Inter- and intramolecular Diels–Alder reaction of benzoxazole-based azadienes

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Inter- and intramolecular Diels–Alder reactions of novel azadienes **2** and **3** are described. The dienes **2** and **3** react with electron-rich dienophiles, vinyl ethers **7a**,**b** and *p*-methoxystyrene derivatives **7c**,**d** to afford the corresponding cycloadducts **8** and **9**, regioselectively. The azadienes **2** and **3** also undergo tandem transesterification and intramolecular cycloaddition with cinnamyl alcohols **13** in the presence of stannoxane catalyst **14** to give tetracyclic compounds **15** and **16** in one step. In a tandem process, the geometries of the dienophile components of **13** were transmitted into the cycloadducts **15** and **16**.

During the last few decades, significant studies have been made to discover reactive 1-azabuta-1,3-dienes, since the hetero-Diels–Alder reactions of 1-azabuta-1,3-dienes directly provide nitrogen-containing six-membered ring systems of biological importance.[1–7] The dienes developed are divided into three classes in view of their electronic characteristics. The first class consists of 1-azadienes having electron-donating groups such as the dimethylamino group, silyloxy group, and alkoxy group, especially at the 1-position.[2] These electron-donating groups make possible normal-type Diels–Alder reactions with electron-deficient dienophiles. The second class is composed of dienes carrying electron-withdrawing groups, acyl groups or sulfonyl groups, in the systems, which cause inverse-type Diels–Alder reactions with electron-rich dienophiles.[3–5] The third class is less common and lies between the two classes described above.[6,7] These various 1-azabuta-1,3-dienes have been applied to asymmetric synthesis[2e,n] and synthesis of natural products.[2g,m,3c,g,4f]

Compared to 1-azabuta-1,3-dienes, cycloadditions of 1,3-diazabuta-1,3-dienes are much more limited.[8–12] 1,3,5-Triazines and 5-nitropyrimidines are known to undergo Diels–Alder reactions with enamines[8a] and/or ketene aminals,[8b–e] as well as cycloadditions of acyclic 1,3-diazabuta-1,3-dienes with ketenes,[9,10] sulfene,[11] dimethyl acetylenedicarboxylate[10c,12] and enamines.[10b] However, cycloaddition of 1,3-diazadiene with a styrene type dienophile, a typical dienophile for inverse dienes, has not been reported. Furthermore, intramolecular cycloaddition of 1,3-diazadiene has rarely been investigated.[13]

In the field of azadiene chemistry, we recently reported that benzylidenecyanomethyl-1,3-benzoxa/thiazoles and ethyl (*E*)-3-(1,3-benzothiazol-2-yl)-3-cyanopropenoate (**1**) act as reactive inverse-type 1-azabuta-1,3-dienes which react with electron-rich dienophiles *endo*-selectively.[5] It was also found that treatment of the diene (**1**) with allyl alcohols in the presence of 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanatodistannoxane causes tandem transesterification and intramolecular Diels–Alder reaction to give polycyclic compounds in one step.[5] We now report the inter- and intramolecular Diels–Alder reactions of benzoxazole derivative (**2**) of diene **1** and the closely related 1,3-diazabuta-1,3-diene (**3**), which is an analogue of **2** by replacement of the C3 carbon atom (which has an electrophilic cyano group) of **2** with an electronegative nitrogen atom (Fig. 1).

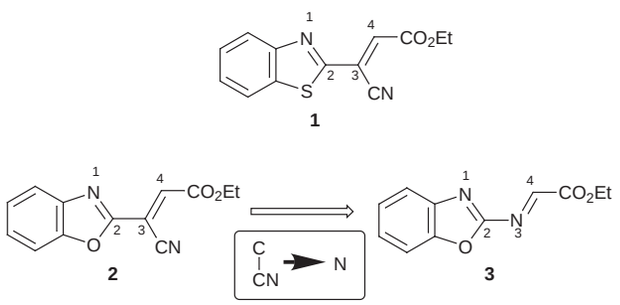


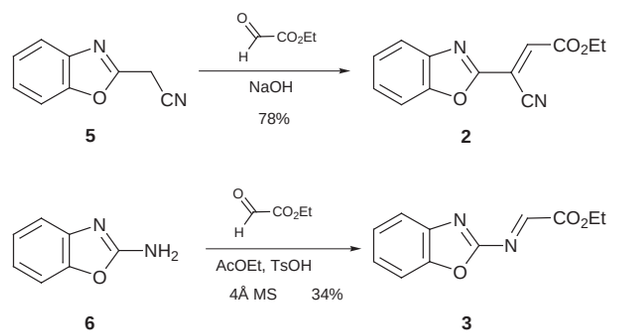
Fig. 1

Results and discussion

1. Calculations and preparation of dienes 2 and 3

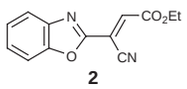
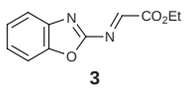
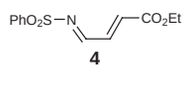
Before experimentation, the lowest unoccupied molecular orbitals (LUMOs) of ethyl (*E*)-(1,3-benzoxazol-2-yl)-3-cyanopropenoate (**2**), ethyl (*E*)-3-aza-3-(1,3-benzoxazol-2-yl)propenoate (**3**) and 1-sulfonyl-1-azabuta-1,3-diene **4**[4e] were calculated using AM1.[14] Since Diels–Alder reactions take place in the s-*cis* form of the diene, the LUMOs of the optimized s-*cis* conformers of the dienes **2**–**4** were estimated. As shown in Table 1, the energy levels of the LUMOs of dienes **2** and **3** were comparable with that of **4**, which is recognized as one of the most reactive inverse-type dienes.[4e] These results strongly suggest that dienes **2** and **3** should have adequate reactivities to react with electron-rich dienophiles. It is also expected that Diels–Alder reactions of **2** and **3** would take place regioselectively because of the large coefficients of the 4-positions of the dienes.

With these theoretical results in hand, we next examined the preparation of dienes **2** and **3** as shown in Scheme 1. (1,3-Benzoxazol-2-yl)acetonitrile **5** underwent condensation by treatment with ethyl glyoxylate in the presence of sodium hydroxide to give **2** in good yield. Since the corresponding diaza-version **3** was unstable under basic conditions, **3** needs to be prepared under acidic conditions. Thus, 2-amino-1,3-



Scheme 1

Table 1 LUMOs of azadienes (**2**–**4**): AM1 results[a]

Diene	LUMO energy/eV	Coefficients N1	C2	C3 (N3)	C4
 **2**	−1.7	0.31	−0.29	−0.45	0.54
 **3**	−1.7	0.35	−0.37	−0.38	0.52
 **4**	−1.5	0.43	−0.46	−0.49	0.46

[a] Spartan version 4.0. All orbital energies were obtained from AM1 optimized geometries of the s-*cis* conformers of the dienes (**2**–**4**).

benzoxazole **6** was treated with ethyl glyoxylate in the presence of toluene-*p*-sulfonic acid and 4 Å molecular sieves (4 Å MS) to afford the desired **3** in moderate yield. These dienes **2** and **3** are crystalline compounds, and can be stored for several months in a refrigerator.

2. Intermolecular cycloaddition of the azadienes 2 and 3

We then investigated the intermolecular Diels–Alder reactions of the dienes with electron-rich dienophiles **7a**–**d** as shown in Table 2. It was found that the 1-azadiene **2** reacts smoothly with 1.5 equivalents of **7a**–**d** at room temperature to give the corresponding Diels–Alder adducts **8a**–**d** with high regio- and *endo*-selectivities (entries 1, 3, 5, 7). Thus, treatment of **2** with ethyl vinyl ether (**7a**) at room temperature underwent regioselective Diels–Alder reaction to afford a 3:1 mixture of *endo* and *exo* cycloadducts (entry 1). Reaction with 2,3-dihydrofuran **7b** gave the *endo* cycloadduct exclusively (entry 3). Diene **2** reacted with dienophiles **7c**,**d** bearing electron-donating aromatic rings, leading to the cycloadducts **8c**,**d** in very high yields as well as with excellent *endo* selectivities (entries 5 and 7).

1,3-Diazadiene **3** also reacted with the dienophiles **7a**–**d**, although it was slightly less reactive than 1-azadiene **2** (entries 2, 4, 6, 8). Thus, treatment of **3** with **7a** in toluene caused only quite a slow cycloaddition. Use of acetonitrile as the solvent at the refluxing temperature induced smooth cycloaddition to rather surprisingly give a 1:1.5 mixture of *endo* and *exo* isomers, *cis*- and *trans*-**9a** (entry 2). 2,3-Dihydrofuran, **7b**, also reacted with the diene **3** in refluxing toluene to afford the tetracyclic cycloadduct **9b** in low yield with moderate *endo* selectivity (entry 4). Reaction of **3** with reactive dienophile **7c** gave only *endo* isomer **9c** in high yield (entry 6). In a similar manner, anethole **7d** also reacted with **3** at the same temperature to give the *endo* cycloadduct **9d** along with a small amount of the *exo* isomer, although the reaction required neat conditions (entry 8). It should be noted that these reactions (entries 2, 4, 6, 8) were the first examples of the Diels–Alder reaction of 1,3-diazabutadiene with vinyl ethers and styrene type dienophiles. In sharp contrast to the reactions in Table 2, Diels–Alder reactions of dienes **2**,**3** with electron-deficient methyl acrylate did not proceed at 110 °C. These results clearly show that the dienes **2**,**3** behave as inverse-type dienes as expected by the calculations (Table 1).

The stereochemistries of the adducts **8a**–**d** were assigned by comparing their ^{1}H-NMR spectra with those of the related Diels–Alder adducts prepared from diene **1**,[5] and the stereostructures of **9a**–**d** were elucidated from the coupling constants and/or NOE experiments in their ^{1}H-NMR spectra as shown in Fig 2.

The observed *endo* selectivities can be rationalized in terms

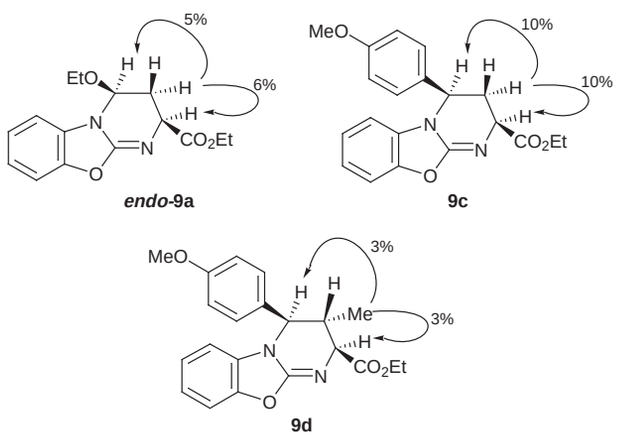


Fig. 2

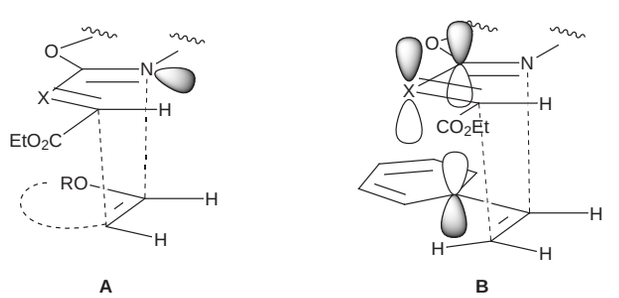


Fig. 3

of a C–O σ*–N antiperiplanar interaction **A**[4e] and/or secondary orbital interaction **B** as depicted in Fig. 3. In the reactions with vinyl ethers (entries 1, 3, 4), the *endo* selectivities may result from both of these factors, while for the styrene derivatives (entries 5–8), the *endo* selectivities would be due to a strong secondary orbital interaction between the C3 of the dienes and the p-orbital of the dienophile **B**. As an exception, reaction of **3** with **7a** in acetonitrile might proceed by a stepwise mechanism[12] in the polar solvent to give the more stable *exo*-product as the main product (Table 2, entry 2).

A simple application of the present cycloaddition of 1,3-diazadiene **3** was made as shown in Scheme 2. Diene **3** reacted with ketene dimethyl acetal **7e** in acetonitrile at room temperature to generate cycloadduct **9e**, which underwent hydrolysis during chromatographic work-up on silica gel to afford the diester **10**. Finally, Boc-protection of **10** followed by oxidative removal of the benzoxazole ring of the resulting **11** afforded aspartic acid derivative **12**. Although optimization of the oxidative step may be required, this scheme offers the possibility of a novel method of synthesis for amino acids.

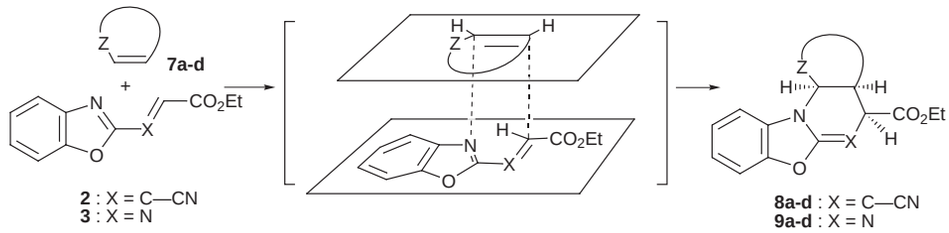
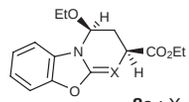
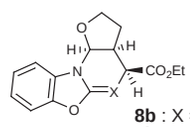
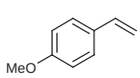
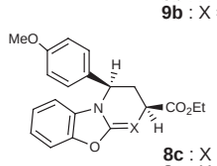
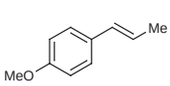
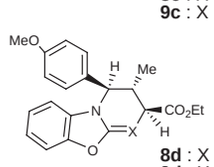
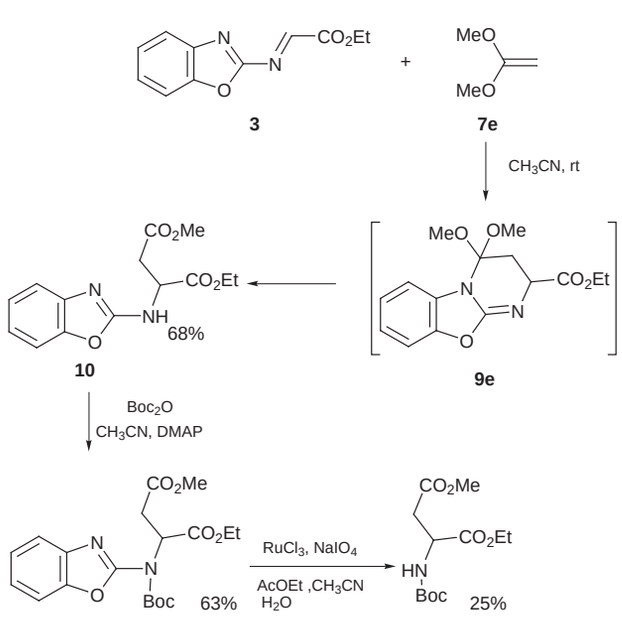


Table 2 Intermolecular Diels–Alder reactions of azadienes (**2** and **3**) with dienophiles (**7a**–**d**)

Entry	Dienophile	Diene	Conditions *T*/°C	Conditions *t*/h	Yield (%)	*endo*:*exo*	Product[a]
1	 **7a**	**2**	rt	27[b]	82	3:1	 **8a** : X = C—CN **9a** : X = N
2		**3**	80	2[c]	66	1:1.5	
3	 **7b**	**2**	rt	19.5[b]	79	Single isomer	 **8b** : X = C—CN **9b** : X = N
4		**3**	110	2[d]	25	3:1	
5	 **7c**	**2**	rt	4[b]	98	Single isomer	 **8c** : X = C—CN **9c** : X = N
6		**3**	110	4[d]	70	Single isomer	
7	 **7d**	**2**	rt	21[b]	93	Single isomer	 **8d** : X = C—CN **9d** : X = N
8		**3**	110	4[e]	55	7.6:1	

[a] The structures of only the *endo*-products are represented in Table 2. [b] Dichloromethane was used as the solvent. [c] Acetonitrile was used as the solvent. [d] Toluene was used as the solvent. [e] Neat conditions were used.



Scheme 2

3. Tandem transesterification and intramolecular cycloaddition of dienes 2 and 3 with cinnamyl alcohols

Next, intramolecular cycloadditions using dienes **2**,**3** and allyl alcohols were investigated. Recently, we have intensively studied intramolecular cycloadditions of *in situ* generated substrates having ester tethers which are constructed by transesterification in the reaction systems.[5,15] Based on aspects shown in Table 2, cinnamyl alcohols would be suitable allyl alcohol counterparts. As shown in Table 3, the tandem transesterification and intramolecular cycloadditions of **2** and **3** were examined by employing four types of cinnamyl alcohol derivatives (**13a**–**d**). Reactions using 1-azadiene **2** were first carried out (entries 1, 3, 5, 7). Treatment of diene (**2**) with 1.5 equivalents of (*E*)-cinnamyl alcohol (**13a**) in the presence of 0.1 equivalents of 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanatodistannoxane (**14**),[16] and 4 Å molecular sieves caused transesterification and intramolecular Diels–Alder reaction to give the *cis*-fused cycloadduct (**15a**) as a single stereoisomer, however, in only 28% yield (entry 1). As could be expected from the electrophilic character of the diene component, use of *p*-methoxycinnamyl alcohol gave **15b** in better yield (entry 3). The stereochemistries of **15a** and **15b** (*vide infra*) strongly suggest that the reaction proceeded *via* transition state **C**. Considering the transition state model **C**, it was expected that the reactions of (*Z*)-cinnamyl alcohol derivatives with the diene (**2**) would be facilitated, since the aromatic rings can occupy the *endo*-position which would be favorable for secondary orbital interaction. Indeed, reactions employing (*Z*)-cinnamyl alcohols (**13c** and **13d**) took place smoothly to afford the corresponding cycloadducts (**15c** and **15d**) in high yields (entries 5 and 7). In the cases employing 1,3-diazadiene **3** (entries 2, 4, 6, 8), the same tendency was observed. While reactions of **3** with (*E*)-cinnamyl alcohols **13a** and **13b** gave only low yields of the cycloadducts **16a** and **16b** (entries 2 and 4), use of (*Z*)-cinnamyl alcohols **13c** and **13d**

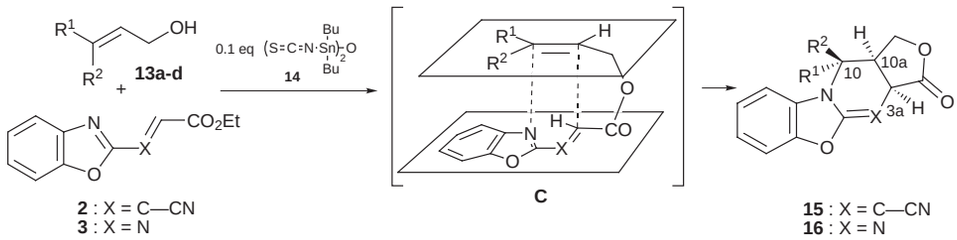
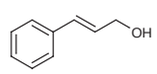
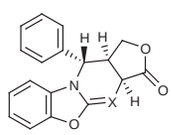
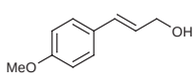
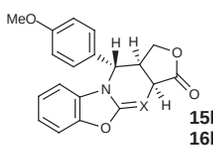
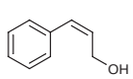
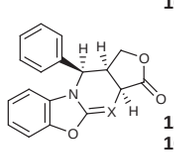
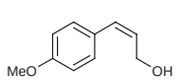
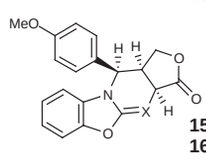


Table 3 Tandem transesterification and intramolecular Diels–Alder reactions of dienes (**2** and **3**) with cinnamyl alcohols (**13a–d**)

Entry	Cinnamyl alcohol	Diene	*t*/h	Yield (%)	Product
1		**2**	10	28	
2	**13a**	**3**	10	44	**15a** : X = C—CN **16a** : X = N
3		**2**	5	67	
4	**13b**	**3**	2	37	**15b** : X = C—CN **16b** : X = N
5		**2**	11	80	
6	**13c**	**3**	4.5	69	**15c** : X = C—CN **16c** : X = N
7		**2**	10.5	77	
8	**13d**	**3**	7.5	70	**15d** : X = C—CN **16d** : X = N

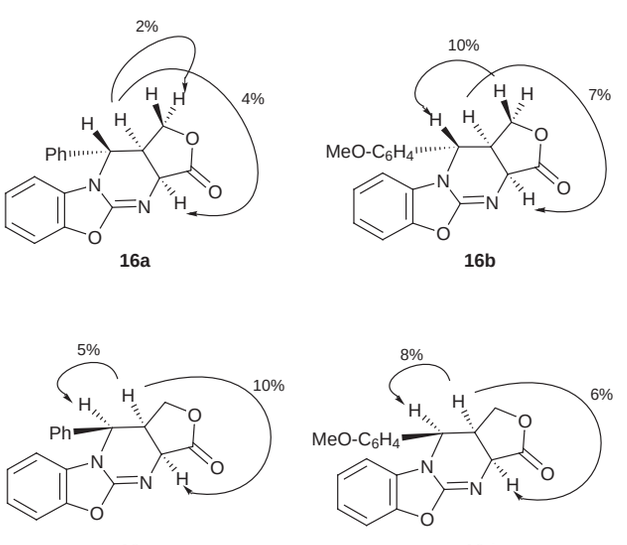


Fig. 4

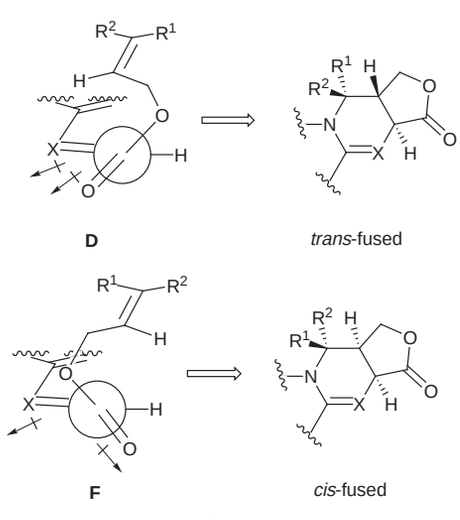


Fig. 5

afforded higher yields of the products **16c** and **16d** (entries 6 and 8). These results strongly suggest that the secondary orbital interaction would also be an important factor in the cases of intramolecular cycloadditions using **3**. It should further be noted that the intramolecular cycloadditions proceed stereospecifically *via* a concerted process, while intramolecular cycloaddition of related 1,3-diazabutadienes takes place *via* a stepwise process.[12] Assignments of stereochemistries of the intramolecular type cycloadducts **15a–d** from **2** were made by comparing their ^{1}H-NMR spectra with those of related cycloadducts. Those of cycloadducts **16a–d** were confirmed by NOE experiments as depicted in Fig 4.

The stereochemical course of the intramolecular cycloaddition can be explained by taking into account the transition state models **D** and **F** as illustrated in Fig. 5. Thus, the *exo*-tethered transition model **D** would have a more severe dipole–dipole interaction between the carbonyl group and the cyano group or electronegative nitrogen atom than the *endo*-tethered model **F**. Accordingly, the intramolecular cycloaddition *via* model **F** affords *cis*-fused lactones.

As stated, we have explored novel benzoxazole-based diene systems **2** and **3**, which behave as inverse-type dienes, in par-

ticular, diene **3** is the first case of a 1,3-diazabuta-1,3-diene reacting with vinyl ethers and styrene-type dienophiles. It has also been found that dienes **2** and **3** undergo tandem transesterification and intramolecular cycloadditions to give intramolecular cycloadducts, which reflect the geometries of the dienophile components. This is also the first case of stereospecific intramolecular Diels–Alder reaction of 1,3-diazabuta-1,3-diene.

Experimental

General

All melting points were determined with a Yanagimoto MP-21 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 and a Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-EX270 (270 MHz), and a JEOL JNM-EX400 (400 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual chloroform ($\delta = 7.25$) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Mass spectra were taken with a JEOL JMS-DX302 mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254, 0.25 mm, Art 5715) were used.

Ethyl (*E*)-3-(1,3-benzoxazol-2-yl)-3-cyanopropenoate (2)

To a stirred solution of **5**[7b] (30 mg, 0.19 mmol) in EtOH (0.3 ml) was added successively a 50% solution of ethyl glyoxylate in toluene (19.4 mg, 0.19 mmol) and a 4% aqueous solution of NaOH (0.019 ml) at room temperature. After stirring with shielding from light for 3 h, water (0.19 ml) was added to the mixture. The precipitated crystals of **2** (35.8 mg, 78%) were collected by suction filtration, mp 115–117 °C (EtOH) (Found C, 64.10; H, 4.14; N, 11.12. $C_{13}H_{10}N_2O_3$ requires C, 64.46; H, 4.16; N, 11.56%) (Found: M$^+$, 242.0696. $C_{13}H_{10}N_2O_3$ requires *M*, 242.0691); ν_{max}(CHCl$_3$)/cm^{-1} 1728, 1300, 1208, 1024; δ_H(CDCl$_3$, 270 MHz) 1.42 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 4.42 (2H, q, *J* 6.9, C*H*$_2$CH$_3$), 7.47 (2 H, dd, *J* 7.6 and 2.0, Ar-H), 7.54 (1 H, s, C*H*CO$_2$Et), 7.61 (1 H, dd, *J* 7.3 and 1.7, Ar-H), 7.87 (1 H, dd, *J* 7.6 and 2.3, Ar-H); *m*/*z* 242 (M$^+$, 67%), 214 (17), 197 (52), 170 (100) and 63 (31).

Ethyl (*E*)-3-aza-3-(1,3-benzoxazol-2-yl)propenoate (3)

To a stirred solution of 2-amino-1,3-benzoxazole[7b] (**6**, 300 mg, 2.23 mmol) in AcOEt (100 ml) was added successively a 50% solution of ethyl glyoxylate in toluene (550 mg, 2.61 mmol), anhydrous toluene-*p*-sulfonic acid (42.0 mg, 0.23 mmol), and 4 Å molecular sieves (200 mg). The mixture was refluxed for 8 h. After filtration, the filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and then brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. Purification by column chromatography on silica gel with hexane–AcOEt (2:1) gave **3** (164 mg, 34%), mp 173–175 °C (Found C, 60.50; H, 4.76; N, 13.03. $C_{11}H_{10}N_2O_3$ requires C, 60.55, H, 4.62; N, 12.84%) (Found: M$^+$, 218.0687. $C_{11}H_{10}N_2O_3$ requires *M*, 218.0691); ν_{max}(CHCl$_3$)/cm^{-1} 3021, 1752, 1638, 1580, 1460, 1219, 1209; δ_H(CDCl$_3$, 270 MHz) 1.24 (3 H, t, *J* 7.3, CO$_2$-CH$_2$C*H*$_3$), 4.32 (2 H, q, *J* 7.3, CO$_2$C*H*$_2$CH$_3$), 5.92 (1 H, s, C*H*CO$_2$Et), 7.07 (1 H, td, *J* 7.6 and 1.0, C6′-H), 7.18 (1 H, td, *J* 7.6 and 1.0, C5′-H), 7.27 (1 H, dt, *J* 7.6 and 0.7, C7′-H), 7.40 (1 H, dt, *J* 7.6 and 0.7, C4′-H); δ_C(CDCl$_3$, 67.8 MHz) 13.9 (CO$_2$CH$_2$*C*H$_3$), 62.7 (C-2), 63.2 (CO$_2$*C*H$_2$CH$_3$), 109.2 (C-7′), 117.0 (C-4′), 121.8 (C-6′), 124.1 (C-5′), 142.0, 148.6, 159.7 (C-2, C-3a′, C-7a′), 167.4 (C-1); *m*/*z* 218 (M$^+$, 82%), 145 (63), 134 (100), 119 (22), 90 (20), 79 (14), 64 (12) and 52 (7).

General procedures for the intermolecular Diels–Alder reactions of 2 and 3 (Table 2)

(a) For Diels–Alder reactions of **2** (entries 1, 3, 5 and 7). A mixture of **2** (1 equiv.) and the dienophile (**7**, 1.5 equiv.) in CH_2Cl_2 was stirred at room temperature for the period indicated in Table 2. The mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel and/or crystallization.

(b) For Diels–Alder reactions of **3** (entries 2, 4, 6 and 8). A mixture of **3** (1 equiv.) and the dienophile (**7**) was stirred in the solvent and under the conditions indicated in Table 2. The mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel and/or crystallization.

Ethyl (1*S,3*R**)-4-cyano-1-ethoxy-2,3-dihydro-1*H*-pyrido-[2,1-*b*][1,3]benzoxazole-3-carboxylate (*cis*-8a) and its (1*R**, 3*R**)-isomer (*trans*-8a) (Table 2, entry 1).** Following the general procedure (a), the diene (**2**, 30.0 mg, 0.12 mmol), ethyl vinyl ether (**7a**, 13 μl, 0.18 mmol) and CH_2Cl_2 (2 ml) gave the crude compound, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to afford *cis*-**8a** (19.6 mg, 62%) as the less polar product and *trans*-**8a** (7.4 mg, 23.6%) as the polar product. *cis*-**8a**, mp 189 °C (hexane–AcOEt) (Found C, 64.88; H, 5.74; N, 8.84. $C_{17}H_{18}N_2O_4$ requires C, 64.96, H, 5.77; N, 8.91%) (Found: M$^+$, 314.1267. $C_{17}H_{18}N_2O_4$ requires *M*, 314.1265); ν_{max}(CHCl$_3$)/cm^{-1} 2194, 1665; δ_H(CDCl$_3$, 270 MHz) 1.05 (3 H, t, *J* 6.9, CH$_2$C*H*$_3$), 1.21 (3 H, t, *J* 7.1, CO$_2$CH$_2$C*H*$_3$), 1.85 (1 H, ddd, *J* 14.1, 6.9 and 2.3, C*H*H), 2.86 (1 H, dt, *J* 14.1 and 2.3, CH*H*), 3.38 (1 H, dd, *J* 6.6 and 2.0, C*H*CO$_2$Et), 3.50 (2 H, m, OC*H*$_2$CH$_3$), 4.11 (2 H, q, *J* 7.1, CO$_2$C*H*$_2$CH$_3$), 5.33 (1 H, t, *J* 2.5, C*H*OEt), 6.9–7.2 (4 H, m, Ar-H); *m*/*z* 314 (M$^+$, 22%), 269 (6), 241 (100), 213 (18) and 195 (27). *trans*-**8a**, mp 98–100 °C (hexane–CH_2Cl_2) (Found C, 64.82; H, 6.00; N, 8.53. $C_{17}H_{18}N_2O_4$ requires C, 64.96, H, 5.77; N, 8.91%) (Found: M$^+$, 314.1267. $C_{17}H_{18}N_2O_4$ requires *M*, 314.1265); ν_{max}(CHCl$_3$)/cm^{-1} 2197, 1732, 1667, 1622, 1480, 1258; δ_H(CDCl$_3$, 270 MHz) 1.23 (3 H, t, *J* 6.9, OCH$_2$C*H*$_3$), 1.34 (3 H, t, *J* 7.3, CO$_2$CH$_2$C*H*$_3$), 2.08 (1 H, ddd, *J* 14.2, 11.2 and 3.3, C*H*H), 2.36 (1 H, ddd, *J* 13.5, 4.3 and 3.6, CH*H*), 3.62–3.73 (3 H, m, C*H*OC*H*$_2$CH$_3$), 4.27 (2 H, qd, *J* 7.3 and 1.3, CO$_2$C*H*$_2$CH$_3$), 5.44 (1 H, t, *J* 2.3, C*H*CO$_2$Et), 7.01–7.24 (4 H, m, Ar-H); *m*/*z* 314 (M$^+$, 22%), 269 (5), 241 (100), 213 (17) and 195 (19).

Ethyl (3a*R,4*S**,11a*R**)-5-cyano-2,3,3a,11-tetrahydro-4*H*-furo[3′,2′:5,6]pyrido[2,1-*b*][1,3]benzoxazole-4-carboxylate (8b) (Table 2, entry 3).** Following the general procedure (a), the diene (**2**, 30.0 mg, 0.12 mmol), **7b** (12.6 mg, 0.18 mmol), and CH_2Cl_2 (1 ml) gave the crude compound, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to give **8b** (29.5 mg, 79%), mp 141–144 °C (hexane–AcOEt) (Found C, 65.23; H, 5.12; N, 8.88. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.16; N, 8.97%) (Found: M$^+$, 312.1111. $C_{17}H_{16}N_2O_4$ requires *M*, 312.1109); ν_{max}(CHCl$_3$)/cm^{-1} 2197, 1667, 1622, 1480, 1260; δ_H(CDCl$_3$, 270 MHz) 1.28 (3 H, t, *J* 7.3, CO$_2$-CH$_2$C*H*$_3$), 2.00 (2 H, m, OC*H*$_2$CH$_2$), 3.00 (1 H, m, OCH$_2$CH$_2$-C*H*), 3.86 (1 H, m, OC*H*HCH$_2$), 3.88 (1 H, d, *J* 5.0, C*H*CO$_2$Et), 4.00 (1 H, dd, *J* 8.4 and 16.8, OCH*H*CH$_2$), 4.22 (2 H, q, *J* 7.3, CO$_2$C*H*$_2$CH$_3$), 5.64 (1 H, d, *J* 5.0, NCHO), 7.08 (1 H, br t, *J* 7.6, Ar-H), 7.18–7.38 (3 H, m, Ar-H); *m*/*z* 312 (M$^+$, 19%), 239 (100), 211 (4), 195 (4) and 70 (7).

Ethyl (1*S,3*R**)-4-cyano-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrido[2,1-*b*][1,3]benzoxazole-3-carboxylate (8c) (Table 2, entry 5).** Following the general procedure (a), the diene (**2**, 30.0 mg, 0.12mmol), **7c** (24.1 mg, 0.18 mmol), and CH_2Cl_2 (1 ml) gave the crude compound, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to give **8c** (23.6 mg, 98%) as an oil (Found: M$^+$, 376.1424. $C_{22}H_{20}N_2O_4$

requires *M*, 376.1422); $\nu_{max}(CHCl_3)/cm^{-1}$ 2195, 1667, 1219, 1211; $\delta_H(CDCl_3$, 270 MHz) 1.07 (3 H, t, *J* 7.3, $CO_2CH_2CH_3$), 2.37 (1 H, td, *J* 14.2 and 5.6, NCHC*H*HCHCO$_2$Et), 2.63 (1 H, qd, *J* 13.9 and 6.2, NCHCH*H*CHCO$_2$Et), 3.52 (1 H, t, *J* 5.9, NCHCH$_2$C*H*CO$_2$Et), 3.72 (3 H, s, OCH_3), 3.80 (2 H, qd, *J* 7.3 and 2.3, $CO_2CH_2CH_3$), 5.04 (1 H, t, *J* 5.6, NC*H*CH$_2$-CHCO$_2$Et), 6.79 (2 H, dd, *J* 8.9 and 2.0, Ar-H), 6.85 (1 H, td, *J* 7.9 and 1.6, Ar-H), 6.93 (1 H, td, *J* 7.6 and 1.3, Ar-H), 7.02 (1 H, dd, *J* 7.3 and 1.0, Ar-H), 7.17 (2 H, dd, *J* 8.9 and 1.7, Ar-H); *m*/*z* 376 (M^+, 31%), 303 (100), 289 (2), 267 (2), 195 (6), 152 (6), 134 (43), 121 (10) and 91 (3).

Ethyl (1*S,2*R**)-4-cyano-1-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrido[2,1-*b*][1,3]benzoxazolo-3-carboxylate (8d) (Table 2, entry 7).** Following the general procedure (a), the diene (**2**, 30.0 mg, 0.12 mmol), **7d** (26.6 mg, 0.18 mmol), and CH_2Cl_2 (2 ml) gave the crude compound, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to give **8d** (43.4 mg, 93%), mp 157–160 °C (recrystallized from hexane–ether) (Found: M^+, 390.1577. $C_{23}H_{22}N_2O_4$ requires *M*, 390.1579); $\nu_{max}(CHCl_3)/cm^{-1}$ 2195, 1732, 1667, 1620, 1514, 1478, 1254, 1179; $\delta_H(CDCl_3$, 270 MHz) 0.99 (3 H, d, *J* 6.9, CHC*H*$_3$), 1.11 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.75 (1 H, br qt, *J* 6.6 and 6.3, C*H*CH$_3$,), 3.17 (1 H, d, *J* 6.6, C*H*CO$_2$Et), 3.73 (3 H, s, OCH_3), 3.86 (2 H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.58 (1 H, d, *J* 6.3, NC*H*CHMe), 5.99 (1 H, dd, *J* 7.6 and 1.3, Ar-H), 6.80 (2 H, dd, *J* 8.6 and 2.0, Ar-H), 6.81 (1 H, td, *J* 7.6 and 1.3, Ar-H), 6.91 (1 H, td, *J* 7.9 and 1.3, Ar-H), 7.02 (2 H, dd, *J* 8.9 and 2.0, Ar-H), 7.14 (1 H, dd, *J* 7.9 and 1.0, Ar-H); *m*/*z* 390 (M^+, 45%), 317 (100), 148 (97) and 121 (24).

Ethyl (2*R,4*S**)-4-ethoxy-3,4-dihydro-2*H*-pyrimido[2,1-*b*]-[1,3]benzoxazole-2-carboxylate (*cis*-9a) and its (2*R**,4*R**)-isomer (*trans*-9a) (Table 7, entry 2).** Following the general procedure (b), the diene (**3**, 20.0 mg, 0.092 mmol), **7a** (1 ml), and CH_3CN gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:1) to afford *trans*-**9a** (10.5 mg, 40%) as the less polar product and *cis*-**9a** (7.1 mg, 27%) as the more polar product. *cis*-**9a,** mp 113–114 °C (AcOEt) (Found C, 61.94; H, 6.25; N, 9.58. $C_{15}H_{18}N_2O_4$ requires C, 62.26, H, 6,25; N, 9.65%) (Found: M^+, 290.1267. $C_{15}H_{18}N_2O_4$ requires *M*, 290.1265); $\nu_{max}(CHCl_3)/cm^{-1}$ 2984, 1746, 1707, 1483, 1260; $\delta_H(CDCl_3$, 270 MHz) 1.10 (3 H, t, *J* 6.9, OCH_2CH_3), 1.21 (3 H, t, *J* 7.3, $CO_2CH_2CH_3$), 1.92 (1 H, ddd, *J* 13.9, 6.9 and 3.6, C*H*H), 2.65 (1 H, dt, *J* 13.9 and 2.3, CH*H*), 3.55 (2 H, qd, *J* 6.9 and 2.3, OCH_2CH_3), 4.01 (2 H, q, *J* 7.3, $CO_2CH_2CH_3$), 4.40 (1 H, dd, *J* 6.3 and 2.3, C*H*CO$_2$Et), 5.23 (1 H, t, *J* 2.3, N*H*CH$_2$), 6.86 (1 H, dd, *J* 7.6 and 1.6, C9-H), 6.96 (1H, td, *J* 7.6 and 1.6, C7-H), 7.02 (1 H, td, *J* 7.6 and 1.3, C8-H), 7.09 (1 H, dd, *J* 7.6 and 1.3, C6-H); $\delta_C(CDCl_3$, 67.8 MHz) 14.6 (OCH_2CH_3), 15.5 ($CO_2CH_2CH_3$), 28.7 (C-3), 54.1 (C-2), 61.5 (OCH_2CH_3), 64.6 ($CO_2CH_2CH_3$), 80.0 (C-4), 107.2, 110.3, 122.6, 123.8 (C-6, C-7, C-8, C-9), 132.5, 144.7, 153.9 (C-5a, C-9a, C-10a), 172.7 ($CO_2CH_2CH_3$); *m*/*z* 290 (M^+, 15%), 245 (7), 218 (17), 217 (100), 189 (6), 171 (10), 145 (4), 120 (4) and 90 (2). *trans*-**9a**, mp 79–81 °C (hexane–AcOEt) (Found: M^+, 290.1269. $C_{15}H_{18}N_2O_4$ requires *M*, 290.1265); $\nu_{max}(CHCl_3)/cm^{-1}$ 2984, 1734, 1705, 1483, 1221, 1213; $\delta_H(CDCl_3$, 270 MHz) 1.26 (3 H, t, *J* 6.9, OCH_2CH_3), 1.33 (3 H, t, *J* 7.3, $CO_2CH_2CH_3$), 1.82 (1 H, ddd, *J* 13.9, 12.5 and 3.6, C*H*H), 2.43 (1 H, ddd, *J* 13.9, 3.6 and 2.0, CH*H*), 3.73 (2 H, qd, *J* 6.9 and 1.0, OCH_2-CH_3), 4.28 (2 H, q, *J* 7.3, $CO_2CH_2CH_3$), 4.47 (1 H, dd, *J* 12.5 and 3.6, C*H*CO$_2$Et, spin saturation at $\delta = 1.82$; NOE→10.2%), 5.33 (1 H, dd, *J* 3.3 and 2.0, NC*H*CH$_2$, spin saturation at $\delta = 2.43$; NOE→7.8%), 6.96 (1 H, dd, *J* 7.6 and 1.3, C9-H), 7.02 (1 H, td, *J* 7.6 and 1.6, C8-H), 7.10 (1 H, td, *J* 7.6 and 1.3, C7-H), 7.14 (1 H, dd, *J* 7.6 and 1.0, C6-H, spin saturation at $\delta = 5.33$; NOE→7.9%); $\delta_C(CDCl_3$, 67.8 MHz) 14.2 (OCH_2CH_3), 15.2 ($CO_2CH_2CH_3$), 28.7 (C-3), 53.2 (C-2), 61.3 (OCH_2CH_3), 64.7 ($CO_2CH_2CH_3$), 79.2 (C-4), 106.7, 109.8, 122.2, 123.3 (C-6, C-7, C-8, C-9), 132.1, 144.4 (C-5a, C-9a), 172.7 ($CO_2CH_2CH_3$); *m*/*z* 290 (M^+, 14%), 245 (6), 218 (17), 217 (100), 189 (6), 171 (10), 145 (4), 120 (4) and 90 (2).

Ethyl (3a*R,4*S**,11a*R**)-2,3,3a,11a-tetrahydro-4*H*-furo[3′,2′:5,6]pyrimido[2,1-*b*][1,3]benzoxazole-4-carboxylate (9b) (Table 2, entry 4).** Following the general procedure (b), the diene (**3**, 20.0 mg, 0.092 mmol), **7b** (0.07 ml, 0.90 mmol), and toluene (1 ml) gave a crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (3:2) to afford **9b** (6.5 mg, 25%) as an inseparable 3:1 mixture of *endo*- and *exo*-products. Significant decomposition was observed during chromatography. Further purification could not be made because of its instability. $\nu_{max}(CHCl_3)/cm^{-1}$ 2986, 1699, 1483, 1248, 1215; $\delta_H(CDCl_3$, 270 MHz) 1.30 (3 H, t, *J* 6.9, $CO_2CH_2CH_3$, minor), 1.34 (3 H, t, *J* 6.9, $CO_2CH_2CH_3$), 2.02 (2 H, m, NCHOCH$_2$C*H*$_2$), 2.25 (2 H, m, NCHOCH$_2$C*H*$_2$, minor), 2.78 (1 H, m, NCHOCH$_2$CH$_2$C*H*, minor), 3.14 (1 H, tdd, *J* 13.9, 9.9 and 3.6, NCHOCH$_2$CH$_2$C*H*), 3.78 (2 H, td, *J* 8.9 and 5.0, NCHOC*H*$_2$CH$_2$), 3.91 (2 H, td, *J* 8.6 and 5.0, NCHOC*H*$_2$CH$_2$, minor), 4.01 (2 H, q, *J* 7.9, $CO_2CH_2CH_3$, minor), 4.31 (3 H, br q, *J* 7.3, $CO_2CH_2CH_3$, C*H*CO$_2$Et, minor), 4.52 (1 H, d, *J* 4.0, C*H*CO$_2$Et), 5.72 (1 H, d, *J* 5.6, NCHO, minor), 5.88 (1 H, d, *J* 5.9, NCHO), 7.00–7.08 (4 H, m, Ar-H, minor), 7.06–7.15 (4 H, m, Ar-H).

Ethyl (2*R,4*S**)-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrimido[2,1-*b*][1,3]benzoxazole-2-carboxylate (9c) (Table 2, entry 6).** Following the general procedure (b), diene (**3**, 10.0 mg, 0.045 mmol), **7c** (0.1 ml, 0.75 mmol), and toluene (4 ml) gave a crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (6:5) to afford **9c** (11 mg, 70%) as an oil (Found: M^+, 352.1420. $C_{20}H_{20}N_2O_4$ requires *M*, 352.1422); $\nu_{max}(CHCl_3)/cm^{-1}$ 3021, 1736, 1698, 1514, 1483, 1252, 1217; $\delta_H(CDCl_3$, 270 MHz) 1.23 (3 H, t, *J* 7.3, CO_2-CH_2CH_3), 2.24 (1 H, td, *J* 13.9 and 9.6, NCHC*H*HCHCO$_2$Et), 2.56 (1 H, td, *J* 13.9 and 4.5, NCHCH*H*CHCO$_2$Et), 3.83 (3 H, s, OMe), 4.12 (2 H, dq, *J* 7.3 and 2.0, $CO_2CH_2CH_3$), 4.47 (1 H, dd, *J* 9.6 and 4.0, NCHCH$_2$C*H*CO$_2$Et, spin saturation at $\delta = 2.56$; NOE→10.4%), 5.03 (1 H, dd, *J* 9.6 and 4.6, NC*H*-CH$_2$CHCO$_2$Et, spin saturation at $\delta = 2.56$; NOE→10.3%), 5.86 (1 H, dd, *J* 7.6 and 1.0, Ar-H), 6.77 (1 H, td, *J* 7.2 and 1.3, Ar-H), 6.90 (1 H, td, *J* 6.9 and 1.3, Ar-H), 6.91 (2 H, d, *J* 8.6, Ar-H), 7.10 (1 H, dd, *J* 7.9 and 1.0, Ar-H), 7.19 (2 H, d, *J* 8.9, Ar-H, spin saturation at $\delta = 5.03$; NOE→14.1%); $\delta_C(CDCl_3$, 67.8 MHz) 14.4 ($CO_2CH_2CH_3$), 34.4 (C-3), 55.6 (OCH_3), 56.6 (C-4), 56.7 (C-2), 61.5 ($CO_2CH_2CH_3$), 109.3 (C-6), 109.6 (C-9), 114.7 (C-2′, C-6′), 121.6, 123.3 (C-7, C-8), 128.5 (C-3′, C-5′), 129.5 (C-1′), 131.6, 144.7, 155.5 (C-5a, C-9a, C-10a), 160.1 (C-4′), 172.6 ($CO_2CH_2CH_3$); *m*/*z* 352 (M^+, 17%), 280 (22), 279 (100), 218 (2), 171 (2), 161 (1), 145 (22), 134 (19), 119 (36) and 90(3).

Ethyl (2*R,3*R**,4*S**)-4-(methoxyphenyl)-3-methyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*][1,3]benzoxazole-2-carboxylate (9d) (Table 2, entry 8).** Following the general procedure (b), the diene (**3**, 10.0 mg, 0.045 mmol) and **7d** (500 μl) gave a crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:1) to afford **9d** (9.6 mg, 55%) as an oil (Found: M^+, 368.1584. $C_{21}H_{24}N_2O_4$ requires *M*, 368.1735); $\nu_{max}(CHCl_3)/cm^{-1}$ 1734, 1698, 1516, 1483, 1254, 1221; $\delta_H(CDCl_3$, 270 MHz) 0.75 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.04 (3 H, t, *J* 7.3, $CO_2CH_2CH_3$), 2.36 (1 H, tq, *J* 6.6 and 9.9, NCH-C*H*CH$_3$), 3.25 (3 H, s, OCH_3), 3.74 (1 H, d, *J* 9.9, NC*H*CO$_2$Et, spin saturation at $\delta = 0.75$; NOE→3.0%), 4.09 (2 H, q, *J* 7.3, $CO_2CH_2CH_3$), 4.15 (1 H, d, *J* 9.9, NC*H*CHMe, spin saturation at $\delta = 0.75$; NOE→2.7%), 5.57 (1 H, dd, *J* 1.3 and 7.6, Ar-H), 6.46 (1 H, td, *J* 1.3 and 7.9, Ar-H), 6.54 (1 H, td, *J* 1.3 and 7.9, Ar-H), 6.81 (1 H, dd, *J* 1.3 and 7.9, Ar-H); $\delta_C(CDCl_3$, 67.8 MHz) 14.1 ($CO_2CH_2CH_3$), 14.7 (CH_3), 36.7 (C-3), 55.3 (OCH_3),

61.2 ($CO_2CH_2CH_3$), 62.5 (C-2), 63.5 (C-4), 108.9 (C-6), 109.2 (C-9), 114.3 (C-2′, C-6′), 121.2, 122.9 (C-7, C-8), 129.0 (C-3′, C-5′), 128.3 (C-1′), 131.5, 144.4, 154.9 (C-5a, C-9a, C-10a), 159.9 (C-4′), 172.5 ($CO_2CH_2CH_3$); *m*/*z* 366 (M^+, 17%), 293 (100), 159 (21), 148 (14), 121 (4) and 90 (2).

1-Ethyl 4-methyl 2-(1,3-benzoxazol-2-ylamino)butane-1,4-dioate (10)

A mixture of the diene **3** (20.0 mg, 0.092 mmol) and 1,1-dimethoxyethylene **7e** (86.8 μl, 0.92 mmol) in acetonitrile (4 ml) was stirred for 15 h. The mixture was concentrated *in vacuo* to give the cycloadduct **9e**, δ_H($CDCl_3$, 270 MHz) 2.13 (1 H, dd, *J* 12.9 and 9.9, C*H*H), 2.45 (1 H, dd, *J* 12.9 and 4.3, CH*H*), 4.45 (1 H, dd, *J* 9.9 and 4.4, C*H*CO_2Et). The crude product was subjected to column chromatography on silica gel (hexane–AcOEt, 3:1) to afford **10** (19.3 mg, 72%) as an oil (Found: M^+, 292.1059. $C_{14}H_{16}N_2O_5$ requires *M*, 292.1058); ν_{max}($CHCl_3$)/cm^{-1} 3414, 2957, 1744, 1644, 1584, 1460, 1242; δ_H($CDCl_3$, 270 MHz) 1.28 (3 H, t, *J* 7.3, $CO_2CH_2CH_3$), 3.15 (2 H, q, *J* 7.3, $CO_2CH_2CH_3$), 3.71 (3 H, s, CO_2CH_3), 4.28 (2 H, q, *J* 7.3, $CO_2CH_2CH_3$), 4.85 (1 H, br t, *J* 7.6, C-5′H), 6.04 (1 H, br, NH), 7.06 (1 H, br t, *J* 7.9, C-6′H), 7.18 (1 H, br t, *J* 7.6, C-5′H), 7.28 (1 H, br d, *J* 7.4, C-7′H), 7.38 (1 H, br d, *J* 7.6, C-4′H); δ_C($CDCl_3$, 67.8 MHz) 14.0 ($CO_2CH_2CH_3$), 36.1 (C-3), 52.1 (CO_2CH_3), 52.3 (C-2), 62.2 ($CO_2CH_2CH_3$), 109.0 (C-7′), 116.7 (C-4′), 121.4 (C-6′), 124.0 (C-5′), 124.2, 148.7, 169.8 (C-2′, C-3a′, C-7a′), 170.3, 171.1 (C-1, C-4); *m*/*z* 292 (M^+, 51%), 261 (12), 247 (4), 233 (7), 219 (100), 187 (57), 177 (19), 159 (32), 145 (23) and 134 (13).

1-Ethyl 4-methyl 2-[1,3-benzoxazol-2-yl(*tert*-butoxycarbonyl)-amino]butane-1,4-dioate (11)

To a stirred solution of **10** (10.8 mg, 0.037 mmol) and di-*tert*-butyl dicarbonate (86.8 μl, 0.92 mmol) in acetonitrile (0.5 ml) was added 4-dimethylaminopyridine (0.45 mg, 0.092 mmol) at room temperature. After 10 min, the mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel (hexane–Et_2O, 5:1) to give **11** (9.1 mg, 63%) as an oil (Found: M^+, 392.1584. $C_{19}H_{24}N_2O_7$ requires *M*, 392.1583); ν_{max}($CHCl_3$)/cm^{-1} 2986, 1740, 1619, 1566, 1458, 1371, 1318, 1281, 1244, 1221, 1213, 1150; δ_H($CDCl_3$, 270 MHz) 1.23 (3 H, t, *J* 6.9, $CO_2CH_2CH_3$), 1.55 (9 H, s, ^{t}Bu), 2.98 (1 H, dd, *J* 16.5 and 6.9, NHCHC*H*H-CO_2Me), 3.39 (1 H, dd, *J* 16.5 and 6.9, NHCHCH*H*CO_2Me), 3.67 (3 H, s, CO_2CH_3), 4.23 (2 H, m, $CO_2CH_2CH_3$), 5.66 (1 H, t, *J* 7.3, NHC*H*CO_2Et), 7.22–7.33 (2 H, m, Ar-H), 7.45–7.49 (1 H, m, Ar-H), 7.59–7.63 (1 H, m, Ar-H); δ_C($CDCl_3$, 67.8 MHz) 13.9 ($CO_2CH_2CH_3$), 27.3, 27.6, 27.7, 27.9 (^{t}Bu), 35.2 (C-3), 51.9 (CO_2CH_3), 57.6 (C-2), 62.0 ($CO_2CH_2CH_3$), 110.0, 119.1, 123.9, 124.4 (C-4′, C-5′, C-6′, C-7′), 140.4, 149.3, 157.0 (C-2′, C-3a′, C-7a′), 150.7 (CO_2^{t}Bu), 168.9, 170.7 (C-1, C-4); *m*/*z* 392 (M^+, 4%), 292 (59), 261 (10), 233 (7), 219 (100), 187 (42), 177 (12), 159 (18), 134 (1), 57 (27), 41 (19).

1-Ethyl 4-methyl 2-[(*tert*-butoxycarbonyl)amino]butane-1,4-dioate (12)

To a stirred solution of **11** (50.0 mg, 0.13 mmol) in ethyl acetate–acetonitrile (1:1, 2 ml) was added successively an aqueous solution of sodium metaperiodate (815 mg, 4 ml) and an aqueous solution of ruthenium trichloride (4 mg ml^{-1}, 1.32 ml, 0.026 mmol). After 15 h, the mixture was diluted with water, and the mixture was extracted with ethyl acetate. After drying ($MgSO_4$), the organic phase was concentrated under reduced pressure to give a residue. The mixture was suspended in ether, and insoluble materials were removed by filtration through a pad of Celite. The filtrate was washed with a saturated solution of sodium bicarbonate and dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. This product was purified by column chromatography on silica gel (hexane–AcOEt, 1:1) to give **12** (9.3 mg, 26%) as an oil, ν_{max}($CHCl_3$)/cm^{-1} 3507, 3353, 3027, 1732, 1553, 1374, 1260, 1252, 1152, 1098, 1046; δ_H($CDCl_3$, 270 MHz) 1.19 (3 H, t, *J* 6.9, $CO_2CH_2CH_3$), 1.43 (9 H, s, ^{t}Bu), 2.61 (1 H, dd, *J* 16.2 and 6.3, NHCHC*H*HCO$_2$Me), 3.38 (1 H, dd, *J* 16.2 and 7.6, NHCHCH*H*CO_2Me), 3.64 (3 H, s, CO_2CH_3), 4.11 (2 H, qd, *J* 6.9 and 1.7 $CO_2CH_2CH_3$), 5.14 (1 H, br, NH), 5.74 (1 H, br, NHC*H*CO_2Et).

General procedure for the tandem transesterification and intramolecular cycloaddition of the dienes 2 and 3 with cinnamyl alcohols 13 (Table 3)

A mixture of diene (**2** or **3**), cinnamyl alcohol (**13**), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanatodistannoxane (**14**), and 4 Å molecular sieves (4 Å MS) in toluene was heated at reflux. After a given period (Table 3), the mixture was cooled to room temperature, filtered, and the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel. The reaction times are listed in Table 3.

(3a*R,11*R**,13a*S**)-4-Cyano-11-phenyl-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzoxazol-3-one (15a) (Table 3, entry 1).** The diene (**2**, 80.0 mg, 0.33 mmol), (*E*)-cinnamyl alcohol (**13a**, 67.0 mg, 0.50 mmol), **14** (19.7 mg, 0.033 mmol), and 4 Å MS (800 mg) in toluene (5 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to afford **15a** (30.0 mg, 28%), mp > 300 °C (CH_2Cl_2–hexane) [Found: $(M + 1)^+$ 331.1071. $C_{20}H_{14}N_2O_3$ + H requires *M* + 1, 331.1082]; ν_{max}-($CHCl_3$)/cm^{-1} 2201, 1792, 1667, 1211; δ_H($CDCl_3$, 270 MHz) 3.07 (1 H, m, *J* 3.3, NHC*H*C*H*$_2$), 3.62 (1 H, d, *J* 7.3, CHCO_2), 4.16 (1 H, dd, *J* 9.9 and 3.6, NHCHCH*H*), 4.41 (1 H, dd, *J* 9.9 and 5.9, NHCHCHC*H*H), 4.60 (1 H, d, *J* 8.3, NC*H*-CHCH$_2$), 5.75 (1 H, d, *J* 6.9, Ar-H), 6.83 (1 H, br d, *J* 7.6, Ar-H), 7.00 (1 H, td, *J* 6.9 and 0.9, Ar-H), 7.22 (1 H, d, *J* 7.6, Ar-H), 7.33–7.38 (2 H, m, Ph), 7.47–7.51 (3H, m, Ph); *m*/*z* 331 [$(M + 1)^+$, 23%], 330 (M^+, 100), 285 (54), 272 (15), 245 (26) and 195 (68).

(3a*R,11*R**,11a*S**)-4-Cyano-11-(4-methoxyphenyl)-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzoxazol-3-one (15b) (Table 3, entry 3).** The diene (**2**, 160.0 mg, 0.66 mmol), (*E*)-*p*-methoxycinnamyl alcohol (**13b**, 162.0 mg, 0.99 mmol), **14** (39.3 mg, 0.066 mmol), and 4 Å MS (1.6 g) in toluene (10 ml) gave a crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to afford **15b** (159.5 mg, 67.1%), mp 274–276 °C (CH_2Cl_2–hexane) [Found: $(M + 1)^+$ 361.1202. $C_{21}H_{16}N_2O_4$ + H requires *M* + 1, 361.1187)]; ν_{max}($CHCl_3$)/cm^{-1} 2199, 1790, 1664, 1622, 1516, 1477, 1259; δ_H($CDCl_3$, 270 MHz) 3.01 (1 H, m, *J* 2.6, NCH-C*H*CH$_2$), 3.63 (1 H, d, *J* 7.3, CHCO_2), 3.87 (3 H, s, OCH_3), 4.13 (1 H, dd, *J* 9.9 and 2.6, NHCHCHC*H*H), 4.39 (1 H, dd, *J* 9.9 and 5.6, NHCHCHCH*H*), 4.53 (1 H, d, *J* 8.9, NC*H*CHCH$_2$), 5.74 (1 H, br d, *J* 7.9, Ar-H), 6.84 (1 H, td, *J* 7.9 and 1.3, Ar-H), 6.99 (1 H, td, *J* 7.3 and 1.0, Ar-H), 7.01 (2 H, d, *J* 6.9, Ar-H), 7.21 (1 H, br d, *J* 7.3, Ar-H), 7.30 (2 H, d, *J* 6.6, Ar-H); *m*/*z* 361 [$(M + 1)^+$, 26%], 360 (M^+, 100), 315 (83), 302 (15), 301 (15), 195 (35), 170 (24) and 147 (21).

(3a*R,11*S**,11a*S**)-4-Cyano-11-phenyl-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzoxazol-3-one (15c) (Table 3, entry 5).** The diene (**2**, 80.0 mg, 0.33 mmol), (*Z*)-cinnamyl alcohol (**13c**, 67.0 mg, 0.50 mmol), **14** (19.7 mg, 0.033 mmol), and 4 Å MS (800 mg) in toluene (4 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:1) to afford **15c** (86.9 mg, 80%), mp >300 °C (CH_2Cl_2–hexane) (Found: M^+, 330.1006. $C_{20}H_{14}N_2O_3$ requires *M*, 330.1003); ν_{max}($CHCl_3$)/cm^{-1} 2203,

1794, 1664, 1211; δ_H($CDCl_3$, 270 MHz) 3.35 (1 H, m, NCH-C*H*CH_2), 3.67 (1 H, d, *J* 7.6, $CHCO_2$), 4.15 (1 H, dd, *J* 9.2 and 6.9, NCHCHC*H*H), 4.34 (1 H, dd, *J* 9.2 and 7.3, NCHCH-CH*H*), 5.20 (1 H, d, *J* 7.6, NC*H*CHCH$_2$), 6.14 (1 H, d, *J* 7.6, Ar-H), 6.92 (1 H, br t, *J* 7.9, Ar-H), 7.04 (1 H, br t, *J* 7.6, Ar-H), 7.22–7.30 (3 H, m, Ar-H), 7.41–7.46 (3 H, m, Ph); *m*/*z* 330 (M^+, 100%), 285 (53), 272 (13), 258 (6), 245 (23), 195 (70) and 170 (8).

(3a*R,11*S**,11a*S*)-4-Cyano-11-(4-methoxyphenyl)-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzoxazol-3-one (15d) (Table 3, entry 7).** The diene (**2**, 160.0 mg, 0.66 mmol), (*Z*)-*p*-methoxycinnamyl alcohol (**13d**, 162.0 mg, 0.99 mmol), **14** (39.3 mg, 0.066 mmol), and 4 Å MS (1.6 g) in toluene (10 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1) to afford **15d** (159.5 mg, 67.1%), mp 274–276 °C (CH_2Cl_2–hexane) [Found: $(M + 1)^+$, 361.1202. $C_{21}H_{16}N_2O_4$ + H requires *M* + 1, 361.1187]; ν_{max}($CHCl_3$)/cm^{-1} 2199, 1790, 1664, 1622, 1516, 1477, 1259; δ_H($CDCl_3$, 270 MHz) 3.01 (1 H, m, NCHC*H*CH_2), 3.63 (1 H, d, *J* 7.3, $CHCO_2$), 3.87 (3 H, s, OCH_3), 4.13 (1 H, dd, *J* 9.9 and 2.6, NCHCHC*H*H), 4.39 (1 H, dd, *J* 9.9 and 5.6, NCHCHCH*H*), 4.53 (1 H, d, *J* 8.9, NC*H*CHCH$_2$), 5.74 (1 H, br d, *J* 7.9, Ar-H), 6.84 (1 H, td, *J* 7.9 and 1.3, Ar-H), 6.99 (1 H, td, *J* 7.3 and 1.0, Ar-H), 7.01 (2 H, d, *J* 6.9, Ar-H), 7.21 (1 H, br d, *J* 7.3, Ar-H), 7.30 (2 H, d, *J* 6.6, Ar-H); *m*/*z* [$(M + 1)^+$, 26%], 360 (M^+, 100), 315 (83), 302 (15), 301 (15), 195 (35), 170 (24), 147 (21).

(3a*R,11*R**,11a*S**)-11-Phenyl-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzoxazol-3-one (16a) (Table 3, entry 2).** The diene (**3**, 20.0 mg, 0.092 mmol), (*E*)-cinnamyl alcohol (**13a**, 24.6 mg, 0.184 mmol), **14** (5.5 mg, 0.0092 mmol), and 4 Å MS (1.6 g) in toluene (8 ml) gave a crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:3) to afford **16a** (12.3 mg, 44%), mp 260 °C (AcOEt–hexane) (Found: M^+, 306.1001. $C_{18}H_{14}N_2O_3$ requires *M*, 306.1003); ν_{max}($CHCl_3$)/cm^{-1} 1794, 1697, 1483; δ_H($CDCl_3$, 270 MHz) 3.23 (1 H, m, NCHC*H*CH_2), 4.04 (1 H, dd, *J* 9.2 and 6.9, NCHCHC*H*H, spin saturation at δ = 3.23; NOE→2.0%), 4.30 (1 H, dd, *J* 9.2 and 7.6, NCHCHCH*H*), 4.52 (1 H, d, *J* 6.6, NC*H*CHCH$_2$), 5.30 (1 H, d, *J* 5.6, $CHCO_2$, spin saturation at δ = 3.23; NOE→4.3%), 6.12 (1 H, br d, *J* 7.9, Ar-H), 6.87 (1 H, br t, *J* 7.9, Ar-H), 6.99 (1 H, br t, *J* 7.9, Ar-H), 7.17 (1 H, br d, *J* 7.9, Ar-H), 7.20–7.25 (2 H, br, Ph), 7.38–7.45 (3 H, m, Ph); *m*/*z* 306 (M^+, 100%), 262 (37), 245 (54), 171 (60), 117 (19) and 115 (20).

(3a*R,11*R**,11a*S**)-11-(4-Methoxyphenyl)-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzoxazol-3-one (16b) (Table 3, entry 4).** The diene (**3**, 30.0 mg, 0.138 mmol), (*E*)-*p*-methoxycinnamyl alcohol (**13b**, 27.1 mg, 0.165 mmol), **14** (8.2 mg, 0.0014 mmol), and 4 Å MS (1.6 g) in toluene (8 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:3) to afford **16b** (17.1 mg, 37%) (Found: M^+, 336.1107. $C_{19}H_{16}N_2O_4$ requires *M*, 336.1109); ν_{max}($CHCl_3$)/cm^{-1} 1794, 1697, 1660, 1481; δ_H($CDCl_3$, 270 MHz) 1.87 (1 H, m, NCHC*H*CH_2), 3.25 (3 H, s, OCH_3), 3.39 (1 H, br d, *J* 9.5, NCHCHC*H*H), 3.48 (1 H, dt, *J* 9.5 and 3.1, NCHCHCH*H*), 3.69 (1 H, d, *J* 8.0, NC*H*CHCH$_2$), 4.17 (1 H, d, *J* 6.8, $CHCO_2$), 5.54 (1 H, d, *J* 7.6, Ar-H), 6.43 (1 H, td, *J* 7.6 and 1.0, Ar-H), 6.54 (1 H, td, *J* 7.7 and 1.2, Ar-H), 6.64 (2 H, s, Ar-H), 6.77 (1 H, d, *J* 7.7, Ar-H), 7.15 (2 H, s, Ar-H); δ_C($CDCl_3$, 270 MHz) 39.8 (C-11a), 54.9 (OCH_3), 56.1 (C-11), 56.3 (C-3a), 65.6 (C-1), 109.3 (C-9), 109.9 (C-6), 114.8 (C-2′, C-6′), 121.8 (C-7), 123.0 (C-8), 128.8 (C-3′, C-5′), 132.0, 144.8, 154.6 (C-4a, C-6a, C-10a), 160.2, 160.5 (C-1′, C-4′).

(3a*R,11*S**,11a*S**)-11-Phenyl-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzoxazol-3-one (16c) (Table 3, entry 6).** The diene (**3**, 10.0 mg, 0,046 mmol), (*Z*)-cinnamyl alcohol (**13c**, 12.3 mg, 0.092 mmol), **14** (2.8 mg, 0.0046 mmol), and 4 Å MS (0.8 g) in toluene (4 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (2:3) to afford **16c** (9.7 mg, 69%), mp 228–231 °C (hexane–AcOEt) (Found: M^+, 306.1010. $C_{18}H_{14}N_2O_3$ requires *M*, 306.1003); ν_{max}($CHCl_3$)/cm^{-1} 3019, 1794, 1698, 1661, 1482, 1460, 1244, 1225, 1206; δ_H($CDCl_3$, 270 MHz) 2.92 (1 H, m, NCHC*H*CH_2, spin saturation at δ = 4.65; NOE→5.4%), 4.20 (1 H, dd, *J* 9.6 and 3.3, NCHCHC*H*H), 4.42 (1 H, dd, *J* 9.9 and 5.9, NCHCHCH*H*), 4.57 (1 H, d, *J* 7.3, $CHCO_2$, spin saturation at δ = 2.92; NOE→9.7%), 4.65 (1 H, d, *J* 7.9, NC*H*CHCH$_2$), 5.80 (1 H, br d, *J* 7.9, Ar-H), 6.79 (1 H, br t, *J* 7.6, Ar-H), 6.96 (1 H, br t, *J* 7.6, Ar-H), 7.15 (1 H, br d, *J* 8.2, Ar-H), 7.34–7.40 (2 H, br, Ph), 7.45–7.50 (3 H, m, Ph); *m*/*z* 306 (M^+, 100%), 262 (50), 245 (64), 171 (76), 134 (18) and 115 (23).

(3a*R,11*S**,11a*S**)-11-(4-Methoxyphenyl)-3,3a,11,11a-tetrahydro-1*H*-furo[3′,4′:4,5]pyrimido[2,1-*b*][1,3]benzoxazol-3-one (16d) (Table 3, entry 8).** The diene (**3**, 10.0 mg, 0.046 mmol), (*Z*)-*p*-methoxycinnamyl alcohol (**13d**, 7.5 mg, 0.046 mmol), **14** (2.6 mg, 0.0046 mmol), and 4 Å MS (0.6 g) in toluene (3 ml) gave the crude product, which was purified by column chromatography on silica gel with hexane–AcOEt (1:1) to afford **16d** (10.8 mg, 70%), mp 195–197 °C (hexane–AcOEt) (Found: M^+, 336.1109. $C_{19}H_{16}N_2O_4$ requires *M*, 336.1109); ν_{max}($CHCl_3$)/cm^{-1} 1797, 1697, 1483; δ_H($CDCl_3$, 270 MHz) 3.20 (1 H, m, NCH-C*H*CH_2), 3.82 (3 H, s, OCH_3), 4.09 (1 H, dd, *J* 9.7 and 7.0, NCHCHC*H*H), 4.29 (1 H, dd, *J* 9.7 and 7.0, NCHCHCH*H*, spin saturation at δ = 3.20; NOE→4.9%), 4.51 (1 H, d, *J* 6.7, $CHCO_2$, spin saturation at δ = 3.20; NOE→5.8%), 5.24 (1 H, d, *J* 6.1, NC*H*CHC$_2$, spin saturation at δ = 3.20; NOE→7.8%), 6.15 (1 H, d, *J* 7.7, Ar-H), 6.87 (1 H, td, *J* 7.7 and 1.0, Ar-H), 6.91 (2 H, d, *J* 8.7, Ar-H), 6.98 (1 H, td, *J* 7.9 and 1.2, Ar-H), 7.14 (2 H, d, *J* 8.7, Ar-H), 7.16 (1 H, d, *J* 7.9, Ar-H); δ_C($CDCl_3$, 270 MHz) 37.5 (C-11a), 54.8 (C-11), 55.3 (OCH_3), 55.8 (C-3a), 66.4 (C-1), 109.2 (C-9), 109.7 (C-6), 114.7 (C-2′, C-6′), 122.3 (C-7), 123.3 (C-8), 128.8 (C-3′, C-5′), 160.2 (C-4′); *m*/*z* 336 (M^+, 100%), 292 (69), 275 (86), 171 (44), 158 (15) and 147 (47).

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