Chiral Synthesis of (+)-Methyl 5-*epi*-Shikimate by Asymmetric Diels–Alder Reaction of $(S)_S$-3-(2-Pyridylsulfinyl)acrylate

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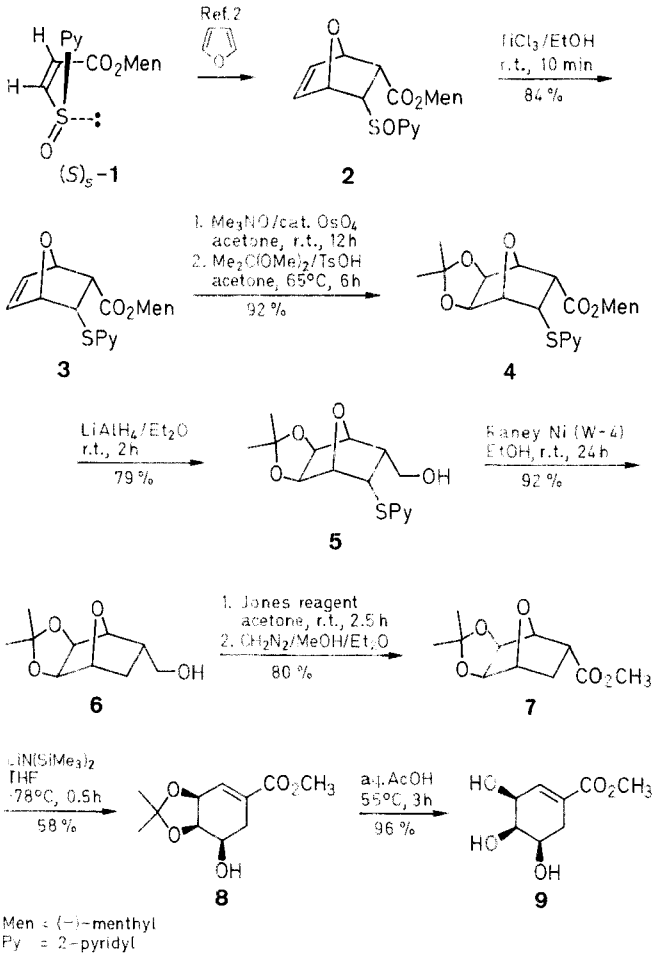
(+)-Methyl 5-*epi*-shikimate **(9)** was synthesized diastereoselectively by asymmetric Diels–Alder reaction of $(S)_S$-3-(2-pyridylsulfinyl)acrylate **(1)** with furan.

Much attention has so far been focused on the asymmetric Diels–Alder reaction of chiral sulfinylethenes, especially 3-arylsulfinylacrylates.[1] We have recently developed a new method for diastereoselective construction of 7-oxabicyclo[2.2.1]hept-5-ene system by the asymmetric Diels–Alder reaction of $(S)_S$-3-(2-pyridylsulfinyl)acrylate **(1)** with furan.[2] As an extension of this novel reaction, we have achieved a chiral synthesis of D-showdomycin and D-2,5-anhydroallose derivative using the *endo*-cycloadduct **2**.[3] This asymmetric Diels–Alder reaction provides us with a powerful tool for the diastereoselective synthesis of a variety of polyoxygenated cyclohexane derivatives. For example, introduction of the *exo*-*cis*-diol function to **2**[3] and a cleavage of the oxide bridge would furnish the triol corresponding to the absolute configuration of (+)-5-*epi*-shikimate **(9)**.



Shikimic acid and related compounds are known to be biologically important.[4] Many synthetic studies have been reported for the chiral synthesis of shikimic acid;[5] however, little information has been available for the synthesis of racemic[6–8] and

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optically active[9,10] 5-*epi*-shikimic acid. There have been no reports for asymmetric synthesis of this acid. We describe here a chiral synthesis of (+)-methyl 5-*epi*-shikimate utilizing the asymmetric Diels–Alder reaction of $(S)_S$-**1** with furan.

Optically pure *endo*-cycloadduct **2** derived from $(S)_S$-**1** and furan,[2] which has the desired absolute configuration for the synthesis of (+)-methyl 5-*epi*-shikimate **(9)**, was reduced with titanium trichloride to give the sulfide **3** in 84% yield. The sulfide **3** was oxidized with osmium tetroxide and trimethylamine *N*-oxide, and the resulting *exo*-diol was protected with 2,2-dimethoxypropane to give the acetonide **4** in 92% yield. The ester **4** was converted to the alcohol **5** by reduction with lithium aluminum hydride in 79% yield. Desulfurization of **5** with Raney nickel (W-4) afforded **6** in 92% yield. Alcohol **6** was oxidized with Jones reagent, and the resulting carboxylic acid was treated with diazomethane to give methyl ester (−)-**7** in 80% yield. Ester **7** was transformed to (+)-methyl 5-*epi*-shikimate **(9)** according to the procedure reported by Campbell et al. in their synthesis of racemic methyl 5-*epi*-shikimate.[7] Cleavage of the oxide bridge of **7** was achieved by treatment with lithium hexamethyldisilazide to give the desired monocyclic triol (−)-**8** in 58% yield. The enantiomeric excess of (−)-**8** was no less than 96% as determined by 270 MHz NMR spectroscopy using a chiral shift reagent, $Eu(hfc)_3$.[11] Deprotection of **8** gave (+)-methyl 5-*epi*-shikimate **(9)** in 96% yield. The spectral data of (−)-**8** and (+)-**9** were consistent with those of the racemic authentic compounds.[7]

The method developed in the present studies thus provides a new and powerful strategy for the chiral synthesis of a series of precursors in the shikimic acid pathway as their natural and unnatural enantiomers. Furthermore, (−)-methyl (3*R*,4*S*,5*S*)-tri-*O*-benzyl-5-*epi*-shikimate has already been transformed to pseudo-β-L-mannopyranose by Suami et al.[10] We are currently studying the transformation of the acetonide **8** to pseudo-β-D-mannopyranose by reference to their procedure.

Melting points were measured with a Yanako melting point apparatus and are uncorrected. The spectroscopic measurements were performed with the following instruments: IR, JASCO A-102; ^{1}H-NMR, Varian XL-200 and JEOL JNM-GX 270; MS, JEOL OISG-2 at 70 eV; optical rotations, JASCO DIP-140 digital polarimeter.

(1′*R*,2′*S*,5′*R*)-Menthyl (1*R*,2*R*,3*S*,4*S*)-3-(2-Pyridylthio)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (3):

A 25 w/v% aq. solution of $TiCl_3$ (0.39 mL, 0.632 mmol) is added dropwise to a solution of **2**[2] (126 mg, 0.313 mmol) in EtOH (2 mL) at room temperature. After 10 min, H_2O (2 mL) is added to the mixture, and the pH is brought to 10 by addition of sat. aq. $NaHCO_3$ at 0 °C. The aqueous layer is extracted with $CHCl_3$ (4 × 10 mL); the combined extract is washed with brine and dried ($MgSO_4$). The solvent is evaporated, and the residue is chromatographed on silica gel (eluent: *n*-hexane/Et_2O, 5:1) to give **3**; yield: 102 mg (84%); syrup; $[\alpha]_D^{26}$ + 75.1° (*c* = 1.17, $CHCl_3$).

HRMS: exact mass calc. for $C_{18}H_{25}NO_2S$ (M^+ − furan), *m/z* = 319.1616, found 319.1631.

IR ($CHCl_3$): ν = 1715, 1575, 1175 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.36–1.96 (m, 9 H); 0.73, 0.76, 0.86 (3d, 9 H, *J* = 7.0 Hz, 3 × CH_3); 3.61 (dd, 1 H, *J* = 9.5, 4.0 Hz, H-2); 4.60 (ddd, 1 H, *J* = 10.5, 10.5, 4.5 Hz, H-1′); 4.90 (dd, 1 H, *J* = 9.5, 4.0 Hz, H-3); 5.16 (d, 1 H, *J* = 4.0 Hz, H-1); 5.22 (d, 1 H, *J* = 4.0 Hz, H-4); 6.55, 6.70 (2dd, 2 H, *J* = 6.0, 1.5 Hz, H-5, H-6); 7.00 (ddd, 1 H, *J* = 8.0, 5.0, 1.0 Hz, H_{arom}); 7.11 (dd, 1 H, *J* = 8.0, 1.0 Hz, H_{arom}); 7.46 (ddd, 1 H, *J* = 8.0, 8.0, 1.0 Hz, H_{arom}); 8.45 (dd, 1 H, *J* = 5.0, 1.0 Hz, H_{arom}).

MS: *m/z* = 319 (M^+ − furan).

(1′*R*,2′*S*,5′*R*)-Menthyl (1*S*,2*R*,3*S*,4*S*,5*S*,6*S*)-5,6-*O*,*O*-Isopropylidene-5,6-dihydroxy-3-(2-pyridylthio)-7-oxabicyclo[2.2.1]heptane-2-carboxylate (4):

A mixture of **3** (531 mg, 1.37 mmol), a 0.1 M solution of OsO_4 in *t*-BuOH (0.14 mL, 0.014 mmol), and trimethylamine *N*-oxide dihydrate (152 mg, 1.37 mmol) in acetone (10 mL) is stirred under nitrogen at room temperature for 12 h. After the solvent is evaporated, the residue is chromatographed on silica gel (eluent: $CHCl_3/CH_3OH$, 98:2) to give (1′*R*,2′*S*,5′*R*)-menthyl (1*S*,2*R*,3*S*,4*S*,5*S*,6*S*)-5,6-dihydroxy-3-(2-pyridylthio)-7-oxabicyclo[2.2.1]heptane-2-carboxylate (770 mg) as pale yellow solid.

A mixture of the diol (770 mg), 2,2-dimethoxypropane (0.84 mL, 6.83 mmol), and TsOH · H_2O (5.0 mg, 0.03 mmol) in acetone (10 mL) is stirred under nitrogen at 65 °C for 6 h. After the solvent is evaporated, the residue is dissolved in CH_2Cl_2, washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue is purified by flash column chromatography on silica gel (eluent: *n*-hexane/Et_2O, 4:1) and by subsequent recrystallization from *n*-hexane/Et_2O to give **4**; yield: 584 mg (92% from **3**); mp 139 °C; $[\alpha]_D^{25}$ + 21.1° (*c* = 0.693, $CHCl_3$).

$C_{25}H_{35}NO_5S$	calc.	C 65.04	H 3.03	N 7.64
(461.2)	found	65.24	2.80	7.71

IR (KBr): ν = 1710, 1580, 1555, 1370 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.76, 0.82, 0.89 (3d, 9 H, *J* = 7.0 Hz, 3 × CH_3); 0.64–1.90 (m, 9 H); 1.29, 1.48 (2s, 6 H, 2 × CH_3); 3.43 (dd, 1 H, *J* = 11.2, 5.5 Hz, H-2); 4.58–4.68 (m, 3 H, H-1, H-3, H-1′); 4.73 (dd, 1 H, *J* = 4.4, 0.9 Hz, H-4); 4.86, 4.90 (2d, 2 H, *J* = 5.7 Hz, H-5, H-6); 6.99 (ddd, 1 H, *J* = 7.3, 5.0, 1.0 Hz, H_{arom}); 7.17 (ddd, 1 H, *J* = 8.1, 1.0, 1.0 Hz, H_{arom}); 7.46 (ddd, 1 H, *J* = 8.1, 7.3, 1.8 Hz, H_{arom}); 8.40 (ddd, 1 H, *J* = 5.0, 1.8, 1.0 Hz, H_{arom}).

MS: *m/z* = 461 (M^+).

(1*S*,2*S*,3*S*,4*S*,5*S*,6*S*)-2-Hydroxymethyl-5,6-*O*,*O*-isopropylidene-5,6-dihydroxy-3-(2-pyridylthio)-7-oxabicyclo[2.2.1]heptane (5):

$LiAlH_4$ (29 mg, 0.764 mmol) is added to a solution of **4** (235 mg, 0.51 mmol) in dry Et_2O (4 mL) at 0 °C, and the mixture is stirred under nitrogen at room temperature for 2 h. The mixture is quenched with sat. aq. Na_2SO_4 at 0 °C. After 0.5 h at room temperature, the precipitate is filtered and washed with THF (10 mL); the combined organic layer is concentrated. The residue is purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc, 1:1) and subsequent recrystallization from *n*-hexane/acetone to give **5**; yield: 124 mg (79%); mp 130–131 °C; $[\alpha]_D^{25}$ + 80.5° (*c* = 0.893, $CHCl_3$).

$C_{15}H_{19}NO_4S$	calc.	C 58.23	H 6.19	N 4.53
(309.1)	found	58.38	6.24	4.45

IR (KBr): ν = 3260, 1580, 1555 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.29, 1.46 (2s, 6 H, 2 × CH_3); 2.76 (m, 1 H, H-2); 3.62 (m, 1 H, HCH); 3.85 (dd, 1 H, *J* = 11.0, 8.8 Hz, HCH); 3.92 (br s, 1 H, OH); 4.10 (dd, 1 H, *J* = 10.4, 5.6 Hz, H-3); 4.35 (d, 1 H, *J* = 5.9 Hz, H-5/H-6); 4.50 (d, 1 H, *J* = 5.4 Hz, H-1); 4.53 (d, 1 H, *J* = 5.9 Hz, H-5/H-6); 4.61 (d, 1 H, *J* = 5.6 Hz, H-4); 7.07 (ddd, 1 H, *J* = 7.3, 4.9, 1.0 Hz, H_{arom}); 7.31 (ddd, 1 H, *J* = 8.1, 1.0, 1.0 Hz, H_{arom}); 7.53 (ddd, 1 H, *J* = 8.1, 7.3, 2.0 Hz, H_{arom}); 8.40 (ddd, 1 H, *J* = 4.9, 2.0, 1.0 Hz, H_{arom}).

MS: *m/z* = 309 (M^+).

(1*R*,2*R*,3*S*,4*S*,5*S*)-5-Hydroxymethyl-2,3-*O*,*O*-isopropylidene-2,3-dihydroxy-7-oxabicyclo[2.2.1]heptane (6):

Raney-Ni (W-4, 0.4 g) is added to a solution of **5** (179 mg, 0.579 mmol) in EtOH (5 mL), and the mixture is stirred under nitrogen at room temperature for 24 h. The metal powder is filtered and washed with EtOH (10 mL); the filtrate is concentrated. The residue is purified by flash column chromatography on silica gel (eluent: *n*-hexane/Et_2O, 1:4) and by subsequent recrystallization from *n*-hexane/Et_2O to give **6**; yield: 107 mg (92%); mp 73–74 °C; $[\alpha]_D^{25}$ − 12.5° (*c* = 0.740, $CHCl_3$).

$C_{10}H_{16}O_4$	calc.	C 59.98	H 8.05	
(200.1)	found	59.92	8.01	

IR (KBr): ν = 3460 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.90 (dd, 1 H, *J* = 12.5, 5.4 Hz, H-6_{endo}); 1.29, 1.48 (2s, 6 H, 2 × CH_3); 1.89 (ddd, 1 H, *J* = 12.5, 12.5, 6.1 Hz, H-6_{exo}); 1.89 (br s, 1 H, OH); 2.33 (m, 1 H, H-5); 3.55 (dd, 1 H, *J* = 11.0, 8.5 Hz, HCH); 3.73 (dd, 1 H, *J* = 11.0, 6.6 Hz, HCH); 4.18 (d, 1 H, *J* = 5.6 Hz, H-2/H-3); 4.39 (d, 1 H, *J* = 6.1 Hz, H-1); 4.41 (d, 1 H, *J* = 5.1 Hz, H-4); 4.57 (d, 1 H, *J* = 5.6 Hz, H-2/H-3).

MS: *m/z* = 201 (M^+ + 1), 185 (M^+ − CH_3).

Methyl (1*R*,2*R*,3*S*,4*S*,5*R*)-2,3-*O*,*O*-Isopropylidene-2,3-dihydroxy-7-oxabicyclo[2.2.1]heptane-5-carboxylate (7):

Jones reagent[12] (0.17 mL) is added dropwise to a solution of **6** (66.0 mg, 0.33 mmol) in acetone (2 mL) at 0 °C, and the mixture is stirred under

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nitrogen at room temperature for 2.5 h. After dilution with Et_2O (10 mL), the organic layer is washed with 1 N aq. HCl (2 mL) and separated; the aqueous layer is extracted with Et_2O (10 × 5 mL); the combined organic phase is dried ($MgSO_4$) and concentrated. The residue is dissolved in CH_3OH/Et_2O (0.2 mL–3 mL) and treated with a diazomethane/Et_2O (0.35 M, 10 mL) solution at 0 °C. After the solvent is evaporated, the residue is purified by flash column chromatography on silica gel (eluent: *n*-hexane/Et_2O, 2:1) and by subsequent recrystallization from *n*-hexane/EtOAc to give **7**; yield: 60.0 mg (80%); mp 91 °C; $[\alpha]_D^{25}$ −11.1° (*c* = 0.640, $CHCl_3$).

$C_{11}H_{16}O_5$	calc.	C 57.88	H 7.07
(228.1)	found	58.11	7.12

IR (KBr): ν = 1725 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.27, 1.42 (2s, 6H, 2 × CH_3); 1.72 (dd, 1H, *J* = 12.8, 5.1 Hz, H-6$_{endo}$); 1.93 (ddd, 1H, *J* = 12.8, 11.4, 6.0 Hz, H-6$_{exo}$); 2.98 (m, 1H, H-5); 3.73 (s, 3H, OCH_3); 4.26, 4.29 (2d, 2H, *J* = 5.6 Hz, H-2, H-3); 4.46 (d, 1H, *J* = 6.0 Hz, H-1); 4.56 (d, 1H, *J* = 5.9 Hz, H-4).

MS: *m/z* = 229 (M^+ + 1), 213 ($M^+ - CH_3$), 197 ($M^+ - OCH_3$).

Methyl (3*S*,4*R*,5*R*)-3,4-*O*,*O*-Isopropylidene-3,4,5-trihydroxycyclohex-2-ene-1-carboxylate (8):

A 10 w/v% solution of BuLi in *n*-hexane (0.13 mL, 0.203 mmol) is added to a solution of hexamethyldisilazane (0.044 mL, 0.209 mmol) in dry THF (1 mL), and the mixture is maintained at −78 °C for 0.5 h under nitrogen. A solution of **7** (40 mg, 0.175 mmol) in dry THF (1 mL) is introduced, and the mixture is stirred for a further 0.5 h at −78 °C before being allowed to warm to 0 °C. The solvent is evaporated, and the residue is dissolved in CH_2Cl_2. The CH_2Cl_2 phase is washed with 1 N aq. HCl and brine, dried ($MgSO_4$), and concentrated. The residue is chromatographed on silica gel (eluent: *n*-hexane/EtOAc, 2:1) to give **8**; yield: 23 mg (58%); syrup; $[\alpha]_D^{25}$ −33.0° (*c* = 0.667, $CHCl_3$).

HRMS: exact mass calc. for $C_{10}H_{13}O_5$ ($M^+ - CH_3$), *m/z* = 213.0763, found 213.0773.

IR ($CHCl_3$): ν = 3600, 3420, 1715, 1655 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.39, 1.41 (2s, 6H, 2 × CH_3); 2.28 (br s, 1H, OH); 2.49 (dddd, 1H, *J* = 16.7, 9.0, 2.3, 2.3 Hz, H-6β); 2.65 (ddd, 1H, *J* = 16.7, 5.1, 0.7 Hz, H-6α); 3.78 (s, 3H, OCH_3); 3.96 (ddd, 1H, *J* = 9.0, 5.1, 2.7 Hz, H-5); 4.42 (dd, 1H, *J* = 5.8, 2.7 Hz, H-4); 4.74 (m, 1H, H-3); 6.79 (m, 1H, H-2).

MS: *m/z* = 213 ($M^+ - CH_3$).

(+)-Methyl 5-*epi*-Shikimate [Methyl (3*S*,4*R*,5*R*)-3,4,5-Trihydroxyhex-2-ene-1-carboxylate] (9):

A solution of **8** (34 mg, 0.149 mmol) in 50% AcOH/H_2O (2 mL) is stirred under nitrogen at 55 °C for 3 h. After the solvent is evaporated, the residue is recrystallized from EtOAc to give **9**; yield: 27 mg (96%); mp 122–123 °C; $[\alpha]_D^{25}$ + 53.7° (*c* = 0.887, EtOH).

$C_8H_{12}O_5$	calc.	C 51.06	H 6.43
(188.1)	found	50.82	6.38

IR (KBr): ν = 3350, 1710, 1645 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.38 (dddd, 1H, *J* = 17.2, 8.6, 3.1, 2.4 Hz, H-6β); 2.50 (dddd, 1H, *J* = 17.2, 5.7, 1.7, 1.7 Hz, H-6α); 3.71 (s, 3H, OCH_3), 3.80–4.40 (m, 5H, H-4, H-5, 3 × OH); 4.25–4.35 (m, 1H, H-3); 6.66 (br s, 1H, H-2).

^{1}H-NMR (acetone-d_6/D_2O/TMS): δ = 2.37 (dddd, 1H, *J* = 17.2, 8.6, 3.1, 2.5 Hz, H-6β); 2.50 (dddd, 1H, *J* = 17.2, 6.0, 1.5, 1.5 Hz, H-6α); 3.71 (s, 3H, OCH_3); 3.85 (ddd, 1H, *J* = 8.6, 6.0, 1.5 Hz, H-5); 3.95 (m, 1H, H-4); 4.30 (br s, 1H, H-3); 6.66 (m, 1H, H-2).

MS: *m/z* = 188 (M^+).

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