Asymmetric Diels–Alder Reaction Using (*S*)-Pyroglutamic Acid Derivatives as Chiral Dienophiles[1)]

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Asymmetric Diels–Alder reaction of cyclopentadiene with chiral dienophiles (3) derived from (*S*)-pyroglutamic acid derivatives was performed in the presence of a Lewis acid such as diethylaluminum chloride in toluene to afford the cycloadducts with high diastereoselectivity.

Keywords asymmetric reaction; Diels–Alder reaction; (*S*)-pyroglutamic acid; chiral dienophile; diethylaluminum chloride; (2+4)cycloaddition

Highly selective asymmetric Diels–Alder reactions have recently been developed employing chiral dienophiles,[2)] chiral dienes,[3)] and chiral Lewis acids as catalysts.[4)] Recently, Koga *et al.*,[5)] reported asymmetric Diels–Alder reactions using an (*S*)-pyroglutamic acid derivative as a chiral auxiliary. We have already described the synthetic utility of optically active pyroglutamic acid derivatives for the asymmetric synthesis of β-lactams by (2+2)cycloaddition[6)] and for natural product synthesis[7)] such as (−)-swainsonine. In a continuation of our work on the utility of optically active pyroglutamic acid derivatives for asymmetric reactions, we describe here the results of asymmetric Diels–Alder reactions employing (*S*)-pyroglutamic acid derivatives (**2**) as chiral dienophiles.

The dienophiles (**2**) were prepared by *N*-acylation of (*S*)-5-(methoxymethoxy)methyl-2-pyrrolidinone (**1**).[6)] Compound **1** was treated with sodium hydride in tetrahydrofuran (THF), followed by addition of acryloyl chloride or (*E*)-crotonyl chloride to afford the corresponding carboximides (**2a** and **2b**) in 38% and 73% yields, respectively. The reaction of the carboximides (**2**) with a large excess of cyclopentadiene in methylene chloride or toluene with or without a Lewis acid such as diethylaluminum chloride gave a diastereomeric mixture of *endo* and *exo* cycloadducts. Since the isomers could not be separated by column chromatography on silica gel, authentic samples of each of the products of this cycloaddition reaction were prepared by condensation of the corresponding racemic *endo* and *exo* acids with the sodium salt of **1** *via* the mixed anhydride in THF, and proton nuclear magnetic resonance (^{1}H-NMR) analysis was used to distinguish among four isomers. *endo*/*exo* ratios and *endo* diastereoface selectivities of the cycloadducts of **2** with cyclopentadiene were deduced by ^{1}H-NMR analysis. The absolute configuration of the major *endo* diastereomer and the optical purity of the *endo* isomer were determined based on the optical rotation after the conversion of **3** to the corresponding methyl ester (**5**). Reaction of the cycloadduct (Table I, run 1) with sodium methoxide (1.6 eq) in methanol at room temperature gave a mixture of an amido-ester (**4**) and the desired methyl ester (ratio about 2:3 by ^{1}H-NMR of the crude product). Although the *endo* isomer (**5a**, $[\alpha]_D^{20}$ −22° (*c*=1, 95% EtOH), corresponding to 16% ee, lit.[8)] $[\alpha]_D^{20}$ −141° (95% EtOH)) was isolated by column chromatography on silica gel, the same treatment of **3b** gave exclusively the amido-ester. Therefore, the adducts (**3**) were hydrolyzed (concentrated HCl–MeOH, reflux, then aqueous KOH) to furnish the corresponding acids and subsequent esterification with diazomethane provided the methyl esters in 28—59% yields, and the absolute structures of the major diastereomers were found to be as illustrated in Chart 1. The results are summarized in Table I. Very high selectivity (*endo*/*exo*=97/3, 95% de) was observed when diethylalu-

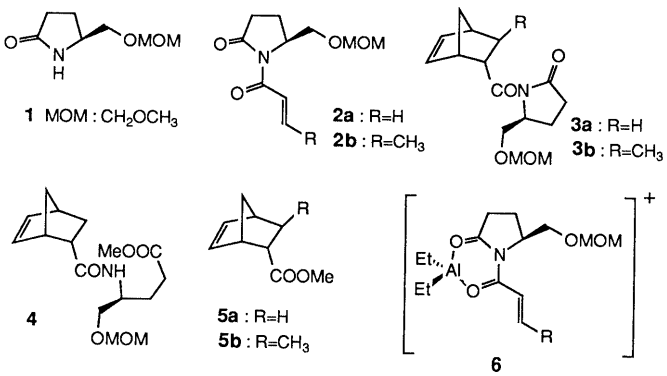

Chart 1

TABLE I. Asymmetric Diels–Alder Reaction of **2** with Cyclopentadiene

Run	Dienophile	Et_2AlCl (eq)	Solvent	Temperature (°C)	Time	Cycloadduct (**3**)			Methyl ester (**5**)	
						Yield (%)	*endo*/*exo*[a)]	Diastereomeric[a,c)] excess (%)	$[\alpha]_D$ (°, 95% EtOH)[e)]	Optical purity (%)
1	**2a**	None	Toluene	20	20 h	48	81/19	15[d)]	−28.2	20
2	**2a**	1	CH_2Cl_2	−78	10 min	20	96/4[b)]	66	−95.9	68
3	**2a**	1	Toluene	−78	10 min	53	94/6[b)]	70	−101.5	72
4	**2b**	None	Toluene	20	10 h	No Reaction	—	—	—	—
5	**2b**	1.12	Toluene	−78	1.2 h	62	97/3	95	−146.8	95

a) Determined by ^{1}H-NMR analysis of the crude cycloadduct. *b*) Determined by ^{1}H-NMR analysis of the corresponding methyl ester **5a**. *c*) For the *endo* isomer. *d*) This value is approximate due to the overlapping of signals. *e*) Value of $[\alpha]_D$ −141° and −155.4° were used for optically pure **5a** and **5b**, respectively. See references 8 and 9.

minum chloride was used at −78 °C in toluene for the synthesis of **5b**.

The stereochemical course could be explained by considering the Lewis acid–dienophile complex **6**,[2c] in which the (methoxymethoxy)methyl group controls the cycloaddition process; cyclopentadiene approaches the complex **6** from the less hindered α-side to yield **3a** and **3b**, predominently.

Further studies of asymmetric reactions employing (*S*)-pyroglutamic acid derivatives are in progress.

Experimental[10]

(*S*)-5-(Methoxymethoxy)methyl-1-(2-propenoyl)-2-pyrrolidinone (2a) Sodium hydride (0.88 g, 60% oil suspension, washed with hexane) was added to a solution of (*S*)-5-(methoxymethoxy)methyl-2-pyrrolidinone (**1**, 3.5 g, 22 mmol) in THF (50 ml) at 0 °C. The mixture was stirred at room temperature for 1 h, then acryloyl chloride (2.7 ml, 33 mmol) was added at 0 °C and the whole was stirred at 0 °C for 13 h. After dilution with AcOEt (200 ml), the reaction mixture was washed with H_2O, 5% aqueous HCl, and saturated aqueous NaCl. Drying followed by evaporation *in vacuo* gave an oily residue, which was purified by column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 10) to give **2a** (1.78 g, 38% yield) as an oil, $[\alpha]_D^{20}$ −113.2° (*c* = 3.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1680, 1620. NMR ($CDCl_3$): 1.9—3.1 (4H, m, 2 × CH_2), 3.4 (3H, s, OCH_3), 3.5—4.0 (2H, m, CH_2O), 4.4—4.7 (1H, m, CH), 4.6 (2H, s, OCH_2O), 5.8 (1H, dd, *J* = 2, 11 Hz, vinyl proton), 6.45 (1H, dd, *J* = 2, 16 Hz, vinyl proton), 7.45 (1H, dd, *J* = 11, 16 Hz, vinyl proton). MS *m/z*: 213 (M^+), 214 ($M^+ + 1$).

(*S*)-1-((*E*)-2-Butenoyl)-5-(methoxymethoxy)methyl-2-pyrrolidinone (2b) This sample was obtained in 73% yield from **1** and (*E*)-crotonyl chloride as described for the preparation of **2a**, $[\alpha]_D^{20}$ −123° (*c* = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1680, 1620. NMR ($CDCl_3$): 1.95 (3H, d, *J* = 6 Hz, CH_3), 2.0—3.0 (4H, m, 2 × CH_2), 3.25 (3H, s, OCH_3), 3.5—4.0 (2H, m, CH_2O), 4.4—4.7 (1H, m, CH), 4.5 (2H, s, OCH_2O), 6.8—7.4 (2H, m, vinyl protons). MS *m/z*: 227 (M^+).

General Procedure for the Preparation of Authentic Mixture of Diels–Alder Adducts Reaction of cyclopentadiene with methyl acrylate and methyl (*E*)-crotonate in benzene at room temperature gave the Diels–Alder cycloadducts (a catalytic amount of $AlCl_3$ was used for the reaction of methyl (*E*)-crotonate). Racemic *endo* and *exo* isomers were isolated by column chromatography (silica gel, ether : hexane = 1 : 10) (methyl 3-*endo*-methyl-5-norbornene-2-*exo*-carboxylate was not completely purified), then hydrolyzed with aqueous NaOH in methanol to afford the corresponding acids. Triethylamine (0.2 mmol) was added at 0 °C to a solution of 0.2 mmol of the acid in THF (1.5 ml) followed by addition of ethyl chloroformate (0.2 mmol). Then the mixture was stirred at 0 °C for 10 min. This solution was added to a suspension of the sodium salt of **1**, prepared from sodium hydride (0.6 mmol) and **1** (0.6 mmol) in THF (2.5 ml) at 0 °C for 5 min, then at room temperature for 1 h. After being stirred at 0 °C for 1 h and at room temperature for 10 h, the mixture was diluted with AcOEt, and washed with H_2O. Drying followed by evaporation *in vacuo* gave a residue, which was purified by column chromatography (silica gel, $CHCl_3$: AcOEt = 1 : 10) to afford the authentic diastereomeric mixture of *endo* and *exo* isomer in 40—60% yields. The ratios for the cycloadduct of **2** with cyclopentadiene (*endo*/*exo* and diastereomeric excess for *endo* isomer) were determined by ^{1}H-NMR analysis based on the following signals. 5-Norbornene-2-*endo*-carboximide: 3.34 and 3.39 (3H, s, OCH_3, each diastereomer), 5.86 (1H, m, vinyl proton); 5-norbornene-2-*exo*-carboximide: 3.36 and 3.37 (3H, s, OCH_3, each diastereomer), 6.20 (2H, m, vinyl protons). The *endo*/*exo* ratio of **3a** was deduced based on the 5.86 (*endo*) and 6.20 (*exo*) signals, and de for the *endo* isomer was deduced based on the 3.34 and 3.39 signals. 3-*exo*-Methyl-5-norbornene-2-*endo*-carboximide: 1.14 (3H, dd, *J* = 7 Hz, $CHC\underline{H}_3$), 3.34 and 3.38 (3H, s, OCH_3, each diastereomer); 3-*endo*-methyl-5-norbornene-2-*exo*-carboximide: 0.86 (3H, dd, *J* = 7 Hz, $CHC\underline{H}_3$). The 2-*endo*/*exo* ratio of **3b** was deduced based on the 1.14 (*endo*) and 0.86 (*exo*) signals, and de for the 2-*endo* isomer was deduced based on the 3.34 and 3.38 signals.

(*S*)-1-((1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carbonyl)-5-(methoxymethoxy)methyl-2-pyrrolidinone (3a) The reaction procedure for cycloaddition of **2a** and cyclopentadiene in toluene at −78 °C with diethylaluminum chloride (Table I, run 3) is described as an example. Diethylaluminum chloride (0.56 ml, 1.8 M in toluene, 1 mmol) was added at −78 °C to a solution of **2a** (213 mg, 1 mmol) and cyclopentadiene (0.66 g, 10 mmol) in toluene (5 ml). After being stirred at −78 °C for 10 min, the mixture was quenched with 10 ml of saturated aqueous NH_4Cl, and extracted with ether. The organic layers were washed with H_2O. Drying followed by filtration and evaporation *in vacuo* gave a residue, which was subjected to column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 10) to give a diastereomeric mixture of the cycloadduct (148 mg, 53% yield) as an oil. IR ν_{max}^{film} cm^{-1}: 1740, 1695. ^{1}H-NMR ($CDCl_3$): 1.2—3.4 (10H, m), 3.34, 3.36 and 3.39 (3H, 3 × s, OCH_3, 3 × isomer), 3.4—3.8 (3H, m, CH_2O), 4.1 (1H, m, CH), 4.35—4.65 (1H, m, CH), 4.6 (2H, m, OCH_2O), 5.8 and 5.85 (1H, 2 × dd, *J* = 3, 6 Hz, vinyl proton), 6.23 (1H, dd, *J* = 3, 6 Hz, vinyl proton). MS *m/z*: 279 (M^+).

(−)-Methyl 2-*endo*-Norbornenecarboxylate (5a) A mixture of the cycloadducts described above (280 mg, 1 mmol), concentrated HCl (0.5 ml), and methanol (10 ml) was heated under reflux for 6 h, then 4 ml of 10% aqueous KOH was added and the mixture was heated under reflux for a further 1 h. After removal of methanol *in vacuo*, 5 ml of H_2O was added, and the aqueous layer was acidified with 10% HCl, and extracted with ether (× 3). The combined organic solutions were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was treated with ethereal diazomethane at room temperature. After addition of a few drops of acetic acid, the mixture was washed with saturated $NaHCO_3$ and H_2O. Drying followed by evaporation *in vacuo* gave the methyl ester (*endo* : *exo* = 94 : 6 by ^{1}H-NMR analysis based on the methyl signal), which was purified by column chromatography (silica gel, ether : hexane = 1 : 10) to give **5a** (43 mg, 28% yield) as an oil, $[\alpha]_D^{20}$ −101.5° (*c* = 0.6, 95% EtOH), corresponding to 72% ee. Its ^{1}H-NMR spectrum ($CDCl_3$) was identical with that of a racemic authentic sample, 1.14—1.54 (3H, m), 1.7—2.1 (1H, m), 2.8—3.08 (2H, m), 3.1—3.3 (1H, br s), 3.62 (3H, s, CH_3), 5.92 (1H, dd, *J* = 3, 6 Hz, vinyl proton), 6.19 (1H, dd, *J* = 3, 6 Hz, vinyl proton).

(*S*)-5-(Methoxymethoxy)methyl-1-((1*S*,2*S*,3*R*,4*R*)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbonyl)-2-pyrrolidinone (3b) 1.1 ml (1.8 M in toluene, 1.98 mmol) of diethylaluminum chloride was added at −78 °C to a solution of **2b** (0.4 g, 1.76 mmol) and cyclopentadiene (1.16 g, 17.6 mmol) in toluene (7 ml). After being stirred at −78 °C for 1 h, the mixture was quenched with 15 ml of saturated aqueous NH_4Cl, and extracted with ether. The organic layers were washed with H_2O. Drying followed by filtration and evaporation *in vacuo* gave a residue, which was subjected to column chromatography (silica gel, AcOEt : $CHCl_3$ = 1 : 10) to give a diastereomeric mixture of the cycloadduct (320 mg, 62% yield, >95% pure by ^{1}H-NMR) as an oil, $[\alpha]_D^{20}$ −116.1° (*c* = 0.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1695. ^{1}H-NMR ($CDCl_3$): 0.86 and 1.14 (3H, 2 × d, *J* = 7 Hz, $CHCH_3$), 1.3—3.3 (9H, m), 3.38 (3H, s, OCH_3), 3.4—3.9 (3H, m, CH_2O, CH), 4.3—4.7 (1H, m, CH), 4.59 (2H, m, OCH_2O), 5.72 (1H, dd, *J* = 3, 6 Hz, vinyl proton), 6.36 (1H, dd, *J* = 3, 6 Hz, vinyl proton). ^{13}C-NMR ($CDCl_3$): 20.47 (q), 21.20 (t), 33.28 (t), 35.67 (d), 46.93 (t), 47.22 (d), 49.66 (d), 53.02 (d), 55.46 (q), 56.48 (d), 68.56 (t), 96.68 (t), 130.79 (d), 139.61 (d), 174. 79 (s), 175.77 (s). MS *m/z*: 293 (M^+).

(−)-Methyl 3-*exo*-Methyl-5-norbornene-2-*endo*-carboxylate (5b) The cycloadduct described above (**3b**, 280 mg, 0.96 mmol) was transformed into the corresponding methyl ester as described for the preparation of **5a**, and **5b** (94 mg, 59% yield) was obtained after column chromatography (silica gel, ether : hexane = 1 : 10), $[\alpha]_D^{20}$ −146.8° (*c* = 1, 95% EtOH), corresponding to 95% ee (lit.[10] $[\alpha]_D^{20}$ −155.4° (95% EtOH)). The ^{1}H-NMR spectrum ($CDCl_3$) was identical with that of racemic authentic sample, 1.2 (3H, d, *J* = 6 Hz, $CHC\underline{H}_3$), 1.3—1.7 (2H, m), 1.7—2.0 (1H, m), 2.4 (1H, t, *J* = 4 Hz, CH), 2.48 (1H, br s, CH), 3.12 (1H, br s, CH), 3.6 (3H, s, $COOCH_3$), 6.05 (1H, dd, *J* = 3, 5.6 Hz, vinyl proton), 6.27 (1H, dd, *J* = 3, 5.6 Hz, vinyl proton).

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References and Notes

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10) Infrared (IR) spectral measurements were performed with a JASCO IRA-1 grating infrared spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured with a Hitachi R-24 (60 MHz) and a JNM-FX-100 (100 MHz) spectrometer. Data are recorded in parts per million (ppm) down-field from internal tetramethylsilane. The following abbreviations are used: singlet(s), doublet(d), triplet(t), quartet(q), and mutiplet(m). Optical rotations were determined with a JASCO DIP-SL. Mass spectra (MS) were recorded with a JEOL JMS-DS302 mass spectrometer. The organic extracts were dried over $MgSO_4$ before vacuum evaporation.