyl-9-(4-nitrophenyl)-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 4e. Yield 14%; yellow crystals; high-resolution FAB MS (Found: *m*/*z*, 317.1136. Calc. for $C_{16}H_{16}N_2O_5$: *M*H$^+$, 317.1138); mp 184–184.5 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 1710 (C=O), 1630; δ_H 1.40 (s, 6H), 2.04 (m, 2H), 2.53 (m, 2H), 3.20 (m, 2H), 7.57 (d, *J* 9.3 Hz, 2H), 8.33 (d, *J* 9.3 Hz, 2H); δ_C 18.43, 30.15, 36.93, 59.07, 124.36, 126.74, 137.41, 146.90, 177.96.

3,5-Dimethyl-9-(4-nitrophenyl)-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 5e. Yield 66%; colorless crystals (Found: C, 60.66; H, 4.98; N, 8.75. Calc. for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.10; N, 8.86%); mp 198–199 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2920, 1715 (C=O), 1625, 1525, 1350; δ_H 1.35 (s, 6H), 2.25 [dd, *J* 7.1, 15.4 Hz, 1H (conformer A)], 2.25 [dd, *J* 2.7, 15.4 Hz, 1H (conformer B)], 2.60 (d, *J* 15.4 Hz, 2H), 2.97 [d, *J* 7.1 Hz, 1H (conformer A)], 2.97 [dd, *J* 1.0, 2.7 Hz, 1H (conformer B)], 7.59 (d, *J* 9.0 Hz, 2H), 8.32 (d, *J* 9.3 Hz, 2H); δ_C 18.37, 29.60, 36.93, 61.22, 124.24, 127.24, 138.33, 146.91, 178.98.

9-(2-*tert*-Butylphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 4f. Yield 44%; colorless crystals (Found: C, 73.41; H, 7.71; N, 4.23. Calc. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28%); mp 164–166 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2968, 1713 (C=O), 1559, 1491, 1440, 1373; δ_H 1.25 (s, 9H), 1.38 (s, 6H), 2.03 (m, 2H), 2.48 (m, 2H), 3.13 (m, 2H), 6.74 (dd, *J* 1.4, 7.8 Hz, 1H), 7.26 (dt, *J* 1.5, 7.6 Hz, 1H), 7.37 (dt, *J* 1.5, 7.8 Hz, 1H), 7.55 (dd, *J* 1.5, 8.0 Hz, 1H); δ_C 18.50, 18.54, 29.89, 31.49, 31.53, 35.51, 37.17, 59.17, 127.34, 128.79, 129.74, 130.16, 130.60, 147.98, 179.90.

An X-ray crystal structure was obtained: $C_{20}H_{25}NO_3$, $M = 327.42$, colorless prismatic crystal, crystal dimensions $0.30 \times 0.40 \times 0.40$ mm, monoclinic, space group $P2_1/c$ (no. 14), $a = 11.665(1)$, $b = 9.667(1)$, $c = 16.100(1)$ Å, $\beta = 98.060(7)°$, $V = 1797.7(3)$ Å^3, $Z = 4$, $D_x = 1.210$ g cm^{-3}, μ(CuKα) = 6.46 cm^{-1}, 3603 reflections measured, 3428 unique ($R_{int} = 0.037$) which were used in all calculations. The final *R* and *wR* were 0.059 and 0.061.

CCDC reference number 207/503. See http://www.rsc.org/suppdata/p1/b0/b004098n/ for crystallographic files in .cif format.

9-(2-*tert*-Butylphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 5f. Yield 20%; colorless crystals (Found: C, 73.39; H, 7.88; N, 4.37%); mp 156–157 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2920, 1715 (C=O), 1450, 1385; δ_H 1.26 (s, 9H), 1.34 (s, 6H), 2.18 [dd, *J* 7.0, 15.1 Hz, 1H (conformer A)], 2.18 [dd, *J* 2.7, 15.1 Hz, 1H (conformer B)], 2.60 (br d, *J* 15.1 Hz, 2H), 2.90 [d, *J* 7.0 Hz, 1H (conformer A)], 2.90 [dd, *J* 1.0, 2.7 Hz, 1H (conformer B)], 7.13 (dd, *J* 2.0, 7.6 Hz, 1H), 7.28 (dt, *J* 1.7, 7.6 Hz, 1H), 7.33 (dt, *J* 1.7, 7.8 Hz, 1H), 7.50 (dd, *J* 1.7, 7.8 Hz, 1H); δ_C 18.46, 29.34, 31.39, 35.18, 37.03, 61.07, 127.42, 127.74, 129.24, 130.55, 131.69, 147.64, 180.62.

9-(2-*tert*-Butylphenyl)-3,5-dimethyl-4-oxa-9-azatricyclo-[5.3.0.0^{3,5}]decane-8,10-dione 4g. Yield 61%; colorless crystals (Found: C, 73.26; H, 7.67; N, 4.23%); mp 172–174 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2926, 1711 (C=O), 1442, 1376; δ_H 1.31 (s, 9H), 1.40 (s, 6H), 2.01 (m, 2H), 2.53 (m, 2H), 3.15 (m, 2H), 6.81 (dd, *J* 1.5, 7.8 Hz, 1H), 7.27 (dt, *J* 1.6, 7.5 Hz, 1H), 7.38 (ddd, *J* 1.5, 7.3, 7.8 Hz, 1H), 7.57 (dd, *J* 1.5, 8.2 Hz, 1H); δ_C 18.36, 29.80, 31.72, 35.78, 37.34, 59.08, 127.55, 128.71, 129.74, 130.64, 130.76, 147.99, 179.74.

Synthesis of 2,5,6-trimethyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione 6

In a two-necked 100 cm^3 flask equipped with a reflux condenser capped with a calcium chloride drying tube and a rubber septum was stirred a solution of *N*-methylmaleimide (300 mg, 2.70 mmol) in toluene (20 cm^3). Then, 2,3-dimethylbuta-1,3-diene (0.915 cm^3, 8.10 mmol) was added and the mixture was heated at 70 °C for 3 h with stirring. After cooling, the solution was concentrated *in vacuo* and compound **6** was separated by column chromatography on silica gel and elution with ethyl acetate. The solid was recrystallized from chloroform–hexane to afford a colorless solid (351.8 mg, 68%) (Found: C, 68.21; H, 7.74; N, 7.24. Calc. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%); mp 73–74 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 2940, 1770, 1700 (C=O), 1440, 1385, 1330; δ_H 1.66 [s, 3H (conformerA)], 1.67 [s, 3H (conformerB)], 2.24 (br d, *J* 15.8 Hz, 2H), 2.42 (d, *J* 14.7 Hz, 2H), 2.94 (s, 3H), 3.02 (t, *J* 2.4 Hz, 2H); δ_C 19.21, 24.90, 30.48, 39.82, 126.70, 180.33.

Competitive oxidation of 1a and 1e

Compounds **1a** (7.0 mg, 0.025 mmol) and **1e** (7.4 mg, 0.025 mmol) were dissolved in chloroform (5 cm^3). A solution of MCPBA [0.0025 mmol, 0.50 mg (purity 80%)] in chloroform (0.1 cm^3) was added and the mixture stirred at 21 °C for 23 h. The proportions of epoxides **4a** (retention time 38 min) **5a** (retention time 112 min), **4e** (retention time 33 min), and **5e** (retention time 134 min) were determined by HPLC [hexane–ethyl acetate (2.5 : 1), detection 254 nm] comparison of their peak areas calibrated with their ε-values at 254 nm.

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