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# Inter- and Intramolecular Diels-Alder Reactions Using a Highly Reactive 1-Aza-1,3-butadiene, Ethyl (*E*)-3-(1,3-Benzothiazol-2-yl)-3-cyanopropenoate

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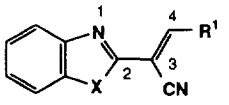
*Abstract:* Inverse type Diels-Alder reactions of ethyl (*E*)-3-(1,3-benzothiazol-2-yl)-3-cyanopropenoate (**2**) as 1-aza-1,3-butadiene are described. The diene (**2**), bearing electron-withdrawing ester group at diene 4-position, reacts with electron-rich dienophiles (**3a-d**) under extremely mild conditions to give corresponding cycloadducts (**4a-d**) with regio- and *endo*-selectivities. Treatment of **2** with electron-donating allyl alcohols (**6a-d**) causes tandem transesterification and intramolecular cycloaddition to afford *cis*-fused polycyclic systems (**7a-d**) in a single step.

One of the most direct approaches to nitrogen compounds containing a six membered ring system is hetero Diels-Alder reaction of a 1-aza-1,3-butadiene.[1] To achieve this concept, various 1-aza-1,3-butadienes carrying modified substituents at the 1-position have been developed during the last decade,[2-5]; 1-acyl,[2] 1-sulfonyl,[3] 1-dimethylamino,[4] and 1-phenyl[5] derivatives are of paticular note. Recently we reported that benzylidene-(cyano)methyl-1,3-benzoxa/thiazoles (**1a,b**) serve as stable 1-aza-1,3-butadienes, and react with some dienophiles to afford Diels-Alder adducts (**Fig. 1**).[6] In this report, we found that the dienes (**1a,b**) having more electron-withdrawing substituents (**Y**) exhibit higher reactivities. Consequently, it was expected that direct introduction of an electron-withdrawing group into the diene 4-position would make possible the generation of a more reactive 1-aza-1,3-diene system. We report here that ethyl (*E*)-3-(1,3-benzothiazol-2-yl)-3-cyano-propenoate (**2**) acts as a highly reactive 1-aza-1,3-diene to electron-donating dienophiles, and also that treatment of **2** with allyl alcohols causes tandem transesterification and intramolecular cycloadddition to afford polycyclic systems in a single step.[7]

**Fig. 1**




**1a**: X = S, $R^1$ = $-C_6H_4-Y$
**1b**: X = O, $R^1$ = $-C_6H_4-Y$
**2**: X = S, $R^1$ = $-CO_2Et$

## 1. Intermolecular Diels-Alder Reactions of 2 with Dienophiles.

The starting diene (**2**) was readily prepared by condensation of (1,3-benzothyazol-2-yl)acetonitrile with ethyl glyoxylate in the presence of a catalytic amount of triethyl amine. The diene (**2**) is a highly stable crystalline compound, and can be stored in air at room temperature for several months.

With the starting diene (**2**) in hand, intermolecular Diels-Alder reactions of **2** with electron-donating

This paper is dedicated to Emeritus Professor Hans Suschitzky on the occasion of his 80th birthday.

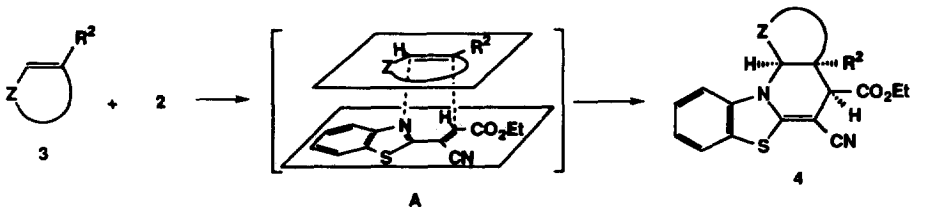
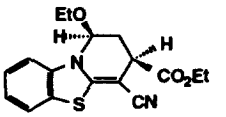
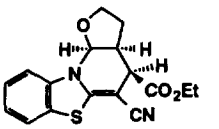
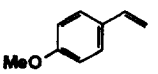
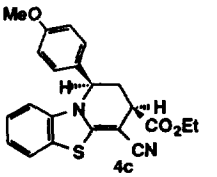
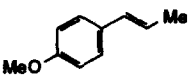
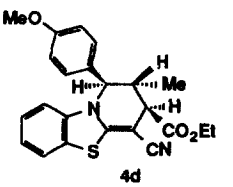
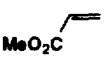
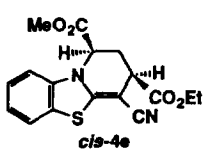
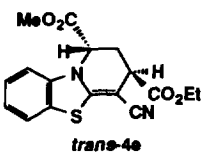


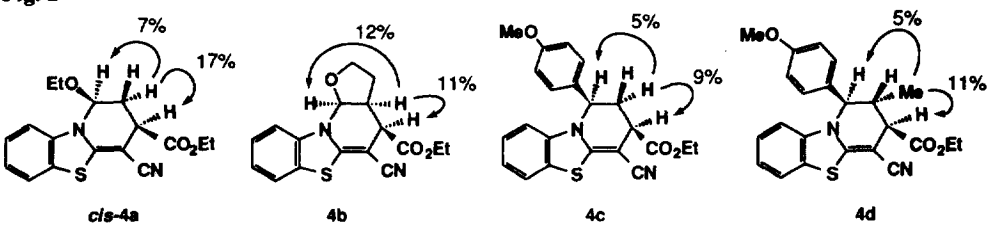
**Table 1.** Intermolecular Diels-Alder reactions of 2 with dienophiles (3a-e).

| Entry | Dienophile | Conditions | Yield (%) | Product |
|---|---|---|---|---|
| 1 |  3a | $CH_2Cl_2$ r.t., 5 h | 98 |  4a (*cis* : *trans* = 10 : 1) |
| 2 |  3b | $ClCH_2CH_2Cl$ 50 °C, 5 h | 87 |  4b |
| 3 |  3c | $CH_2Cl_2$ r.t., 24 h | 98 |  4c |
| 4 |  3d | $CH_2Cl_2$ r.t., 14 h | 76 |  4d |
| 5 |  3e | toluene 100 °C, 56 h | 31 |  *cis*-4e  *trans*-4e |

dienophiles (**3a-d**) and electron-poor dienophile (**3e**) were first examined as shown **Table 1**. The diene reactivity of **2** is extremely high, and causes Diels-Alder reaction with dienophiles to afford cycloadducts with high regio- and *endo*-selectivities under mild conditions. Thus, treatment of **2** with 10 fold excess of ethyl vinyl

ether (**3a**) in dichloromethane at room temperature afforded a 10 : 1 mixture of *cis*-**4a** and *trans*-**5a** in excellent yield (entry 1). Although the reaction of **2** with cyclic vinyl ether (**3b**) required a slightly higher reaction temperature, the reaction similarly proceeded to give *endo*-cycloadduct (**4b**) in good yield (entry 2). In the same manner, olefins bearing electron-donating aromatic ring (**3c,d**) acted as good dienophiles to the diene (**2**), affording exclusively *endo*-cycloadducts (**4c,d**) in high yields (entries 3,4).[8] In contrast to these reactions (entries 1-4), heating diene (**2**) with 10 equivalents of methyl acrylate (**3e**) in toluene at 100 °C for 56 h gave the corresponding cycloadducts (*cis*- and *trans*-**4e**) in only 31% yield with low *endo*-selectivity (1.9 : 1). This may show that the electrophilic character of the diene (**2**) is an inverse type diene.[2,3,8] The stereochemical assignments of the adducts were made based on their $^1$H-NMR spectra including NOE experiments as depicted in **Fig. 2**. Since all the reactions in **Table 1** afforded *endo*-cycloadducts, predominantly, they may proceed *via* transition state **A** due to secondary orbital interactions.

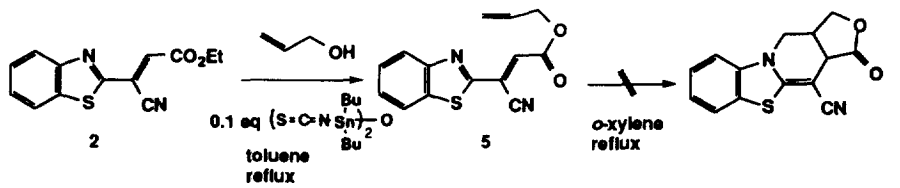
**Fig. 2**




## 2. Tandem transesterification and intramolecular cycloaddition of 2 with allyl alcohols.

Intramolecular Diels-Alder reaction is recognized as a powerful method for construction of various carbon frameworks, since it makes possible regio- and stereoselective polycyclization in one step. With the results of the intermolecular reaction of **2** with **3** in hand, our attention turned to the application of this reaction to an intramolecular version by employing the ester group as a linker moiety. To achieve this idea, we took a tandem transesterification-intramolecular cycloaddition approach.[9] The approach was first attempted using simple allyl alcohol. However, heating diene **2** with allyl alcohol in refluxing toluene in the presence of a catalytic amount of distanoxane catalyst[10] gave only a transesterification product (**5**). The reactivity of **5** is extremely low, and the desired intramolecular Diels-Alder reaction did not take place even in refluxing *o*-xylene (**Scheme 1**).

**Scheme 1**




Taking into account the electrophilic character of the diene system, more electron-rich allyl alcohols (**6a-d**) were next examined as shown in **Table 2**. In all cases, *cis*-fused lactones (**7a-d**) were obtained exclusively. Thus, reactions of **2** with **6a** and **6b** gave 3a,10a-*cis*-10,10a-*trans*-cycloadduct **7a** and 3a,10a-*cis*-10,10a-*trans*-

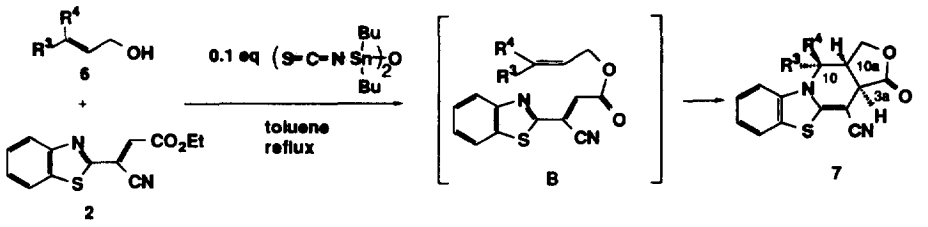
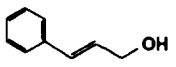
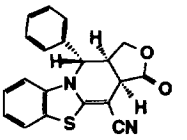
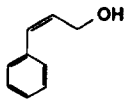
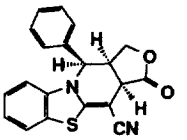
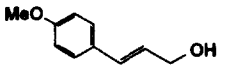
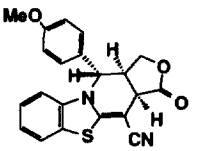
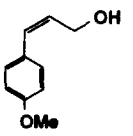
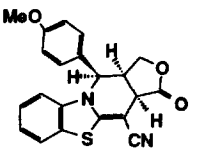
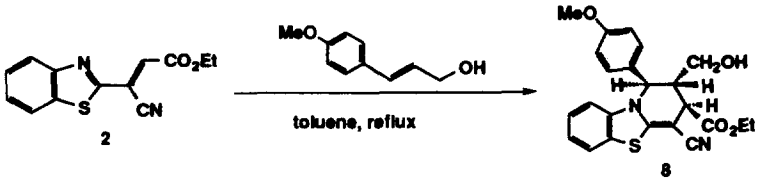



**Table 2.** Tandem transesterification and intramolecular cycloaddtion of **2** with allyl alcohols (**6a-d**).

| Entry | Allyl Alchohol | Reaction Time | Yield (%) | Product |
|---|---|---|---|---|
| 1 |  6a | 26 h | 49 |  7a |
| 2 |  6b | 28 h | 35 |  7b |
| 3 |  6c | 10 h | 49 |  7c |
| 4 |  6d | 4 h | 84 |  7d |

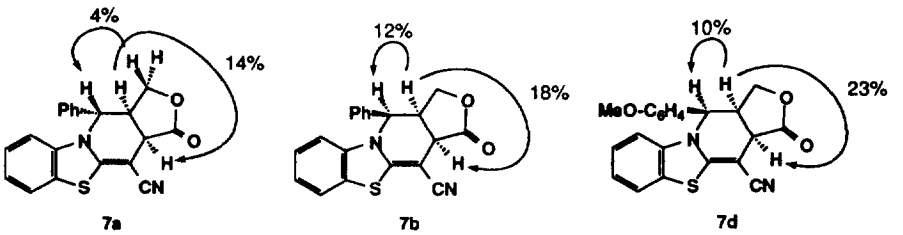
cycloadduct **7b**, respectively (entries 1,2). These facts clearly show that the present intramolecular process is concerted because it reflects the olefinic geometries of dienophiles (**6a,b**) into the products (**7a,b**), and also suggests that the stereochemical courses of the reactions are not affected by secondary orbital interactions. As expected, more electron-rich allyl alcohols (**6c,d**) reacted with **2** more smoothly to afford **7c,d** in higher yield (entries 3,4), suggesting that the intramolecular Diels-Alder reaction is classified as an inverse type cycloaddition. In contrast to the reaction of entry 3, heating **2** with **6** in the absence of the catalyst in refluxing toluene gave **8** bearing the opposite stereochemistry (**Scheme 2**). Accordingly, products (**7a-d**) are probably produced by intramolecular cycloaddition of initially formed intermediate (**B**) instead of intermolecular cycloaddition and lactonization.

**Scheme 2**




The stereochemical assignments of **7a,b,d** were made based on NOE experiments of their $^1$H-NMR spectra, and that of **7c** was done by comparing its $^1$H-NMR spectrum with those of **7a,b,d** (**Fig. 3**).

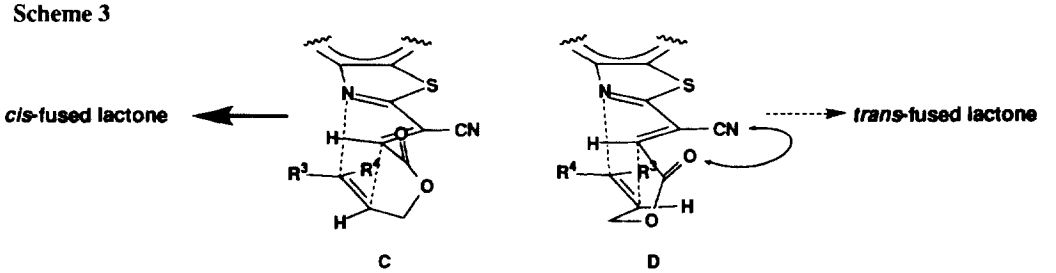
**Fig. 3**




As mentioned above, the tandem process gives only *cis*-fused lactones (**7a-d**) independent of the olefinic geometries. The stereochemical course of the intramolecular cycloaddition can be rationalized by considering the transition state models (**C** and **D**) as depicted in **Scheme 3**. Thus, the tether-*ex* transition model (**D**) would have higher strain to form the cyclic system, and more severe electrostatic interaction between the carbonyl group and the cyano group than the tether-*endo* model (**C**). Accordingly, intermediate (**B**) would undergo intramolecular cycloaddition *via* model (**C**) to afford *cis*-fused lactones.

Intramolecular cycloaddition can generally proceed under milder conditions than intermolecular one. The present intramolecular cycloaddition, however, required a higher temperature than the intermolecular cycloaddition of **2** does. This may also be rationalized taking into account the conformation of transition state (**C**). The π-systems of the 1-azadiene of **C** would lie almost perpendicular to that of the ester carbonyl group. The perpendicularity would decrease the electrophilicity of the 1-azadiene system due to interference of conjugation between the diene and the carbonyl group.

**Scheme 3**



## Conclusion

As stated, we have explored novel inverse type hetero Diels-Alder reaction of highly reactive diene, ethyl (*E*)-3-(benzothiazol-2-yl)-3-cyanopentenoate, with electron-rich dienophiles. This cycloaddition was successfully extended to tandem transesterification and intramolecular cycloaddition by employing electron-rich allyl alcohols. These methods may facilitate access to various heterocycles of biological interest. The tandem transesterification and intramolecular cycloaddition process, in paticular, might be applied to other electrophilic 1-aza-1,3-butadienes.

## Experimental

*General.* All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Infrared (IR) 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-LA500 (500 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. The following abbreviations were used for solvents: diethyl ether ($Et_2O$), ethyl acetate (AcOEt), ethanol (EtOH), methanol (MeOH), dimethylsulfoxide (DMSO), and dichloromethane ($CH_2Cl_2$).

**Ethyl (*E*)-3-(1,3-Benzothiazol-2-yl)-3-cyanopropenoate (2)**
To a stirred solution of (1,3-benzothiazol-2-yl)acetonitrile (0.871 g, 5 mmol) in EtOH (10 ml) was added dropwise a solution of ethyl glyoxylate (0.510 g, 5 mmol) and $Et_3N$ (a few drops) in EtOH (3 ml) at room temperature. After additional stirring for 1 h, the mixture was concentrated *in vacuo* to give a crude product, which was purified by column chromatography on silica gel ($CH_2Cl_2$-hexane, 5 : 1) to afford **2** (1.025 g, 79%) as yellow crystals. mp: 158-161 °C (recrystallized from acetone). IR ($CHCl_3$): 2184, 1732 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.41 (3 H, t, J = 7.3 Hz, $CH_2$*Me*), 4.41 (2 H, q, J = 7.3 Hz, C*H*$_2$Me), 7.52 (1 H, s, C*H*$CO_2$Et), 7.54-7.62 (2 H, m, ArH), 7.96 (1 H, d, J = 8.3 Hz, ArH), 8.14 (1 H, d, J = 8.6 Hz, ArH). MS m/z: 258 ($M^+$, 100%), 213 (83), 186 (77). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.89; N, 10.83. Found: C, 60.45; H, 3.90; N, 10.85.

**General Procedure for the intermolecular Diels-Alder reaction of 2 and 3 (Table 1).**
A mixture of the diene (**2**) and a dienophile (**3**) in a solvent was stirred. After a given period, the mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel. The reaction temperature and the reaction time are listed in **Table 1**.

**Ethyl (1*R**,3*S**)-1-Ethoxy-4-cyano-2,3-dihydro-1*H*-pyrido[2,1-*b*]benzothiazole-3-carboxylate (*cis*-4a) and Its (1*R**, 3*R**)-Isomer (*trans*-4a) (Table 1, entry 1)** The crude product was obtained from **2** (65.0 mg, 0.25 mmol), ethyl vinyl ether (**3a**, 0.24 ml, 2.5 mmol), and $CH_2Cl_2$ (0.6 ml). Purification by column chromatography on silica gel (hexane-AcOEt, 2 : 1) afforded ***cis*-4a** (73.6 mg, 89%) as the polar product and ***trans*-4a** (7.3 mg, 9%) as the less polar product. ***cis*-4a**, mp: 203-204 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 2190, 1734 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.11 (3 H, t, J = 6.9 Hz, $OCH_2CH_3$), 1.30 (3 H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.90 (1 H , ddd, J = 14.0, 6.8, 2.3 Hz, C*H*H), 3.03 (1 H, dt, J = 14.0, 2.3 Hz, CH*H*), 3.35 (1 H, dd, J = 6.8, 1.7 Hz, C*H*$CO_2$Et, spin saturation at $\delta$ = 1.90; NOE → 16.6%), 3.54 (2 H, m, $OCH_2CH_3$), 4.18 (2 H, m, $CO_2CH_2CH_3$), 5.46 (1 H, t, J = 2.3 Hz, C*H*OEt, spin saturation at $\delta$ = 1.90; NOE → 7.3%), 6.94 (1 H, br d, J = 7.6 Hz, ArH), 7.07 (1 H, br t, J = 7.6 Hz, ArH), 7.23 (1 H, br t, J = 7.6 Hz, ArH), 7.39 (1 H, br t, J = 7.6 Hz, ArH). MS m/z: 330 ($M^+$, 22%), 257 (100), 213 (25), 186 (28), 149, (32). Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.66; H, 5.45; N, 8.37. ***trans*-4a**, mp: 111-112 °C (recrystallized from hexane-AcOEt). IR (CHCl3): 2184, 1725 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.20 (3 H, t, J = 7.1 Hz, $OCH_2CH_3$), 1.35 (3 H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.03 (1 H, td, J = 13.4, 2.6 Hz, C*H*H), 2.46 (1 H, ddd, J = 13.4, 5.9, 2.6 Hz, CH*H*), 3.62 (2 H, m,

$OCH_2CH_3$), 3.68 (dd, J = 13.4, 5.9 Hz, $CHCO_2Et$), 4.28 (2 H, m, $CO_2CH_2CH_3$), 5.50 (1 H, t, J = 2.6 Hz, CHOEt), 7.01 (1 H, br d, J = 7.8 Hz, ArH), 7.07 (1 H , br t, J = 7.8 Hz, ArH), 7.25 ( 1 H, br t, J = 7.8 Hz, ArH), 7.38 (1 H, br t, J = 7.8 Hz, ArH). $^1$H-NMR ($C_6D_6$, 270 MHz): 0.74 (3 H, t, J = 6.9 Hz, $OCH_2CH_3$), 1.10 (3 H, t, J = 6.9 Hz, $CO_2CH_2CH_3$), 1.66 (1 H, ddd, J = 13.5, 12.5, 2.6 Hz, CHH), 1.97 (1 H, ddd, 13.5, 5.3, 3.0 Hz, CHH), 2.89 (2 H, m, $OCH_2CH_3$), 3.69 (1 H, dd, J = 12.5, 5.3 Hz, $CHCO_2Et$), 4.10 (2 H, m, $CO_2CH_2CH_3$), 4.55 (1 H, dd, J = 3.0, 2.6 Hz, CHOEt), 6.31 (1H, br d, J = 8.3 Hz, ArH), 6.57 (2 H, br d, J = 4.0 Hz, ArH), 6.78 (1 H, m, ArH). MS m/z: 330 ($M^+$, 22%), 257 (100), 213 (25), 186 (28), 149 (32). HRMS. Calcd for $C_{17}H_{18}N_2O_3S$: 330.1038. Found: 330.1045.

**Ethyl (3a*R**,4*S**,10c*R**)-5-Cyano-2,3,3a,10c-tetrahydro-4*H*-furano[3',2':5,6]pyrido[2,1-b]-benzothiazole-4-carboxylate (4b) (Table 1, entry 2).** This (33.3 mg, 87%) was obtained from **2** (30.0 mg, 0.116 mmol), 2,3-dihydrofuran (**3b**, 89 µl, 1.16 mmol), and $CH_2ClCH_2Cl$ (1 ml) after purification by column chromatography on silica gel (hexane-AcOEt, 4 : 1). mp: 198-200°C (hexane-AcOEt). IR ($CHCl_3$): 2190, 1731, 1226 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.34 (3 H, t, J = 7.3 Hz, $CO_2CH_2CH_3$), 2.10 (2 H, m, $OCH_2CH_2$), 3.11 (1 H, m, NCHCHCHCO$_2$Et), 3.86 (1 H, d, J = 4.6 Hz, NCHCHCHCO$_2$Et, spin saturation at δ = 3.11; NOE → 10.8%), 3.90 (1 H, m, $OCHHCH_2$), 4.02 (1 H, br q, J = 8.3 Hz, $OCHHCH_2$), 4.29 (2 H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 5.76 (1 H, d, J = 5.6 Hz, NCHCHCHCO$_2$Et, spin saturation at δ = 3.11; NOE → 11.8%), 7.08 (1 H, br t, J = 7.6 Hz, ArH), 7.18-7.38 (3 H, m, ArH). MS m/z: 328 ($M^+$, 23%), 255 (100), 227 (4), 225 (4), 211 (5). HRMS Calcd for $C_{17}H_{16}N_2O_3S$: 328.0882. Found: 328.0881. Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.04; H, 4.97; N, 8.45.

**Ethyl (1*R**,3*R**)-4-Cyano-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrido[2,1-*b*]benzothiazole-3-carboxylate (4c) (Table 1, entry 3).** This (72.5 mg, 98%) was obtained from **2** (50.0 mg, 0.194 mmol), 4-methoxystyrene (**3c**, 51.9 mg, 0.387 mmol), and $CH_2Cl_2$ (1 ml) after purification by column chromatography on silica gel ($CH_2Cl_2$ : hexane = 5 : 1 → $CH_2Cl_2$). mp: 233-234°C (recrystallized from AcOEt-hexane). IR ($CHCl_3$): 2186, 1726, 1580 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 0.94 (3 H, t, J = 7.3 Hz, $CO_2CH_2CH_3$), 2.35 (1 H, ddd, J = 13.9, 6.6 5.3 Hz, NCHCHHCHCO$_2$Et, spin saturation at δ = 3.29; NOE → 4.7%, spin saturation at δ = 5.26; NOE → 4.7%), 2.93, (1 H, dt, J = 13.9, 2.0 Hz, NCHCHHCHCO$_2$Et), 3.29 (1 H, dd, J = 6.6, 2.0 Hz, NCHCH$_2$CHCO$_2$Et, spin saturation at δ = 2.35; NOE → 8.7%), 3.52 (2 H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 3.67 (3 H, s, $OCH_3$), 5.26 (1 H, dd, J = 5.3, 2.0, NCHCH$_2$CHCO$_2$Et, spin saturation at δ = 2.35; NOE → 5.2%), 6.51 (1 H, d, J = 8.3 Hz, ArH), 6.71 (2 H, d, J = 8.7 Hz, Ar), 6.87 (2 H, d, J = 8.7 Hz), 6.93-7.06 (2 H, m, ArH), 7.35 (1 H, d, J = 7.6 Hz, ArH). MS m/z: 392 ($M^+$,31%), 319 (100), 211 (6), 160 (5), 134 (36). HRMS Calcd for $C_{22}H_{20}N_2O_3S$: 392.1194. Found: 329.1198.

**Ethyl (1*R**,2*R**,3*R**)-4-Cyano-1-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrido[2,1-*b*]benzothiazole-3-carboxylate (4d) (Table 1, entry 4).** This (77.3 mg, 76%) was obtained from **2** (65.0 mg, 0.25 mmol), 4-propenylanisole (**3d**, 80 mg, 0.5 mmol), and $CH_2Cl_2$ (1 ml) after purification by column chromatography on silica gel ($CH_2Cl_2$). mp: 178-180 °C (recrystallized from ether). IR ($CHCl_3$): 2188, 1729 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.02 (3 H, t, J = 7.3 Hz, $CO_2CH_2CH_3$), 1.26 (3 H, d, J = 7.0 Hz, $CHCH_3$), 3.01 (1 H, br s, $CHCO_2Et$, spin saturation at δ = 1.26; NOE → 11.3%), 3.22 (1 H, br qt, 7.0, 1.6 Hz, $CHCH_3$, spin saturation at δ = 1.26; NOE → 9.0%), 3.55 (2 H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 3.73 (3 H, s, $OCH_3$), 5.00 (1 H, br s, NCHAr, spin saturation at δ = 1.26; NOE → 6.7%), 6.58 (1 H, d, J = 7.6 Hz, ArH), 6.77 (2 H, d, J = 8.6 Hz, ArH), 6.92 (2 H, d, J = 8.6 Hz, ArH), 7.01-7.14 (2 H, m, ArH), 7.44 (1 H, dd, J = 7.4, 1.3 Hz, ArH). MS m/z: 406 ($M^+$, 44%), 333 (100), 148 (94), 121 (33). HRMS: Calcd for $C_{23}H_{22}N_2O_3S$: 406.1351. Found: 406.1347.

**Ethyl 1-Methyl (1*R**,3*S**)-4-Cyano-2,3-dihydro-1*H*-pyrido[2,1-*b*]benzothiazole-1,3-dicarboxylate (*cis*-4e) and Its (1*R**, 3*R**)-Isomer (*trans*-4e) (Table 1, entry 5).** The crude product was obtained from **2** (10.0 mg, 0.039 mmol), methyl acrylate (**5a**, 33.4 mg, 0.39 mmol), and toluene (2 ml). Purification by preparative TLC on silica gel ($CH_2Cl_2$) afforded a 1.9 : 1 mixture (4.1 mg, 31%) of ***cis*-4e** and ***trans*-4e**. Further purification by preparative TLC on silica gel ($CH_2Cl_2$ : hexane = 3 : 1) afforded pure ***cis*-4e** and ***trans*-4e**. ***cis*-4e**, mp: 189-190°C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 2190, 1728

$cm^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.31 (3 H, t, J = 7.3 Hz, $CO_2CH_2CH_3$), 2.20 (1 H, br dt, J = 14.5, 6.6 Hz, NCHC*H*HCHCO$_2$Et), 3.10 (1 H, br t, J = 14.5, 1.3 Hz, NCHCH*H*CHCO$_2$Et), 3.44 (1 H, dd, J = 6.3, 1.3 Hz, NCHCH$_2$C*H*CO$_2$Et), 4.18 (2 H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 4.81 (1 H, dd, J = 6.6, 1.3 Hz, NC*H*CH$_2$CHCO$_2$Et), 6.71 (1 H, br d, J = 7.9 Hz, ArH), 7.08 (1 H, br t, J = 7.6 Hz, ArH), 7.22 (1 H, br t, J = 7.9 Hz, ArH), 7.41 (1 H, br d, J = 7.6 Hz, ArH). MS m/z: 344 ($M^+$, 24%), 271 (100), 211 (64). HRMS Calcd for $C_{17}H_{16}N_2O_4S$: 344.0831. Found. 344.0828. ***trans*-4e**, mp: 122-124 °C (recrystallized from acetone-hexane). IR ($CHCl_3$): 2190, 1736 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 1.34 (3 H, t, J = 6.9 Hz, $CO_2CH_2CH_3$), 2.41 (1 H, ddd, J = 13.9, 11.6, 5.6 Hz, NCHC*H*HCHCO$_2$Et), 2.68 (1 H, ddd, J = 13.9, 5.0, 3.0 Hz, NCHCH*H*CHCO$_2$Et), 3.45 (1 H, dd, J = 11.9, 5.0 Hz, NCHCH$_2$C*H*CO$_2$Et), 4.28 (2 H, br q, J = 6.9 Hz, $CO_2CH_2CH_3$), 4.87 (1 H, dd, J = 5.6, 3.0 Hz, NC*H*CH$_2$CHCO$_2$Et), 6.77 (1 H, br d, J = 8.6 Hz, ArH), 7.09 (1 H, td, J = 8.6, 1.0 Hz, ArH), 7.24 (1 H, dd, J = 8.6, 1.0 Hz, ArH), 7.40 (1 H, dd, J = 7.9, 1.0 Hz, ArH). MS m/z: 344 ($M^+$, 26%), 271 (100), 211 (81). HRMS Calcd for $C_{17}H_{16}N_2O_4S$: 344.0831. Found. 344.0829.

**General Procedure for the tandem transesterification and intramolecular cycloaddition of 2 with 6 (Scheme 1 and Table 2).** A mixture of the diene (**2**), an allyl alcohol (**6**), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distannoxane,[10] and molecular sieves 4A (MS4A) in toluene was heated at reflux. After a given piriod, 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 time are listed in **Table 2.**

**Allyl (*E*)-3-(1,3Benzothiazol-2-yl)-3-cyanopropenoate (5) (Scheme 1).** The crude product was obtained from **2** (80.0 mg, 0.31 mmol), allyl alcohol (180 mg, 3.1 mmol), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distanoxane (17.4 mg, 0.031 mmol), MS4A (800 mg), and toluene (4 ml). Purification by column chromatography on silica gel ($CH_2Cl_2$ : hexane = 4 : 1) to afford **5** (55.1 mg, 66%). mp: 138-140 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 2193, 1728 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 4.76 (2 H, br d, J = 5.9 Hz, C*H*$_2$CH=CH$_2$), 5.28 (1 H, br dd, J = 10.2, 2.3 Hz, CH=C*H*H), 5.38 (1 H, br dd, J = 17.2, 2.3 Hz, CH=CH*H*), 5.94 (1 H, ddt, 17.2, 10.2, 5.9 Hz, C*H*=CH$_2$), 7.46 (1 H, s, C*H*CO$_2$Et), 7.35-7.62 (2 H, m, ArH), 7.88 (1 H, d, J = 7.6 Hz, ArH), 8.06 (1 H, d, J = 7.6 Hz, ArH). MS m/z: 270 ($M^+$, 65%), 225 (55), 213 (100), 186 (96), 159(19). HRMS Calcd for $C_{14}H_{10}N_2O_2S$: 270.0463. Found. 270.0466.

**Ethyl (3a*R**,10*R**,10a*S**)-4-Cyano-10-phenyl-1,3,3a,10a-tetrahydro-10*H*-furano[3',4':4,5]-pyrido[2,1-*b*]benzothiazole-3-one (7a) (Table 2, entry 1).** The crude product was obtained from **2** (60.0 mg, 0.23 mmol), (*E*)-cinnamyl alcohol (**6a**, 46.7 mg, 0.35 mmol), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distanoxane (13.0 mg, 0.023 mmol), MS4A (300 mg), and toluene (3 ml). Purification by column chromatography on silica gel ($CH_2Cl_2$ : hexane = 4 : 1) to afford **7a** (39.4 mg, 49%). mp: 257-257.5 °C (recrystallized $CH_2Cl_2$-hexane). IR (KBr): 2181, 1775, 1556 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$, 270 MHz): 3.17 (1 H, d, J = 7.9 Hz, C*H*CO$_2$, spin saturation at δ = 3.54; NOE → 14.0%), 3.54 (1 H, ddd, J = 10.9, 8.6, 7.9 Hz, NCHC*H*CH$_2$, spin saturation at δ = 3.17; NOE → 7.6%, spin saturation at δ = 4.55; NOE → 14.0%), 4.10 (1 H, dd, J = 10.9, 8.6 Hz, NCHCHC*H*H, spin saturation at δ = 4.55; NOE → 28.5%), 4.55 (1 H, t, J = 8.6 Hz, NCHCHCH*H*, spin saturation at δ = 4.10; NOE → 20.0%), 5.67 (1 H, br s, NC*H*CHCH$_2$, spin saturation at δ = 4.10; NOE → 4.0%), 6.95 (1 H, br d, J = 8.3 Hz, ArH), 7.03 (1 H, br t, J = 7.9 Hz, ArH), 7.13-7.35 (6 H, m, ArH), 7.65 (1 H, br d, J = 7.9 Hz, ArH). MS m/z: 346 ($M^+$, 72%), 302 (61), 288 (11), 225 (14), 211 (100). HRMS Calcd for $C_{20}H_{14}N_2O_2S$: 346.0776. Found: 346.0768.

**Ethyl (3a*R**,10*S**,10a*S**)-4-Cyano-10-phenyl-1,3,3a,10a-tetrahydro-10*H*-furano[3',4':4,5]-pyrido[2,1-*b*]benzothiazole-3-one (7b) (Table 2, entry 2).** The crude product was obtained from **2** (60.0 mg, 0.23 mmol), (*Z*)-cinnamyl alcohol (**6b**, 46.7 mg, 0.35 mmol), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distanoxane (13.0 mg, 0.023 mmol), MS4A (300 mg), and toluene (4 ml). Purification by column chromatography on silica gel ($CH_2Cl_2$ : hexane = 4 : 1) to afford **7b** (29.4 mg, 35%). mp: 300 °C<. IR (KBr): 2180, 1767, 1592 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$, 270 MHz): 3.37 (1 H, br q, J = 6.9 Hz, NCHC*H*CH$_2$, ), 3.94 (1 H, d, J = 6.9 Hz, C*H*CO$_2$, spin saturation at δ = 3.37; NOE → 18.6%), 4.21 (1 H, d, J = 9.9 Hz, NCHCHC*H*H, ), 4.45 (1 H, dd, J = 9.9, 6.3 Hz, NCHCHCH*H*, spin saturation at δ = 3.37; NOE → 9.5%),

5.57 (1 H, d, J = 6.9 Hz, NC*H*CHCH$_2$, spin saturation at δ = 3.37; NOE → 11.7%), 6.94 (1 H, br d, J = 7.9 Hz, ArH), 7.05 (1 H, br t, J = 7.6 Hz, ArH), 7.19 (1 H, br t, J = 7.6 Hz, ArH), 7.27 (5 H, br s, Ph), 7.66 (1 H, br d, J = 7.9 Hz). MS m/z: 346 (M$^+$, 91%), 302 (56), 288 (11), 267 (9), 225 (19), 211 (100). HRMS Calcd for $C_{20}H_{14}N_2O_2S$: 346.0776. Found: 346.0775.

**Ethyl (3a*R**,10*R**,10a*S**)-4-Cyano-10-(4-methoxyphenyl)-1,3,3a,10a-tetrahydro-10*H*-furano[3',4':4,5]pyrido-[2,1-*b*]benzothiazole-3-one (7c) (Table 2, entry 3).** The crude product was obtained from **2** (30.0 mg, 0.12 mmol), (*E*)-*p*-methoxycinnamyl alcohol (**6c**, 28.6 mg, 0.17 mmol), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distanoxane (6.5 mg, 0.012 mmol), MS4A (300 mg), and toluene (3 ml). Purification by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to afford **7c** (21.6 mg, 49%). mp: 133-135 °C (recrystallized from hexane-AcOEt). IR ($CHCl_3$): 2186, 1780, 1566 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz): 3.30 (1 H, d, J = 7.6 Hz, C*H*CO$_2$), 3.39 (1 H, dddd, J = 10.6, 7.9, 7.6, 1.5 Hz, NCHC*H*CH$_2$), 3.78 (3 H, s, OMe), 4.16 (1 H, dd, J = 10.6, 8.9 Hz, NCHCHC*H*H), 4.60 (1 H, dd, J = 8.9 Hz, 7.9 Hz, NCHCHCH*H*), 5.15 (1 H, br d, J = 1.5 Hz, NC*H*CHCH$_2$), 6.75 (1 H, br d, J = 7.9 Hz, ArH), 6.88 (2 H, br d, J = 8.6 Hz, ArH), 7.04-7.12 (1 H, ArH), 7.10 (2 H, br d, J = 8.6 Hz, ArH), 7.17 (1 H, br td, J = 7.9, 0.8 Hz, ArH), 7.44 (1 H, dd, J = 7.9, 1.0 Hz, ArH). MS m/z: 376 (M$^+$, 100%), 331 (67), 317 (15), 211 (53), 186 (27). HRMS Calcd for $C_{21}H_{16}N_2O_3S$: 376.0882. Found. 376.0879.

**Ethyl (3a*R**,10*S**,10a*S**)-4-Cyano-10-(4-methoxyphenyl)-1,3,3a,10a-tetrahydro-10*H*-furano[3',4':4,5]pyrido-[2,1-*b*]benzothiazole-3-one (7d) (Table 2, entry 4).** The crude product was obtained from **2** (30.0 mg, 0.12 mmol), (*Z*)-*p*-methoxycinnamyl alcohol (**6d**, 28.6 mg, 0.17 mmol), 1,1,3,3-tetra-*n*-butyl-1,3-diisothiocyanate distanoxane (6.5 mg, 0.012 mmol), MS4A (300 mg), and toluene (4 ml). Purification by column chromatography on silica gel ($CH_2Cl_2$) to afford **7d** (36.8 mg, 84%). mp: 300 °C< (recrystallized from $CH_2Cl_2$). IR (KBr): cm$^{-1}$. $^1$H-NMR (DMSO-d$_6$, 500 MHz): 3.34 (1 H, ddd, J = 7.7, 7.0, 5.6 Hz, NCHC*H*CH$_2$, ), 3.69 (3 H, s, OMe), 3.91 (1 H, d, J = 7.7 Hz, C*H*CO$_2$, spin saturation at δ = 3.34; NOE → 22.6%), 4.20 (1 H, d, J = 10.1 Hz, NCHCHC*H*H, ), 4.45 (1 H, dd, J = 10.1, 5.6 Hz, NCHCHCH*H*, spin saturation at δ = 3.34; NOE → 5.6%), 5.60 (1 H, d, J = 7.0 Hz, NC*H*CHCH$_2$, spin saturation at δ = 3.34; NOE → 10.2%), 6.73 (2 H, d, J = 9.2 Hz, ArH), 6.94 (1 H, br d, J = 7.6 Hz, ArH), 7.05 (1 H, td, J = 7.6, 1.3 Hz, ArH), 7.19 (2 H, d, J = 9.2 Hz, ArH), 7.19 (1 H, td, J = 7.6, 1.3 Hz, ArH), 7.64 (1 H, dd, J = 7.6, 1.3 Hz ArH). MS m/z: 376 (M$^+$, 100%), 332 (55), 318 (12), 225 (10), 211 (57), 186 (26), 147 (19). HRMS Calcd for $C_{21}H_{16}N_2O_3S$: 376.0882. Found: 376.0879.

**Ethyl (1R*,2S*,3R*)-4-Cyano-2-hydroxymethyl-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrido[2,1-b]benzothiazole-3-carboxylate (8) (Scheme 2).** A mixture of **2** (30.0 mg, 0.12 mmol), **6c** (28.6 mg, 0.17 mmol), and MS4A (300 mg) in toluene (2 ml) was heated at reflux for 20 h. After cooling, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give the crude product. Purification by column chromatography on silica gel (hexane : AcOEt = 3 : 2) afforded **8** (25.6 mg, 61%). mp: 98-100 °C (recrystallized from EtOH). IR ($CHCl_3$): 3450, 2188, 1730 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 500 MHz): 1.01 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.72 (1 H, br, OH), 3.21 (1 H, br s, NCHCHC*H*CO$_2$Et), 3.23 (1 H, br dd, J = 9.5, 6.7 Hz, NCHC*H*CHCO$_2$Et), 3.57 (1 H, dq, J = 10.9, 7.2 Hz, $CO_2CHHCH_3$), 3.60 (1 H, dq, J = 10.9, 7.2 Hz, $CO_2CHHCH_3$), 3.61 (1 H, dd, J = 10.7, 9.5 Hz, C*H*HOH), 3.70 (1 H, J = 10.7, 6.5 Hz, CH*H*OH), 5.47 (1 H, br s, NC*H*CHCHCO$_2$Et), 6.64 (1 H, br d, J = 7.7 Hz, ArH), 6.78 (2 H, br d, J = 8.9 Hz, ArH), 6.95 (2 H, br d, J = 8.9 Hz, ArH), 7.04 (1 H, td, J = 7.7, 1.3 Hz, ArH), 7.11 (1 H, td, J = 7.7, 1.3 Hz, ArH), 7.42 (1 H, dd, J = 7.7, 1.3 Hz, ArH). MS m/z: 422 (M$^+$, 57%), 390 (10), 349 (87), 331 (100), 319 (17), 283 (20), 211 (26). HRMS Calcd for $C_{23}H_{22}N_2O_4S$: 442.1301. Found. 442.1299.

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8. In contrast to the reaction of **2** with **3d** (entry 4), reaction of **1a** (Y = H) with **3d** takes 24 h at 120°C under neat condition. Reactivity of diene (**2**) introduced ester group at diene 4-position is apparently much higher than that of **1a**. Brief AM1 calculation of *s-cis* conformation of **1a** (Y = H) and **2** supports this difference of reactivities. Thus, the calculation shows that the diene (**2**) has lower LUMO (-1.6 eV) than **1a** (Y = H) (-1.2 eV). In addition, the magnitude of C4 coefficient of **2** (0.47) is larger than that of **1a** (0.44). These values in the calculation of **2** are favorable for regio-selective diene-LUMO controlled (inverse type) Diels-Alder reaction with high regioselectivity. Accordingly, diene (**2**) smoothly reacts with electron-rich dienophiles (**3a-e**) (HOMO: between -9.5 and -8.5 eV). For discussions on reactivity of 1-aza-1,3-butadiene using computation, see ref. 4b and 6b. For AM1, see, Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
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