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Internal Activation of Acrylate-Type Dienophiles for the Diels-Alder Reaction. Stereoselective Synthesis of Conformationally Constrained Glutamate Analogs.

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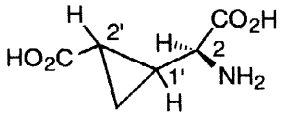
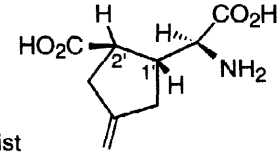
Abstract: The [4+2] cycloaddition reaction of the unreactive acrylate-type dienophiles such as **5a** and **6a** was accomplished by introducing an electronegative or electron-withdrawing group as the ester counterpart. Among them, the pentafluorophenyl (PFP) group was found to be an excellent ester counterpart in view of its rate acceleration and chemical stability under the reaction conditions. The ^{13}C NMR spectral data of the dienophiles with the PFP group suggested that the conjugated CC-double bond was strongly polarized. The internal activation was found to be effective for the related dienophile or other dienes, in particular, unstable to Lewis acid catalysts. A successful application of this method is demonstrated by the syntheses of conformationally restricted analogs of L-glutamate, **3** and **4**.

Naturally occurring and artificial analogs of L-glutamate have been employed as useful pharmacological tools in the field of neuroscience. Recently, we have developed a series of conformationally constrained glutamate analogs possessing a carbocyclic ring on its side chain such as L-2-(2-carboxycyclopropyl)glycines, CCGs (**1**),[2a] and L-2-(2-carboxy-4-methylenecyclopentyl)glycines, CPGs (**2**).[3] These analogs have proven the hypothesis that a specific conformation of L-glutamate (extended or folded conformation) is one of the crucial factors for activating distinct types of glutamate receptors (Figure 1).[2] Our further interest regarding the conformational requirement of glutamate receptors prompted us to develop new glutamate analogs L-2-(2-

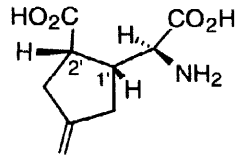
Figure 1. Structures of CCGs (**1**), CPGs (**2**), and CHGs (**3**) and (**4**).



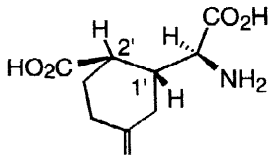
1a: (2S,1'S, 2'S)-CCG-I, potent mGluRs agonist
1b: (2S,1'R, 2'R)-CCG-II, transport inhibitor
1c: (2S,1'S, 2'R)-CCG-III, transport inhibitor
1d: (2S,1'R, 2'S)-CCG-IV, potent NMDA agonist



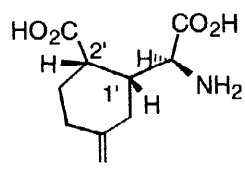
2a: CPG-II
transport inhibitor



2b: CPG-IV,
potent KA agonist



3: CHG-II

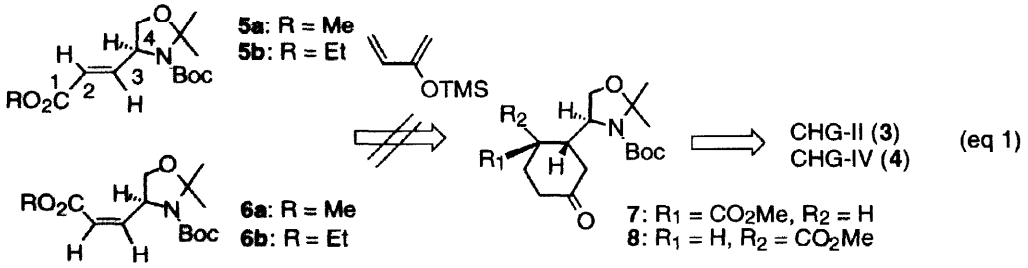


4: CHG-IV

CCG: 2-(2-carboxycyclopropyl)glycine
CPG: 2-(2-carboxy-5-methylenecyclopentyl)glycine
CHG: 2-(2-carboxy-5-methylenecyclohexyl)glycine

PII: S0040-4020(98)00219-I

carboxy-5-methylenecyclohexyl)glycines, CHGs (**3**) and (**4**), possessing a 6-membered carbocyclic ring. The most straightforward route to the synthesis of CHGs seemed to be the Diels-Alder reaction (eq 1) involving the optically active acrylate derivatives **5** and **6** as the dienophile which have been employed as useful chiral synthons for the syntheses of a variety of unusual amino acids.[4] Unfortunately, the cycloaddition reaction of the methyl or ethyl acrylates with 2-trimethylsilyloxy-1,3-butadiene was unsuccessful (Table 1). The reaction did not proceed even when heated to 160 °C (entries 1,2). Upon further heating (180 °C) or an addition of a mild Lewis acid catalyst, $Eu(fod)_3$,[5] the reaction only resulted in decomposition of the diene and/or the dienophile (entries 3,4). The lability of these reactants under these conditions suggested that other known activation methods would also be unsuitable.[6] A new and mild activation method for the present reaction was needed. In this paper, we wish to report a new method for the activation of the acrylate-type dienophile[7] and its successful application to the syntheses of CHGs.



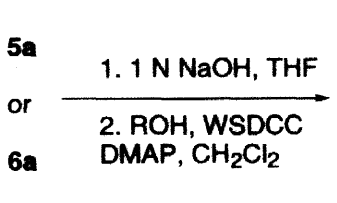
In order to enhance the electron-deficient nature of the dienophiles, our idea was an exchange of the methyl or the ethyl group with an electronegative ester counterpart. Thus, we chose *p*-nitrophenyl (PNP) and several fluorinated alcohols such as 2,2,2-trifluoroethyl (TFE), 1,1,1,3,3,3-hexafluoroisopropyl (HFI) and pentafluorophenyl (PFP) alcohols. Each alcohol was introduced to the acrylates **5** and **6** in two steps: (i) 1 *N* NaOH in tetrahydrofuran (THF), and (ii) 4-dimethylaminopyridine (DMAP) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in CH_2Cl_2.

Table 1. Diels-Alder reactions of **5** and **6** with 2-trimethylsilyloxy-1,3-butadiene.[a]

Entry	Dienophile	Temperature (°C)	Yield (%)[b,c]	Product (1'*R* : 1'*S*)
1	**5a** R = CH_3 or **5b** R = Et	160	no reaction	——
2	**6a** R = CH_3 or **6b** R = Et	160	no reaction	——
3	**5a**	180 (24 h)	decomposition	——
4	**5a** (0.1 equiv $Eu(fod)_3$)	130	no reaction	——
5	**5c** R = CH_2CF_3 (TFE)	130	47	**7** (4 : 1)
6	**5e** R = $CH(CF_3)_2$ (HFI)	130	71	**7** (1 : 0)
7	**5f** R = C_6H_5 (Phe)	130	no reaction	——
8	**5g** R = p-NO_2-Phe (PNP)	130	52	**7** (1 : 0)
9	**5h** R = C_6F_5 (PFP)	130	84	**7** (1 : 0)
10	**6c** R = R = CH_2CF_3 (TFE)	130	no reaction	——
11	**6e** R = $CH(CF_3)_2$ (HFI)	130	12	**8** (1 : 0)
12	**6h** R = C_6F_5 (PFP)	130	54	**8** (1 : 0)

[a]The reactions were performed in toluene for 3 days using a sealed tube. [b]Isolated yield. [c]Starting material was recovered as the methyl ester **5a** or **6a** (**5c**, 34%; **5e**, 20 %; **5f**, 36%; **5g**, 0%; **6e**, 71%; **6h**, 22%).

Scheme 1. Syntheses of the esters **5c-5h** and **6c-6h** from the methyl esters **5a** and **6a**.

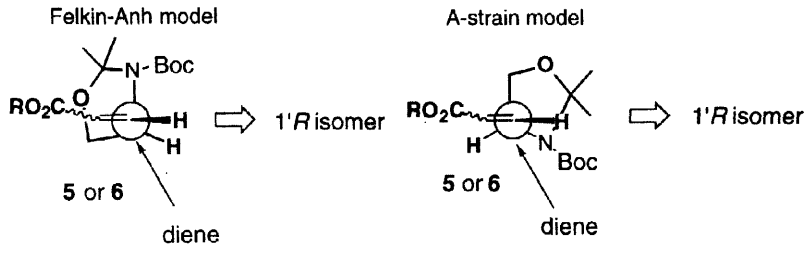


5c: R = CH_2CF_3 (75%) **6c**: R = CH_2CF_3 (75%)
5d: R = $CH(CH_3)_2$ (37%) **6d**: R = $CH(CH_3)_2$ (26%)
5e: R = $CH(CF_3)_2$ (87%) **6e**: R = $CH(CF_3)_2$ (51%)
5f: R = Phe (86%) **6f**: R = Phe (76%)
5g: R = PNP (76%) **6g**: R = PNP (86%)
5h: R = PFP (93%) **6h**: R = PFP (88%)

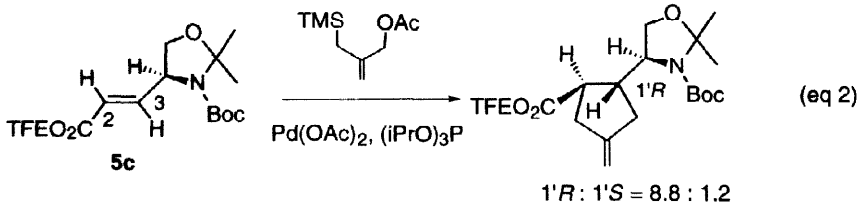
Diels-Alder reactions of the activated acrylates with 2-trimethylsilyloxy-1,3-butadiene. Upon heating to 130 °C in a sealed tube, treatment of a series of the activated acrylates with 2-trimethylsilyloxy-1,3-butadiene gave, for the first time, the desired cycloadducts in moderate to good yields (Table 1). The cycloadducts were isolated as the methyl ester **7** or **8** by the following sequence of reactions: (i) alkaline hydrolysis and (ii) esterification with diazomethane. This procedure was performed only for the purpose for removing the resulting polymetic diene residue from the reaction mixture. Among the 2*E*-esters, the PFP derivative **5h** gave the best result in terms of both yield and stereoselectivity. Excellent rate enhancement was also observed in the case of the 2*Z*-PFP derivative **6h** to give the corresponding cycloadduct **8** in 54% yield. The fact that no reaction took place using the phenyl ester **5f** apparently indicates that the activation by the PFP or PNP group is not due to steric and/or stereoelectronic effects of the phenyl group. These results revealed that the introduction of either an electronegative or an electron-withdrawing ester counterpart activated the acrylate-type dienophiles for the Diels-Alder reaction.

It is necessary to inspect the reaction to determine whether the internal activation is dependent upon the stability of the activated dienophiles (avoidance of decomposition, isomerization and racemization). The stability of the PFP esters under the thermal conditions was proven by an isolation of the cycloadducts and the starting acrylate as the unchanged PFP esters. The TFE and HFI esters, **5c,e** and **6c,e**, were also stable under the reaction conditions and the unreacted acrylates were recovered (Table 1, footnote). On the other hand, the PNP ester **5g** appeared to be labile upon heating and none of the starting **5g** was recovered (entry 8). Therefore, the fluorinated groups can be viewed as a superior activating counterpart to the PNP group. More significant was the stability of the PFP-acrylates towards the racemization at C4. No racemization throughout the synthetic procedure (preparation and thermal reaction) was confirmed by the following experiments: conversion of the recovered and the prepared PFP esters into the corresponding methyl esters, **5a** and **6a**, by an initial hydrolysis (1 *N* NaOH, THF) and subsequent esterfication (CH_2N_2, Et_2O). Their $[\alpha]_D$ values were in accord with the authentic samples, respectively. These results strongly suggested that the PFP group activates only the conjugated double bond without causing an enolization (vide infra).

Figure 2. Proposed mechanisms for the stereoselective cycloaddition which affords the 1'*R* isomer, **7** or **8**.

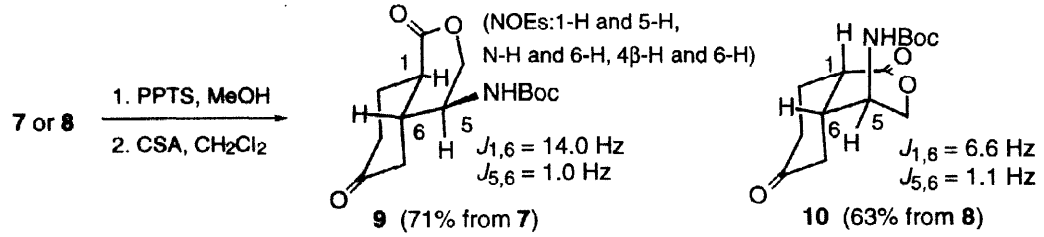


A further characteristic feature of this reaction is that the cycloadduct was obtained as a single diastereomer except in the case of the TFE ester **5c**. The notable diastereofacial selectivity can be rationalized as illustrated in Figure 2 where the diene attacked to the dienophile along the trajectory anti to the neighboring nitrogen atom in the Felkin-Ahn model[8] and an open face in the A-strain model.[9] Since both models can be used to explain the same configuration of 1'*R* in **7** and **8**, it is not possible to determine which model the reaction followed. Similar facial selectivity to these acrylates has been reported by us in the Pd-catalyzed [3+2] cycloaddition reaction of the TFE-acrylate **5c** and **6c** with a trimethylenemethane equivalent (eq 2).[3]



The structures of the cycloadducts **7** and **8** were determined by converting them into the corresponding lactones **9** and **10**, respectively. These transformations were performed in a stepwise manner by a selective removal of the acetonide group with pyridinium *p*-toluenesulfonate (PPTS) followed by an acid-catalyzed lactonization with *dl*-camphorsulfonic acid (CSA). The structures of **9** and **10** possessing the (1*R*,5*S*,6*R*)- and (1*S*,5*S*,6*R*)-stereochemistry were determined by their ^{1}H NMR data and NOESY experiments, respectively.

Scheme 2. Structure determination of the cycloadducts **7** and **8** by the conversion into **9** and **10**.



^{13}C NMR profile of the activated dienophiles. Since the electronegative and the electron-withdrawing ester counterparts largely accelerated the rate of the Diels-Alder reactions, we assumed that these ester counterparts strongly polarized the reacting CC-double bond at C2 and C3.[10] It is well accepted that ^{13}C NMR chemical shifts are sensitive to electronic properties at the observed carbon.[11] Thus, we compared the ^{13}C chemical shifts at C1-C4 of the ethyl ester **6b** with those of the TFE ester **6c**. The chemical shifts of the C4 and other carbons of both compounds were quite similar (cf. experimental section). These data clearly indicated that the C1 and C2 carbons of the TFE ester shifted to upper field and the C3 carbon to lower field (entry 1,2 in Table 2). Similar up- or downfield shifts at the C1 and C2 carbons, and at the C3 carbon were observed when the polar esters and the corresponding isopropyl or phenyl esters (HFI ester **5e** and isopropyl ester **5d**, PNP ester **5g** and phenyl ester **5f**, and PFP ester **5h** and phenyl ester **5f**) were compared. The same comparisons were made in the case of the 2*Z*-acrylates. In particular, the largest difference in the chemical shift change (shown as Δ = δC2 of the activated ester - δC2 of the corresponding alkyl or phenyl ester) was demonstrated by the PFP esters which were the most reactive dienophile (entries 7,14). These data suggest that the electronegative alcohols in the acrylates increase the negative charge density at the β-carbon (C3) and the positive charge density at the α-carbon (C2).[12] The remarkable polarization of the CC-double bond

appeared to be one of the crucial factors in the present internal activation method, while these analyses remain at a qualitative level.

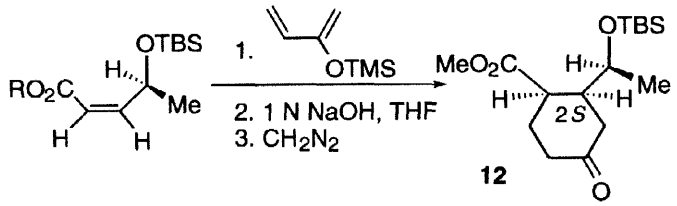
Table 2. ^{13}C NMR (100 MHz, $CDCl_3$) data of the dienophiles **5b-5h** and **6b-6h**.[a]

Entry	Dienophile	C1 (ppm)	C2 (ppm)	C3 (ppm)	C4 (ppm)
1	**5b** R = CH_2CH_3 (Et)	166.1	122.3	145.9	80.2
2	**5c** R = CH_2CF_3 (TFE)	164.2	120.2	148.9	80.5
	Δ(5c - 5b)	**(-1.9)**	**(-2.1)**	**(+3.0)**	**(+0.3)**
3	**5d** R = $CH(CH_3)_2$ (*i*-Pr)	166.6	121.9	146.3	80.3
4	**5e** R = $CH(CF_3)_2$ (HFI)	162.5	118.9	151.3	80.6
	Δ(5e - 5d)	**(-4.1)**	**(-3.0)**	**(+5.0)**	**(+0.3)**
5	**5f** R = C_6H_5 (Phe)	164.4	125.8	148.0	80.3
6	**5g** R = p-NO_2-Phe (PNP)	163.4	120.7	149.6	80.5
	Δ(5g - 5f)	**(-1.0)**	**(-5.1)**	**(+1.6)**	**(+0.2)**
7	**5h** R = C_6F_5 (PFP)	161.6	118.9	151.0	80.8
	Δ(5h - 5f)	**(-2.8)**	**(-6.9)**	**(+3.0)**	**(+0.5)**
8	**6b** R = CH_2CH_3 (Et)	165.8	119.5	152.0	80.0
9	**6c** R = CH_2CF_3 (TFE)	163.8	117.4	154.1	80.1
	Δ(6c - 6b)	**(-2.0)**	**(-2.1)**	**(+2.1)**	**(+0.1)**
10	**6d** R = $CH(CH_3)_2$ (*i*-Pr)	165.4	120.1	152.7	80.5
11	**6e** R = $CH(CF_3)_2$ (HFI)	161.9	115.9	157.2	80.9
	Δ(6e - 6d)	**(-3.5)**	**(-4.2)**	**(+4.5)**	**(+0.4)**
12	**6f** R = C_6H_5 (Phe)	164.1	125.9	153.7	80.4
13	**6g** R = p-NO_2-Phe (PNP)	163.0	118.4	155.6	80.8
	Δ(6g -6f)	**(-0.9)**	**(-7.5)**	**(+1.9)**	**(+0.4)**
14	**6h** R = C_6F_5 (PFP)	161.1	115.9	158.0	80.5
	Δ(6h - 6f)	**(-3.0)**	**(-10.0)**	**(+4.3)**	**(+0.1)**

[a] ^{13}C NMR signals (δ, ppm) at C3 and C4 were observed as two separate signals (each singlet), respectively, due to the rotamer at the *N*-Boc group. The chemical shift of the lower field signal at the C3 and C4 carbons is shown, respectively.

Diels-Alder reactions of other acrylate derivatives or with other dienes. As an extention of the internal activation method for applications, we first examined the activation of other unreactive dienophiles. Methyl acrylate**11a** was known to be an unreactive dienophile to 2-trimethylsilyloxybutadiene.[13] In fact, the reaction (160 °C, 5 days) resulted in a complete recovery of the starting material. Remarkable rate acceleration

Scheme 3

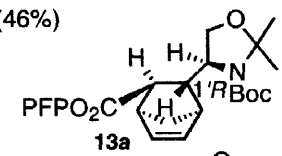
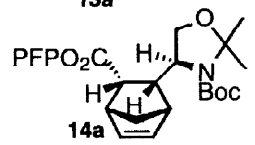
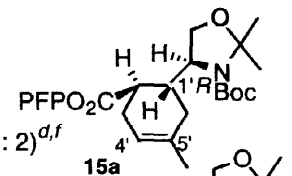
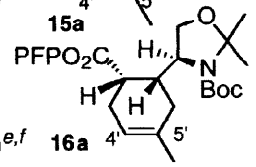
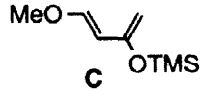
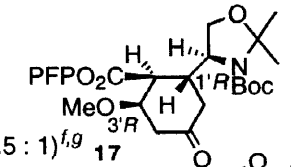
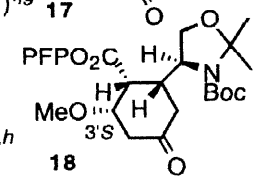


11a R = Me (130 °C, 5 days; no reaction)
11b R = PFP (130 °C, 5 days; 94% yield; 2*S*-**12** : 2*R*-isomer = 93 : 7)

was observed when the corresponding PFP ester **11b** was employed. The reaction proceeded at 130 °C to give the desired cycloadduct which was isolated as the methyl ester **12**, whose $[\alpha]_D$ value was in accord with the authentic sample,[13] indicating that no racemization occurred at the γ-position.

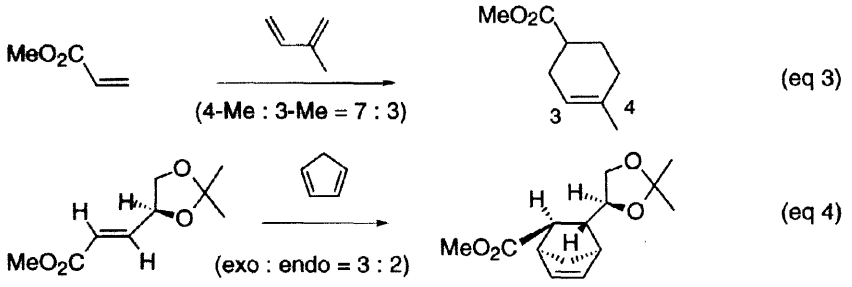
Next, we examined whether other dienes would react with the PFP dienophiles **5h** and **6h**. If they react, it would be of interest to inspect the stereoselectivity of the cycloadducts regarding diastereofacial, regio, and endo/exo selectivities. It is well known that a Lewis acid catalyst not only accelerates the reaction rate but also affects the stereoselectivities in Diels-Alder reactions. Many examples are reported of Lewis acid catalysts which increase the endo-selectivities with cyclopentadiene[14] and regio-selectivities with isoprene.[15] Thus, we employed cyclopentadiene (**A**), isoprene (**B**), and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**C**). To obtain comparative data, the reaction with the methyl esters **5a** and **6a** were also examined (Table 3).

Table 3. Reaction profiles of the acrylates **5a** and **5h**, and **6a** and **6g** with the dienes **A**-**C**.[a]

Entry	Dienes	Dienophile	Temperature (°C)	Time (day)	Products (yield)
1	 **A**	**5a** (2*E* Me ester)	130	3	Me ester of **13** (46%) (3 : 3 : 1 : 1)[b]
2		**5h** (2*E* PFP ester)	25	3	**13** (77%) (5 : 3 : 1 : 1)[b]  **13a**
3		**6a** (2*Z* Me ester)	130	3	no reaction
4		**6h** (2*Z* PFP ester)	50	3	**14** (71%) (40 : 4 : 3 : 1)[c]  **14a**
5	 **B**	**5a**	130	5	no reaction
6		**5h**	130	3	**15** (79%) (**15a**/**15b** = 3 : 2)[d,f]  **15a**
7		**6a**	130	5	no reaction
8		**6h**	130	5	**16** (68%) (**16a**/**16b** = 3 : 2)[e,f]  **16a**
9	 **C**	**5a**	130	5	no reaction
10		**5h**	80	5	**17** (84%) (**17a**/**17b** = 2.5 : 1)[f,g]  **17**
11		**6a**	130	5	no reaction
12		**6h**	80	5	**18** (67%) (**18a**/**18b** = 3 : 1)[f,h]  **18**

[a]All reactions were carried out in toluene using a sealed tube. The products were isolated as a mixture of the PFP esters. The yields were isolated yields as a mixture of the cycloadducts. The products ratio was determined by ^{1}H NMR. [b]The products were a mixture of the 1'*R*/1'*S* and endo/exo isomers (1'*R*-endo (**13a**) : 1'*R*-exo (**13b**) : 1'*S*-endo : 1'*S*-exo). [c]The products were a mixture of the 1'*R*/1'*S* and endo/exo isomers (1'*R*-endo (**14a**) : 1'*R*-exo (**14b**) : 1'*S*-endo : 1'*S*-exo). [d]The products were a mixture of **15a** and its 4'-Me regioisomer **15b**. [e]The products were a mixture of **16a** and its 4'-Me regioisomer **16b**. [f]None of the 1'*S* isomers were detected. [g]The products were a mixture of **17a** and its 3'*S* isomer **17b**. [h]The products were a mixture of **18a** and its 3'*R* isomer **18b**.

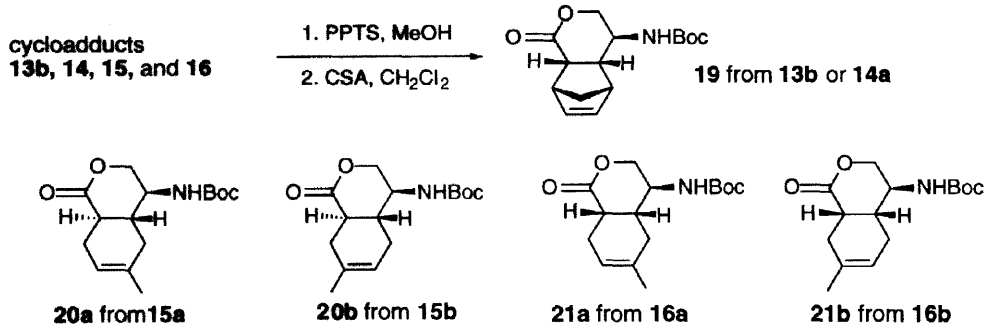
As expected, the reaction proceeded smoothly with the use of the PFP esters. In particular, the use of the reactive dienes **A** and **C** effected the cycloaddition even at room temperature or 80 °C (entries 2,4,10,12). The methyl esters were unreacted except **5a** with **A** (entry 1) where the reaction did not complete even at 130 °C (3 days, 48%). Regarding the stereoselectivity, the following points are noted. (i) The cycloaddition with **B** and **C** proceeded in a highly diastereofacial-selective manner to give the 1'*R* isomers, respectively. The use of reactive and sterically small diene **A** by-produced considerable amounts of the 1'*S* isomers as a mixture of endo- and exo-isomers (20% in **13** and 8% in **14**). These 1'*R* selectivities can be explained by the transition state models in Figure 2. (ii) None of the regioisomers were produced using the diene **C**. Contrary to this, poor regioselectivities were observed using isoprene (**B**) to give a mixture of the 4'- and 5'-methyl derivatives (5'-isomer/4'-isomer = 3:2) (entries 6,8). The low electron-releasing properties of the methyl group to the diene **B** would attribute to this poor selectivity. Similar regioselectivity has been reported in the case of methyl acrylate with **B**: a mixture of methyl 3- and 4-methylcyclohex-3-ene caboxylate are produced (4-methyl/3-methyl = 7:3) (eq 3).[16] (iii) In view of the endo/exo selectivity, the reactions with both dienes **A** and **C** showed moderate to good endo-selectivities (entries 2,4,10,12). Similar endo-selectivity has also been reported using the related acrylate derivatives, methyl 2*E*- and 2*Z*-4,5-(isopropylidenedioxy)pentenoate: the reaction with **A** affords a mixture of endo- and exo-cycloadducts in 3:2 ratio in the *E*-isomer and 85:15 in the *Z*-isomer, respectively (eq 4),[17] and with the diene **C** results in a pronounced decrease in the endo selectivity.[18]



Initially, we presumed that the electronegative ester counterpart affects not only the rate enhancement but also the stereoselectivity, which was often observed in the Lewis acid-catalyzed Diels-Alder reaction.[19] However, the reactions of the PFP acrylates using the dienes **A**-**C** were almost in accord with the un-catalyzed Diels-Alder reaction of the related acrylate systems having an unactivated ester counterpart. Therefore, it is proposed that the present internal activation method mainly affects the acceleration of the reaction rate by polarizing the CC-double bond of the dienophile.

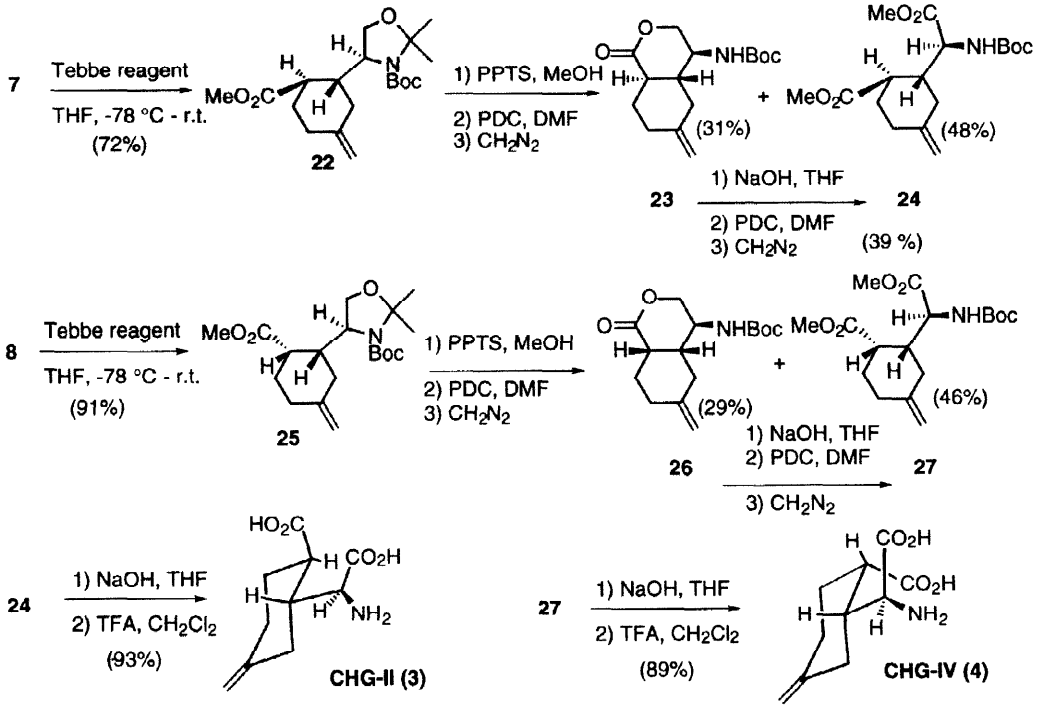
The structures of the cycloadducts in Table 3 were determined by the ^{1}H NMR studies (as the corresponding methyl esters with COSY and NOESY experiments) or those of the corresponding δ-lactones **19**-**21** (Scheme 4). In the case of the cyclopentadiene adducts, acidic treatment of the α-exo adduct **13b** underwent an initial epimerization at C2 and subsequent lactonization to give the δ-lactone **19**, while the α-endo adduct **13a** was recovered unchanged. The resulting lactone **19** was identical in all respects with that derived from **14a**. Finally, the structure of **19** was determined by 2D-NOESY experiments. Thus, the structures of both exo-**13b** and its endo-isomer **13a**, and **14a** were unambiguously determined. Since the isoprene adducts **15** and **16** could not be separated by column chromatography, these compounds were also converted to the corresponding lactones **20** and **21**, respectively.

Scheme 4. Structure determination of the cycladducts **13-16** by converting them into the lactones **19-21**.



Conversion of the Diels-Alder adducts 7 and 8 into CHG-II (3) and CHG-IV (4). Next, we examined the conversion of the cycloadducts **7** and **8** into the conformationally restricted analogs of L-glutamate **3** and **4**, respectively. In our previous studies, the exo-methylene group was ascertained to play a crucial role for the activation of kainate-type glutamate receptors.[3] Introduction of an exo-methylene group into **7** was achieved by using the Tebbe reagent to give methylene cyclohexane **22**. After removal of the acetonide group under the mild acidic conditions, oxidation of the resulting alcohol with pyridinium dichromate (PDC) in the presence of molecular sieves 4A followed by esterfication with CH_2N_2 gave dimethyl ester **24** together with lactone **23** which was reconverted into **24** in 3 steps: (i) 1 *N* NaOH in THF, (ii) PDC in DMF, and (iii) CH_2N_2 in Et_2O in 39% yield. Finally, the synthesis of CHG-II (**3**) from **24** was accomplished by the following sequence of reactions: (i) hydrolysis with 1 *N* NaOH, (ii) removal of the Boc group with TFA, and (iii) purification with Dowx 50Wx4 (H^+ form, elution with 10% NH_4OH) to give **3**. Following the same procedure, the cycloadduct **8** was successfully transformed into CHG-IV (**4**).[20]

Scheme 5. Syntheses of CHGs (**3**) and (**4**).



Experimental

Melting points are uncorrected. ^1H (400 MHz) and ^{13}C NMR (100 MHz) were measured on JEOL EX-400 spectrometer in $CDCl_3$ or D_2O. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$ or sodium 3-(trimethylsilyl)-propionate-d_4 (TSP) (0.00) as an internal standard in D_2O. IR spectra were measured on a Perkin Elmer FT-IR 1640 spectrophotometer. High resolution mass spectra (HRMS) under fast atom bombardment ionization (FAB) were obtained with JEOL JMX-HX 110. Optical rotations were taken on a Perkin Elmer 241 polarimeter. All reactions were monitored by thin-layer chromatography (TLC), carried on 2 x 5 cm precoated TLC plates (silica gel 60F-254; layer thickness, 0.25 mm) manufactured by Merck. Silica gel (Merck 60, 70-230 mesh) was used for column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials unless otherwise stated.

General procedure for the Syntheses of the dienophiles 5c-5h and 6c-6h: (1'*S*,2*E*)-pentafluorophenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5h). A solution of **5a** (6.00 g, 21.9 mmol) in THF (100 mL) and 1 *N* NaOH (25 mL) was stirred at 0 °C for 3 h. After additional stirring at room temperature for 15 h, THF was evaporated in vacuo. The aqueous solution was acidified with 1 *N* HCl to pH 2, saturated with NaCl, and extracted with Et_2O for several times. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give an oily residue. The residue was used for the subsequent esterification without chromatographic purification. To a solution of the crude residue in CH_2Cl_2 (100 mL) was added pentafluorophenol (4.50 g, 24.2 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (5.00 g, 26.4 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ether/hexane = 1:6) to give crude crystals. Recrystallization from pentane gave **5h** (8.90 g, 93%) as colorless crystals: mp 58.0 °C; $[\alpha]^{28}_D$ +63.9° (*c* 1.15, $CHCl_3$); FT-IR (film) 2984, 2938, 2886, 1763, 1703, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44, 1.50 (each s, total 9 H), 1.54, 1.56, 1.64, 1.67 (each s, total 6 H), 3.87 (dd, 1 H, *J* = 2.2, 9.0 Hz), 4.16 (dd, 1 H, *J* = 8.5, 9.0 Hz), 4.50, 4.66 (each m, total 1 H), 6.14, 6.18 (each d, total 1 H, *J* = 16.0 Hz), 7.14, 7.17 (each dd, 1 H , *J* = 6.8, 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.5, 26.4, 27.3, 28.3, 31.6, 58.2, 67.0, 80.8, 81.4, 94.4, 94.9, 118.9, 136.2, 136.3, 139.5, 139.6, 151.4, 151.4, 152.5, 161.6, 164.4;[10] HRMS *m/z* calcd for $C_{19}H_{21}O_5NF_5$ $(M+H)^+$ 438.1340, found 438.1353.

(1'*S*,2*E*)-2,2,2-Trifluoroethyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5c).[3] In a manner similar to that used to prepare **5h**, the reaction of **5a** (500 mg, 1.4 mmol) gave **5c** (800 mg, 75%) as a colorless oil: $[\alpha]^{28}_D$ +50.1° (*c* 1.64, $CHCl_3$); FT-IR (film) 2982, 2940, 2877, 1743, 1699, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41, 1.48 (each s, total 9 H), 1.51, 1.54, 1.61, 1.64 (each s, total 6 H), 3.82 (dd, 1 H, *J* = 2.4, 8.8 Hz), 4.11 (dd, 1 H, *J* = 2.3, 8.8 Hz), 4.16 (dd, 1 H, *J* = 6.4, 8.8 Hz), 4.45 (m, 2 H), 4.53 (m, 1 H), 5.85, 6.02 (each d, total 1 H, *J* = 16.1 Hz), 6.96, 6.98 (each dd, 1 H, *J* = 6.3, 16.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.6, 26.4, 27.3, 28.3, 58.0, 59.6, 60.1, 60.6, 61.1, 67.1, 80.5, 81.0, 94.5, 94.7, 120.2, 121.1, 148.7, 148.9, 152.0, 152.9, 164.2;[10] HRMS *m/z* calcd for $C_{15}H_{23}O_5NF_3$ $(M+H)^+$ 354.1528, found 354.1514.

(1'*S*,2*E*)-Isopropyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5d). In a manner similar to that used to prepare **5h**, the reaction of **5a** (160 mg, 0.62 mmol) gave **5d** (70 mg, 37%) as a colorless oil: $[\alpha]^{23}_D$ +51.6° (*c* 1.15, $CHCl_3$); FT-IR (film) 2982, 2938, 2878, 1735, 1703, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, 6 H, *J* = 7.0 Hz), 1.42, 1.49 (each s, total 9 H), 1.53, 1.63, 1.66 (each s, total 6 H), 3.79 (dd, 1 H, *J* = 2.4, 9.5 Hz), 4.11 (dd, 1 H, *J* = 6.2, 9.5 Hz), 4.37, 4.57 (each m, total 1 H), 5.08 (m, 1 H), 5.86, 5.91 (each d, total 1 H, *J* = 15.5 Hz), 6.79, 6.81 (each dd, 1 H, *J* = 6.2, 15.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.6, 26.4, 28.4, 51.7, 58.0, 67.3, 80.3, 80.7, 94.0, 94.5, 107.2, 121.9, 146.1, 146.3, 151.6, 166.6;[10] HRMS *m/z* calcd for $C_{16}H_{28}O_5N$ $(M+H)^+$ 314.1968, found 314.1968.

(1'*S*,2*E*)-1,1,1,3,3,3-Hexafluoropropyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5e). In a manner similar to that used to prepare **5h**, the reaction of **5a** (500 mg, 1.40 mmol) gave **5e** (850 mg, 87%) as colorless crystals: mp 72 °C; $[\alpha]^{23}_{D}$ +46.5° (*c* 3.29, $CHCl_3$); FT-IR (film) 2982, 2941, 2883, 1759, 1701, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41, 1.49 (each s, total 9 H), 1.54, 1.55, 1.64, 1.66 (each s, total 6 H), 3.85 (dd, 1 H, *J* = 2.3, 9.8 Hz), 4.13 (dd, 1 H, *J* = 6.0, 9.8 Hz), 4.46, 4.62 (each m, total 1 H,), 5.82 (m, 1 H), 6.07, 6.25 (each d, total 1 H, *J* = 15.8 Hz), 7.07, 7.10 (each dd, total 1 H, *J* = 6.0, 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.5, 27.3, 28.3, 58.0, 66.0, 66.3, 66.6, 67.0, 67.3, 80.3, 80.7, 94.0, 94.5, 116.2, 118.9, 119.1, 121.9, 124.7, 151.2, 151.3, 162.5;[10] HRMS *m/z* calcd for $C_{16}H_{22}O_5N_2F_6$ $(M+H)^+$ 422.1402, found 422.1394.

(1'*S*,2*E*)-Phenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5f). In a manner similar to that used to prepare **5h**, the reaction of **5a** (160 mg, 0.62 mmol) gave **5f** (180 mg, 86%) as colorless crystals: mp 43 °C; $[\alpha]^{23}_{D}$ +87.0° (*c* 0.40, $CHCl_3$); FT-IR (film) 2980, 2936, 2878, 1739, 1699, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48, 1.56 (each s, total 9 H), 1.57, 1.63, 1.67 (each s, total 6 H), 3.83 (dd, 1 H, *J* = 3.5, 9.0 Hz), 4.16 (dd, 1 H, *J* = 6.0, 9.0 Hz), 4.47, 4.63 (each m, total 1 H), 6.10, 6.15 (each d, total 1 H, *J* = 15.5 Hz), 7.02, 7.06 (each dd, total 1 H, *J* = 6.5, 15.5 Hz), 7.10-7.40 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.6, 26.4, 27.3, 28.3, 58.0, 67.0, 67.2, 80.3, 80.9, 94.1, 94.6, 121.5, 125.8, 129.4, 148.0, 148.2, 150.6, 151.5, 152.1, 164.4;[10] HRMS *m/z* calcd for $C_{19}H_{26}O_5N$ $(M+H)^+$ 348.1811, found 348.1815.

(1'*S*,2*E*)-4-Nitrophenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5g). In a manner similar to that used to prepare **5h**, the reaction of **5a** (260 mg, 1.00 mmol) gave **5g** (300 mg, 76%) as colorless crystals: mp 77 °C; $[\alpha]^{23}_{D}$ +87.3° (*c* 0.40, $CHCl_3$); FT-IR (film) 2980, 2938, 2882, 1746, 1697, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44, 1.50 (each s, total 9 H), 1.51, 1.54, 1.60, 1.70 (each s, total 6 H), 3.85 (dd, 1 H, *J* = 2.2, 9.0 Hz), 4.17 (dd, 1 H, *J* = 8.5, 9.0 Hz), 4.55, 4.64 (each m, total 1 H), 6.11, 6.14 (each d, total 1 H, *J* = 15.7 Hz), 7.10 (dd, 1 H, *J* = 6.5, 15.7 Hz), 7.30 (m, 2 H), 8.25 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.6, 26.5, 27.3, 28.4, 58.1, 67.0, 80.5, 81.1, 94.3, 94.8, 120.7, 122.4, 125.2, 145.4, 149,6. 149.9, 155.4, 163.4;[10] HRMS *m/z* calcd for $C_{19}H_{25}O_7N_2$ $(M+H)^+$ 393.1662, found 393.1665.

(1'*S*,2*Z*)-2,2,2-Trifluoroethyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6c).[3] In a manner similar to that used to prepare **5h**, the reaction of **6a** (500 mg, 1.4 mmol) gave **6c** (800 mg, 75%) as a colorless oil: $[\alpha]^{23}_{D}$ -20.3° (*c* 2.42, $CHCl_3$); FT-IR (film) 2982, 2938, 2880, 1738, 1703, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38, 1.48 (each s, total 9 H), 1.51, 1.53, 1.59, 1.64 (each s, total 6 H), 3.76 (dd, 1 H, *J* = 2.9, 9.3 Hz), 4.25 (m, 1 H), 4.48 (m, 2 H), 5.28 (m, 1 H), 5.88, 5.93 (each d, total 1 H, *J* = 11.2 Hz), 6.40, 6.49 (each dd, total 1 H, *J* = 8.8, 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.9, 26.6, 27.3, 28.3, 28.4, 55.6, 56.5, 59.5, 59.9, 60.4, 60.8, 65.8, 68.5, 68.6, 80.1, 80.4, 94.1, 94.6, 117.4, 118.1, 152.3, 154.1, 154.8, 163.8;[10] HRMS *m/z* calcd for $C_{15}H_{23}O_5NF_3$ $(M+H)^+$ 354.1528, found 354.1518.

(1'*S*,2*Z*)-Isopropyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6d). In a manner similar to that used to prepare **5h**, the reaction of **6a** (160 mg, 0.62 mmol) gave **6d** (50 mg, 26%) as a colorless oil: $[\alpha]^{23}_{D}$ -11.5° (*c* 0.68, $CHCl_3$); FT-IR (film) 2982, 2939, 2876, 1710, 1705, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, 6 H, *J* = 7.0 Hz), 1.40, 1.50 (each s, total 9 H) 1.51, 1.53, 1.60, 1.63 (each s, total 6 H), 3.78 (dd, 1 H, *J* = 3.0, 9.4 Hz), 4.23 (m, 1 H), 5.06 (m, 1 H), 5.38 (m, 1 H), 5.78, 5.79 (each d, total 1 H, *J* = 11.0 Hz), 6.22, 6.32 (each dd, total 1 H, *J* = 8.0, 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.9, 26.6, 28.3, 55.7, 55.7, 68.9, 80.5, 82.2, 94.4, 94.4, 120.1, 120.6, 150.8, 151.8, 165.4;[10] HRMS *m/z* calcd for $C_{16}H_{28}O_5N$ $(M+H)^+$ 314.1967, found 314.1957.

(1'*S*,2*Z*)-1,1,1,3,3,3-Hexafluoropropyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6e). In a manner similar to that used to prepare **5h**, the reaction of **6a** (500 mg, 0.14 mmol) gave **6e** (500 mg, 51%) as colorless crystals: mp 72 °C; $[\alpha]^{23}_{D}$ -21.1° (*c* 1.16, $CHCl_3$); FT-IR (film) 2982, 2939, 2881, 1755, 1705, 1643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37, 1.48 (each s, total 9 H), 1.51, 1.54, 1.60, 1.64 (each s, total 6 H), 3.77 (dd, 1 H, *J* = 2.5, 9.2 Hz), 4.24 (m, 1 H), 5.32 (m, 1 H), 5.76 (m, 1 H), 5.96, 5.98 (each d, total 1 H, *J* = 11.2 Hz), 6.55, 6.65 (each

dd, total 1 H, J = 8.8, 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.8, 26.5, 27.2, 28.3, 55.8, 56.8, 65.4, 65.8, 66.1, 66.3, 66.8, 67.0, 67.2, 68.3, 80.3, 81.0, 94.0, 94.7, 115.9, 116.5, 118.8, 122.3, 151.7, 157.2, 158.0, 161.9;[10] HRMS *m/z* calcd for $C_{16}H_{22}O_5N_2F_6$ $(M+H)^+$ 422.1402, found 422.1411.

(1'*S*,2*Z*)-Phenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6f). In a manner similar to that used to prepare **5h**, the reaction of **6a** (160 mg, 0.62 mmol) gave **6f** (160 mg, 76%) as colorless crystals: mp 84 °C; $[\alpha]^{23}_D$ -45.2° (*c* 1.07, $CHCl_3$); FT-IR (film) 2980, 2935, 2877, 1736, 1701, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40, 1.53 (each s, total 9 H), 1.55, 1.62, 1.65 (each s, total 6 H), 3.82 (dd, 1 H, J = 2.6, 9.1 Hz), 4.28 (m, 1 H), 5.21 (m, 1 H), 6.06, 6.09 (each d, total 1 H, J = 10.8 Hz), 6.45, 6.54 (each dd, total 1 H, J = 8.9, 10.8 Hz), 7.10-7.40 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.8, 26.6, 27.3, 28.4, 55.6, 56.8, 68.8, 70.0, 80.4, 81.0, 94.6, 115.3, 118.6, 119.5, 120.7, 121.4, 121.5, 125.9, 126.0, 129.4, 129.6, 150.2, 153.7, 154.4, 155.5, 164.3;[10] HRMS *m/z* calcd for $C_{19}H_{26}O_5N$ $(M+H)^+$ 348.1811, found 348.1810.

(1'*S*,2*E*)-4-Nitrophenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6g). In a manner similar to that used to prepare **5h**, the reaction of **6a** (130 mg, 0.50 mmol) gave **6g** (150 mg, 79%) as colorless crystals: mp 77 °C; $[\alpha]^{23}_D$ -71.6° (*c* 1.06, $CHCl_3$); FT-IR (film) 2980, 2938, 2874, 1742, 1697, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43, 1.53 (each s, total 9 H), 1.54, 1.62, 1.63, 1.65 (each s, total 6 H), 3.80 (dd, 1 H, J = 2.0, 9.0 Hz), 4.28 (m, 1 H), 5.40 (m, 1 H), 6.07, 6.08 (each d, total 1 H, J = 11.3 Hz), 6.53, 6.59 (each dd, total 1 H, J = 8.5, 11.3 Hz), 7.30 (m, 2 H), 8.30 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.9, 26.6, 27.3, 28.6, 55.7, 56.5, 68.5, 80.1, 80.8, 94.0, 94.7, 117.6, 118.4, 122.3, 122.4, 125.2, 128.3, 145.5, 151.7, 152.4, 155.2, 155.6, 163.0;[10] HRMS *m/z* calcd for $C_{19}H_{25}O_7N_2$ $(M+H)^+$ 393.1662, found 393.1664.

(1'*S*,2*Z*)-Pentafluorophenyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6h). In a manner similar to that used to prepare **5h**, the reaction of **6a** (7.00 g, 26.0 mmol) gave **6h** (10.3 g, 88%) as colorless crystals: mp 89.3 °C; $[\alpha]^{23}_D$ -52.1° (*c* 1.17, $CHCl_3$); FT-IR (film) 2984, 2938, 2876, 1753, 1707, 1649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41, 1.50 (each s, total 9 H), 1.51, 1.54, 1.61, 1.66 (each s, total 6 H), 3.80 (dd, 1 H, J = 2.5, 9.0 Hz), 4.25 (dd, 1 H, J = 6.5, 9.0 Hz), 5.28 (m, 1 H), 6.14, 6.15 (each d, total 1 H, J = 11.8 Hz), 6.60, 6.72 (each dd, total 1 H, J = 8.2, 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.7, 24.9, 26.6, 27.2, 28.3, 55.8, 56.9, 56.9, 68.3, 80.5, 81.1, 93.9, 94.7, 115.9, 116,5, 124.9, 132.1, 136.9, 139.3, 140.0, 142.3, 157.1, 158.0, 161.1;[10] HRMS *m/z* calcd for $C_{19}H_{21}O_5NF_5$ $(M+H)^+$ 438.1340, found 438.1341.

^{13}C NMR (100 MHz, $CDCl_3$) data of (1'*S*,2*E*)-ethyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (5b). δ 14.2, 23.6, 24.7, 26.4, 27.3, 28.4, 58.0, 60.5, 67.3, 80.2, 94.5, 122.3, 145.7, 145.9, 152.0, 166.1.[3,10]

^{13}C NMR (100 MHz, $CDCl_3$) data of (1'*S*,2*Z*)-ethyl 3-[5-(*tert*-butyl)oxycarbonyl-4,4-dimethyl-3,5-oxazolidinyl]prop-2-enoate (6b). δ 14.2, 22.7, 23.8, 26.6, 28.3, 31.6, 55.6, 56.6, 56.7, 60.2, 68.8, 69.0, 69.1, 80.0, 94.4, 119.5, 151.9, 152.0, 165.8.[3,10]

Typical procedure for the Cycloaddition of 5 or 6 with 2-trimethylsilyloxy-1,3-butadiene. Synthesis of (5*S*,1'*R*,6'*R*)-*tert*-butyl 5-[6-(methoxycarbonyl)-3-oxocyclohexyl]-2,2-dimethyl-3,1-oxazolidinecarboxylate (7). A solution of the PFP ester **5h** (1.50 g, 3.43 mmol) and 2-trimethylsilyloxy-1,3-butadiene (3.0 mL) in toluene (3.0 mL) was heated at 130 °C in a sealed tube for 75 h. The reaction mixture was filtered through short-pass silica gel column (elution with Et_2O) and the resulting solution was concentrated in vacuo. The residue was dissolved in THF (50 mL) and H_2O (10 mL). To this solution was added 1 *N* NaOH (10 mL) and the solution was stirred at 0 °C for 1 h and at room temperature for 15 h. After removal of THF in vacuo, the aqueous solution was acidified with 1 *N* HCl to pH 2, saturated with NaCl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in MeOH (50 mL) and was treated with CH_2N_2 in ether. The resulting solution was concentrated in vacuo to give a crude residue, which, upon purification by column chromatography

on silica gel (ether/hexane = 1:4), gave **7** (1.00 g, 82%) as a colorless oil: $[\alpha]^{23}_{D}$ +16.6° (*c* 3.54, $CHCl_3$); FT-IR (film) 2986, 2976, 2944, 1726, 1703, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45, 1.62 (each s, 3 H), 1.48 (s, 9 H), 1.81 (m, 1 H), 2.21-2.46 (m, 6 H), 2.83 (ddd, 1 H, *J* = 4.2, 9.8, 9.8 Hz), 3.72 (m, 1 H), 3.73 (s, 3 H), 3.99 (dd, 1 H, *J* = 6.3, 9.2 Hz), 4.24 (m, 1 H); HRMS *m/z* calcd for $C_{18}H_{30}O_6N$ $(M+H)^+$ 356.2074, found 356.2073.

(5*S*,1'*R*,6'*S*)-*tert*-Butyl 5-[6-(methoxycarbonyl)-3-oxocyclohexyl]-2,2-dimethyl-3,1-oxazolidinecarboxylate (8). In a manner similar to that used to prepare **7**, the reaction of **6h** (2.00 g, 4.20 mmol) with 2-trimethylsilyloxy-1,3-butadiene (5.0 mL) in toluene (5.0 mL) gave a mixture of the recovered **6a** and **8**. The mixture was isolated by column chromatography on silica gel (ether/hexane = 4:1, then 1:1) to give recovered **6a** (250 mg, 22%) and the cycloadduct **8** (840 mg, 54%). **8**: Oily compound; $[\alpha]^{23}_{D}$ +2.28° (*c* 1.84, $CHCl_3$); FT-IR (film) 2986, 2976, 2944, 1726, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41, 1.50 (each s, total 9 H), 1.47, 1.48 (each s, total 6 H), 1.87, 1.91 (each ddd, total 1 H, *J* = 5.0, 5.0, 13.9 Hz), 2.21-2.42 (m, total 3 H), 2.87-3.01 (m, total 2 H), 2.72, 2.83 (each dd, total 1 H, *J* = 6.2, 14.1 Hz), 2.87-3.01 (m, total 2 H) 3.76, 3.78 (each s, total 3 H), 3.84, 4.40 (each m, total 2 H), 4.10, 4.15 (each m, total 1 H); HRMS *m/z* calcd for $C_{18}H_{30}O_6N$ $(M+H)^+$ 356.2074, found 356.2073.

(4"*S*,4a"*R*,8a"*R*)-*tert*-Butoxy-*N*-[1,6-dioxo(5,7,8,4a,8a-pentahydroisochroman-4-yl)]formamide (9). To a solution of **7** (50 mg, 0.14 mmol) in methanol (2.0 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (5.0 mg). The solution was stirred at room temperature for 15 h, and concentrated in vacuo to give an oily residue. To a solution of the crude residue in CH_2Cl_2 (2.0 mL) was added *dl*-camphorsulfonic acid (CSA) (5.0 mg). The mixture was stirred for 1 h, quenched with triethylamine and concentrated in vacuo to give an oily residue, which, upon column chromatography on silica gel (AcOEt/benzene = 3:7), gave **9** (28 mg, 71%) as colorless crystals (recrystallized from ether): mp 170.5 °C; $[\alpha]^{23}_{D}$ -24.1° (*c* 0.63, $CHCl_3$); FT-IR (film) 3339, 2974, 2930, 1713, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1,71 (dddd, 1 H, *J* = 4.5, 12.5, 14.0, 14.0 Hz), 1.92 (dddd, 1 H, *J* = 4.0, 8.1, 14.1, 14.1 Hz), 2.34 (dd, 1 H, *J* = 14.1, 14.1 Hz), 2.38 (ddd, 1 H, *J* = 6.5, 14.0, 14.0 Hz), 2.53 (ddd, 1 H, *J* = 2.1, 2.4, 6.5 Hz), 2.55-2.65 (m, 2 H), 2.76 (dddd, 1 H, *J* = 2.3, 4.0, 14.1, 14.1 Hz), 3.94 (m, 1 H), 4.12 (dd, 1 H, *J* = 4.8, 11.5 Hz), 4.48 (dd, 1 H, *J* = 5.7, 11.5 Hz), 4.74 (m, 1 H); HRMS *m/z* calcd for $C_{14}H_{22}O_5N$ $(M+H)^+$ 284.1498, found 284.1498.

(4"*S*,4a"*R*,8a"*S*)-*tert*-Butoxy-*N*-[1,6-dioxo(5,7,8,4a,8a-pentahydroisochroman-4-yl)]formamide (10). In a manner similar to that used to prepare **9**, the reaction of **8** (50 mg, 0.14 mmol) gave **10** (25 mg, 63%) as colorless crystals: mp 157.5-158.0 °C; $[\alpha]^{23}_{D}$ +19.2° (*c* 0.53, $CHCl_3$); FT-IR (film) 3339, 2974, 2930, 1713, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.92 (dddd, 1 H, *J* = 5.0, 5.0, 11.5, 15.0 Hz), 2.42 (dd, 1 H, *J* = 15.1, 15.1 Hz), 2.32 (dddd, 1 H, *J* = 1.5, 4.5, 4.5, 15.0 Hz), 2.51-2.67 (m, 3 H), 3.17 (m, 1 H), 3.59 (dddd, 1 H, *J* = 5.7, 7.2, 11.5, 12.5 Hz), 4.29 (dd, 1 H, *J* = 11.5, 11.5 Hz), 4.46 (dd, 1 H, *J* = 5.7, 11.5 Hz), 4.83 (m, 1 H); HRMS *m/z* calcd for $C_{14}H_{22}O_5N$ $(M+H)^+$ 284.1498, found 284.1492.

(4*S*,2*Z*)-Pentafluorophenyl 4-*tert*-butyldimethylsilyloxypent-2-enoate (11b). In a manner similar to that used to prepare **5h**, the reaction of (4*S*,2*Z*)-methyl 4-*tert*-butyldimethylsilyloxypent-2-enoate (**11a**)[13] (100 mg, 0.41 mmol) gave **11b** (140 mg, 88%) as a colorless oil: $[\alpha]^{23}_{D}$ +58.2° (*c* 3.57, $CHCl_3$); FT-IR (film) 2957, 2934, 2893, 2881, 1767, 1543, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06, 0.07 (each s, 3 H), 0.95 (s, 9 H), 1.38 (d, 1 H, *J* = 6.7 Hz), 5.94 (ddd, 1 H, *J* = 6.7, 6.7, 11.2 Hz), 5.37 (d, 1 H, *J* = 12.5 Hz), 6.55 (dd, 1 H, *J* = 11.2, 12.5 Hz); HRMS *m/z* calcd for $C_{17}H_{22}O_3F_5Si$ $(M+H)^+$ 397.1258, found 397.1258.

(1*R*,2*S*,1'*S*)-Methyl 4-oxo-2-(*tert*-butyldimethylsilyloxyethyl)cyclohexanecarboxylate (12). In a manner similar to that used to prepare **7**, the reaction of **11b** (70 mg, 0.18mmol) with 2-trimethylsilyloxy-1,3-butadiene (0.5 mL) in toluene (0.5 mL) at 130 °C for 120 h gave a mixture of **12** (47 mg, 87.5%) and its 2*R*-isomer (4 mg, 6.5%). **12**: Oily compound; $[\alpha]^{23}_{D}$ +7.6° (*c* 0.91, $CHCl_3$); FT-IR (film) 2957, 2934, 2859, 1767, 1543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (each s, 6 H), 0.87 (s, 9 H), 1.17 (d, 3 H, *J* = 6.3 Hz), 1.94 (m, 1 H), 2.03 (m, 1 H), 2.26 (m, 1 H), 2.32 (m, 1 H), 2.52 (dd, 1 H, *J* = 4.4, 15.5 Hz), 2.56 (m, 1 H), 2.66 (dd, 1 H, *J* = 9.8, 15.5 Hz), 2.91 (dd, 1 H, *J* = 5.0,

5.1 Hz), 3.73 (s, 3 H), 3.83 (ddd, 1 H, J = 6.3, 6.5, 6.5 Hz); HRMS m/z calcd for $C_{16}H_{31}O_4Si$ $(M+H)^+$ 315.1921, found 315.1989.

Cycloaddition of 5h with cyclopentadiene. A solution of **5h** (80.0 mg, 0.18 mmol) and freshly distilled cyclopentadiene (0.50 mL) in toluene (0.50 mL) was stood at room temperature in a sealed tube for 75 h. The reaction mixture was subjected to column chromatography on silica gel (ether/hexane = 1:4) to give a mixtureof **13** (**13a/13b**/1'*S*-endo/1'*S*-exo = 5:3:1:1) (70 mg, 77%) as a colorless oil. The mixture was further purified by preparative TLC (ether/hexane = 9/1, 2 times) to give diastereomerically pure **13a** (Rf 0.70, ether/hexane = 1:1) and **13b** (Rf 0.75, ether/hexane = 1:1), respectively, as an oily compound. α–Endo isomer **13a**: $[\alpha]^{23}_D$ -11.0° (c 0.33, $CHCl_3$); FT-IR (film) 2974, 2936, 1784, 1696, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.42, 1.45 (each s, total 9 H), 1.55, 1.72 (each s, total 6 H), 1.55, 1.58 (each d, 1 H, J = 7.2 Hz), 2.24 (ddd, 1 H, J = 2.5, 3.2, 6.2 Hz), 2.85 (dd, 1 H, J = 3.2, 5.5 Hz), 2.93, 3.16 (each m, total 1 H), 3.65, 3.67 (each dd, total 1 H, J = 2.8, 2.8 Hz), 3.85 (m, 2 H), 6.28 (dd, 1 H, J = 3.4, 5.2 Hz), 6.46 (dd, 1 H, J = 2.8, 5.2 Hz); HRMS m/z calcd for $C_{26}H_{28}O_7NF_5$ $(M+H)^+$ 504.1810, found 504.1811. α–Exo isomer **13b**: $[\alpha]^{23}_D$ +19.0° (c 1.03, $CHCl_3$); FT-IR (film) 2976, 2876, 1778, 1697, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.48, 1.5 0 (each s, total 9 H), 1.50, 1.57, 1.64, 1.69 (each s, total 6 H), 1.72, 1.80 (each d, 1 H, J = 7.2 Hz), 2.19, 2.20 (each ddd, 1 H, J = 1.8, 4.7, 4.7 Hz), 2.87, 2.91 (each dd, total 1 H, J = 3.8, 3.8 Hz), 2.89, 2.92 (each m, total 1 H), 3.40 (m, 1 H), 3.79 (dd, 1 H, J = 5.3, 8.9 Hz), 3.89, 4.03 (each dd, total 1 H, J = 5.3, 10.6 Hz), 3.96, 3.98 (each dd, 1 H, J = 5.3, 5.3 Hz), 6.09, 6.10 (each dd, 1 H, J = 2.7, 6.1 Hz), 6.32 (dd, 1 H, J = 2.5, 6.1 Hz); HRMS m/z Calcd for $C_{26}H_{28}O_7NF_5$ $(M+H)^+$ 504.1810, found 504.1834.

Cycloaddition of 6h with cyclopentadiene. In a manner similar to that used for the cycloaddition of **5h**, a solution of **6h** (80.0 mg, 18.0 mmol) and cyclopentadiene (0.50 mL) in toluene (0.50 mL) was heated at 50 °C for 72 h gave a mixture of **14** (**14a/14b**/1'*S*-endo/1'*S*-exo = 40:4:3:1) (65 mg, 72%). Further purification was performed with preparative TLC (ether/hexane = 1:9) to give the α-endo isomer **14a** as a colorless oil: $[\alpha]^{23}_D$ +20.3° (c 0.49, $CHCl_3$); FT-IR (film) 2984, 1778, 1696, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.42, 1.48 (each d, 1 H, J = 6.0 Hz), 1.47, 1.49 (each s, total 9 H), 1.55, 1.60, 1.66, 1.72 (each s, total 6 H), 2.70 (ddd, 1 H, J = 3.5, 8.0, 8.0 Hz), 2.85 (m, 1 H), 3.40 (m, 1 H), 3.47 (dd, 1 H, J = 3.4, 9.2 Hz), 3.60 (d, 1 H, J = 9.3 Hz), 3.98 (dd, 1 H, J = 5.0, 9.3 Hz), 4.10 (dd, 1 H, J = 5.0, 11.9 Hz), 6.09 (dd, 1 H, J = 2.9, 5.5 Hz), 6.64 (dd, 1 H, J = 2.9, 5.5 Hz); HRMS m/z calcd for $C_{26}H_{28}O_7NF_5$ $(M+H)^+$, 504.1808, found 504.1834.

Cycloaddition of 5h with isoprene. In a manner similar to that used for the cycloaddition of **5h** with cyclopentadiene, a solution of **5h** (110 mg, 0.25 mmol) and isoprene (0.5 mL) in toluene (0.5 mL) was heated at 130 °C for 3 days. Purification of the crude product by column chromatography on silica gel (ether/hexane = 1:4) gave an inseparable mixture of **15** (**15a/15b** = 3:2) (100 mg, 80%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.75 (m, total 18 H), 1.95-3.04 (m, 6 H), 3.80 (m, 0.6 H), 4.04 (m, 0.4 H), 4.15 (m, 0.6 H), 4.70 (m, 0.6 H), 4.45 (m, 0.4 H), 5.36-5.44 (m, 1 H).

Cycloaddition of 6h with isoprene. In a manner similar to that used for the cycloaddition of **5h** with cyclopentadiene, a solution of **6h** (110 mg, 0.25 mmol) and isoprene (0.5 mL) in toluene (0.5 mL) was heated at 130 °C for 5 days. Purification of the crude product by column chromatography on silica gel (ether/hexane = 1:4) gave an inseparable mixture of **16** (**16a/16b** = 3:2) (105 mg, 68%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.75 (m, total 17.50 H), 1.84-2.40 (m, 4.15 H), 3.16 (m, 0.50 H), 3.22 (m, 0.33 H), 3.75-4.32 (m, 3 H), 5.13 (m, 0.50 H), 5.37 (m, 0.33 H), 6.14, 6.15 (each d, total 0.17 H, J = 16.0 Hz), 6.60, 6.72 (each dd, total 0.17 H, J = 8.2, 11.8 Hz).

Cycloaddition of 5h with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene. In a manner similar to that used for the cycloaddition of **5h** with cyclopentadiene, a solution of **5h** (50 mg, 0.11 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (0.5 mL) in toluene (0.5 mL) was heated at 80 °C for 5 days. The reaction mixture was concentrated in vacuo and stirred with silica gel (50 mg) in benzene (1 mL) at room temperature for 1 h. Purification of the crude product by column chromatography on silica gel (ether/hexane = 1:4) gave a mixture of **17** (**17a/17b** = 2.5:1) (45 mg,

84%) as a colorless oil. Further purification of the mixture was performed by preparative TLC (ether/hexane = 1:4, 2 times) to give diastereomerically pure **17a** (*Rf* 0.46, ether/hexane = 1:1)) and **17b** (*Rf* 0.30, ether/hexane = 1:1), respectively, as a colorless oil. 3'*R*-Isomer **17a**: $[\alpha]^{23}_{D}$ -27.5° (*c* 0.65, $CHCl_3$); FT-IR (film) 2978, 2934, 1790, 1724, 1694, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.42, 1.50 (each s, total 9 H), 1.55, 1.70 (each s, 3 H), 2.33 (dd, 1 H, *J* = 13.8, 13.8 Hz), 2.55 (dd, 1 H, *J* = 1.8, 15.8 Hz), 2.58 (dd, 1 H, *J* = 1.8, 13.8 Hz), 2.77 (dddd, 1 H, *J* = 1.8, 4.1, 12.8, 12.8 Hz), 2.90 (ddd, 1 H, *J* = 2.6, 2.6, 15.1 Hz), 3.21 (dd, 1 H, *J* = 2.6, 12.8 Hz), 3.34 (s, 3 H), 3.75 (dd, 1 H, *J* = 1.8, 9.8 Hz), 4.05 (dd, 1 H, *J* = 7.3, 9.8 Hz), 4.41 (ddd, 1 H, *J* = 2.6, 2.6, 2.9 Hz), 4.54 (ddd, 1 H, *J* = 1.8, 1.8, 7.3 Hz); HRMS *m/z* calcd for $C_{24}H_{29}O_7NF_5$ $(M+H)^+$, 538.1864, found 538.1844. 3'*S*-Isomer **17b**: $[\alpha]^{23}_{D}$ -13.0° (*c* 1.62, $CHCl_3$); FT-IR (film) 2980, 2937, 1780, 1723, 1697, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.39, 1.43 (each s, total 9 H), 1.46, 1.50 (each s, 3 H), 2.24 (dd, 1 H, *J* = 12.4, 14.8 Hz), 2.45 (dd, 1 H, *J* = 2.1, 15.2 Hz), 2.48 (dd, 1 H, *J* = 2.1, 14.8 Hz), 2.77 (m, 1 H), 2.82 (ddd, 1 H, *J* = 2.5, 2.5, 15.2 Hz), 3.27 (s, 3 H), 3.31 (m, 1 H), 3.68 (dd, 1 H, *J* = 1.2, 9.6 Hz), 4.01 (dd, 1 H, *J* = 7.2, 9.6 Hz), 4.32 (ddd, 1 H, *J* = 2.1, 2.1, 2.5 Hz), 4.41 (m, 1 H); HRMS *m/z* calcd for $C_{24}H_{29}O_7NF_5$ $(M+H)^+$ 538.1864, found 538.1841.

Cycloaddition of 6h with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene. In a manner similar to that used for the cycloaddition of **5h** with cyclopentadiene, a solution of **6h** (50 mg, 0.11 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (0.5 mL) in toluene (0.5 mL) was heated at 80 °C for 5 days. The reaction mixture was concentrated in vacuo and stirred with silica gel (50 mg) in benzene (1 mL) at room temperature for 1 h. Purification of the crude product by column chromatography on silica gel (ether/hexane = 1:4) gave a mixture of **18** (**18a/18b** = 3:1) (40 mg, 67%) as a colorless oil. Further purification of the mixture was performed by preparative TLC (ether/hexane = 1:4, 2 times) to give diastereomerically pure**18a** (*Rf* 0.65, ether/hexane = 1:1)) and **18b** (*Rf* 0.55, ether/hexane = 1:1) as a colorless oil, respectively. 3'*S*-Isomer **18a**: $[\alpha]^{23}_{D}$ -13.4° (*c* 0.55, $CHCl_3$); FT-IR (film) 2976, 2931, 1782, 1720, 1694, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.50, 1.52 (each s, total 9 H), 1.56, 1.70 (each s, 3 H), 2.00 (m, 1 H), 2.40 (dd, 1 H, *J* =4.1, 14.1 Hz), 2.51 (dd, 1 H, *J* = 3.3, 15.4 Hz), 2.57 (ddd, 1 H, *J* = 4.1, 10.0, 10.0 Hz), 2.71 (dd, 1 H, *J* = 2.9, 15.4 Hz), 3.02 (dd, 1 H, *J* = 14.0, 14.0 Hz), 3.38 (s, 3 H), 3.44 (dd, 1 H, *J* = 4.1, 4.1 Hz), 3.84 (dd, 1 H, *J* = 5.1, 9.3 Hz), 3.92 (d, 1 H, *J* = 9.3 Hz), 4.30 (dd, 1 H, *J* = 5.1, 10.0 Hz), 4.36 (ddd, 1 H, *J* = 2.9, 2.9, 3.2 Hz); HRMS *m/z* calcd for $C_{24}H_{29}O_7NF_5$ $(M+H)^+$ 538.1864, found 538.1879. 3'*R*-Isomer **18b**: $[\alpha]^{23}_{D}$ -6.4° (*c* 0.33, $CHCl_3$); FT-IR (film) 2978, 2936, 1778, 1721, 1697, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42, 1.48 (each s, total 9 H), 1.52, 1.55, 1.62, 1.70 (each s, total 6 H), 1.70 (m, 1 H), 2.35 (ddd, 1 H, *J* = 3.5, 3.5, 14.2 Hz), 2.69 (m, 1 H), 2.80 (m, 1 H), 3.01 (m, 1 H), 3.36, 3.38 (each s, total 3 H), 3.46 (dd, 1 H, *J* = 7.1, 14.1 Hz), 3.50 (m, 1 H), 3.89 (m, 1 H), 4.01 (dd, 1 H, *J* = 14.1, 14.1 Hz), 4.23 (m, 1 H); HRMS *m/z* calcd for $C_{24}H_{29}O_7NF_5$ $(M+H)^+$ 538.1864, found 538.1846.

(1'*R*,2'*R*,3'*S*,7'*S*,8'*S*)-*tert*-Butoxy-*N*-(5-oxa-6-oxotricyclo[6.2.1.0^{2,7}]undec-9-en-3-yl)formamide (19). In a manner similar to that used to prepare **9**, treatment of **13b** (8.0 mg, 16.0 mmol) gave **19** (3.0 mg, 65%) as an amorphous powder: $[\alpha]^{23}_{D}$ -12.5° (*c* 0.51, $CHCl_3$); FT-IR (film) 1722, 1695, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33, 1.59 (d, 1 H, *J* = 9.0 Hz), 1.46 (s, 9 H), 2.38 (ddd, 1 H, *J* = 2.5, 10.5, 10.5 Hz), 3.05 (dd, 1 H, *J* = 4.0, 10.5 Hz), 3.08 (m, 1 H), 3.25 (m, 1 H), 3.38 (m, 1 H), 3.86 (dd, 1 H, *J* = 10.0, 10.0 Hz), 4.21 (dd, 1 H, *J* = 3.5, 10.0 Hz), 4.42 (m, 1 H), 6.20 (m, 1 H), 6.33 (dd, 1 H, *J* = 2.3, 5.5 Hz).

(4"*S*,4a"*R*,8a"*R*)-*tert*-Butoxy-*N*-(6-methyl-1-oxo(5,8,4a,8a-tetrahydroisochroman-4-yl)formamide (20a) and its methyl isomer (20b). In a manner similar to that used to prepare **9**, treatment of the mixture of **15** (**15a/15b** = 3:2) (50 mg, 0.099 mmol) gave a mixture of δ-lactones (**20a/20b** = 3:2) (15 mg, 54%). Further purification of the mixture was performed by preparative TLC (ether/hexane = 1:1, 2 times) to afford **20a** and **20b**, respectively, as an amorphous solid. **20a**: $[\alpha]^{23}_{D}$ -40.6° (*c* 0.33, $CHCl_3$); FT-IR (film) 1738, 1686, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.48, 1.59 (each s, total 9 H), 1.70 (s, 3 H), 1.74 (m, 1 H), 2.04 (ddd, 1 H, *J* = 5.0, 14.0, 14.0 Hz), 2.22 (m, 1 H), 2.32-2.40 (m, 2 H), 2.47 (m, 1 H), 3.80 (m, 1 H), 4.12 (dd, 1 H, *J* = 5.0, 11.7 Hz), 4.40 (dd, 1 H, *J* = 4.0, 11.7 Hz), 4.70 (m, 1 H), 5.43 (m, 1 H); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1706, found 282.1718. **20b**: $[\alpha]^{23}_{D}$ -30.5° (*c* 0.22, $CHCl_3$); FT-IR (film) 1738, 1701, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.45, 1.57 (each s, total 9 H), 1,70 (s, 3 H), 2.00-2.06 (m, 2 H), 2.11-2.26 (m, 2 H), 2.39 (ddd, 1 H, *J* = 5.9, 11.5, 13.0 Hz), 2.63 (ddd, 1 H, *J* =

3.6, 5.1, 12.6 Hz), 4.05 (m, 1 H), 4.46 (dd, 1 H, J = 2.1, 10.6 Hz), 4.78 (dd, 1 H, J = 2.8, 10.6 Hz), 4.87 (m, 1 H), 5.40 (m, 1 H); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1706, found 282.1707.

(4"*S*,4a"*R*,8a"*S*)-*tert*-Butoxy-*N*-(6-methyl-1-oxo(5,8,4a,8a-tetrahydroisochroman-4-yl)formamide (21a) and its methyl isomer (21b). In a manner similar to that used to prepare **9**, treatment of the mixture of **16** (**16a/16b** = 3:2) (50 mg, 0.099 mmol) gave a mixture of δ-lactones (**21a/21b** = 3:2) (10 mg, 35%). Further purification of the mixture was performed by preparative TLC (ether/hexane = 1:1, 2 times) to afford **21a** and **21b**, respectively, as an amorphous solid. **21a**: $[\alpha]^{23}_D$ -12.5° (*c* 0.51, $CHCl_3$); FT-IR (film) 1745, 1682, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.50 (s, 9 H), 1.60 (s, 3 H), 1.95 (m, 2 H), 2.12-2.30 (m, 2 H), 2.59 (m, 1 H), 3.00 (ddd, 1 H, J = 5.0, 5.0, 5.2 Hz), 3.79 (m, 1 H), 4.06 (dd, 1 H, J =7.9, 11.6 Hz), 4.54 (dd, 1 H, J = 4.4, 11.6 Hz), 4.67 (m, 1 H), 5.36 (m, 1 H); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1706, found 282.1705. Methyl isomer **21b**: $[\alpha]^{23}_D$ -11.0° (*c* 2.1, $CHCl_3$); FT-IR (film) 1736, 1701, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, -20 °C) δ 1.47, 1.58 (each s, total 9 H), 1,70 (s, 3 H), 1.93 (m, 1 H), 2.03-2.25 (m, 2 H), 2.56 (m, 1 H), 2.74 (m, 1 H), 2.80 (ddd, 1 H, J =1.1, 5.0 Hz), 4.11 (dd, 1 H, J = 7.4, 11.8 Hz), 4.38 (m, 1 H), 4.53 (dd, 1 H, J = 5.8, 11.8 Hz), 4.63 (m, 1 H), 5.39 (m,1 H); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1706, found: 282.1718.

(5*S*,1'*R*,6'*R*)-*tert*-Butyl 5-[6-(methoxycarbonyl)-3-methylenecyclohexyl]-2,2-dimethyl-3,1-oxazolidinecarboxylate (22). To a solution of **7** (2.50 g, 7.04 mmol) in THF (100 mL) at -78 °C was added a 0.5 M toluene solution of μ-chloro-μ-methylene-[bis(cyclopentadienyl)titanum]dimethylaluminum (Tebbe reagent) (15 mL, 7.50 mmol). The reaction was stirred at -78 °C for additional 1 h, and then gradually warmed to 0 °C (1 h). The mixture was poured into saturated aqueous $NaHCO_3$ solution, filtered through a celite pad and the filtrate was extracted with ether for several times. The combined extracts were washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give **22** (1.80 g, 72%) as a colorless oil: $[\alpha]^{23}_D$ +15.4° (*c* 0.42, $CHCl_3$); FT-IR (film) 2978, 2943, 2878, 1734, 1697, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44, 1.46 (each s, 3 H), 1.47 (s, 9 H), 1.56 (m, 1 H), 1.91 (dd, 1 H, J= 12.4, 12.4 Hz), 2.20, 2.33 (each m, 2 H), 2.51 (dd, 1 H, J = 3.9, 12.1 Hz), 3.67 (s, 3 H), 3.76 (dd, 1 H, J = 2.0, 8.1 Hz), 3.97 (dd, 1 H, J = 5.2, 8.1 Hz), 4.16 (m, 1 H), 4.67 (m, 2 H); HRMS *m/z* calcd for $C_{19}H_{32}O_5N$ $(M+H)^+$ 354.2281, found 354.2274.

(2*S*,1'*R*,2'*R*)-2-(*N*-*tert*-Butoxycarbonyl-5-methylenecyclohexyl)glycine methyl ester (24). To a solution of **22** (960 mg, 2.72 mmol) in MeOH (300 mL) at room temperature was added PPTS (400 mg). After stirring at 60 °C for 30 min, the solvent was removed in vacuo and the residue was filtrated through a short pass column of silica gel (ether) to give crude residue. To a solution of the residue in DMF (40 mL) was added molecular sieves 4A (10 g) and pyridinium dichromate (5.10 g, 14.0 mmol). The reaction was stirred at room temperature for 15 h, poured into ether (200 mL), and filtered through a celite pad. The filtrate was concentrated in vacuo to give a crude residue, which was dissolved in MeOH (50 mL). The solution was treated with CH_2N_2 in ether. After removal of the solvent in vacuo, the residue was dissolved in ether (300 mL), washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ether/hexane = 1:4, then 1:1) to give **24** (450 mg, 48%) and the δ-lactone **23** (245 mg, 31%), respectively, as colorless crystals. **24** (Recrystallized from hexane): mp 89.0-89.5 °C; $[\alpha]^{23}_D$ +59.9° (*c* 1.16, $CHCl_3$); FT-IR (film) 3366, 2947, 2980, 1736, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.51 (ddd, 1 H, J = 4.6, 11.3, 11.3 Hz), 1.87 (ddd, 1 H, J= 1.0, 11.3, 11.3 Hz), 1.95-2.12 (m, 3 H), 2.29-2.39 (m, 3 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 4.63 (dd, 1 H, J= 1.0, 8.5 Hz), 4.65 (d, 1 H, J = 1.5 Hz), 4.69 (d, 1 H, J = 1.5 Hz), 5.05 (d, 1 H, J = 8.5 Hz); HRMS *m/z* calcd for $C_{17}H_{28}O_6N$ $(M+H)^+$ 342.1917, found 342.1940. δ-Lactone **23** (Recrystallized from ether): mp 154.5-155.0 °C; $[\alpha]^{23}_D$ -24.0° (*c* 1.16, $CHCl_3$); FT-IR (film) 3351, 2978, 2942, 1742, 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36-1.51 (m, 2 H), 1.45 (s, 9 H), 2.01 (dd, 1 H, J = 12.1, 16.0 Hz), 2.06 (m, 1 H), 2.22-2.36 (m, 2 H), 2.43 (ddd, 1 H, J = 1.8, 1.8, 13.4 Hz), 2.69 (dd, 1 H, J = 2.4, 13.4 Hz), 3.83 (m, 1 H), 4.13 (dd, 1 H, J = 3.9, 12.1 Hz), 4.40 (dd, 1 H, J = 4.2, 12.1 Hz), 4.65 (d, 1 H, J = 7.9 Hz), 4.76 (d, 1 H, J = 1.7 Hz), 4.74 (d, 1 H, J = 1.7 Hz); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1740, found 282.1705. To a solution of the δ-lactone **23** (500 mg, 1.80 mmol) in THF (20 mL) and H_2O (10 mL) was added 1 *N* NaOH (10 mL). The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 15 h. After removal of THF in vacuo, the

mixture was washed with ether and the aqueous layer was acidified with 1 *N* HCl to pH 2, saturated with NaCl and extracted with ether for several times. The combined extracts were washed with brine and dried over $MgSO_4$ and concentrated in vacuo to give crude glycinol. This was subjected to the same sequence of reactions as above ((i) PDC oxidation and (ii) esterification with diazomethane) to give the recovered **23** (100 mg, 16%) and the desired product **24** (200 mg, 39%).

(2*S*,1'*R*,2'*R*)-2-(2-Carboxy-5-methylencyclohexyl)glycine (CHG-II) (3). To a solution of **24** (100 mg, 0.69 mmol) in THF (2.8 mL) was added 1 *N* NaOH (0.7 mL, 0.7 mmol). The solution was stirred at room temperature for 48 h and concentrated in vacuo. The residue was dissolved into H_2O and washed with ether. The aqueous layer was acidified with 1 *N* HCl to pH 2, saturated with NaCl, extracted with AcOEt, dried over $MgSO_4$ and concentrated in vacuo to give an oily residue. A solution of the residue in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) was stirred at 0 °C for 30 min and at room temperature for 30 min. The reaction mixture was concentrated in vacuo to give a crude crystalline solid. The crude crystals were dissolved with H_2O (5 mL) and evaporated in vacuo. This process was repeated for several times to remove trace amounts of TFA. A solution of the crude product in H_2O was subjected to a column of ion-exchange resin (Dowex 50W x 4, H_2O then 1% aqueous NH_3) to give **3** (58 mg, 93%) as colorless crystals: mp 109-110.0 °C; $[\alpha]^{23}_D$ +35.3° (*c* 1.05, H_2O/TFA = 1:1); FT-IR (film) 3070, 3040, 2940, 2918, 1620, 1559 cm^{-1}; ^1H NMR (400 MHz, D_2O/TFA-d = 2:1) δ 1.47 (dddd, 1 H, *J* = 3.7, 12.5, 12.5, 12.5 Hz), 2.00 (ddd, 1 H, *J* = 2.6, 12.3,12.3 Hz), 2.12 (ddd, 1 H, *J* = 2.0, 12.3,12.3 Hz), 2.16 (m, 1 H), 2.24-2.35 (m, 2 H), 2.38 (ddd, 1 H, *J* = 3.0, 3.0, 15.9 Hz), 2.55 (ddd, 1 H, *J* = 3.2, 10.5, 10.5 Hz), 4.12 (d, 1 H, *J* = 2.3 Hz), 4.70 (s, 1 H), 4.72 (s, 1 H); HRMS *m/z* calcd for $C_{19}H_{16}O_4N$ $(M+H)^+$ 214.1079, found 214.1081.

(5*S*,1'*R*,6'*S*)-*tert*-Butyl 5-[6-(methoxycarbonyl)-3-methylenecyclohexyl]-2,2-dimethyl-3,1-oxazolidinecarboxylate (25). In a manner similar to that used to prepare **22**, **25** (1.8 g, 91%) was obtained from **8** (2.00 g, 5.60 mmol). **25**: Oily compound; $[\alpha]^{23}_D$ +8.3° (*c* 0.31, $CHCl_3$); FT-IR (film) 2978, 2939, 2876, 1734, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46, 1.48 (each s, 3 H), 1.57 (s, 9 H), 1.77-2.20 (m, 4 H), 2.37 (m, 1 H), 2.58 (m, 1 H), 2.79 (m, 1 H), 3.66, 3.67 (each s, total 3 H), 3.81, 3.99 (each m, total 2 H), 4.10, 4.15 (each m, total 1 H), 4.64 (m, 2 H); HRMS *m/z* calcd for $C_{19}H_{32}O_5N$ $(M+H)^+$ 354.2280, found 354.2316.

(2*S*,1'*R*,2'*S*)-2-(*N*-*tert*-Butoxycarbonyl-5-methylenecyclohexyl)glycine methyl ester (27). In a manner similar to that used to prepare **24**, **27** (1.0 g, 46%) and **26** (300 mg, 29%) were obtained from **25** (2.1 g, 5.95 mmol), respectively, as colorless crystals. **27** (Recrystallized from hexane): mp 104.5-105.0 °C; $[\alpha]^{23}_D$ -16.8° (*c* 1.16, $CHCl_3$); FT-IR (film) 3364, 2984, 2955, 1745, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.74 (m, 1 H), 2.02 (m, 1 H), 2.13 (m, 1 H), 2.15 (dd, 1 H, *J* = 4.5, 13.2 Hz), 2.25-2.35 (m, 2 H), 2.53 (dd, 1 H, *J* = 9.7, 13.2 Hz), 2.73 (ddd, 1 H, *J* = 3.8, 3.8, 5.4 Hz), 3.72, 3.76 (each s, 3 H), 4.51 (dd, 1 H, *J* = 4.8, 4.8 Hz), 4.61, 4.70 (each s, 1 H), 5.14 (d, 1 H, *J* = 4.8 Hz); HRMS *m/z* calcd for $C_{17}H_{28}O_6N$ $(M+H)^+$ 342.1916, found 342.1925. **26** (Recrystallized from ether): colorless crystals; mp 154.5-155.0 °C; $[\alpha]^{23}_D$ +45.0° (*c* 0.41, $CHCl_3$); FT-IR (film) 3340, 2978, 2939, 1748, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 2.02 (dd, 1 H, *J* =3.2, 10.7 Hz), 1.56 (m, 1 H), 2.16 (m, 2 H), 2.28 (m, 1 H), 2.41 (dd, 1 H, *J* = 4.4, 13.2 Hz), 2.95 (ddd, 1 H, *J* = 4.9, 4.9, 4.9 Hz), 3.73 (m, 1 H), 4.12 (dd, 1 H, *J* = 10.0, 12.2 Hz), 4.48 (dd, 1 H, *J* = 6.4, 12.1 Hz), 4.69 (m, 1 H), 4.71, 4.74 (each m, 1 H); HRMS *m/z* calcd for $C_{15}H_{24}O_4N$ $(M+H)^+$ 282.1705, found 282.1710.

(2*S*,1'*R*,2'*S*)-2-(2-Carboxy-5-methylencyclohexyl)glycine (CHG-IV) (4). In a manner similar to that used to prepare **3**, **4** (50 mg, 90%) was prepared from **27** (100 mg, 0.69 mmol) as colorless crystals: mp 167 °C; $[\alpha]^{23}_D$ -30.7° (*c* 0.55, H_2O/TFA = 1:1); FT-IR (film) 3071, 3042, 2984, 1667, 1593 cm^{-1}; ^1H NMR (400 MHz, D_2O/TFA-d = 4:1) δ 1.53 (dddd, 1 H, *J* = 4.2, 4.2, 18.6, 18.6 Hz), 2.00 (ddd, 1 H, *J* = 4.4, 12.0, 12.0 Hz), 2.17 (dd, 1 H, *J* = 8.3, 8.3 Hz), 2.24 (m, 1 H), 2.28 (m, 1 H), 2.35 (dd, 1 H, *J* = 8.3, 8.3 Hz), 2.87 (ddd, 1 H, *J* = 3.6, 3.6, 3.6 Hz), 4.17 (d, 1 H, *J* = 7.2 Hz), 4.65, 4.67 (each s, 1 H); HRMS *m/z* calcd for $C_{10}H_{16}O_4N$ $(M+H)^+$ 214.1079, found 214.1079.

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10. Only slight differences in the IR (absorption of the unsaturated ester group) and ^{1}H NMR (chemical shift of C-2H and C-3H, and *J* value between C-2H and C-3H) data between each set of the alkyl or phenyl ester and fluorinated or PNP ester were observed. The ^{1}H NMR signals of both C-2H and C-3H appeared as a set of d (C-2H) or dd (C-3H) due to the presence of the rotamers around the *N*-Boc group. *E*-Isomers (δ): **5b** (5.85 and 5.91 (C-2H), 6.78 and 6.81 (C-3H), *J* = 15.6 Hz) and **5c** ((5.95 and 6.05 (C-2H), 6.94 and 6.97 (C-3H), *J* = 16.1 Hz); **5d** ((5.90 and 5.95 (C-2H), 6.80 and 6.85 (C-3H), *J* = 15.5 Hz) and **5e** ((6.02 and 6.07 (C-2H), 7.05 and 7.08 (C-3H), *J* = 15.8 Hz); **5f** (6.10 and 6.15 (C-2H), 7.02 and 7.06 (C-3H), *J* = 15.5 Hz), **5g** (6.11 and 6.15 (C-2H), 7.10 (C-3H), *J* = 15.7 Hz) and **5h** (6.13 and 6.18 (C-2H), 7.14 and 7.17 (C-3H), *J* = 16.0 Hz). *Z*-Isomers (δ): **6b** (5.80 and 5.81 (C-2H), 6.22 and 6.32 (C-3H), *J* = 11.0 Hz) and **6c** ((5.90 and 5.93 (C-2H), 6.40 and 6.49 (C-3H), *J* = 11.2 Hz); **6d** (5.78 and 5.79 (C-2H), 6.21 and 6.23 (C-3H), *J* = 11.0 Hz) and **6e** (5.97 and 5.98 (C-2H), 6.33 and 6.47 (C-3H), *J* = 11.2 Hz); **6f** (6.06 and 6.09 (C-2H), 6.45 and 6.55 (C-3H), *J* = 10.8 Hz), **6g** (6.07 and 6.08 (C-2H), 6.53 and 6.59 (C-3H), *J* = 11.3 Hz) and **6h** (6.13 and 6.15 (C-2H), 6.60 and 6.72 (C-3H), *J* = 11.7 Hz). IR spectral data (cm^{-1}) of the *E*-Isomers: **5b** (1701, 1671) and **5c** (1699, 1670); **5d** (1703, 1660) and **5e** (1701, 1658); **5f** (1699, 1657), **5g** (1697, 1656) and **5h** (1703, 1657). Z-Isomers: **6b** (1703, 1653) and **6c** (1703, 1647); **6d** (1705, 1651) and **6e** (1705, 1643); **6f** (1701, 1647), **6g** (1697, 1648) and **6h** (1707, 1647).
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12. Similar differences in ^{13}C chemical shift between ethyl acrylate and 2,2,2-trifluoroethyl (TFE) acrylate

were observed. Ethyl acrylate ($CDCl_3$): δ 166.14, 128.70, 130.27; 2,2,2-trifluoroethyl acrylate ($CDCl_3$): δ 164.35, 128.61, 132.99. The Δ(TFE - ethyl) values are as follows: C1 (-1.79), C2 (-0.09), and C3 (+2.72).

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