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PRACTICAL SYNTHESIS OF A 3, 4, 4a, 5, 8, 8a-HEXAHYDRO-2*H*-ISOQUINOLIN-1, 6-DIONE RING SYSTEM BY THE DIELS-ALDER REACTION OF AN OPTICALLY ACTIVE DIENOPHILE, A 5, 6-DIHYDRO-1*H*-PYRIDIN-2-ONE DERIVATIVE, WITH SILOXYDIENE

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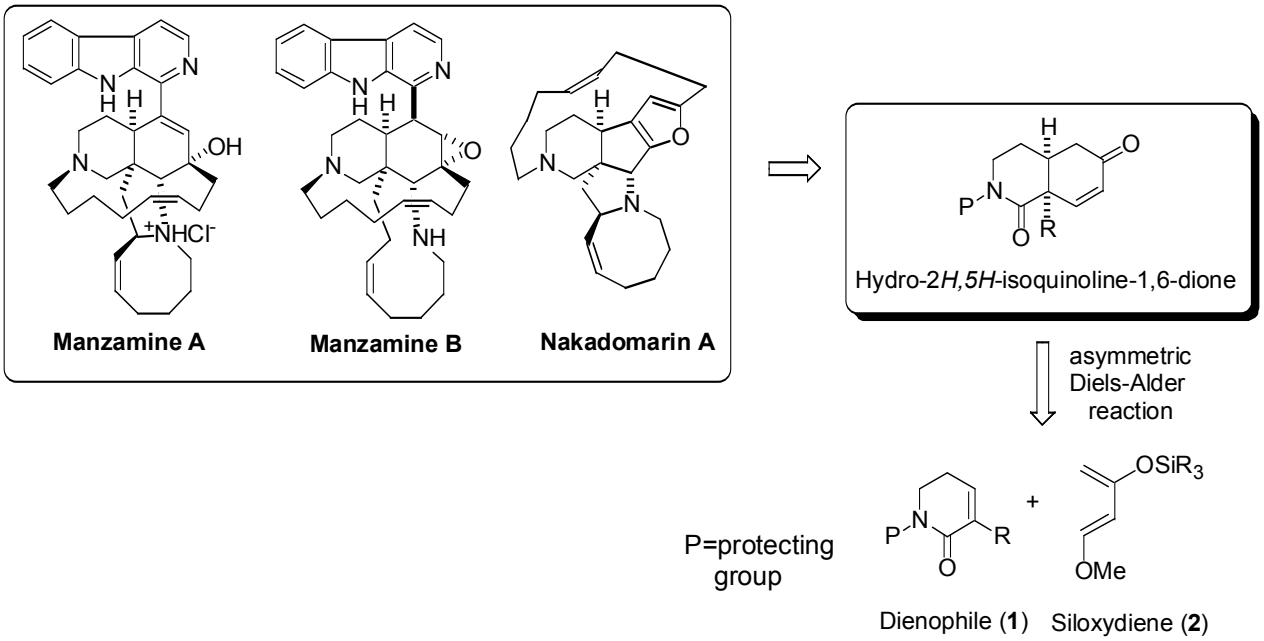
Abstract - An efficient method for preparing chiral 3-substituted-5, 6-dihydro-1*H*-pyridin-2-one (**1**) in large scale, based on a modification of our previous method, is described. The large scale Diels-Alder reaction of **1** with siloxydiene (**2**) to synthesize hexahydroisoquinoline-1, 6-dione, which is a key intermediate for the synthesis of manzamine alkaloids, was also studied.

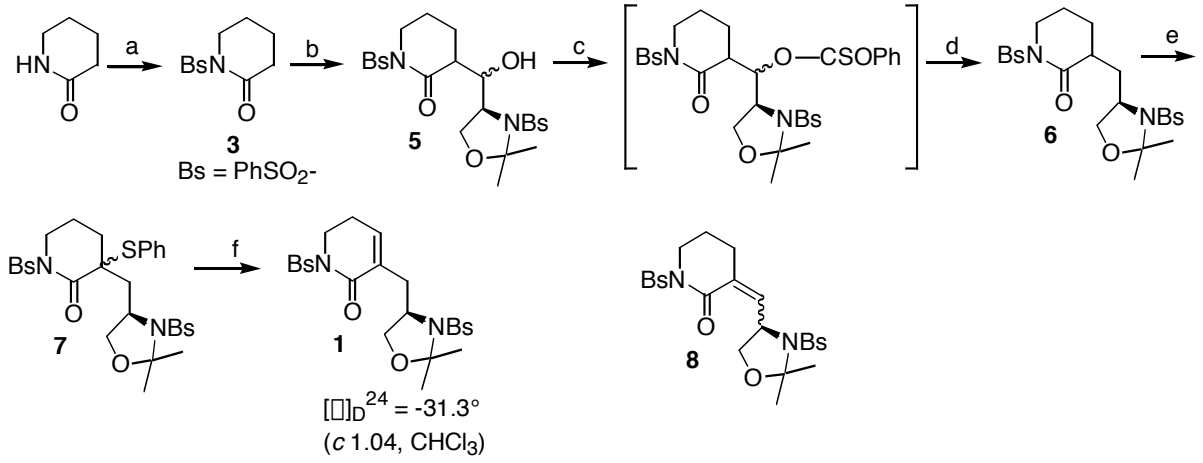
Manzamines, which are a group of marine alkaloids, are attractive molecules because of their remarkable biological properties, such as their cytotoxic, antibiotic and antimalarial activities, as well as their unique structures, which include functionalized heterocyclic ring systems.[2] While the simplest congener, manzamine C, and related compounds have been synthesized by us[3] and afterwards by Gerlach[4a] and Langlois,[4b] the total synthesis of more complex manzamine alkaloids has been a challenge. Recently, Winkler[5a] and Martin[5b, c] have succeeded in the total synthesis of manzamine A and related compounds. In our ongoing studies toward the synthesis of manzamine alkaloids such as manzamine A, manzamine B, nakadomarin A and related compounds, we have been actively exploring the Diels-Alder reaction of 1,3-disubstituted hydropyridinones with siloxy-1,3-dienes, and have previously reported our original method for synthesizing the optically active tetracyclic ring system of manzamine A.[6] Our method is based on the Diels-Alder reaction of a novel dienophile (**1**) with siloxydiene (**2**) (Scheme 1) to construct the highly functionalized hydroisoquinoline ring system, which is a common framework of manzamines A, B and a possible precursor for nakadomarin A. Furthermore, this ring system may also be useful for the development of new lead compounds for pharmaceuticals. In this paper, we describe in detail a practical synthesis of chiral hydroisoquinoline-1,6-dione by the Diels-Alder reaction.

The Diels-Alder reaction of α, β-unsaturated cycloalkanones with 1,3-dienes is a useful method for forming *cis*-fused bicyclic ring systems stereoselectively,[7] and suitable to construct a *cis* fused AB ring system of manzamine alkaloids (Scheme 1).



Scheme 1. Synthetic Strategy for Manzamine Alkaloids.

Our original synthesis of **1** is based on the aldol reaction of *N*-benzenesulfonyl-2-piperidone (**3**) with protected serinal (**4a**) which was obtained from L-serine as shown in Scheme 3,[8] followed by reduction of the aldol (**5**) to **6** by a radical process. Overall, this process proceeded with high efficiency to give optically active **1**.

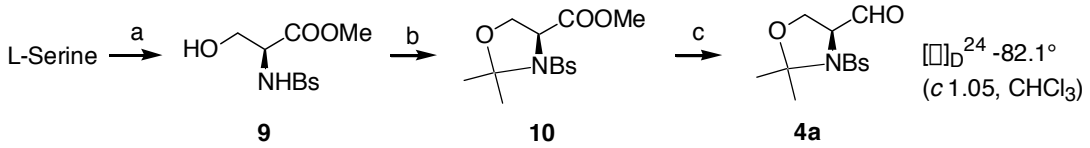


a $PhSO_2Cl$, *n*BuLi, THF, -78 to -40 °C, 94%; **b** **4a**, $LiN(TMS)_2$, THF, -78 °C, 72%; **c** $LiN(TMS)_2$, PhOC(S)Cl, THF, -30 °C; **d** nBu_3SnH, AIBN, benzene, reflux, 80% (2 steps); **e** $PhSO_2SPh$, $LiN(TMS)_2$, THF, -30 °C, 85%; **f** 1) *m*CPBA, aq. $NaHCO_3$, CH_2Cl_2, 0 °C, 2) 50 °C, 91% (2 steps).

Scheme 2. Small-Scale Preparation of Chiral Dienophile (**1**).

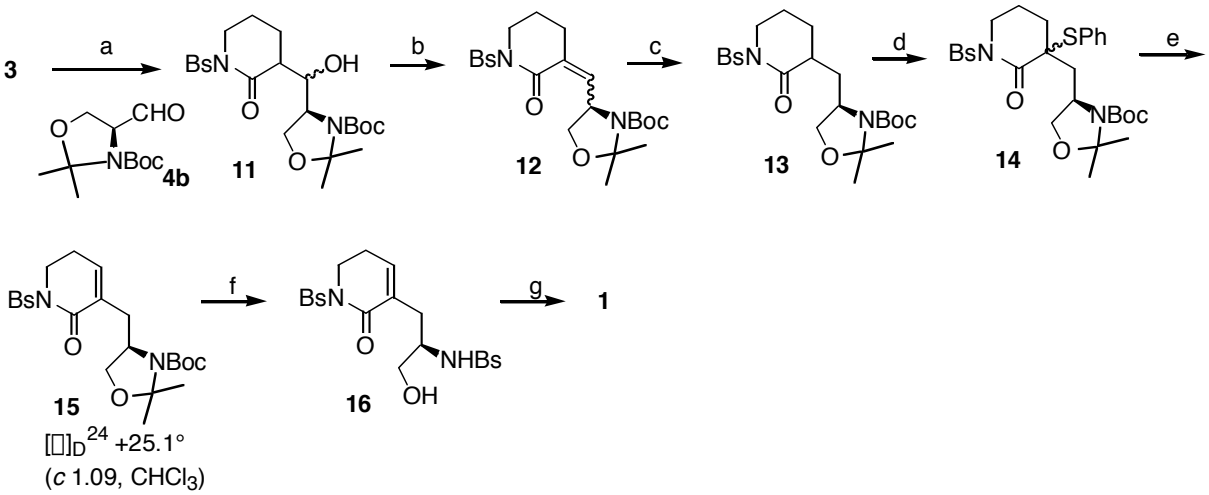
However, in a large scale synthesis of **1** (100-150 g scale) using this method, a considerable amount of highly toxic tributyltin hydride is required. Therefore, we decided to develop an alternative tin-free synthesis of **1**. First, we examined the reduction of **5** and its derivatives without using a tin reagent under various conditions. However, none of the attempted conditions gave the desired **6**. Moreover, re-

examination of the isomerization of the double bond in **8**, which was obtained from **5** by mesylation followed by elimination using DBU, to **1** by a Rh complex gave poor results.[6a] Hydrogenation of **8** proceeded very slowly to give **6** in low yield.



a 1) AcCl, MeOH, reflux, 2) BsCl, Et_3N, CH_2Cl_2, 76% (2 steps); **b** dimethoxypropane, *p*TsOH, benzene, reflux, 90%; **c** *i*Bu_2AlH, toluene, -78 °C, 92%.

Scheme 3. Preparation of Protected Serinal (**4a**).



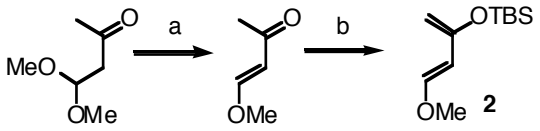
a **4b**, $LiN(TMS)_2$, THF, -78 °C, 67%; **b** 1) MsCl, Et_3N, -30 to 0 °C, 2) DBU, CH_2Cl_2, -10 °C, 71% (2 steps); **c** H_2, 5% Pd-C, AcOEt, 95%; **d** $PhSO_2SPh$, $LiN(TMS)_2$, THF, -30 °C, 70%; **e** 1) *m*CPBA, aq. $NaHCO_3$, CH_2Cl_2, 0 °C, 2) benzene, reflux, 87% (2 steps); **f** 1) HCl, 2) BsCl, aq. $NaHCO_3$, CH_2Cl_2, 80% (2 steps); **g** dimethoxypropane, PPTS, $ClCH_2CH_2Cl$, reflux, 89%.

Scheme 4. Large Scale Preparation of Dienophile (**1**).

Therefore, we next examined the hydrogenation of **12**, which has a smaller Boc group instead of a benzenesulfonyl group, as shown in Scheme 4. Accordingly, **3** and Garner aldehyde (**4b**)[9] were subjected to an aldol reaction using lithium bis(trimethylsilyl)amide in THF at –78 °C to give alcohol (**11**) in 67% yield. Subsequent dehydration of **11** by mesylation followed by treatment with DBU afforded **12** in 71% yield. In contrast to **8**, hydrogenation of **12** proceeded in the presence of 5% Pd/C in AcOEt to give **13** in 95% yield. Introduction of a phenylthio group to **13** followed by oxidative elimination gave the desired chiral dienophile (**15**) in 61% yield (3 steps). Since the Boc group in **15** is not suitable for a Diels-Alder reaction at higher temperature, the Boc group was changed to a benzenesulfonyl group as follows. The acetonide (**15**) was deprotected with hydrochloric acid to give an amino alcohol, which was carefully protected with a benzenesulfonyl group, using sat. aq. $NaHCO_3$ instead of Et_3N or pyridine as a base, to give 16. Reconstruction of acetonide moiety gave **1** in 89% yield.

In the large scale synthesis of **1**, we needed to pay special attention to the reaction conditions, which could be generally ignored in the small scale reaction. 1) In the elimination of mesylated compound obtained from **11**, the solvent was changed from benzene to CH_2Cl_2 to keep the reaction at a lower temperature.

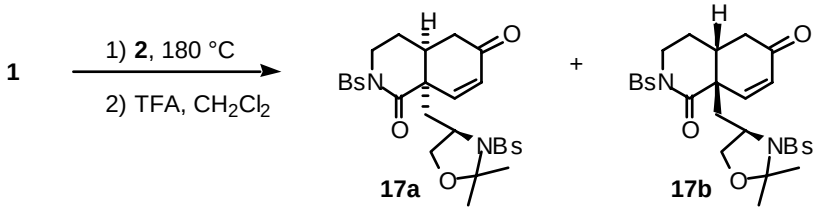
Otherwise, the exothermic reaction led to severe racemization of the substrate. 2) In the hydrogenation of **12**, the solvent was changed from MeOH to AcOEt, which increased the reaction rate. In the present experiment, 5% Pd/C purchased from Kojima Chemical Ltd. (Tokyo, Japan) gave the best results to obtain reproducible results. 3) During the hydrogenation of **12**, partial isomerization of the alkene occurred, which caused partial racemization. However recrystallization of the crude product gave optically pure **1**.



a AcONa, toluene, reflux, 82%; **b** TBSCl, $KN(TMS)_2$, THF, -78 to 0 °C, 68%.

Scheme 5. Preparation of Siloxy Diene (**2**).

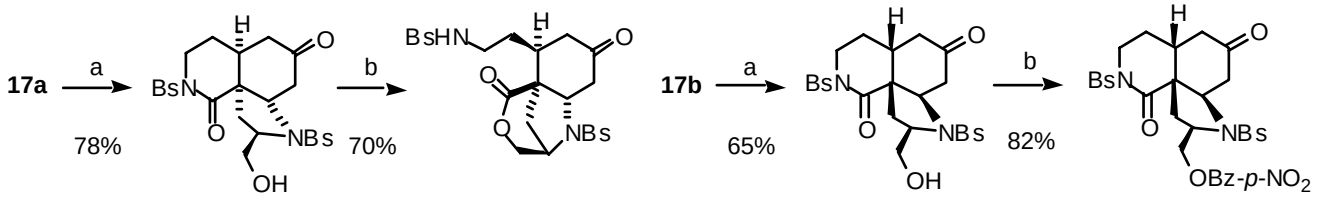
TBS-protected siloxydiene (**2**) was prepared according to the reported method with slight modification (Scheme 5).[10] In the large scale preparation of **2**, in contrast to the original method, we found that **2** could be obtained simply by distillation, and the yield of **2** was dramatically increased, when the amount of $KN(TMS)_2$ was reduced.



run	**1** (amount)	**2** (equiv.)	solvent	time (h)	yield (%)	**17a** : **17b**
1	2.5 g	5	*p*-cymene	15	75	1.4 : 1
2	7 g	5	*p*-cymene	20	85	1.1 : 1
3	50 mg	5	neat	8	81	1.3 : 1
4	31 g	3	neat	1	87	1.5 : 1
5	40 g	2	neat	1	83	1.3 : 1

Table 1. Diels-Alder Reaction of **1** with **2**.

The Diels-Alder reaction of **1** with **2** was carried out under thermal conditions (Table 1). When **1** and 5 equivalents of **2** were refluxed in *p*-cymene for 15 h and then treated with TFA for deprotection, the reaction proceeded regioselectively to give a mixture of enones (**17a** and **17b**, 1.4:1) in 75% yield (run 1).



a 1*N* HCl, THF, reflux; **b** pNO_2BzCl, pyridine.

Scheme 6. Determination of Stereochemistry of **17a** and **17b**.

A longer reaction time increased the yield to 85% (run 2). In contrast, the reaction of **1** with **2** proceeded faster without a solvent. The reaction was completed within 1 h and gave a similar yield and diastereoselectivity (run 3). With 30-40 g of **1**, 3 or 2 equivalents of **2** were sufficient to give the Diels-Alder adduct (**17**) (runs 4 and 5). The desired stereochemistry of **17a** was confirmed by chemical transformation and ^{1}H-NMR spectral analysis (Scheme 6).[6b]

In summary, we have developed an efficient method for preparing 3-substituted-5,6-dihydro-1*H*-pyridin-2-one (**1**) and siloxydiene (**2**) based on a modification of our previous method. We also established conditions for the large scale Diels-Alder reaction of **1** with **2**. Further studies toward the synthesis of manzamine alkaloids are currently underway in our laboratory.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded using a KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, and DMSO-d_6, unless otherwise noted, at 400, 500 or 600 MHz, with TMS as an internal standard. E. Merck silica gel 60 was used for column chromatography, and E. Merck precoated TLC plates and silica gel F_{254}, were used for preparative thin layer chromatography. The organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4.

N-Benzenesulfonyl-2-piperidone (3)

To a THF (600 mL) solution of 2-piperidone (30.0 g, 303 mmol) was added *n*-BuLi (1.6 M solution in *n*-hexane, 200 mL, 333 mmol) at - 78 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. To this mixture was added benzenesulfonyl chloride (46.0 mL, 364 mmol) and the mixture was stirred at - 78 ℃ for 3 h. The reaction was quenched by sat. aq. NH_4Cl and separated aqueous layer was extracted with AcOEt. Organic layers were washed with brine, dried, filtered and concentrated in vacuo. The crude residue was crystallized from a mixture of AcOEt and *n*-hexane to give **3** (68 g, 94%) as colorless prism. mp 72-73 ℃. IR (KBr) ν cm^{-1}: 3060, 2952, 1699, 1448, 1291, 1179, 1142. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.75-1.82 (2H, m), 1.88-1.94 (2H, m), 2.42 (2H, t, J = 6.8 Hz), 3.93 (2H, t, J = 6.0 Hz), 7.50-7.54 (2H, m), 7.60-7.64 (1H, m), 8.01-8.04 (2H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 19.9, 22.8, 33.7, 46.6, 128.1, 128.3, 133.3, 138.7, 169.9. LR-FABMS m/z: 240 [$(M+H)^+$, 100]. *Anal.* Calcd for C_5H_9NO: C, 55.23; H, 5.44; N, 5.86. Found: C, 54.97; H, 5.35; N, 5.72.

(*RS*)-1-Benzenesulfonyl-3-[(*RS*)-[(4*S*)-3-benzenesulfonyl-2,2-dimethyloxazolidin-4-yl]hydroxy-methyl]piperidin-2-one (5)

To a solution of *N*-benzenesulfonyl-2-piperidone (**3**) (11.7 g, 48.8 mmol) in THF (75.0 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 88.0 mL, 87.8 mmol) dropwisely at - 78 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. To this mixture was added **4a** (19.7 g, 73.2 mmol) in THF (50.0 mL) and the mixture was stirred at - 60 ℃ for 12 h. The reaction was quenched by addition of sat. aq. NH_4Cl (50 mL) and the separated aqueous layer was extracted with AcOEt (50 mL x 3). The combined AcOEt layers were washed with brine, dried and evaporated. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 2/1) to afford **5** as a mixture of diastereomers (less polar fraction, 12.6 g, 51%, and more polar fraction, 5.3 g, 21%) as a colorless amorphous. Less polar

isomer: IR (KBr) ν cm^{-1}: 3515, 2985, 2938, 2879, 1681, 1346, 1162. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.42 (3H, s), 1.58 (3H, s), 1.94-2.09 (4H, m), 3.09 (1H, d, J = 11.2 Hz), 3.31 (1H, dd, J = 4.8, 9.3 Hz), 3.37 (1H, ddd, J = 2.3, 7.0, 8.7 Hz), 3.49 (1H, ddd, J = 1.9, 8.7, 11.2 Hz), 3.75 (1H, ddd, J = 5.8, 8.4, 12.7 Hz), 4.00 (1H, dd, J = 4.8, 8.7 Hz), 4.10 (1H, d, J = 9.3 Hz), 4.41 (1H, dt, J = 4.6, 12.7 Hz), 7.36-7.64 (8H, m), 7.98-8.03 (2H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 22.3, 22.9, 23.6, 31.0, 42.3, 44.2, 61.5, 65.8, 72.7, 98.3, 127.7, 128.0, 128.3, 128.5, 128.6, 128.8, 129.0, 132.6, 133.4, 139.0, 139.8, 175.0. LR-FABMS m/z: 509 [$(M+H)^+$, 10]. HR-FABMS m/z: Calcd for $C_{23}H_{30}O_7N_2S_2$: 509.1416, Found: 509.1411. More polar isomer: IR (KBr) ν cm^{-1}: 3502, 2987, 2940, 2879, 1691, 1346, 1153. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.33 (3H, s), 1.56 (3H, s), 1.87-2.14 (4H, m), 2.83-2.88 (1H, m), 2.92 (1H, d, J = 6.8 Hz), 3.53 (1H, dd, J = 5.6, 9.1 Hz), 3.93-4.20 (5H, m), 7.46-7.67 (8H, m), 7.96-8.03 (2H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 21.8, 22.3, 24.0, 30.1, 46.6, 46.8, 61.0, 65.4, 69.8, 98.0, 127.5, 128.3, 128.5, 128.6, 129.0, 129.1, 132.7, 133.5, 139.0, 140.3, 173.0. LR-FABMS m/z: 509 [$(M+H)^+$, 10]. HR-FABMS m/z: Calcd for $C_{23}H_{30}O_7N_2S_2$: 509.1416, found: 509.1411.

(*RS*)-1-Benzenesulfonyl-3-[(4*R*)-3-benzenesulfonyl-2,2-dimethyloxazolidin-4-ylmethyl]piperidin-2-one (6)

To a solution of alcohol (**5**) (11.0 g, 21.6 mmol) in THF (540 mL) was added $LiN(TMS)_2$ (1.00 M solution in THF, 26 mL, 25.9 mmol) at - 78 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. PhOC(S)Cl (4.5 mL, 32.4 mmol) was added and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched by sat. aq. NH_4Cl (100 mL) and aqueous layer was extracted with AcOEt (100 mL x 2). The combined AcOEt layers were washed with brine, dried and concentrated in vacuo to give a residue which was dissolved in benzene (300 mL). To this benzene solution were added AIBN (1.80 g, 10.8 mmol) and *n*-$BuSn_3H$ (12 mL, 43.2 mmol). The mixture was refluxed for 30 min and the solvent was removed in vacuo. The resulting residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 3/1) to afford **6** (8.5 g, 2 steps, 80%) as a white amorphous. $[\alpha]_D^{24}$ - 77.2° (*c* 1.05, $CHCl_3$). IR (KBr) ν cm^{-1}: 3066, 2938, 1698, 1340, 1162, 1089. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.41 (3H, s), 1.62 (3H, s), 1.44-1.55 (1H, m), 1.65-1.72 (1H, m), 1.93-2.00 (4H, m), 2.80 (1H, ddd, J = 2.9, 5.6, 8.3 Hz), 3.53 (1H, dd, J = 4.9, 9.0 Hz), 3.56 (1H, d, J = 9.1 Hz), 3.86 (1H, m), 4.00 (1H, dd, J = 6.1, 12.0 Hz), 4.16 (1H, dt, J = 5.3, 10.5, 12.5 Hz), 7.39-7.62 (8H, m), 7.98-8.04 (2H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 13.5, 22.0, 24.0, 26.0, 26.7, 27.7, 30.6, 36.7, 39.9, 45.3, 58.1, 68.9, 97.7, 127.4, 128.3, 128.6, 128.8, 132.4, 133.4, 139.1, 140.8, 173.8. LR-FABMS m/z: 493 [$(M+H)^+$, 20]. HR-FABMS m/z: Calcd for $C_{23}H_{29}O_6N_2S_2$: 493.1467, found: 493.1469.

(*RS*)-1-Benzenesulfonyl-3-[(4*R*)-3-benzenesulfonyl-2,2-dimethyloxazolidin-4-ylmethyl]-3-phenylthiopiperidin-2-one (7)

To a solution of **6** (10.5 g, 21.4 mmol) in THF (200 mL) was dropwisely added $LiN(TMS)_2$ (1.00 M solution in THF, 35 mL, 32.1 mmol) at − 30 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. To this mixture was added $PhSSO_2Ph$ (6.40 g, 25.7 mmol) in THF (20 mL) and the mixture was stirred at − 30 ℃ for 2 h. The reaction was quenched by addition of sat. aq. NH_4Cl (50 mL) and separated aqueous layer were extracted with AcOEt (50 mL x 2). The combined AcOEt layers

were washed with brine, dried and evaporated. Resulting residue was subjected to chromatography (SiO_2, *n*-hexane/AcOEt = 3/1) to afford the **7** (10.9 g, 85%) as a mixture of diastereo isomers. IR (KBr) ν cm^{-1}: 3060, 2987, 2935, 1685, 1344, 1170, 1089. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.32 (3H, s), 1.62 (3H, s), 1.92-1.97 (1H, m), 1.99-2.01 (4/5H, m), 2.03-2.06 (1H, m), 2.10 (4/5H, dd, *J* = 5.8, 8.3 Hz), 2.34-2.36 (2/5H, m), 2.42-2.54 (1H, m), 2.98 (1H, ddd, *J* = 4.2, 10.7, 15.1 Hz), 3.18 (4/5H, dd, *J* = 5.0, 9.0 Hz), 3.45 (4/5H, d, *J* = 8.3 Hz), 3.55-3.56 (1/5H, m), 3.92 (4/5H, ddd, *J* = 4.8, 8.7, 9.3 Hz), 3.98 (1/5H, d, *J* = 4.4 Hz), 4.01 (1H, dd, *J* = 4.4, 11.2 Hz), 4.26-4.29 (1/5H, m), 4.31 (1H, dt, *J* = 3.9, 9.3, 10.2 Hz), 7.15-7.56 (12H, m), 7.94-8.06 (3H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 14.1, (20.1, 20.5), (23.9, 24.1), (30.2, 30.8), (32.2, 33.5), (41.9, 43.3), (47.0, 47.2), (56.2, 56.3), (56.8, 57.6), (68.9, 69.5), (97.4, 97.8), 127.5, 128.2, 128.73, 128.74, 128.8, 128.9, 129.0, 129.4, 130.6, 132.4, 132.5, 133.1, 133.6, 136.6, 138.1, 139.5, 140.6, (169.8, 170.6). LR-FABMS m/z: 601 [$(M+H)^+$, 20]. HR-FABMS m/z: Calcd for $C_{29}H_{33}O_6N_2S_3$: 601.1501, found: 601.1526.

1-Benzenesulfonyl-3-[(4*R*)-(3-benzenesulfonyl-2,2-dimethyloxazolidin-4-ylmethyl]-5,6-dihydro-1*H*-pyridin-2-one (1)

To a solution of **7** (14.6 g, 24.3 mmol) in CH_2Cl_2 (300 mL) were added sat. aq. $NaHCO_3$ (300 mL) and a solution of *m*-CPBA (70 %, 6.60 g, 26.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C for 2 h. The mixture was stirred at ambient temperature for 1 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (100 mL) and aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined CH_2Cl_2 layers were washed with sat. aq. $Na_2S_2O_3$ (100 mL), brine, dried and evaporated at 50 °C. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 2/1) to give **1** (10.8 g, 91%) as a colorless amorphous. $[\alpha]_D^{24}$ - 31.3 ° (*c* 1.04, $CHCl_3$). IR (KBr) ν cm^{-1}: 3066, 2987, 2938, 2881, 1685, 1342, 1166, 1095. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.34 (3H, s), 1.63 (3H, s), 2.43-2.67 (4H, m), 3.43 (1H, dd, *J* = 5.3, 9.0 Hz), 3.57 (1H, d, *J* = 9.0 Hz), 3.96 (1H, dt, *J* = 4.3, 9.2 Hz), 4.09 (1H, m), 4.30 (1H, ddd, *J* = 5.9, 10.9, 11.5 Hz), 6.58 (1H, t, *J* = 4.1 Hz), 7.31-7.53 (8H, m), 7.56-8.05 (2H, m). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 23.9, 25.3, 30.7, 36.9, 44.1, 57.9, 68.3, 97.7, 127.4, 128.4, 128.5, 128.7, 132.0, 132.3, 133.2, 139.2, 140.8, 140.9, 164.3. LR-FABMS m/z: 491 [$(M+H)^+$, 35]. HR-FABMS m/z: Calcd for $C_{23}H_{27}O_6N_2S_2$: 491.1311, found: 491.1309.

Methyl *N*-Benzenesulfonyl-L-serinate (9)

Acetyl chloride (10 mL, 1.50 mol) was added dropwise to MeOH (400 mL) at 0 ° C, and the mixture was stirred at ambient temperature for 10 min. After L-serine (55.0 g, 0.52 mol) was added, the resulting solution was refluxed for 2 h. The resulting solution was concentrated to give white solid which was recrystallized from Et_2O-MeOH to give methyl L-serinate hydrochloride (77 g, 94%) as a white crystal. To a suspension of methyl L-serinate hydrochloride (30 g, 193 mmol) in CH_2Cl_2 (385 mL) were added Et_3N (67 mL, 483 mmol) and $PhSO_2Cl$ (27 mL, 212 mmol) at 0 °C under Ar atmosphere. After stirring for 12 h at rt, the solution was poured into sat. aq. $NaHCO_3$ and aqueous layer was extracted with CH_2Cl_2 (500 mL x 2). Combined organic layers were washed with 1*N* aq. HCl (100 mL), H_2O (100 mL), sat. aq. $NaHCO_3$ (100 mL), and brine (50 mL) successively. The dried solvent was evaporated in vacuo to give a residue which was recrystallized from AcOEt to give **9** (40 g, 81%) as white crystal. $[\alpha]_D^{23}$ -12.5°(*c* 1.06,

MeOH). mp 120-121 °C. IR (KBr) ν cm^{-1}: 3488, 3274, 1743, 1328. ^{1}H-NMR ; 400 MHz (CD_3OD) δ ppm: 3.44 (3H, s), 3.65 (1H, dd, *J* = 5.4, 11.0 Hz), 3.73 (1H, dd, *J* = 4.9, 11.3 Hz), 3.99 (1H, dd, *J* = 4.9, 5.4 Hz), 7.51-7.62 (3H, m), 7.80-7.88 (2H, m). ^{13}C-NMR; 100 MHz (CD_3OD) δ ppm: 52.6, 59.3, 64.0, 128.1, 130.0, 133.6, 142.0, 171.8. LR-FABMS m/z: 260 [$(M+H)^+$, 45]. *Anal.* Calcd for $C_{10}H_{13}NO_5S$: C, 46.33; H, 5.05; N, 5.40. Found: C, 46.24; H, 4.95; N, 5.43.

Methyl (4*S*)-3-Benzenesulfonyl-2, 2-dimethyloxazolidine-4-carboxylate (10)

To a solution of **9** (13.4 g, 52.0 mmol) in benzene (170 mL) were added 2,2-dimethoxypropane (11.0 mL, 94.0 mmol) and *p*-TsOH•H_2O (1.0 g, 5.2 mmol). The reaction mixture was refluxed for 2 h and then poured into sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with AcOEt (100 mL x 2). The combined organic layers were washed with brine, dried and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, AcOEt/Hexane = 1/2) to give **10** (13.8 g, 90%) as white prism. $[\alpha]_D^{24}$ - 80.5° (*c* 1.03, $CHCl_3$). mp 49-52 °C (Et_2O). IR (KBr) ν cm^{-1}: 1758, 1348, 1162. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.57 (3H, s), 1.69 (3H, s), 3.56 (3H, s), 4.03 (1H, dd, *J* = 2.9, 9.3 Hz), 4.10 (1H, dd, *J* = 7.1, 9.3 Hz), 4.43 (1H, dd, *J* = 2.7, 7.8 Hz), 7.46-7.51 (2H, m), 7.53-7.58 (1H, m), 7.86-7.88 (2H, m). ^{13}C-NMR;100 MHz ($CDCl_3$) δ ppm: 25.3, 27.4, 52.3, 59.8, 67.0, 98.7, 127.4, 128.7, 128.9, 132.7, 132.9, 140.4. LR-FABMS m/z: 300 [$(M+H)^+$, 80]. HR-FABMS m/z: Calcd for $C_{13}H_{18}O_5NS$: 300.0906, found: 300.0883.*Anal*. Calcd for $C_{12}H_{21}NO_5$: C, 52.16; H, 5.72; N, 4.68. Found: C, 52.27; H, 5.71; N. 4.76.

(4*S*)-3-Benzenesulfonyl-4-formyl-2, 2-dimethyl-3-oxazolidine (4a)

To a stirring solution of **10** (11.5 g, 38.5 mmol) in toluene (65.0 mL) was added DIBAH (1.00 M solution in toluene, 65 mL, 65 mmol) dropwisely over 1 h at - 78 °C under Ar. After stirring at ambient temperature for 2 h, MeOH (5 mL) and sat. aq. Rochell salt (50 mL) were added to the mixture. The mixture was then diluted with AcOEt (100 mL), and stirred for 2 h at rt. The organic layer was separated and the aqueous layer was extracted with AcOEt (50 mL x 3). Combined organic layers were washed with brine, dried and evaporated in vacuo. The resulting residue was subjected to column chromatography (SiO_2, AcOEt/*n*hexane = 1/2) to give **4a** (9.5 g, 92%) as a pale yellow oil. $[\alpha]_D^{24}$ - 82.1° (*c* 1.05, $CHCl_3$). IR (neat) ν cm^{-1}: 1735, 1346, 1160. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm: 1.57 (3H, s), 1.69 (3H, s), 3.98 (1H, dd, *J* = 6.4, 8.3 Hz), 4.11-4.02 (2H, m), 7.49-7.53 (2H, m) 7.57-7.61 (1H, m), 7.83-7.85 (2H, m), 9.53 (1H, d, *J* = 2.9 Hz). ^{13}C-NMR; 100 MHz ($CDCl_3$) δ ppm: 24.5, 28.6, 64.5, 65.3, 98.8, 127.9, 129.2, 137.3, 139.9, 199.0. LR-FABMS m/z: 270 [$(M+H)^+$, 70]. HR-FABMS m/z: Calcd for $C_{12}H_{15}O_4NS$: 270.0800, found: 270.0794.

1, 1-Dimethyethyl (4*S*)-4-[(*RS*)-[(3*RS*)-3-Benzenesulfonyl-2-oxopiperidin-3-yl]hydroxymethyl]-2, 2-dimethyloxazolidine-3-carboxylate (11)

To a solution of **3** (43 g, 183.4 mmol) in THF (400 mL) was added $LiN(TMS)_2$ (1.00 M solution in THF, 203 mL, 201.7 mmol) dropwisely at - 78 °C under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. To this mixture was added a solution of aldehyde (**4b**) (46.3 g, 201.7 mmol) in THF (100 mL) and the mixture was stirred for 12 h at - 78 °C. The reaction was quenched by addition of sat. aq. NH_4Cl (300 mL). Separated aqueous layer was extracted with AcOEt (300 mL x 3) and combined

organic layers were washed with brine, dried and evaporated. The residue was subjected to column chromatography (SiO_2, *n*hexane/AcOEt = 2/1) to afford the alcohol (**11**) (58.8 g, 67%). $[\alpha]_D^{23}$ - 30.2° (*c* 1.56, $CHCl_3$). IR (neat) ν cm^{-1}: 3566, 2976, 2936, 2884, 1692, 1448, 1389, 1365, 1260, 1171, 1088. ^{1}H-NMR; 400 MHz (DMSO-d_6, 110 ℃) δ ppm: 1.38 (9H, s), 1.39 (3H, s), 1.45 (3H, s), 1.71-1.80 (2H, m), 1.81-1.89 (1H, m), 1.95-2.01 (1H, m), 2.58 (1H, ddd, *J* = 4.1, 4.3, 8.7 Hz), 3.72 (1H, dd, *J* = 6.5, 8.7 Hz), 3.79-3.89 (3H, m), 3.91 (1H, dd, *J* = 2.3, 8.9 Hz), 4.01 (1H, ddd, *J* = 2.9, 3.6, 6.5 Hz), 4.56 (1H, d, *J* = 6.1 Hz), 7.58 (2H, t, *J* = 7.8 Hz), 7.68 (1H, t, *J* = 7.1 Hz), 7.92 (2H, d, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6, 110 ℃) δ ppm: 21.3, 23.4, 25.9, 27.5, 45.4, 46.5, 71.6, 78.7, 92.6, 127.1, 128.1, 132.8, 139.2, 151.3, 170.7. LR-FABMS m/z: 469 [$(M+H)^+$, 40]. HR-FABMS m/z: Calcd for $C_{22}H_{33}N_2O_7S$: 469.2008, found: 469.2016.

1, 1-Dimethylethyl (4*R*)-(*E*)-4-(1-Benzenesulfonyl-2-oxopiperidin-3-ylidene)methyl-2, 2-dimethyloxazolidine-3-carboxylate and 1-Dimethylethyl (4*R*)-(*Z*)-4-(1-Benzenesulfonyl-2-oxopiperidin-3-ylidene)methyl-2, 2-dimethyloxazolidine-3-carboxylate [(*E*) and (*Z*)-12]

To a solution of alcohol (**11**) (36.0 g, 83.3 mmol) in CH_2Cl_2 (500 mL) were added Et_3N (29 mL, 208.3 mmol) and MsCl (9.7 mL, 125.0 mmol) at - 30 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 2 h, and 0 ℃ for 1.5 h. To the mixture was added sat. aq. $NaHCO_3$ (100 mL) and organic compounds were extracted with CH_2Cl_2 (300 mL x 2). The combined CH_2Cl_2 layers were washed with brine, dried and evaporated. The residue was dissolved in CH_2Cl_2 (300 mL), and to the mixture was added DBU (50 mL, 333.2 mmol). The mixture was stirred at - 10 ℃ for 1 h and to the reaction mixture was added H_2O (100 mL) and organic compounds were extracted with AcOEt (100 mL x 2). The combined CH_2Cl_2 layers were washed with brine, dried and evaporated. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt=2/1) to afford a mixture of (*E*)- and (*Z*)-**12** (26.5 g, 71%) as a colorless syrup. A small amount of (*E*)-and (*Z*)-**12** was separated by column chromatography; (*E*)-**12**: $[\alpha]_D^{23}$ - 2.8° (*c* 1.1, $CHCl_3$), IR (neat) ν cm^{-1}: 2981, 2933, 1700, 1636, 1449, 1395, 1250, 1107. ^{1}H-NMR; 400 MHz (DMSO-d_6, 110 ℃) δ ppm: 1.33 (9H, s), 1.44 (3H, s), 1.49 (3H, s), 1.83-1.97 (2H, m), 2.42-2.45 (1H, m), 2.60-2.67 (1H, m), 3.59 (1H, dd, *J* = 3.6, 9.0 Hz), 3.88-3.99 (2H, m), 4.07 (1H, dd, *J* = 6.5, 9.0 Hz), 4.55 (1H, ddd, *J* = 3.6, 6.5, 9.5 Hz), 6.48 (1H, ddd, *J* = 1.9, 2.1, 9.3 Hz), 7.56-7.60 (2H, m), 7.66-7.70 (1H, m), 7.93-7.95 (2H, m). ^{13}C-NMR ; 100 MHz (DMSO-d_6, 110 ℃) δ ppm: 21.9, 22.9, 23.9, 25.9, 27.4, 45.7, 54.0, 66.4, 78.9, 92.9, 127.1, 128.2, 129.1, 132.8, 139.1, 140.1, 150.6, 162.9. LR-FABMS m/z: 451 [$(M+H)^+$, 30]. HR-FABMS m/z: Calcd for $C_{22}H_{33}N_2O_6S$: 451.1903, found: 451.1880. (*Z*)-**12**: $[\alpha]_D^{23}$ - 2.4° (*c* 1.5, $CHCl_3$). ^{1}H-NMR; 400 MHz (DMSO-d_6, 110 ℃) δ ppm: 1.29 (9H, s), 1.38 (3H, s), 1.48 (3H, s), 1.78-1.88 (1H, m), 1.91-2.07 (1H, m), 2.48 (2H, dt, *J* = 1.9, 3.9 Hz), 3.45 (1H, dd, *J* = 3.4, 9.0 Hz), 3.84 (1H, ddd, *J* = 4.6, 6.8, 11.7 Hz), 3.,93 (1H, ddd, *J* = 4.6, 7.8, 12.4 Hz), 4.00 (1H, dd, *J* = 6.8, 9.0 Hz), 4.92 (1H, td, *J* = 3.4, 7.3 Hz), 5.95 (1H, dt, *J* = 1.7, 7.5 Hz), 7.55-7.59 (2H, m), 7.65-7.67 (1H, m), 7.92-7.94 (2H, m). ^{13}C-NMR: 100 MHz (DMSO-d_6, 110 ℃) δ ppm: 22.3, 23.5, 25.9, 27.4, 28.9, 46.0, 55.4, 67.7, 78.5, 92.9, 127.1, 128.0, 128.2, 132.9, 139.1, 145.7, 150.7, 163.5. LR-FABMS m/z: 451 [$(M+H)^+$, 40]. HR-FABMS m/z: Calcd for $C_{22}H_{33}N_2O_6S$: 451.1903, found: 451.1867.

1, 1-Dimethylethyl (4*R*)-4-[(3*RS*)-1-Benzenesulfonyl-2-oxopiperidin-3-yl]methyl-2, 2-dimethyl-oxazolidine-3-carboxylate (13)

To a solution of a mixture of (*E*)- and (*Z*)-**12** (26.5 g, 58.8 mmol) in AcOEt (300 mL) was added 5%Pd-C (7.80 g) under Ar atmosphere. The Ar gas was exchanged with H_2 gas. The mixture was stirred at rt temperature for 48 h. The solution was filtered using Cerite and mother liquor was evaporated. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 2/1) to afford **13** (25.3 g, 95%) as a colorless syrup. $[\alpha]_D^{23}$ - 2.4° (*c* 1.8, $CHCl_3$). IR (neat) ν cm^{-1}: 2977, 2933, 2875, 1690, 1389, 1364, 1257, 1170, 1089. ^{1}H-NMR (400 MHz, DMSO-d_6, 110 ℃) δ ppm: 1.39 (9H, s), 1.40 (3H, s), 1.45 (3H, s), 1.47-1.56 (2H, m), 1.81-1.94 (2H, m), 1.99 (1H, td, *J* = 6.5, 12.7 Hz), 2.09 (1H, dt, *J* = 5.5, 13.9 Hz), 2.39-2.45 (1H, m), 3.62 (1H, ddd-like, *J* = 1.2, 1.7, 7.5 Hz), 3.79-3.85 (2H, m), 3.87-3.94 (2H, m), 7.56-7.61 (2H, m), 7.66-7.68 (1H, m), 7.91-7.93 (2H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, 110 ℃) δ ppm: Some signals were observed as a pair because of a presence of rotaional isomers due to N-Boc group which are shown in parentheses. (20.9, 21.1), 23.3, 24.7, 25.6, 26.4, 27.5, (34.1, 34.3), 45.7, 78.6, 92.3, 127.1, 128.2, 132.8, 139.1, (150.6, 150.9), (172.1, 172.2). LR-FABMS m/z: 453 [$(M+H)^+$, 50]. HR-FABMS m/z: Calcd for $C_{22}H_{33}N_2O_6S$: 453.2059, found: 453.2034.

1, 1-Dimethylethyl (4*R*)-4-[(1*RS*)-1-Benzenesulfonyl-2-oxo-3-phenylthiopiperidin-3-yl]methyl-2, 2-dimethyloxazolidine-3-carboxylate (14)

A solution of **13** (25.2 g, 55.6 mmol) in THF (400 mL) was dropwisely added $LiN(TMS)_2$ (1.00 M solution in THF, 70 mL, 66.7 mmol) at - 78 ℃ under Ar atmosphere. The mixture was stirred at ambient temperature for 30 min. To the mixture was added a solution of $PhSSO_2Ph$ (16.7 g, 66.7 mmol) in THF (100 mL) and the mixture was stirred at - 78 ℃ for 2 h. To the mixture, sat. aq. NH_4Cl (100 mL) was added and organic compounds were extracted with AcOEt (200 mL x 2). The combined AcOEt layers were washed with brine, dried and evaporated. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 4/1) to afford **14** (21.6 g, 70%) as a colorless amorphous. IR (neat) ν cm^{-1}: 2977, 2935, 2875, 1684, 1391, 1170, 1088. ^{1}H-NMR (400 MHz, DMSO-d_6, 110 ℃) δ ppm: 1.38 (9H, s), 1.39 (3H, s), 1.42 (3H, s), 1.80-2.04 (5H, m), 2.10-2.20 (1H, m), 3.81 (2H, d, *J* = 3.1 Hz), 3.83-3.95 (2H, m), 4.01-4.09 (1H, m), 7.17-7.21 (4H, m), 7.32-7.34 (2H, m), 7.60-7.64 (2H, m), 7.72-7.74 (1H, m), 7.94-7.96 (1H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, 110 ℃) δ ppm: 19.1, 23.0, 23.3, 26.4, 26.5, 27.5, 27.6, 31.2, 47.4, 53.4, 55.7, 68.1, 79.2, 91.9, 127.5, 128.0, 128.2, 128.6, 129.5, 133.1, 135.6, 138.9, 150.9, 169.0. LR-FABMS m/z: 561 [$(M+H)^+$, 20]. HR-FABMS m/z: Calcd for $C_{28}H_{37}N_2O_6S_2$: 561.2093, found: 561.2104.

1, 1-Dimethylethyl (4*R*)-4-[1-Benzenesulfonyl-2-oxo-1, 2, 5, 6-tetrahydropyridin-3-yl]methyl-2, 2-dimethyloxazolidine-3-carboxylate (15)

A solution of **14** (21.6 g, 38.5 mmol) in CH_2Cl_2 (300 mL) was added sat. aq. $NaHCO_3$ (300 mL), and dropwisely added *m*-CPBA (70 %, 10.5 g, 42.4 mmol) in CH_2Cl_2 (100 mL) at 0 ℃. The mixture was stirred at ambient temperature for 1 h. To the reaction mixture was added sat. aq. $NaHCO_3$. (100 mL) and the mixture were extracted with CH_2Cl_2 (100 mL x 2). The combined CH_2Cl_2 layers were washed with sat. aq. $Na_2S_2O_3$ (100 mL), brine, dried and evaporated. The residue was dissolved in benzene (300 mL)

and the solution was refluxed for 30 min and then concentrated. The residue was purified by column chromatography (SiO_2, *n*-hexane/AcOEt = 3/1) to give **15** (15.1 g, 87%) as a colorless prism. mp 160-161 ℃ (AcOEt/*n*-hexane). $[\alpha]_D^{24}$ +25.1 ° (*c* 1.10 $CHCl_3$). IR (KBr) ν cm^{-1}: 2997, 2937, 2874, 1687, 1646, 1395, 1170, 1051. ^{1}H-NMR (400 MHz, DMSO-d_6, 110 ℃) δ ppm: 1.37 (3H, s), 1.39 (9H, s), 1.44 (3H, s), 2.33-2.45 (2H, m), 2.51-2.55 (2H, m), 3.55 (1H, d-like, *J* = 9.1 Hz), 3.76 (1H, dd, *J* = 5.8, 8.7 Hz), 3.86 (1H, dd, *J* = 5.6, 11.5 Hz), 3.93-4.05 (2H, m), 6.65 (1H, t, *J* = 4.1 Hz), 7.58 (2H, t, *J* = 7.8 Hz), 7.68 (1H, dd, *J* = 6.9, 7.8 Hz), 7.95 (2H, d, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6, 110 ℃) δ ppm: 23.3, 24.3, 26.5, 27.5, 33.1, 43.4, 55.5, 65.6, 78.5, 92.4, 127.0, 128.2, 130.8, 132.8, 138.9, 141.1, 150.9, 162.9. LR-FABMS m/z: 451 [$(M+H)^+$, 40]. HR-FABMS m/z: Calcd for $C_{22}H_{31}N_2O_6S$: 451.1903, found: 451.1886. *Anal*. Calcd for $C_{22}H_{30}N_2O_6S$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.74; H, 6.63; N. 6.28.

1-Benzenesulfonyl-3-(2*R*)-2-benzenesulfonylamino-3-hydroxypropyl-1, 2, 5, 6-tetrahydropyridin-2-one (16)

To a solution of dienophile (**15**) (6.47 g, 15.0 mmol) in CH_2Cl_2 (150 mL) was added *c* HCl (7.5 mL) and the reaction mixture was stirred at rt for 1 h, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), and to this solution were added sat. aq. $NaHCO_3$ (100 mL) and benzenesulfonyl chloride (1.90 mL, 15.0 mmol) at 0 ℃. After stirring for 12 h, the mixture was poured into sat. aq $NaHCO_3$ (100 mL) and products were extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried and evaporated in vacuo. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt = 5/1) to give **16** (5.4g, 80% 2 steps) as a white amorphous. $[\alpha]_D^{23}$ +17.9 ° (*c* 1.00, $CHCl_3$). IR (KBr) ν cm^{-1}: 3063, 2943, 2878, 1718, 1685, 1348, 1169, 755. ^{1}H-NMR ; 400 MHz ($CDCl_3$) δ ppm: 2.26-2.35 (5H, m), 3.16-3.34 (3H, m), 3.87-3.94 (1H, m), 4.09-4.14 (1H, m), 5.33 (1H, d, *J* = 7.6 Hz), 6.62 (1H, t, *J* = 4.2 Hz), 7.42-7.65 (8H, m), 8.03-8.06 (2H, m). ^{13}C-NMR ; 100 MHz ($CDCl_3$) δ ppm: 25.1, 32.6, 44.1, 55.2, 64.3, 126.9, 128.5, 128.8, 129.1, 131.3, 132.5, 133.7, 138.7, 140.3, 143.0, 165.1. LR-FABMS m/z: 451 [$(M+H)^+$, 12]. HR-FABMS m/z: Calcd for $C_{20}H_{23}O_6N_2S_2$: 451.0998, found: 451.0886.

Preparation of 1 from 16.

To a stirring solution of **16** (5.40 g, 11.9 mmol) in $ClCH_2CH_2Cl$ (120 mL), was added 2,2-dimethoxypropane (7.4 mL, 29.8 mmol) and PPTS (400 mg, 3.6 mmol) and the mixture was refluxed for 3 h. After cooling to rt, the mixture was poured into H_2O, and the products were extracted with $CHCl_3$. Combined organic layers were washed with brine, dried and evaporated in vacuo. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt=1/1) to give **1** (5.20 g, 89%) as a white amorphous.

(*E*)-3-*tert*-Butyldimethylsilyloxy-1-methoxy-1, 3-butadiene (2)

To a THF (280 mL) solution of TBSCl (41.9 g, 275 mmol) cooled at - 78 ℃ was added 4-methoxy-3-buten-2-one (25.5 mL, 250 mmol) and the mixture was stirred for 15 min. A solution of $KN(TMS)_2$ (63.0 g, 300 mmol) in toluene (250 mL) was added dropwise to the mixture for 1 h and the mixture was warmed to 0 ℃ for 4 h. The reaction was quenched by addition of sat. aq. NH_4Cl (150 mL) and warmed to rt.

After separation of the organic layer, the aqueous layer was extracted with petr. ether (300 mL). Combined organic layers were washed with sat. aq. NH_4Cl and brine successively. Dried solvent was evaporated to give crude **2** which was purified by distillation to give pure **2** (36.2 g) in 68% yield. bp 83-84 ℃ (4 mmHg). IR (neat) ν cm^{-1}: 2956, 2930, 2858, 1653, 1319, 1254, 1211, 1024. ^{1}H-NMR; 400 MHz ($CDCl_3$) δ ppm : 0.18 (6H, s), 0.96 (9H, s), 3.58 (3H, s), 4.07 (2H, d, *J*= 12.9 Hz), 5.35 (1H, d, J = 12.2 Hz), 6.87 (1H, d, *J*= 12.2 Hz). ^{13}C-NMR ; 100 MHz (CDCl3) δ ppm: -4.7, 25.6, 25.7, 56.2, 90.7, 103.2, 150.1. LR-FABMS m/z: 215 [$(M+H)^+$, 100]. HR-FABMS m/z: Calcd for $C_{11}H_{23}O_2Si$: 215.1467, found: 215.1476.

(4a*S*, 8a*S*)-2-Benzenesulfonyl-8a-[(4*R*)-3-benzenesulfonyl-2, 2-dimethyloxazolidin-4-yl]methyl-1, 2, 3, 4, 4a, 5, 6, 8a-octahydroisoquinoline-1, 6-dione (17a) and (4a*R*, 8a*R*)-2-Benzenesulfonyl-8a-[(4*R*)-3-benzenesulfonyl-2, 2-dimethyloxazolidin-4-yl]methyl-1, 2, 3, 4, 4a, 5, 6, 8a-octahydroisoquinoline-1, 6-dione (17b)

To a stirring solution of dienophile (**1**) (6.70 g, 13.7 mmol) in *p*-cymene (34 mL) was added TBS-diene (**2**, 14.6 mL, 68.5 mmol) under Ar atmosphere. The mixture was stirred at 180 ℃ for 20 h, and *p*-cymene and excess diene were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (140 mL), and added TFA (0.960 mL, 12.3 mmol). The mixture was stirred at rt for 2 h and the reaction was quenched by addition of sat. aq. $NaHCO_3$ (50.0 mL) and products were extracted with CH_2Cl_2 (50 mL x 2). The combined CH_2Cl_2 layers were washed with brine, dried and evaporated. The residue was subjected to column chromatography (SiO_2, *n*-hexane/AcOEt=2/1) to afford **17a** (3.39 g, 45%) and **17b** (3.04 g, 40%) as a yellow amorphous. **17a** : $[\alpha]_D^{19}$ –71.2° (*c* 1.07, $CHCl_3$). IR (neat) ν cm^{-1} : 2985, 2938, 1733, 1685, 1340, 1172. ^{1}H-NMR ; 400 MHz ($CDCl_3$) δ ppm: 1.33 (3H, s), 1.60 (3H, s), 1.89-2.04 (2H, m), 2.32-2.33 (2H, m), 2.38 (1H, dd, *J* = 4.3, 19.0 Hz), 2.89-2.95 (2H, m), 3.33 (1H, dd, *J* = 5.1, 9.5 Hz), 3.63 (1H, d, *J* = 9.3 Hz), 3.81-3.88 (2H, m), 4.14 (1H, ddd, *J* = 2.9, 4.8, 12.9 Hz), 5.96 (1H, d, *J* = 10.2 Hz), 6.56 (1H, dd, *J* = 1.5, 10.2 Hz), 7.45-7.64 (6H, m), 7.73-7.75 (2H, m), 7.99-8.02 (2H, m). ^{13}C-NMR ; 100 MHz ($CDCl_3$) δ ppm: 24.2, 26.4, 30.4, 34.9, 39.6, 41.5, 46.6, 51.1, 57.0, 69.3, 97.4, 127.8, 129.2, 129.4, 129.5, 129.8, 133.5, 134.7, 139.1, 141.7, 150.5, 172.8, 196.9. LR-FABMS m/z: 559 [$(M+H)^+$, 10]. HR-FABMS m/z: Calcd for $C_{27}H_{31}O_7N_2S_2$: 559.1551, found: 559.1590. **17b** : $[\alpha]_D^{24}$ –60.7° (*c* 1.18, $CHCl_3$). IR (neat) ν cm^{-1} : 3067, 2985, 2938, 1734, 1684, 1339, 1173. ^{1}H-NMR ; 400 MHz ($CDCl_3$) δ ppm: 1.42 (3H, s), 1.64 (3H, s), 1.83 (1H, ddd, *J* = 4.8, 8.3, 13.1 Hz), 2.13-2.21 (2H, m), 2.27-2.41 (3H, m), 2.54 (1H, dd, *J* = 4.4, 16.0 Hz), 3.40 (1H, d, *J* = 9.7 Hz), 3.59 (1H, dd, *J* = 4.4, 9.7 Hz), 3.90-4.02 (3H, m), 6.03 (1H, d, *J* = 10.2 Hz), 6.84 (1H, d, *J* = 10.2 Hz), 7.48-7.67 (6H, m), 7.81 (2H, d, *J* = 7.3 Hz), 7.99 (2H, d, *J* = 7.3 Hz). ^{13}C-NMR ; 100 MHz ($CDCl_3$) δ ppm: 24.3, 25.2, 29.8, 27.6, 39.1, 43.5, 45.1, 49.2, 55.8, 68.9, 97.2, 127.3, 128.6, 128.9, 129.1, 129.3, 132.8, 134.2, 138.1, 140.9, 148.5, 171.9, 195.7. LR-FABMS m/z: 559 [$(M+H)^+$, 10]. HR-FABMS m/z: Calcd for $C_{27}H_{31}O_7N_2S_2$: 559.1551, found : 559.1573.

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REFERNCES

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2 For isolation and reviews. a) R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli, *J. Am. Chem. Soc.,* 1986, **108**, 6404. b) H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotaka, T. Matsuzaki, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, 1987, **28**, 621. c) R. Sakai,; T. Kohmoto, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, 1987, **28**, 5493. d) D. Watanabe, M. Tsuda, and J. Kobayashi, *J. Nat. Prod.*, 1998, **61**, 689. e) K. Kondo, H. Shigemori, Y. Kikuchi, M. Ishibashi, T. Sasaki, and J. Kobayashi, *J. Org. Chem.*, 1992, **57**, 2480.

3 a) Y. Torisawa, A. Hashimoto, M. Nakagawa, and T. Hino, *Tetrahedron Lett.*, 1989, **30**, 6549. b) Y. Torisawa, A. Hashimoto, M. Nakagawa, H. Seki, R. Hara, and T. Hino, *Tetrahedron*, 1991, **47**, 8067. c) M. Arisawa, C. Kato, H. Kaneko, A. Nishida, and M. Nakagawa, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1873.

4 a) W. Nowak and H. Gerlach, *Liebigs Ann. Chem.*, 1993, 153. b) T. Vidal, E. Magnier, and Y. Langlois, *Tetrahedron*, 1998, **54**, 5959.

5 a) J. D. Winkler and J. M. Axten, *J. Am. Chem. Soc.*, 1998, **120**, 6425. b) S. F. Martin, J. M. Humphrey, A. Ali, and M. C. Hillier, *J. Am. Chem. Soc.*, 1999, **121**, 866. c) J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.–L. Wong, H.–J. Chen, A. K. Courtney, and S. F. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 8584.

6 a) Y. Torisawa, T. Soe, C. Katoh, Y. Motohashi, A. Nishida, T. Hino, and M. Nakagawa, *Heterocycles*, 1998, **47**, 655. b) H. Uchida, A. Nishida, and M. Nakagawa, *Tetrahedron Lett.*, 1999, **40**, 113. c) M. Nakagawa, Y. Torisawa, H. Uchida, and A. Nishida, *J. Synth. Org. Chem., Jpn.*, 1999, **57**, 1004. d) M. Nakagawa, *J. Heterocycl. Chem.*, 2000, **37**, 567.

7 K. C. Nicolaou, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668.

8 P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3072.

9 a) P. Garner and R. Ramakanth, *J. Org. Chem.*, 1986, **51**, 2609. b) P. Garner, *Tetrahedron Lett.*, 1984, **25**, 5855.

10 a) S. Danishefsky, M. Bednarski, T. Izawa, and C. Maring, *J. Org. Chem.*, 1984, **49**, 2290. b) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1986, **108**, 7060. c) S. Rafel, G. Cabarrocas, M. Ventura, and T. Parella, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3837.