Synthetic and mechanistic study of the acid-promoted aromatisation of the Diels–Alder adduct: 6,7-dimethoxy-1-(4-pyridyl)-1,4-epoxytetrahydronaphthalene-2,3-dicarboxylate

Masakatsu Sugahara,*[a] Yasunori Moritani,[a] Tooru Kuroda,[b] Kazuhiko Kondo[b] and Tatsuzo Ukita[a]

[a] *Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa, Osaka 532-8505, Japan. E-mail: m-suga@tanabe.co.jp*
[b] *Product & Technology Development Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa, Osaka 532-8505, Japan*

Received (in Cambridge, UK) 9th November 2001, Accepted 11th February 2002
First published as an Advance Article on the web 26th February 2002

A synthetic study of a 1-arylnaphthalene lignan having a heteroaryl group, such as the pyridyl group, at the C(1) position was conducted in detail. The Diels–Alder reaction of 1-pyridylisobenzofuran precursor **1** with dimethyl maleate or dimethyl fumarate gave desired 1,4-epoxides **2**–**5** in good yields as mixtures of *exo* and *endo* diastereoisomers. Intensive investigation of the following acid-promoted aromatisation using a Lewis acid or a Brønsted acid as a reaction promoter revealed that $BF_3{\cdot}Et_2O$ was the most suitable acid for this step. Examination of the reaction rates in aromatisation of 1,4-epoxides **2**–**5** provided information for the elaboration of reaction mechanisms in these reactions. Both the neighbouring-group effect of the 2-methoxycarbonyl substituent stabilising the benzyl cation intermediate and the longer length of the C(1)–O bond in 1,4-epoxide in 2-*endo* form **3** (or **5**) than that of the C(4)–O bond presumably contribute to enhancing the reaction rate, and aromatisation of the 2-*endo* form would be greatly favoured over that of the 2-*exo* form.

Introduction

In recent years, much attention has been focused on 1-arylnaphthalene lignans and their heterocyclic analogues because many of them exhibit intriguing biological activities, such as antihyperlipidaemic,[1] and 5-lipoxygenase- and phosphodiesterase-inhibitory activities.[2,3] One of the most successful methods for the synthesis of these compounds involves the application of the Diels–Alder reaction of 1-arylisobenzofurans with dienophiles to construct the basic skeletons, followed by aromatisation.[4] This method provides an efficient and general route for the synthesis of 1-arylnaphthalene lignans having an aryl group with methoxy substituents at the C(1) position. However, there were few papers that investigated the synthesis of their analogues having a heteroaryl group, such as the pyridyl group, at the C(1) position.[2,5] We recently reported a practical synthesis of 1-pyridylnaphthalene derivatives, heterocyclic analogues of 1-arylnaphthalene lignans.[6] In that paper, we reported that the Diels–Alder reaction of **1** with dienophiles followed by aromatisation by $BF_3{\cdot}Et_2O$ furnished 1-pyridylnaphthalene derivatives in moderate to good yields. Although intensive investigations have been done on the Diels–Alder reaction (reactivity, regio- and stereoselectivity) of C(1)-substituted isobenzofurans with dienophiles,[7] there are few reports that illustrate the ring opening of a 1,4-epoxide, followed by dehydration.[8] It was reported that the ring opening of a 1,4-epoxide having an aryl group at the C(1) position smoothly proceeds *via* a benzyl cation, resulting in the successful formation of a desired 1-arylnaphthalene lignan.[9] However, the reaction was carried out only with regard to the *endo* form of the 1,4-epoxide and was not examined with regard to the reactivity. In this paper, we would like to report our synthetic and mechanistic studies of the acid-promoted aromatisation of the Diels–Alder adducts **2**–**5**.

Results and discussion

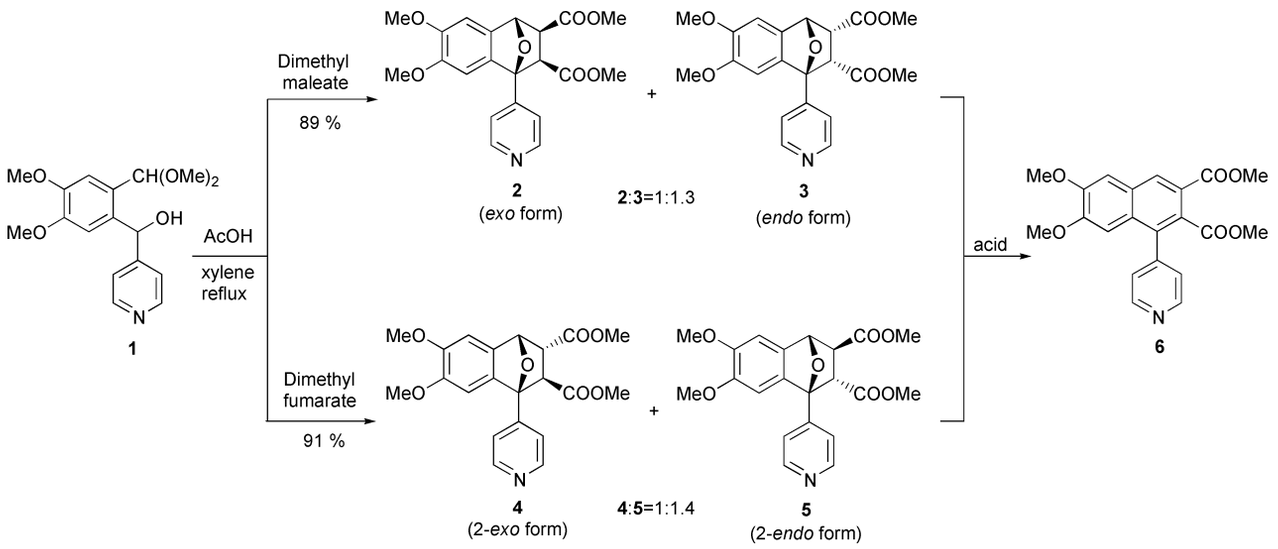
The Diels–Alder adducts **2**–**5** were first synthesised for the synthetic and mechanistic study into their transformation to **6**. As shown in Scheme 1, the treatment of compound **1**[3b] with dimethyl maleate in refluxing xylene–acetic acid (5 : 1) for 3 h gave a mixture of *exo*- and *endo*-cycloadduct **2** and **3** (1 : 1.3) in 89% yield. In similar manner, treatment of compound **1** with dimethyl fumarate under the same reaction conditions gave a mixture of 2-*exo*- and 2-*endo*-cycloadduct **4** and **5** (1 : 1.4) in 91% yield. These isomers **2**–**5** were isolated by silica gel column chromatography and/or recrystallisation. Their structures were determined by ^{1}H NMR spectra and X-ray crystallographic analyses. Because of the chemical stability of 1-(4-pyridyl)-1,4-epoxytetrahydronaphthalene, the four isomers **2**–**5** were isolated for the first time and their structures were determined. According to the X-ray crystallographic analyses, the O–C(1)–C(py) angles in **2**–**5** are 112°, 110°, 112°, and 110°, respectively; therefore, the C(1)–O–C(4) in 1,4-epoxide is located on the same side of the tetrahydrogenated ring as the pyridyl group, and the C(1)–O distances in **3** and **5** [1.457(2) and 1.448(2) Å, respectively] are statistically longer than the C(4)–O distances [1.439(2) and 1.436(2) Å, respectively] (Fig. 1).

The aromatisation of the mixture of **2** and **3** (1 : 1.3) was first investigated by means of three mol of Lewis acid in refluxing CH_3CN for 2 h (runs 1–5, in Table 1). All Lewis acids except for $ZnCl_2$ gave **6** in good to high yield without the formation of anhydride **7** as a by-product. In particular, $BF_3{\cdot}Et_2O$ furnished **6** in the highest chemical yield as we reported in our previous paper.[6] The use of one or two mol of $BF_3{\cdot}Et_2O$ resulted in the formation of **6** in lower yields with the recovery of starting materials (runs 6 and 7).

We next turned our attention to Brønsted acids instead of Lewis acids. The reaction was carried out in the presence of

 DOI: 10.1039/b110265f

This journal is © The Royal Society of Chemistry 2002



Scheme 1

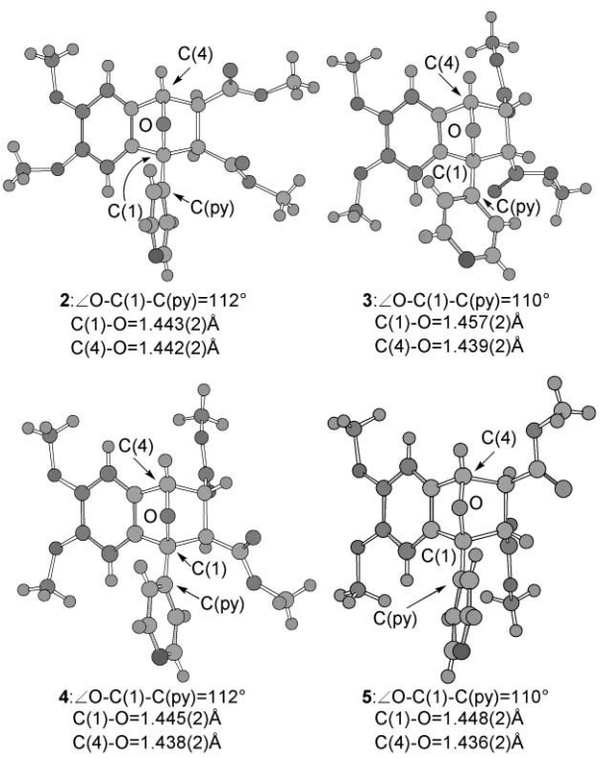
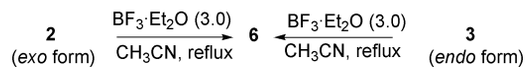


Fig. 1 Computer-generated perspective drawing of adducts **2**–**5** as determined by X-ray crystallography.

three mol of an acid like *p*-TsOH, $MeSO_3H$, AcOH, or TFA in refluxing CH_3CN for 2 h (runs 8, 11, 13, and 15, in Table 1). Although both *p*-TsOH and $MeSO_3H$ gave small amounts of **6**, AcOH and TFA were not efficient as reaction promoters at all. Even if AcOH or TFA was used as a reaction solvent under reflux conditions, **6** was obtained only in a low yield (runs 14 and 16). When the reaction was examined in the presence of *p*-TsOH in refluxing toluene, **6** was obtained in a moderate yield (run 9); however, in refluxing xylene, both *p*-TsOH and $MeSO_3H$ gave a considerable amount of **7** (runs 10 and 12). $BF_3{\cdot}Et_2O$ is thought to react easily with water produced in the aromatisation, and that could be the reason why no anhydride **7** was produced.[10] On the basis of these results, we concluded that the stronger acid was favourable for aromatisation of the 1,4-epoxide; in particular, $BF_3{\cdot}Et_2O$ was one of the most suitable acids.

In order to obtain information of the reaction mechanism in the aromatisation, we examined the reaction rate employing each isomer **2** and **3** in the presence of $BF_3{\cdot}Et_2O$, respectively (Scheme 2). Fig. 2 shows the yield of **6** *versus* reaction time in the



Scheme 2

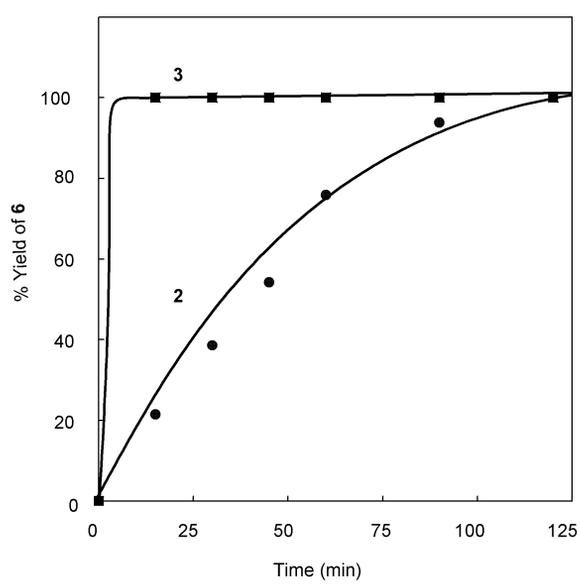


Fig. 2 Plots of yield percent of **6** *versus* time in the $BF_3{\cdot}Et_2O$-promoted aromatisation of stereoisomers **2** and **3** *via* ring opening and dehydration. Yields were determined by HPLC analysis.

$BF_3{\cdot}Et_2O$-promoted aromatisation of **2** and **3**; yields of **6** were determined by HPLC analyses. The aromatisation of *endo* form **3** was complete within 15 min under these reaction conditions. On the other hand, the reaction of *exo* form **2** took about 2 h for completion of the reaction. In these reactions, no by-product was detected by HPLC. These results showed that the aromatisation of *endo* form **3** would be greatly favoured over that of *exo* form **2**.

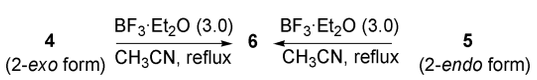
We next examined the reaction rate employing each isomer **4** and **5** under the same conditions (Scheme 3). The reaction of 2-*endo* form **5** proceeded successfully to give **6** within 15 min whereas, in the case of 2-*exo* form **4**, the reaction did not go to completion even after 2 h; this reaction proceeded with the recovery of starting material and the formation of unidentified

Table 1 Effects of acid on aromatisation of Diels–Alder adducts **2** + **3**[a]

7

Run	Acid	Yield of **6** (%)[b]	Yield of **7** (%)[b]	Recovery of **2** + **3** (**2** : **3**) (%)[b]
1	$ZnCl_2$	0	0	90 (1 : 1.3)
2	$SnCl_4$	67	0	21 (1 : 0)
3	$TiCl_4$	68	0	17 (1 : 0)
4	$AlCl_3$	77	0	15 (1 : 0)
5	$BF_3{\cdot}Et_2O$	90	0	6 (1 : 0)
6	$BF_3{\cdot}Et_2O$[c]	68	0	25 (1 : 0)
7	$BF_3{\cdot}Et_2O$[d]	trace	0	96 (1 : 1.2)
8	*p*-$TsOH{\cdot}H_2O$	6	0	81 (1 : 1.2)
9	*p*-$TsOH{\cdot}H_2O$[e]	68	7	3 (1 : 0)
10	*p*-$TsOH{\cdot}H_2O$[f]	34	39	0
11	$MeSO_3H$	2	0	93 (1 : 1.4)
12	$MeSO_3H$[f]	47	25	0
13	AcOH	0	0	98 (1 : 1.4)
14	AcOH[g]	2	0	90 (1 : 1.2)
15	TFA	0	0	93 (1 : 1.4)
16	TFA[g]	29	0	66 (1 : 0.7)

[a] Experiments were carried out with 3.0 mol equiv. of acid in refluxing CH_3CN for 2 h except where noted. [b] Isolated yields. [c] 2.0 mol equiv. of $BF_3{\cdot}Et_2O$ was used. [d] 1.0 mol equiv. of $BF_3{\cdot}Et_2O$ was used. [e] In toluene. [f] In xylene. [g] AcOH or TFA was used as the reaction solvent.



Scheme 3

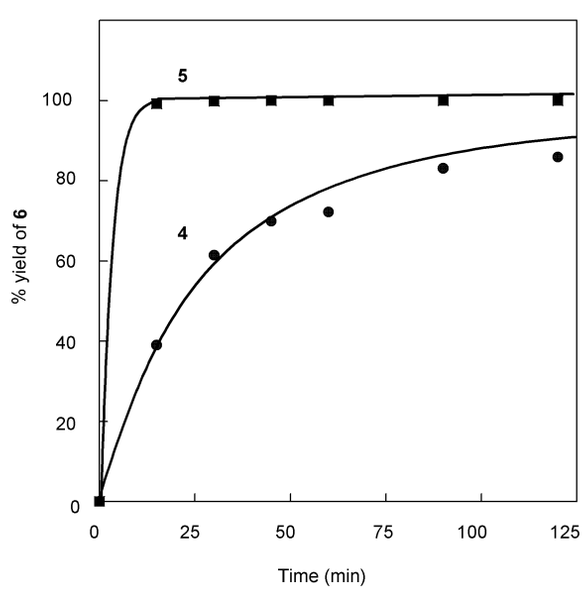
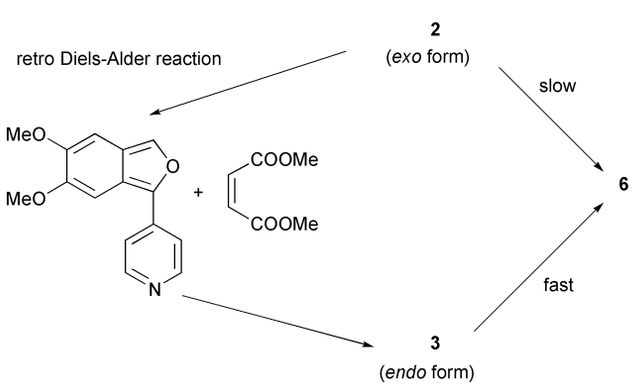


Fig. 3 Plots of yield percent of **6** *versus* time in the $BF_3{\cdot}Et_2O$-promoted aromatisation of stereoisomers **4** and **5** *via* ring opening and dehydration. Yields were determined by HPLC analysis.

by-products (Fig. 3). These results indicated that the aromatisation of 2-*endo* form **5** would be greatly favoured over that of 2-*exo* form **4**.

On the basis of the above results, we propose that the ring opening of 2-*endo* form **3** proceeds *via* four-membered transition structures by the neighbouring-group effect illustrated in Fig. 4a. It is well known that neighbouring-group participation by ester, amide, *etc.* can control reactivity.[11] In this Figure, the neighbouring-group effect of the 2-methoxycarbonyl group would be expected to stabilise the benzyl cation intermediate in the ring opening. This orientation of the 2-methoxycarbonyl group also allowed for delocalisation of the developing positive charge by the ester carbonyl group, as the ester moiety was situated in the plane of the developing unoccupied orbital. This transition structure could contribute to lowering of the reaction energy in the ring opening of the 1,4-epoxide. Support for this ring opening has been furnished by X-ray crystallographic analyses; that is, the length of C(1)–O in **3** is statistically longer than that of C(4)–O (Fig. 1). Thus, we predict that the C(1)–O bond could be cleaved more easily than the C(4)–O bond. In contrast, the ring opening of 2-*exo* form **2** could not proceed *via* cyclic intermediate structures by the neighbouring-group effect because of its steric demands (Fig. 4b). The 2-*exo* form **2** could only react to give the benzyl cation intermediate without delocalisation of the developing positive charge by the ester carbonyl group. These processes were energetically less favourable than those of the 2-*endo* form **3**. These proposed transition structures of *exo* form **2** and *endo* form **3** were assumed to be similar to those of 2-*exo* form **4** and 2-*endo* form **5**, respectively.

Next we confirmed whether *exo* form **2** reacted directly to yield **6** or instead isomerised to *endo* form **3** (*via* retro-Diels–Alder reaction) followed by the transformation to **6** (Scheme 4).



Scheme 4

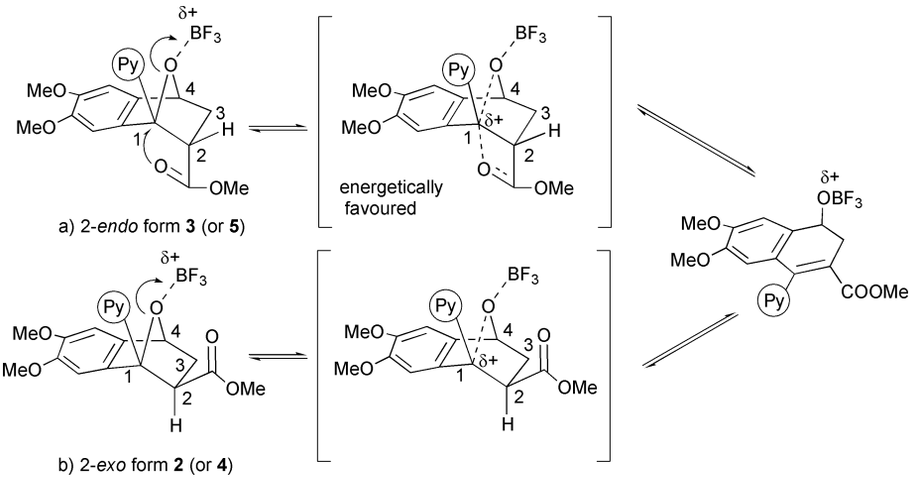
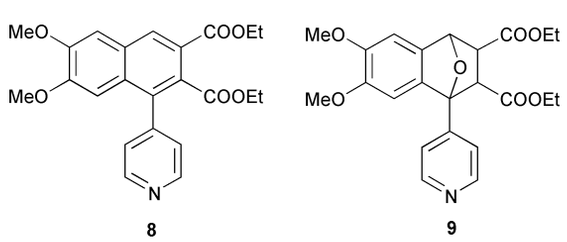


Fig. 4 Proposed transition structures in the $BF_3{\cdot}Et_2O$-promoted ring opening of the Diels–Alder adducts. The methoxycarbonyl group at the C(3) position was omitted.

exo Form **2** was treated with $BF_3{\cdot}Et_2O$ in the presence of diethyl maleate in refluxing CH_3CN for 2 h. Under these reaction conditions, diethyl ester **8** was not obtained at all, and dimethyl ester **6** was obtained in 92% yield. The comparable reactivity of dienophiles was confirmed by treating **1** with dimethyl maleate and diethyl maleate in the presence of AcOH in refluxing xylene for 3 h. Dimethyl ester **2+3** and diethyl ester **9** were afforded in 47% and 44% yield, respectively. These results showed that isomerisation between *exo* form **2** and *endo* form **3** did not occur at all, and that the aromatisation from *exo* form **2** proceeded directly to yield **6**. We propose that the transformation from *exo* form **2** to **6** proceeds through the transition structure illustrated in Fig. 4b. It would also be predicted that this proposed transition structure of *exo* form **2** is similar to that of 2-*exo* form **4**.

From these results, we concluded that the neighbouring-group effect of the 2-methoxycarbonyl substituent to stabilise the benzyl cation intermediate in 2-*endo* form **3** (or **5**) presumably contributes to enhancing the reaction rate, and that the aromatisation of the 2-*endo* form would be greatly favoured over that of the 2-*exo* form. These experimental results also gave the important information that stereoselective synthesis of *endo* form **3** and **5** could make this procedure more effective and useful for the synthesis of 1-arylnaphthalenes and related compounds.



Conclusions

A synthetic study of a new class of 1-arylnaphthalene lignans having a heteroaryl group, such as the pyridyl group, at the C(1) position was conducted. Combination of the Diels–Alder reaction and the following acid-promoted aromatisation of the 1,4-epoxide **2**–**5** was extremely effective in the synthesis of product **6**. Lewis acids generally gave good results in the aromatisation, and $BF_3{\cdot}Et_2O$, which is one of the strongest acids, was one of the most suitable reagents. On the other hand, Brønsted acids did not afford satisfactory results: a low yield of product **6** with the recovery of starting material or the formation of anhydride **7**. A mechanistic study of the aromatisation was also made by the treatment of each of four isomers **2**–**5** with $BF_3{\cdot}Et_2O$. The difference in reaction rates suggested that the neighbouring-group effect of ester at the C(2) position would be expected to stabilise the benzyl cation intermediate in the ring opening of 2-*endo* form **3** (or **5**), which was energetically favourable compared with that of the 2-*exo* form **2** (or **4**). In addition, the longer bond length of C(1)–O over that of C(4)–O in the 1,4-epoxide would be also imply that the C(1)–O bond was cleaved more easily than the C(4)–O bond. The best result was obtained when the reaction of the mixture of **2** and **3** was carried out in the presence of three mol equiv. of $BF_3{\cdot}Et_2O$ in refluxing CH_3CN to afford **6** in 90% isolated yield without **7**. $BF_3{\cdot}Et_2O$ is thought to react easily with water produced in the aromatisation and that could be the reason no anhydride **7** was produced. This is the first example which clarifies the reaction mechanism in the transformation from 1-aryltetrahydronaphthalene-1,4-epoxides **2**–**5** to 1-arylnaphthalene derivative **6**. This efficient method should find wide application in the synthesis of biologically active 1-arylnaphthalene lignan derivatives having an electron-deficient group at the C(1) position. Further synthetic and mechanistic investigation along these lines are continuing.

Experimental

Melting points were determined on a Büchi 545 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II analyser. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 (200 MHz) spectrometer with Me_4Si as internal standard. *J*-Values are given in Hz. Mass spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer. Column chromatography was performed with silica gel (E. Merck, 70–230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F254 (E. Merck) glass plates. All reagents were purchased from commercial sources and used without further purification. Xylene refers to the commercial mixture of isomers.

The Diels–Alder reaction of 1 with dimethyl maleate (Scheme 1)

A solution of compound **1** (15.0 g, 47.0 mmol), dimethyl maleate (6.3 mL, 50.4 mmol), and acetic acid (30 mL) in xylene (150 mL) was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$–acetone = 5 : 1), followed by crystallisation from diisopropyl ether, gave a mixture of adducts **2** and **3** (16.7 g, 89%). The residue obtained by silica gel chromatography was analysed by ^{1}H NMR to

determine the isomer ratios (**2** : **3** = 1 : 1.3). Purification of a mixture of **2** and **3** by silica gel chromatography ($CHCl_3$–acetone = 8 : 1), followed by recrystallisation from AcOEt gave **2** (5.4 g, 29%) and **3** (7.1 g, 38%), respectively.

***exo* Form 2.** Mp 204–207 °C (Found: C, 62.80; H, 5.12; N, 3.31. $C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.30; N, 3.51%); ν_{max} (KBr)/cm^{-1} 1746 and 1094; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.09 (1 H, d, *J* 9.2, C_2H), 3.34 (3 H, s, $COOCH_3$), 3.48 (1 H, d, *J* 9.2, C_3H), 3.69 (3 H, s, $COOCH_3$), 3.79 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 6.03 (1 H, s, C_4H), 6.57 (1 H, s, aryl-*H*), 6.96 (1 H, s, aryl-*H*), 7.50 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*), 8.70 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*); *m*/*z* (SIMS) 400 (MH^+, 34%) and 256 (100).

***endo* Form 3.** Mp 166–167 °C (Found: C, 62.89; H, 5.10; N, 3.40. $C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.30; N, 3.51%); ν_{max} (KBr)/cm^{-1} 1746 and 1111; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.56 (6 H, s, 2 × $COOCH_3$), 3.65 (1 H, d, *J* 10.5, C_2H), 3.80 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.97 (1 H, dd, *J* 10.5, 4.9, C_3H), 5.61 (1 H, d, *J* 4.9, C_4H), 6.69 (1 H, s, aryl-*H*), 6.92 (1 H, s, aryl-*H*), 7.58 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*), 8.70 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*); *m*/*z* (SIMS) 400 (MH^+, 62%) and 256 (100).

The Diels–Alder reaction of 1 with dimethyl fumarate (Scheme 1)

A solution of compound **1** (15.0 g, 47.0 mmol), dimethyl fumarate (7.2 g, 50.0 mmol), and acetic acid (30 mL) in xylene (150 mL) was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$–acetone = 5 : 1), followed by crystallisation from diisopropyl ether, gave a mixture of adducts **4** and **5** (17.1 g, 91%). The residue obtained by silica gel chromatography was analysed by ^1H NMR to determine the isomer ratios (**4** : **5** = 1 : 1.4). Purification of a mixture of **4** and **5** by recrystallisation from AcOEt gave **4** (6.3 g, 34%), while concentration of the mother liquor under reduced pressure, followed by recrystallisation from EtOH, gave **5** (6.8 g, 36%).

2-*exo* Form 4. Mp 183–185 °C (Found: C, 63.02; H, 5.06; N, 3.47. $C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.30; N, 3.51%); ν_{max} (KBr)/cm^{-1} 1733 and 1099; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.37 (3 H, s, $COOCH_3$), 3.42 (1 H, d, *J* 4.4, C_2H), 3.61 (3 H, s, $COOCH_3$), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.01 (1 H, dd, *J* 5.2, 4.4, C_3H), 5.78 (1 H, d, *J* 5.2, C_4H), 6.65 (1 H, s, aryl-*H*), 6.87 (1 H, s, aryl-*H*), 7.50 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*), 8.72 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*); *m*/*z* (SIMS) 400 (MH^+, 34%) and 256 (100).

2-*endo* Form 5. Mp 119–120 °C (Found: C, 62.98; H, 5.13; N, 3.41. $C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.30; N, 3.51%); ν_{max} (KBr)/cm^{-1} 1733 and 1087; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.25 (1 H, d, *J* 3.8, C_2H), 3.51 (3 H, s, $COOCH_3$), 3.77 (3 H, s, $COOCH_3$), 3.82 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 4.12 (1 H, d, *J* 3.8, C_2H), 5.73 (1 H, s, C_4H), 6.55 (1 H, s, aryl-*H*), 7.00 (1 H, s, aryl-*H*), 7.70 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*), 8.72 (2 H, dd, *J* 4.5, 1.7, pyridyl-*H*); *m*/*z* (SIMS) 400 (MH^+, 24%) and 256 (100).

Analysis of acid-promoted aromatisation of the Diels–Alder adducts 2 and 3 (2 : 3 = 1 : 1.3) (Table 1)

A solution of the Diels–Alder adducts **2** and **3** (**2** : **3** = 1 : 1.3) (399 mg, 1.0 mmol) and an acid (3.0 mmol) in CH_3CN (10 mL) was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature and was then poured into a mixture of AcOEt and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$–acetone = 10 : 1), followed by crystallisation from diisopropyl ether, gave aromatic products **6**, **7**, and (or) recovery of **2** and **3**. The residue obtained by silica gel chromatography was analysed by ^1H NMR to determine the proportions of **2**, **3**, **6**, and **7**.

Dimethyl 6,7-dimethoxy-1-(4-pyridyl)naphthalene-2,3-dicarboxylate 6. Mp 211–212 °C (Found: C, 66.30; H, 4.82; N, 3.64. $C_{21}H_{19}NO_6$ requires C, 66.13; H, 5.02; N, 3.67%); ν_{max} (KBr)/cm^{-1} 1741, 1708, 1248 and 1165; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.61 (3 H, s, $COOCH_3$), 3.75 (3 H, s, $COOCH_3$), 3.95 (3 H, s, OCH_3), 4.04 (3 H, s, OCH_3), 6.67 (1 H, s, aryl-*H*), 7.27 (1 H, s, aryl-*H*), 7.33 (2 H, dd, *J* 4.4, 1.6, pyridyl-*H*), 8.50 (1 H, s, aryl-*H*), 8.75 (2 H, dd, *J* 4.4, 1.6, pyridyl-*H*); *m*/*z* (EIMS) 381 (M^+, 100%).

6,7-Dimethoxy-1-(4-pyridyl)naphthalene-2,3-dicarboxylic anhydride 7. Mp 270–272 °C (Found: C, 68.19; H, 3.78; N, 4.09. $C_{19}H_{13}NO_5$ requires C, 68.06; H, 3.91; N, 4.18%); ν_{max} (KBr)/cm^{-1} 1832, 1781, 1241 and 915; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.83 (3 H, s, OCH_3), 4.11 (3 H, s, OCH_3), 6.98 (1 H, s, aryl-*H*), 7.37 (1 H, s, aryl-*H*), 7.41 (2 H, d, *J* 4.5, pyridyl-*H*), 8.42 (1 H, s, aryl-*H*), 8.86 (2 H, d, *J* 4.5, pyridyl-*H*); *m*/*z* (EIMS) 335 (M^+, 100%).

Analysis of BF_3·Et_2O-promoted aromatisation of the Diels–Alder adducts 2–5 (Figs. 2 and 3)

A solution of a Diels–Alder adduct **2**, **3**, **4**, or **5** (100 mg, 0.25 mmol), BF_3·Et_2O (107 mg, 0.75 mmol), and 4-methoxybiphenyl (100 mg), which was added as an internal standard, in CH_3CN (5 mL) was heated under reflux. At different time intervals, 0.5 mL of the reaction solution was removed, and poured into a mixture of AcOEt and saturated aqueous $NaHCO_3$. The organic layer was concentrated under reduced pressure. The residue was analysed by reversed-phase HPLC on a CAPCELL PAK C_{18} column (4.6 × 150 mm; 5 μm particle size; SHISEIDO, type SG120 Å) at 30 °C. Solvent A: H_2O and solvent B: CH_3CN with a gradient of 30–80% of B in A over a period of 12 min, at a flow rate of 1.0 mL min^{-1}, were used as the eluent. Detection was at 254 nm. Retention times for **2**–**6** were 5.9, 6.5, 6.7, 7.2, and 9.1 min, respectively.

Aromatisation of *exo* form 2 in the presence of diethyl maleate

A solution of the *exo* form **2** (399 mg, 1.0 mmol), BF_3·Et_2O (426 mg, 3.0 mmol), and diethyl maleate (172 mg, 1.0 mmol) in CH_3CN (10 mL) was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature and was poured into a mixture of AcOEt and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$–acetone = 10 : 1) gave only dimethyl ester **6** (351 mg, 92%).

The Diels–Alder reaction of 1 with dimethyl maleate and diethyl maleate

A solution of compound **1** (319 mg, 1.0 mmol), dimethyl maleate (151 mg, 1.05 mmol), and diethyl maleate (181 mg, 1.05 mmol), and acetic acid (2 mL) in xylene (10 mL) was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue

by silica gel chromatography ($CHCl_3$–acetone = 5 : 1) gave a mixture of dimethyl ester **2+3** and diethyl ester **9** (**2+3** : **9** = 1.1 : 1) (376 mg, 91%), which was analysed by ^{1}H NMR to determine the ratios of **2+3** and **9**.

Crystal structure determinations of adducts 2–5 †

Data for compounds **2**–**5** were measured on an AFC 5R (RIGAKU) diffractometer with graphite-monochromated Cu–Ka (λ = 1.541 78 Å) radiation. The unit-cell dimensions were determined from the angular setting of 25 reflections (2θ-values in the range 70–90°). No absorption correction was applied. These structures were solved by a direct method using SHELXS-97 [12] and subsequent difference Fourier method. The refinement of atomic parameters was carried out using SHELXL-97 [13] with anisotropic thermal parameters for non-H atoms. All hydrogen atoms were located geometrically and fixed.

Detailed crystallographic results have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 156919 (**2**), CCDC 156920 (**3**), CCDC 156921 (**4**), CCDC 156922 (**5**)).

Crystal data for *exo* form 2. $C_{21}H_{21}NO_7$, M = 399.39, monoclinic, space group $P2_1/c$, a = 9.159(2), b = 16.895(1), c = 13.252(1) Å, β = 109.87(1)°, V = 1928.6(4) Å^3, Z = 4, D_c = 1.375 g mL^{-1}, μ = 0.872 cm^{-1}, F(000) = 840, colourless needle, crystal dimensions 0.5 × 0.2 × 0.2 mm. 3296 Unique reflections (2θ < 130°) were measured, of which 2914 with $|F_o| > 2.0\sigma(F_o)$ were considered reliable. The final R_1 and wR_2 were 0.0462 and 0.1726, respectively.

Crystal data for *endo* form 3. $C_{21}H_{21}NO_7$, M = 399.39, monoclinic, space group C2/c, a = 34.619(2), b = 6.874(2), c = 16.426(2) Å, β = 98.73(1)°, V = 3863.7(10) Å^3, Z = 8, D_c = 1.373 g mL^{-1}, μ = 0.870 cm^{-1}, F(000) = 1680, colourless needle, crystal dimensions 0.3 × 0.3 × 0.3 mm. 3288 Unique reflections (2θ < 130°) were measured, of which 2972 with $|F_o| > 2.0\sigma(F_o)$ were considered reliable. The final R_1 and wR_2 were 0.0492 and 0.1788, respectively.

Crystal data for 2-*exo* form 4. $C_{21}H_{21}NO_7$, M = 399.39, monoclinic, space group $P2_1/n$, a = 8.529(2), b = 13.759(1), c = 16.822(1) Å, β = 98.84(1)°, V = 1950.7(4) Å^3, Z = 4, D_c = 1.360 g mL^{-1}, μ = 0.862 cm^{-1}, F(000) = 840, colourless needle, crystal dimensions 0.4 × 0.3 × 0.3 mm. 3322 Unique reflections (2θ < 130°) were measured, of which 2785 with $|F_o| > 2.0\sigma(F_o)$ were considered reliable. The final R_1 and wR_2 were 0.0564 and 0.1715, respectively.

† CCDC reference number(s) 156919–156922. See http://www.rsc.org/suppdata/p1/b1/b110265f/ for crystallographic files in .cif or other electronic format.

Crystal data for 2-*endo* form 5. $C_{21}H_{21}NO_7$, M = 399.39, monoclinic, space group $P2_1/c$, a = 10.839(1), b = 11.534(1), c = 15.677(1) Å, β = 105.51(1)°, V = 1888.5(3) Å^3, Z = 4, D_c = 1.405 g mL^{-1}, μ = 0.890 cm^{-1}, F(000) = 840, colourless needle, crystal dimensions 0.4 × 0.2 × 0.2 mm. 3224 Unique reflections (2θ < 130°) were measured, of which 2911 with $|F_o| > 2.0\sigma(F_o)$ were considered reliable. The final R_1 and wR_2 were 0.0423 and 0.1413, respectively.

Acknowledgements

We thank Mr H. Hiramatsu for acquisition of the X-ray crystal structures.

References

1 T. Iwasaki, K. Kondo, T. Nishitani, T. Kuroda, K. Hirakoso, A. Ohtani and K. Takashima, *Chem. Pharm. Bull.*, 1995, **43**, 1701.
2 D. Delorme, Y. Ducharme, C. Brideau, C.-C. Chan, N. Chauret, S. Desmarais, D. Dubé, J.-P. Falgueyret, R. Fortin, J. Guay, P. Hamel, T. R. Jones, C. Lépine, C. Li, M. McAuliffe, C. S. McFarlane, D. A. Nicoll-Griffith, D. Riendeau, J. A. Yergey and Y. Girard, *J. Med. Chem.*, 1996, **39**, 3951.
3 (*a*) T. Iwasaki, K. Kondo, T. Kuroda, Y. Moritani, S. Yamagata, M. Sugiura, H. Kikkawa, O. Kaminuma and K. Ikezawa, *J. Med. Chem.*, 1996, **39**, 2696; (*b*) T. Ukita, M. Sugahara, Y. Terakawa, T. Kuroda, K. Wada, A. Nakata, Y. Ohmachi, H. Kikkawa, K. Ikezawa and K. Naito, *J. Med. Chem.*, 1999, **42**, 1088; (*c*) T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, M. Takahashi, J. Kotera and T. Ikeo, *J. Med. Chem.*, 1999, **42**, 1293.
4 (*a*) R. Rodrigo, *J. Org. Chem.*, 1980, **45**, 4538; (*b*) S. P. Forsey, D. Rajapaksa, N. J. Taylor and R. Rodrigo, *J. Org. Chem.*, 1989, **54**, 4280.
5 A. C. Spivey, T. Fekner, S. E. Spey and H. Adams, *J. Org. Chem.*, 1999, **64**, 9430.
6 M. Sugahara, Y. Moritani, Y. Terakawa, T. Ogiku, T. Ukita and T. Iwasaki, *Tetrahedron Lett.*, 1998, **39**, 1377.
7 (*a*) D. Tobia and B. Rickborn, *J. Org. Chem.*, 1987, **52**, 2611; (*b*) R. Rodrigo, S. M. Knabe, N. J. Taylor, D. Rajapaksa and M. J. Chernishenko, *J. Org. Chem.*, 1986, **51**, 3973; (*c*) R. N. Warrener, B. C. Hammer and R. A. Russell, *J. Chem. Soc. Chem. Commun.*, 1981, 942; (*d*) M. A. Makhlouf and B. Rickborn, *J. Org. Chem.*, 1981, **46**, 2734.
8 N. Jotterand, P. Vogel and K. Schenk, *Helv. Chim. Acta*, 1999, **82**, 821 and references cited therein.
9 T. Kuroda, M. Takahashi, K. Kondo and T. Iwasaki, *J. Org. Chem.*, 1996, **61**, 9560.
10 (*a*) H. Heymann and L. F. Fieser, *J. Am. Chem. Soc.*, 1951, **73**, 5252; (*b*) L. F. Fieser, *J. Am. Chem. Soc.*, 1954, **76**, 1945; (*c*) G. H. Posner, E. M. Shulman-Roskes, C. H. Oh, J.-C. Carry, J. V. Green, A. B. Clark, H. Dai and T. E. N. Anjeh, *Tetrahedron Lett.*, 1991, **32**, 6489.
11 (*a*) B. Capon, *Quart. Rev.*, 1964, **18**, 45; (*b*) C. J. Easton, C. A. Hutton, P. D. Roselt and E. R. T. Tiekink, *Tetrahedron*, 1994, **50**, 7327; (*c*) C. J. Easton, C. A. Hutton, M. C. Merrett and E. R. T. Tiekink, *Tetrahedron*, 1996, **52**, 7025.
12 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
13 G. M. Sheldrick, *SHELXL-97. Program for Crystal Structure Refinement*, University of Gottingen, Germany, 1997.