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ENANTIOSELECTIVE SYNTHESIS OF CARBOCYCLIC SHOWDOMYCIN DERIVATIVE *VIA* ASYMMETRIC DIELS-ALDER REACTION OF (S_S)-3-(2-PYRIDYLSULPHINYL)ACRYLATE

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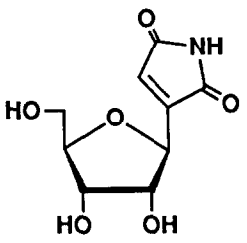
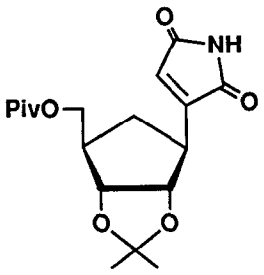
Abstract: The first enantioselective synthesis of a carbocyclic analogue of showdomycin, 3-[(1*S*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-(pivaloxymethyl)cyclopentyl]maleimide **1**, has been accomplished using the asymmetric Diels-Alder reaction of the (S_S)-3-(2-pyridylsulphinyl)acrylate **2** with cyclopentadiene as the key step.

A number of new nucleoside analogues with unique properties have been produced by transformation of the sugar moiety of the parent compounds into the carbocyclic ring.[1] An advantageous feature of the carbocyclic nucleosides is the increased stability to enzymic and acid hydrolysis, which is conferred by the replacement of the ring oxygen by a methylene group. In the present studies, we have focused on carbocyclic C-nucleosides which have so far received little attention.[2] We have targeted a carbocyclic analogue **1** of D-showdomycin (Chart 1).

Chart 1



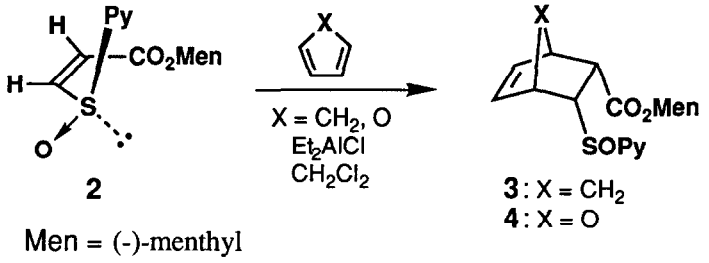
D-showdomycin



1

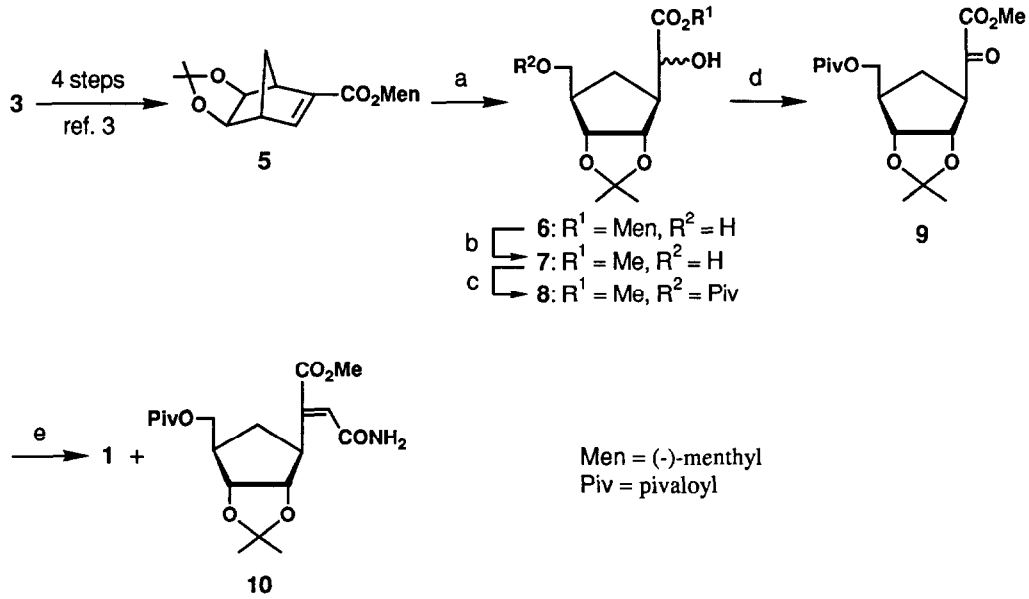
Piv = pivaloyl

Scheme 1



In earlier work, we have reported that an asymmetric Diels-Alder reaction of (S_S)-3-(2-pyridylsulphinyl)acrylate **2** with cyclopentadiene and furan proceeded in the presence of Et_2AlCl giving the cycloadducts **3**[3] and **4**[4] with high diastereoselectivity (Scheme 1). This novel asymmetric reaction have provided us with a powerful tool for the chiral synthesis of D-showdomycin,[5] pseudo-sugars[6] and the precursor for the preparation of (-)-aristeromycin and (-)-neplanocin A.[3] With these backgrounds, we planned the synthetic route to the carbocyclic showdomycin **1** starting from the cycloadduct **3**.

Scheme 2



a, (1) O_3, CH_2Cl_2, -78 °C; Me_2S; (2) $NaBH_4$, MeOH, 0 °C; b, (1) LiOH, DME-H_2O, 70 °C;

(2) CH_2N_2; c, PivCl, pyridine; d, $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O; e, $H_2NCOCH{=}PPh_3$, CH_2Cl_2.

The *endo* cycloadduct **3** (d.e. > 96% by ^{1}H NMR spectrum and HPLC) was converted in four steps to the unsaturated ester **5** according to the method described before[3] (Scheme 2). The absolute configuration of **5** has been determined by transformation into the known lactone, (+)-(1*R*,5*R*,6*R*,7*S*)-6,7-(isopropylidenedioxy)-3-oxabicyclo[3.2.1]octan-2-one.[3] Ozonolysis of the unsaturated ester **5** (O_3, CH_2Cl_2, -78 °C; Me_2S) followed by reduction with sodium borohydride gave the diol **6** in 74% yield. The menthyl ester **6** was converted into the corresponding methyl ester **7** in two steps [LiOH, 1,2-dimethoxyethane (DME)-H_2O, 70 °C; CH_2N_2][7] in 62% yield. The primary hydroxy group of **7** was protected as pivaloate ester (PivCl, pyridine) to give **8** in 56% yield together with the unreacted starting material **7** (33%). Oxidation of the secondary hydroxy group of **8** ($RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O)[8,9] afforded the keto ester **9**. The crude ester **9** was subjected to the next reaction without purification because of its instability. Formation of maleimide ring by utilizing the keto ester moiety of **9** proceeded under Wittig conditions ($H_2NCOCH{=}PPh_3$, CH_2Cl_2)[8] to give the expected carbocyclic showdomycin **1**, $[\alpha]_D$ -2.5° (*c* 0.79, $CHCl_3$), in 53% yield from **8** along with the acrylamide **10** (36% from **8**).[10]

To the best of our knowledge, this is the first synthesis of carbocyclic showdomycin. The method developed in the present studies will be useful for preparing both enantiomers of some carbocyclic C-nucleosides.

Experimental Section

Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Centre of Toyama Medical & Pharmaceutical University. Spectroscopic measurements were carried out with the following instruments: IR, JASCO A-102 for solutions in $CHCl_3$; ^{1}H NMR, JEOL JNM-GX 270 (270 MHz) for solutions in $CDCl_3$ with Me_4Si as internal standard; mass (MS) and high resolution mass spectra (HRMS), JEOL JMS D-200; optical rotations, JASCO DIP-140 digital polarimeter. *J* values are given in Hz. Column chromatography and preparative TLC (PLC) were performed on Kieselgel 60 (Merck, Art. 9385 and Art. 7748, respectively).

(1'*R*,2'*S*,5'*R*)-Menthyl 2-Hydroxy-2-[(1*R*,2*S*,3*R*,4*R*)-4-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentyl]acetate (6).

Ozone in oxygen was passed through a solution of the unsaturated ester **5**[3] (1.111 g, 3.19 mmol) in dry CH_2Cl_2 (25 ml) at -78 °C until persistence of a blue colour. After the excess ozone was purged with nitrogen, dimethyl sulphide (2.34 ml, 31.9 mmol) was added and the temperature was allowed to rise to ambient temperature. After evaporation of the solvent, the residue was dissolved in dry MeOH (30 ml) and $NaBH_4$ (362 mg, 9.57 mmol) was added portionwise to the solution at 0 °C. After 5.5 h at 0 °C, the reaction mixture was acidified (pH 3) with 1 N HCl and the solvent was evaporated. The residue was extracted with CH_2Cl_2 (5 x 30 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography [hexane-AcOEt (2:1) followed by hexane-AcOEt (1:1)] afforded the diol **6** [a 1:1 epimeric mixture at C(6)] (904 mg, 74%) as an oil; IR 3500, 1730 cm^{-1}; ^{1}H NMR δ 0.72-2.56 (m, 22H), 1.26 (s, 3/2H), 1.32 (s, 3/2H), 1.46 (s, 3/2H), 1.53 (s, 3/2H), 3.34 (br, 1H), 3.65-3.72 (m, 2H), 4.10 (d, *J* 3.7, 1/2H), 4.31-4.40 (m, 3/2H), 4.47 (dd, *J* 4.5, 7.0, 1/2H), 4.65 (dd, *J* 4.9, 7.1,

1/2H), 4.73-4.86 (m, 1H); MS *m/z* 385 (M^++1), 383 (M^+-1), 369 (M^+-15); HRMS calcd for $C_{20}H_{33}O_6$ (M^+-CH_3) 369.2275. found 369.2254.

Methyl 2-Hydroxy-2-[(1*R*,2*S*,3*R*,4*R*)-4-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentyl]acetate (7).

A mixture of the menthyl ester **6** (45 mg, 0.12 mmol) and LiOH•H_2O (25 mg, 0.59 mmol) in 1,2-dimethoxyethane (DME)-H_2O (2:1) (3 ml) was heated at 70 °C for 4 h. After addition of AcOEt (4 ml), the mixture was acidified (pH 2) with 1 N HCl at 0 °C and extracted with AcOEt (5 x 10 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 2-hydroxy-2-[(1*R*,2*S*,3*R*,4*R*)-4-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentyl]acetic acid (38 mg) as a pale yellow oil. The crude acid in dry MeOH (8 ml) was esterified with diazomethane in ether at 0 °C. After evaporation of the solvent, the residual oil was purified by column chromatography [hexane-AcOEt (1:1) followed by AcOEt] to give the methyl ester **7** (19 mg, 62%) as an oil; IR 3500, 1730 cm^{-1}; ^1H NMR δ 1.29 (s, 3H), 1.48 (s, 3H), 1.32-1.62 (m, 1H), 2.06 (m, 1H), 2.27 (m, 1H), 2.45 (m, 1H), 2.99 (d, *J* 5.4, 1H), 3.51-3.78 (m, 2H), 3.82 (s, 3H), 4.18 (t, *J* 4.8, 1H), 4.37 (dd, *J* 4.7, 7.0, 1H), 4.47 (dd, *J* 6.3, 6.6, 1H); MS *m/z* 260 (M^+), 259 (M^+-1), 245 (M^+-15); Anal. calcd for $C_{12}H_{20}O_6$: C 55.37, H 7.74 %. Found: C 55.59, H 7.68 %.

Methyl 2-Hydroxy-2-[(1*R*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-(pivaloxymethyl)cyclopentyl]acetate (8).

Pivaloyl chloride (109 μl, 0.88 mmol) was added dropwise to a solution of the diol **7** (191 mg, 0.735 mmol) in dry pyridine (1.5 ml) at 0 °C and the mixture was stirred at room temperature for 2 days under nitrogen. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (6 ml) and water (2 ml), and extracted with CH_2Cl_2 (3 x 4 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was separated by column chromatography [hexane-AcOEt (2:1)] to give the monopivaloate ester **8** (oil, 141 mg, 56%) and the starting diol **7** (63 mg, 33%); IR 3550, 1720 cm^{-1}; ^1H NMR δ 1.21 (s, 9H), 1.25 (s, 3H), 1.46 (s, 3H), 1.50-1.63 (m, 1H), 2.02 (m, 1H), 2.42 (m, 2H), 2.96 (br, 1H), 3.81 (s, 3H), 4.08 (dd, *J* 6.4, 11.1, 1H), 4.16 (dd, *J* 6.1, 11.5, 1H), 4.18 (d, *J* 4.6, 1H), 4.30 (dd, *J* 5.1, 6.8, 1H), 4.44 (dd, *J* 6.5, 6.6, 1H); MS *m/z* 344 (M^+); Anal. calcd for $C_{17}H_{28}O_7$: C 59.29, H 8.19 %. Found: C 59.41, H 8.56 %.

Methyl 2-[(1*R*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(pivaloxymethyl)cyclopentyl]-2-oxoacetate (9).

An aqueous solution (1 ml) of $NaIO_4$ (93 mg, 0.44 mmol) was added dropwise to a mixture of the ester **8** (50 mg, 0.15 mmol) and $RuCl_3$•$3H_2O$ (10 mg, 0.015 mmol) in CCl_4-MeCN (1:1) (2 ml). After stirring at room temperature for 4 h, *i*-PrOH (1 ml) was added to the mixture to terminate the reaction. The precipitates were removed on Celite and the filtrate was extracted with CH_2Cl_2 (3 x 4 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was passed through a short column of silica gel [hexane-AcOEt (1:1)] to give the keto ester **9** (51 mg) as a pale yellow oil; IR 3550, 1725 cm^{-1}; ^1H NMR (a 54:46 mixture of keto and enol tautomers in $CDCl_3$) δ 1.20 (s, 4.9H), 1.23 (s, 4.1H), 1.24 (s,1.6H), 1.31 (s, 1.6H), 1.32 (s, 1.4H), 1.51 (s, 1.4H), 1.4-1.8 (m, 1H), 2.35-2.6 (m, 2H), 3.7-3.8 (m, 1H), 3.89 (s, 1.6H),

3.90 (s, 1.4H), 3.9-4.2 (m, 2H), 4.42 (dd, *J* 4.2, 6.8, 0.54H), 4.51 (d, *J* 4.9, 0.46H), 4.87 (dd, *J* 5.1, 6.8, 0.54H), 5.15 (t, *J* 6.2, 0.46H); MS *m/z* 343 (M^++1), 342 (M^+), 327 (M^+-15).

The crude ester **9** was subjected to the next reaction without purification because of its instability.

3-[(1*S*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(pivaloxymethy)cyclopentyl]maleimide (1).
3-[(1*S*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(pivaloxymethyl)cyclopentyl]-*Z*-3-methoxycarbonylacrylamide (10).

Carbamoylmethylenetriphenylphosphorane[11] (139 mg, 0.435 mmol) was added portionwise to a solution of the keto ester **9** (51 mg) in dry CH_2Cl_2 (3 ml). After stirring at room temperature for 2 h, the solvent was evaporated. The maleimide **1** (feathers 27 mg, 53% from **8**) and the acrylamide **10** (oil 20 mg, 36% from **8**) were obtained by PLC [hexane-AcOEt (1:1)] of the residue.

For **1**: mp 118-120 °C; $[\alpha]_D^{25}$ -2.5 (*c* 0.79, $CHCl_3$); IR 3450, 1720 cm^{-1}; ^1H NMR δ 1.22 (s, 9H), 1.31 (s, 3H), 1.53 (s, 3H), 1.61-1.77 (m, 1H), 2.30 (m, 1H), 2.51 (m, 1H), 3.12 (m, 1H), 4.12 (dd, *J* 6.3, 11 4, 1H), 4.19 (dd, *J* 5.9, 11.1, 1H), 4.48 (dd, *J* 5.4, 6.6, 1H), 4.66 (t, *J* 6.7, 1H), 6.40 (s, 1H), 7.29 (br, 1H); MS *m/z* 351 (M^+); Anal. calcd for $C_{18}H_{25}NO_6$: C 61.53, H 7.17, N 3.99 %. Found: C 61.40, H 7.18, N 4.11 %.

For **10**: $[\alpha]_D^{26}$ -3.0 (*c* 0.30, $CHCl_3$); IR 3540, 3420, 1725, 1680, 1635, 1450 cm^{-1}; ^1H NMR δ 1.21 (s, 9H), 1.29 (s, 3H), 1.50 (s, 3H), 1.57 (m, 1H), 2.10 (m, 1H), 2.42 (m, 1H), 2.92 (m, 1H), 3.83 (s, 3H), 4.10 (dd, *J* 4.6, 10.3, 1H)), 4.15 (dd, *J* 5.9, 11.2, 1H), 4.36 (dd, *J* 4.9, 7.1, 1H), 4.52 (t, *J* 7.0, 1H), 5.44 (br, 1H), 5.71 (br, 1H), 5.93 (d, *J* 1.5, 1H); MS *m/z* 383 (M^+), 368 (M^+-15); HRMS calcd for $C_{18}H_{26}NO_7$ (M^+-CH_3) 368.1707. found 368.1701.

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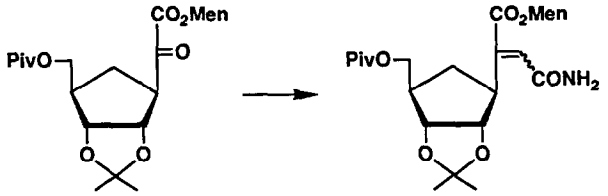
10. However, treatment of the corresponding menthyl ester **11** with the phosphorane resulted in the formation of an *E*, *Z*-mixture (1:1) of **12** which could not be cyclized.



11 **12** (1:1)

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