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Total Synthesis of Catunaregin and Preliminary Evaluation of its Antitumor Activity

Hideki Abe*[a,b], Takuma Hikichi[a], Kosuke Emori[a], Akihito Yokosuka[c], Yoshihiro Mimaki[c], Toyoharu Kobayashi[a], and Hisanaka Ito*[a]

Abstract: Total synthesis of catunaregin in both racemic and optically active forms was accomplished. This enantioselective synthesis employs Evans aldol methodology using oxazolidinone or thiazolidinethione as the chiral auxiliary. The key features include a *syn* selective aldol reaction to form the Evans-*syn* or Non-Evans-*syn* product, and successive ketalization of a furanyl diol derivative under acidic conditions. The biological properties of the synthetic racemate and both enantiomers were evaluated against A549 and HL-60 human cancer cells.

Introduction

The mangrove plant is a rich source for biologically active natural products.[1] Many kinds of natural products, alkaloids, flavonoids, lignans, limonoids, and terpenoids, have been isolated from mangrove plants and mangrove-associated fungi or bacteria.[2] In 2010, Zhang and co-workers reported two unprecedented norneolignans, catunaregin (**1**) and epicatunaregin (**2**), isolated from the stem bark of *Catunaregam spinosa* Tirveng, a Chinese mangrove associate (Figure 1).[3a] They were found to exhibit inhibition against mammary cancer F10 cell lines. In an additional report, Luo and Yao described that catunaregin (**1**) inhibited different VEGF-induced angiogenic phenotypes of HUVECs in vitro and vessel formation in transgenic zebrafish.[3b] The optical rotation value of the natural catunaregin (**1**) is very low {$[\alpha]_D^{20}$ = +1.4 (c 0.8, MeOH)}, leading Zhang to surmise that the natural catunaregin is virtually racemic as a result of its biosynthetic pathway, which includes the production of benzofuran norneolignans with no enantioselective reduction. The structural features and biological properties of **1** attracted our attention, and we began a synthetic study of the unique norneolignan **1** in optically pure form. Very recently, we reported the total synthesis of (+)-catunaregin (**1**) in enantiomerically pure form using the Evans aldol strategy.[4]

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Herein, we describe in detail the stereoselective synthesis of (±)-catunaregin and the asymmetric synthesis of (+)- and (–)-catunaregin, which include a *syn* selective aldol reaction and construction of the oxygen-bridged furopyran skeleton by successive ketalization. In addition, their cytotoxic activities against human non-small cell lung cancer A549 cells and human promyelocytic leukemia HL-60 cells were investigated.

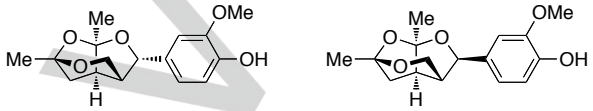
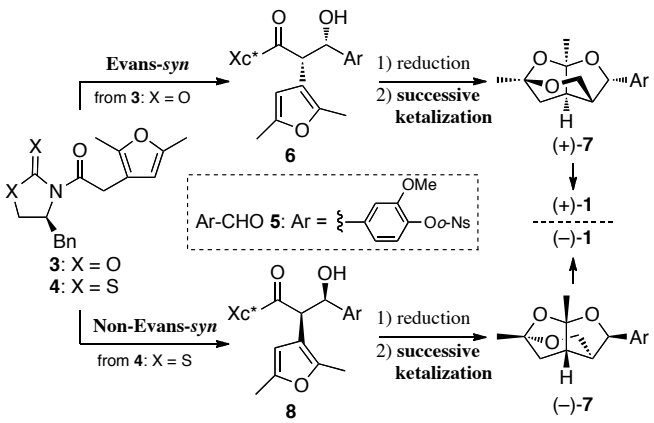


Figure 1. Structures of catunaregin (**1**) and epicatunaregin (**2**).

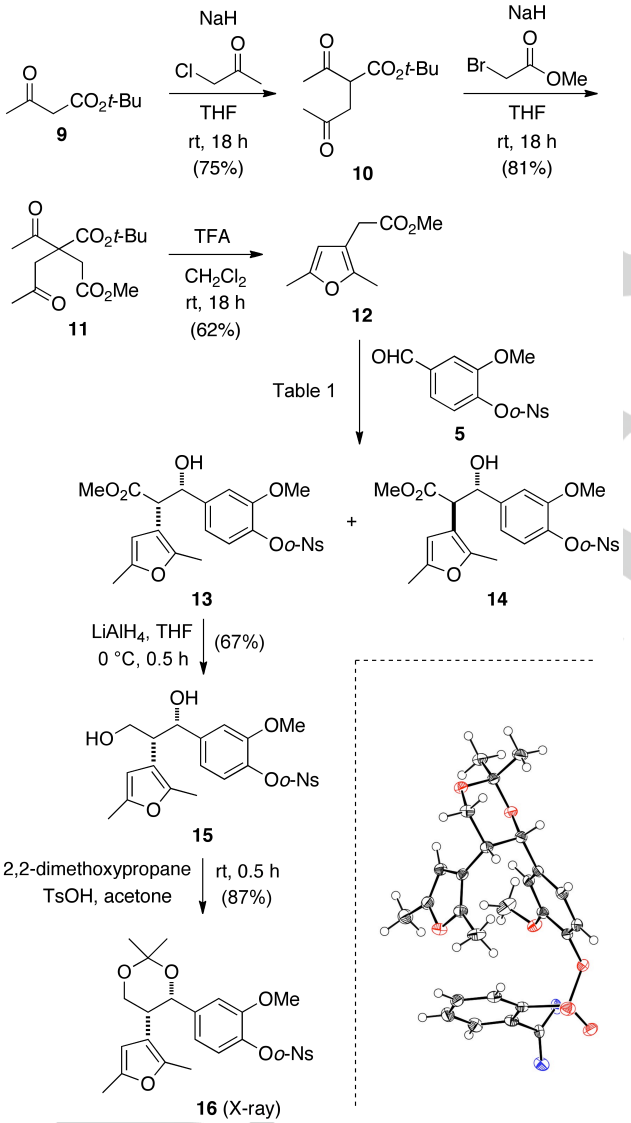
Results and Discussion

The synthetic strategy for both enantiomers of novel tricyclic norneolignan **1** is outlined in Scheme 1. The target norneolignan (+)-**1** or (–)-**1** could be obtained by the construction of the tricyclic skeleton **7** by successive ketalization of furanyl diol derivatives, which would be obtained by reductive cleavage of the chiral auxiliary of aldol products **6** or **8**, respectively, followed by removal of the protecting group of the phenolic hydroxyl group. The aldol product **6** would be produced by *syn* selective aldol reaction with vanillin derivative **5** and the furan derivative **3** with the 4-benzyloxazolidinone tether as a chiral auxiliary. On the other hand, the aldol product **8** would be obtained as the Non-Evans-*syn* product by aldol reaction between thiazolidinethione derivative **4** and vanillin derivative **5**.



Scheme 1. Synthetic strategy for the optically active catunaregin (**1**).

Our investigation started from the synthesis of (±)-catunaregin in order to study the successive ketalization, which is an important key step in this project (Scheme 1). The furan derivative **12** was synthesized from *tert*-butyl acetoacetate (**9**) in three steps according to the reported procedure.[5] Results of the aldol reaction of the furan derivative **12** with *O*-*o*-nitrobenzenesulfonyl (Ns)[6] vanillin derivative **5** are shown in Table 1. Aldol reactions via lithium or sodium enolate intermediates using LHMDS or NHMDS as bases gave a mixture of *syn*- and *anti*-adducts **13** and **14** in moderate yield (entries 1 and 2). However the desired *syn*-adduct **13** was obtained in low yield or as the minor product. On the other hand, reaction via the borane enolate with a combination of di-*n*-butylboryl trifluoromethanesulfonate and diisopropyl(ethyl)amine afforded the *syn*-adduct **13** in 87% yield with high selectivity. Although the relative configuration of these aldol adducts were not determined at this stage, they were assigned by X-ray crystallography of the acetonide derivatives **16**,[7] derived in a two-step operation including reduction of the ester moiety, followed by protection of the resulting 1,3-diol as an acetonide group.



Scheme 2. Synthesis of the *syn*-adduct **13** and its acetonide derivative **16**.

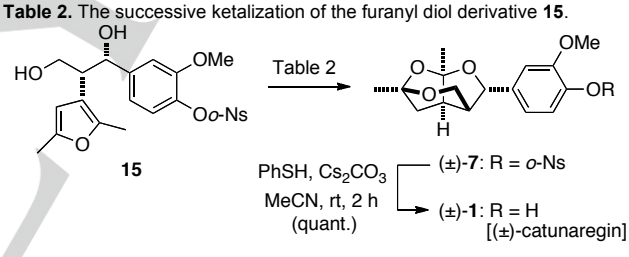
Table 1. Aldol reaction of the furan derivative **12** and *O*-*o*-Ns-vanillin derivative **5**.

entry	conditions	yield (%)[a]	
		13	**14**
1	LHMDS, THF, –78 °C, 1 h	25	23
2	NHMDS, THF, –78 °C, 2 h	15	46
3	*n*-Bu_2BOTf, *i*-Pr_2NEt, THF, –78 °C, 2 h	87	4

[a] Isolated yields.

With the desired diol **15** in hand, our investigation advanced to the main stage of this synthetic study. Construction of the tricyclic skeleton of catunaregin **1** by successive ketalization of the furanyl diol derivative was attempt as shown in Table 2. First, the ketalization reaction under aqueous conditions was carried out (entries 1–4). Although the reaction using of acetic acid as a Brønsted acid at room temperature did not proceeded, the

Table 2. The successive ketalization of the furanyl diol derivative **15**.

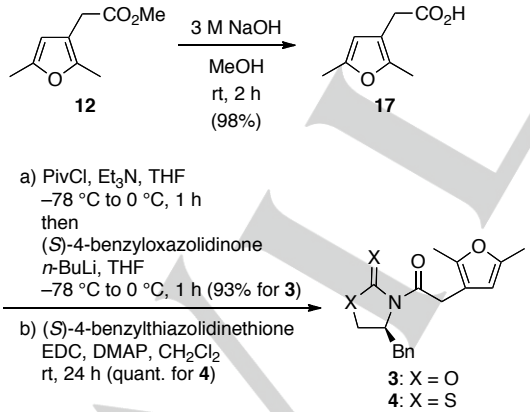


entry	conditions	yield (%)[a] [brsm] [b]
1	AcOH, H_2O, rt, 144 h	n.r.
2	AcOH, H_2O, 80 °C, 48 h	30 [39]
3	$EtCO_2H$, H_2O, 80 °C, 48 h	trace
4	CF_3CO_2H, H_2O, 80 °C, 18 h	12
5	CF_3CO_2H, CH_2Cl_2, rt, 14 h	59
6	AcOH, CH_2Cl_2, rt, 144 h	n.r.
7	conc. H_2SO_4 (10 equiv.), THF, rt, 48 h	68
8	$MeSO_3H$ (10 equiv.), MeOH, rt, 96 h	64
9	$TsOH·H_2O$ (10 equiv.), CH_2Cl_2, rt, 42 h	quant.
10	$MeSO_3H$ (10 equiv.), CH_2Cl_2, rt, 1 h	83
11	$MeSO_3H$ (1.0 equiv.), CH_2Cl_2, rt, 1 h	quant.

[a] Isolated yields. [b] Based on recovered starting material.

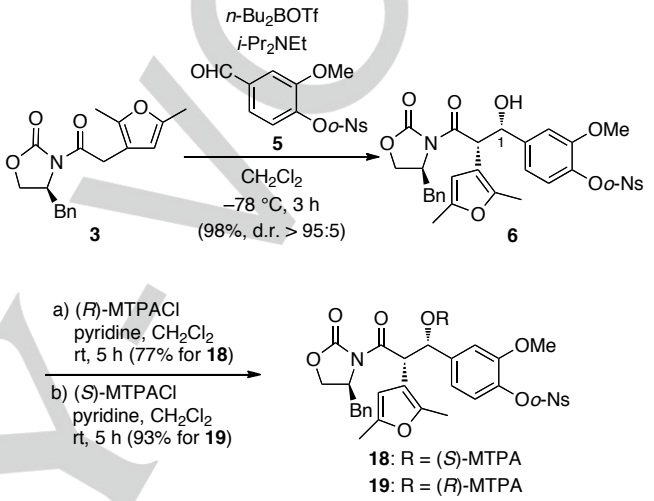
heated condition in presence of acetic acid afforded the desired product in 30% yield along with small amount of diol **15** (entry 2). When the use of propionic acid, which is a weaker acid than acetic acid at 80 °C, a trace amount of the tricyclic compound was detected in ^{1}H NMR spectrum of the crude product (entry 3). Treatment with trifluoroacetic acid, stronger acid than acetic acid yielded the compound **7** in 12% yield along with the complex mixture (entry 4). In absence of water, compound **7** was obtained in good yield (entries 5, 7–11) except in the case of acetic acid (entry 6). Treatment of **15** with concentrated sulfuric acid in THF afforded **7** in 68% yield.[8] It was found that methanesulfonic acid and *p*-toluenesulfonic acid were the best acid reagents in this ketalization reaction. The reaction conditions using methanesulfonic acid (1.0 equiv.) in CH_2Cl_2 at room temperature for 1 h gave the desired tricyclic compound **7** in quantitative yield (entry 11). Finally, removal of the *o*-Ns group of (±)-**7** by treatment with thiophenol and cesium carbonate[6] gave the target compound **1** in quantitative yield. The NMR, IR and mass spectral data of the synthetic sample were identical to those of natural catunaregin.

With the establishment of the synthetic route of (±)-catunaregin by successive ketalization, we focused our efforts on the asymmetric synthesis of catunaregin in enantiomerically pure form. For the Evans aldol methodology,[9] introduction of the chiral auxiliary to the furan derivative was carried out as shown in Scheme 3. Installation of the (*S*)-4-benzyloxazolidinone group as the chiral auxiliary was achieved by a three-step operation: saponification of methyl ester **12** to give carboxylic acid **17**,[10] and transformation of the carboxylic acid to the mixed anhydride, followed by addition of the lithiated oxazolidinone to afford **3** in 93% yield. On the other hand, the thiazolidinethione derivative **4** was obtained by condensation of carboxylic acid **17** and (*S*)-4-benzylthiazolidinethione using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in high yield.



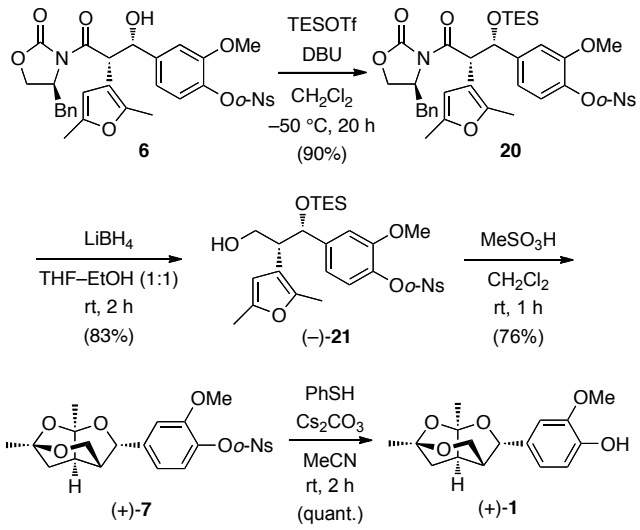
Scheme 3. Installation of chiral auxiliaries to carboxylic acid **17**.

Having the desired furan derivatives with tethered chiral auxiliaries in hand, the asymmetric synthesis of catunaregin using the oxazolidinone derivative **3**[4] was worked out as shown in Scheme 4. The *syn* selective Evans aldol reaction[9] of **3** with *O*-*o*-Ns-vanillin derivative **5** using di-*n*-butylboryl trifluoromethanesulfonate and diisopropyl(ethyl)amine gave the desired Evans-*syn* product **6** exclusively in 98% yield. The absolute stereochemistry at C1 of **6** was determined by the improved Mosher's method.[11] Thus, the alcohol **6** was transformed with (*R*)- and (*S*)-MTPA chlorides to (*S*)- and (*R*)-MTPA esters **18** and **19**, respectively. From ^{1}H NMR spectral analysis, the absolute configuration at the C1 asymmetric carbon was determined as *S*.[12]



Scheme 4. Synthesis of the Evans-*syn*-product **6** and its MTPA esters for determination of the absolute configuration.

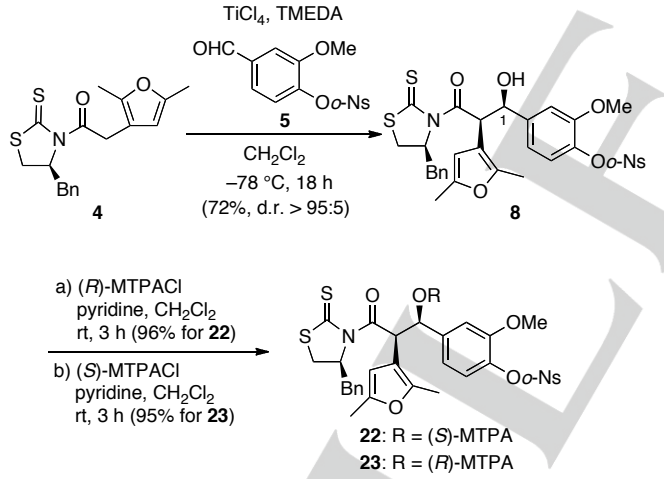
Although direct removal of the chiral oxazolidinone auxiliary of **6** by reduction was carried out, all attempts for a retro aldol reaction caused by the naked hydroxyl group at the benzylic position of **6** failed. Thus, after treatment of **6** with TESOTf and



Scheme 5. Synthesis of (+)-catunaregin [(+)-**1**].

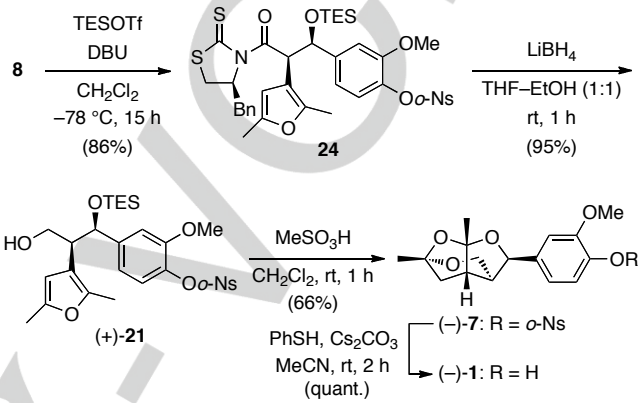
DBU at –50 °C, hydride reduction of the resulting TES ether **20** with $LiBH_4$ under mild conditions gave the primary alcohol (–)-**21**, the precursor to successive ketalization, in 75% yield over 2 steps (Scheme 5). Treatment of **21** with methanesulfonic acid in CH_2Cl_2 at room temperature for 1 h gave the desired tricyclic compound (+)-**7** in 76% yield. Finally, elimination of the *o*-Nsgroup of **7** gave the target molecule **1** in quantitative yield. The spectral data of the synthetic sample **1** was identical to those of the reported natural catunaregin (**1**). The optical rotation of the synthetic sample was $[\alpha]_D^{25}$ +38.6 (c 1.00, MeOH). This result confirms that natural catunaregin was isolated in the racemic form as speculated by Zhang.

With (+)-catunaregin [(+)-**1**] in enantiomerically pure form synthesized, the asymmetric synthetic study using the thiazolidinethione derivative **4** was undertaken. After many attempts toward the *syn* selective aldol reaction of **4** with vanillin derivative **5** to produce the Non-Evans-*syn* product, the combination of titanium tetrachloride and tetramethylethylenediamine gave the best result to afford the desired aldol product **8** in 72% yield as the sole product. The absolute configuration of the newly produced asymmetric carbon of **8** was also assigned by the improved Mosher's method.[11] From the ^{1}H NMR spectral analysis of (*S*)- and (*R*)-MTPA esters **22** and **23**, prepared from (*R*)- and (*S*)-MTPA chlorides, respectively, the absolute configuration at the C1 asymmetric carbon was determined as *R*.[12]



Scheme 6. Synthesis of the Non-Evans-*syn*-product **8** and its MTPA esters to determination for the absolute configuration.

After reductive cleavage of the chiral auxiliary of **8** in a two-step procedure, protection of the secondary hydroxy group as a TES ether, followed by hydride reduction of **24** with lithium borohydride, the successive ketalization precursor (+)-**21** was afforded in 82% yield for the 2 steps. Subsequent successive ketalization, and cleavage of the Ns group of the resulting tricyclic compound (–)-**7** afforded the desired product **1** in moderate yield. All spectral data were identical with those of the previously synthesized (+)-**1**.[4] In addition, the optical rotation of the synthetic sample {$[\alpha]_D^{25}$ –38.6 (c 1.00, MeOH)} derived from the Non-Evans-*syn* product **8** had the opposite rotation of compound (+)-**1** {$[\alpha]_D^{25}$ +38.6 (c 1.00, MeOH)} synthesized from the Evans-*syn* adduct **6**. As a result, asymmetric total synthesis of (+)/(–)-catunaregin was achieved by the Evans aldol strategy. This is the first report of catunaregin in both enantiomerically pure forms.



Scheme 7. Synthesis of (–)-catunaregin [(–)-**1**].

Since racemic sample (±)-catunaregin and enantiomerically pure samples (+)- and (–)-catunaregin were obtained by this synthetic project, we were interested in their biological activities. To explore new possibilities, the biological properties of our synthetic samples were evaluated for their in vitro cytotoxic activities against A549 human lung adenocarcinoma cells and HL-60 human promyelocytic leukemia cells. Unfortunately, none of the three synthetic compounds, (±)-**1**, (+)-**1**, and (–)-**1** exhibited cytotoxic activities (> 30 μM) against these cell lines. This result is only a part for the biological research of catunaregin. As there is room for consideration using other cell lines, these synthetic samples remain biological attractive.

Conclusions

In summary, the total synthesis of catunaregin **1**, isolated from the stem bark of *Catunaregam spinosa* Tirveng, a Chinese mangrove associate, was achieved. The key features include a *syn* selective aldol reaction including Evans aldol methodology, and successive ketalization of the furanyl alcohol derivative under acidic conditions. This synthetic methodology led us to a very concise total synthesis of the tricyclic natural product. Further biological investigations of enantiomerically pure catunaregin are now in progress in our laboratory.

Experimental Section

General

All reactions involving air- and moisture-sensitive reagents were carried out using standard syringe-septum cap techniques. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. Routine monitoring of reactions were carried out Merck silica gel 60 F254 TLC plates. Column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 60–230 μm) with the solvents indicated. Measurement of optical rotations was performed with a JASCO P-2200 automatic digital polarimeter. Melting points were taken on a Yanako MP-S3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a JASCO ECZ 400S (400 MHz) or a Burker AV-600 (600 MHz) spectrometer. Chemical shifts were expressed in ppm using $CHCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) in $CDCl_3$ as internal standard. Infrared spectral measurements were carried out with a JASCO FT/IR-4700 and only noteworthy absorptions were listed. HRMS spectra were measured on a Micromass LCT spectrometer. X-ray crystallographic analysis was taken with Burker APEX2 Ultra TXS.

*tert-Butyl 2-acetyl-4-oxopentanoate (**10**).*

To a stirred suspension of sodium hydride (55% dispersion in mineral oil, 6.58 g, 157 mmol) in THF (400 mL) was added dropwise *tert*-butyl acetoacetate (**9**) (20.0 mL, 19.1 g, 121 mmol) at 0°C. After stirred for 0.5 h at 0°C, to this reaction mixture was added dropwise α-chloroacetone (12.5 mL, 14.5 g, 157 mmol) at 0 °C, and then stirred for 18 h at room temperature. The reaction mixture was quenched with 1.0 M HCl aqueous solution (100 mL) at 0 °C, and extracted with ether (2 × 300 mL). The combined organic layers were washed with brine, and the washed solution was dried over $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 7:1) to afford the intermediate **10** (19.5 g, 91.0 mmol, 75%) as a colorless liquid. Those spectra data were identified for those of previous report.[4]

*1-tert-Butyl 4-methyl 2-acetyl-2-(2-oxopropyl)succinate (**11**).*

To a stirred suspension of sodium hydride (55% dispersion in mineral oil, 2.88 g, 65.8 mmol) in THF (170 mL) was added dropwise **10** (10.9 g, 50.9 mmol) at 0 °C. After stirred for 0.5 h at room temperature, to this mixture was added dropwise methyl bromoacetate (5.30 mL, 8.56 g, 56.0 mmol) at 0 °C, and then stirred for 18 h at room temperature. The reaction mixture was quenched with 1.0 M HCl aqueous solution (80 mL) and extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine, and the washed solution was dried over $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 4:1) to afford the intermediate **11** (11.8 g, 41.2 mmol, 81%) as a colorless liquid. Those spectra data were identified for those of previous report.[4]

*Methyl 2-(2,5-dimethylfuran-3-yl)acetate (**12**).*

To a stirred solution of **11** (11.8 g, 41.2 mmol) in CH_2Cl_2 (140 mL) was added trifluoroacetic acid (24.5 mL, 37.6 g, 330 mmol) at 0 °C. After stirred for 18 h at room temperature, the mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 9:1) to afford **12** (4.30 g, 25.6 mmol, 62%) as a pale yellow oil. Those spectra data were identified for those of previous report.[4]

(2R,3S*)-Methyl 2-(2,5-dimethylfuran-3-yl)-3-hydroxy-3-(3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl)propanoate (**13**) and (2S*,3S*)-methyl 2-(2,5-dimethylfuran-3-yl)-3-hydroxy-3-(3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl)propanoate (**14**).*

To a stirred solution of **12** (698 mg, 4.15 mmol) in CH_2Cl_2 (17 mL) were added dropwise *N*,*N*-diisopropylethylamine (2.59 mL, 1.92 g, 14.8 mmol), and di-*n*-butylboryl trifluoromethanesulfonate (1.0 M in CH_2Cl_2, 4.80 mL, 4.80 mmol) at 0 °C. After stirred for 30 min at 0 °C, to this mixtre was added dropwise a solution of *O*-*o*-Ns-vanillin **5** (1.00 g, 2.96 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After stirred for 4 h at –78 °C, the reaction was quenched with MeOH (5 mL) and saturated NH_4Cl aqueous solution (15 mL) at –78 °C, and extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were washed with brine, and the washed solution was dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **13** (1.30 g, 2.57 mmol, 87%) as pale yellow amorphous solids and **14** (62.8 mg, 0.124 mmol, 4%) as pale yellow amorphous solids.

Data for **13**

IR (neat) 3541, 3098, 3020, 2952, 2921, 2885, 2849, 1732, 1604, 1587, 1547, 1503, 1464, 1438, 1420, 1386, 1272, 1200, 1176, 1147, 1112, 1060, 1032, 1010, 925, 864, 853, 827, 758, 654, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, dd, *J* = 8.0, 1.4 Hz), 7.87 (1H, dd, *J* = 7.8, 1.4 Hz), 7.81 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.70 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.13 (1H, d, *J* = 8.2 Hz), 6.82 (1H, dd, *J* = 8.2, 1.8 Hz), 6.75 (1H, d, *J* = 1.8 Hz), 6.03 (1H, s), 5.17 (1H, d, *J* = 5.5 Hz), 3.63 (3H, s), 3.53 (1H, d, *J* = 5.5 Hz), 3.48 (3H, s), 2.22 (3H, s), 1.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 151.1, 149.8, 148.6, 148.3, 141.6, 137.5, 134.9, 131.8, 131.5, 129.9, 124.6, 123.6, 118.5, 112.3, 111.1, 106.6, 73.5, 55.5, 52.1, 49.9, 13.4, 10.9; HRMS (ESI–TOF) calcd for $C_{23}H_{23}NO_{10}SNa$ ([M + Na]+) 528.0940, found 528.0945.

Data for **14**

IR (neat) 3548, 3489, 3099, 3022, 2952, 2922, 2849, 1736, 1604, 1547, 1503, 1386, 1269, 1200, 1112, 1059, 1031, 853, 758, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 7.8, 1.4 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 7.81 (1H, ddd, *J* = 7.5, 7.5, 1.4 Hz), 7.69 (1H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 7.04 (1H, dd, *J* = 8.5, 2.1 Hz), 6.71 (1H, d, *J* = 9.1 Hz), 6.66 (3H, d, *J* = 1.8 Hz), 2.16 (3H, s), 1.66 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 150.9, 149.9, 148.4, 147.8, 141.8, 137.6, 134.8, 131.8, 131.5, 130.1, 124.7, 123.6, 118.7, 113.5, 111.0, 105.5, 74.9, 55.6, 52.3, 50.9, 13.4, 10.7; HRMS (ESI–TOF) calcd for $C_{23}H_{23}NO_{10}SNa$ ([M + Na]+) 528.0940, found 528.0939.

4-((1S,2R*)-2-(2,5-Dimethylfuran-3-yl)-1,3-dihydroxypropyl)-2-methoxyphenyl 2-nitrobenzenesulfonate (**15**).*

To a stirred suspension of $LiAlH_4$ (7.51 mg, 0.198 mmol) in THF (2 mL) was added a solution of **13** (50.0 mg, 0.0989 mmol) in THF (0.2 mL) at 0 °C. After stirred for 0.5 h at 0 °C, the reaction was quenched with saturated potassium sodium tartrate aqueous solution (10 mL) at 0 °C, and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with brine, and the washed solution was dried over $MgSO_4$. The dried solution was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–EtOAc, 1:11) to afford the intermediate **15** (31.6 mg, 0.0662 mmol, 67%) as colorless gum.

IR (neat) 3558, 3399, 3099, 3008, 2921, 1717, 1604, 1546, 1502, 1465, 1419, 1384, 1271, 1199, 1175, 1110, 1059, 1031, 864, 853, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, dd, *J* = 8.0, 1.1 Hz), 7.87 (1H, dd, *J* = 7.8, 1.4 Hz), 7.81 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 7.71 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.14 (1H, d, *J* = 8.2 Hz), 6.81 (1H, dd, *J* = 8.5, 1.2 Hz), 6.75 (1H, d, *J* = 1.8 Hz), 5.95 (1H, s), 4.92 (1H, d, *J* = 5.5 Hz), 3.75 (2H, d, *J* = 6.4 Hz), 3.50 (3H, s), 2.83 (1H, q, *J* = 6.1 Hz), 2.23 (3H, s), 1.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 149.9, 148.3, 143.5, 137.3, 134.9, 131.8, 131.6, 130.0, 124.7, 123.6, 118.6, 114.8, 111.0, 106.1, 74.2, 63.9, 55.5, 46.1, 29.6, 13.5, 11.1; HRMS (ESI–TOF) calcd for $C_{22}H_{23}NO_9SNa$ ([M + Na]+) 500.0991, found 500.0995.

4-((4S,5R*)-5-(2,5-Dimethylfuran-3-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxyphenyl 2-nitrobenzenesulfonate (**16**).*

To a stirred solution of **15** (70.0 mg, 0.147 mmol) in acetone (1.6 mL) was added 2,2-dimethoxypropane (0.4 mL, 340 mg, 3.26 mmol) and *p*-toluenesulfonic acid monohydrate (2.8 mg, 14.7 μmol) at room temperature. After stirred for 0.5 h, the reaction was quenched with triethylamine, and the mixture was concentrated in vacuo. The resulting residue purified by column chromatography (hexane–AcOEt, 3:2) to afford **16** (66.3 mg, 0.128 mmol, 87%) as colorless needles.

Mp. 176-179 ºC (AcOEt); IR (KBr) 3568, 3456, 3097, 2994, 2941, 2920, 2876, 1605, 1579, 1547, 1503, 1465, 1442, 1419, 1383, 1261, 1235, 1217, 1200, 1181, 1150, 1112, 1086, 1062, 1034, 1020, 854, 822, 783, 758, 593, 541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, dd, *J* = 7.8, 1.4 Hz), 7.87 (1H, dd, *J* = 7.8, 1.4 Hz), 7.79 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.69 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.07 (1H, d, *J* = 8.7 Hz), 6.71 (1H, dd, *J* = 8.2, 1.8 Hz), 6.52 (1H, d, *J* = 1.8 Hz), 6.36 (1H, s), 5.23 (1H, d, *J* = 3.2 Hz), 4.46 (1H, dd, *J* = 11.4, 3.2 Hz), 3.90 (1H, dd, *J* = 11.7, 1.1 Hz), 3.35 (3H, s), 2.51 (1H, ddd, *J* = 3.0, 3.0, 1.2 Hz), 2.18 (3H, d, *J* = 2.7 Hz), 1.62 (3H, s), 1.59 (3H, s), 1.50 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.3, 148.2, 146.6, 141.3, 137.1, 134.7, 131.8, 131.6, 130.0, 124.7, 123.2, 118.3, 116.6, 111.3, 108.8, 99.3, 73.5, 65.0, 55.3, 36.4, 29.7, 18.9, 13.4, 10.6; HRMS (ESI–TOF) calcd for $C_{25}H_{27}NO_9SNa$ ([M + Na]$^+$) 540.1304, found 540.1309.

4-((1R,3S*,3aR*,6S*,7aR*)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenyl 2-nitrobenzenesulfonate [(±)-**7**].*

To a stirred solution of **15** (50.0 mg, 1.05 mmol) in CH_2Cl_2 (1 mL) was added methanesulfonic acid (6.8 μL, 10.1 mg, 1.05 mmol) at room temperature. After stirred for 1 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, and dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 1:9) to afford (±)-**7** (52.8 mg, 0.105 mmol, quant.) as colorless amorphous solids.

IR (neat) 3502, 3096, 2985, 2936, 2879, 2360, 2341, 1732, 1604, 1546, 1505, 1465, 1453, 1385, 1274, 1200, 1166, 1112, 1059, 1032, 942, 896, 852, 758, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, dd, *J* = 8.0, 1.6 Hz), 7.87 (1H, d, *J* = 7.8 Hz), 7.82 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 7.71 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.15 (1H, dd, *J* = 8.7, 1.8 Hz), 6.86–6.82 (2H, m), 4.97 (1H, d, *J* = 4.1 Hz), 3.76 (2H, d, *J* = 1.8 Hz), 3.56 (3H, d, *J* = 0.9 Hz), 2.68 (1H, dd, *J* = 10.5, 3.7 Hz), 2.47 (1H, dddd, *J* = 10.2, 3.9, 2.0, 1.9 Hz), 2.26 (1H, d, *J* = 12.8 Hz), 1.88 (1H, dd, *J* = 12.6, 3.9 Hz), 1.60 (3H, s), 1.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 148.3, 143.5, 137.5, 134.8, 131.9, 131.6, 130.1, 124.7, 124.3, 117.8, 115.5, 110.2, 106.1, 84.6, 62.9, 55.6, 48.0, 45.5, 33.2, 24.7, 22.5; HRMS (ESI–TOF) calcd for $C_{22}H_{23}NO_9SNa$ ([M + Na]+) 500.0991, found 500.0989.

4-((1R,3S*,3aR*,6S*,7aR*)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenol [(±)-catunaregin (**1**)].*

To a stirred solution of (±)-**7** (50.0 mg, 0.105 mmol) and cesium carbonate (171 mg, 0.524 mmol) in MeCN (1 mL) was added dropwise thiophenol (33 μL, 34.7 mg, 0.314 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution, and the mixture was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 1:1) to afford (±)-**1** (30.8 mg, 0.105 mmol, quant.) as colorless amorphous solids.

IR (neat) 3408, 2984, 2937, 2879, 1608, 1603, 1517, 1460, 1450, 1432, 1385, 1331, 1270, 1238, 1195, 1170, 1113, 1057, 1032, 942, 847, 819, 794, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (1H, d, *J* = 8.2 Hz), 6.81–6.77 (2H, m), 5.71 (1H, br s), 4.93 (1H, d, *J* = 4.1 Hz), 3.87 (3H, s), 3.76–3.73 (2H, m), 2.70 (1H, dd, *J* = 10.5, 4.1 Hz), 2.48 (1H, dddd, *J* = 10.5, 4.1, 1.8, 1.8 Hz), 2.25 (1H, d, *J* = 12.4 Hz), 1.88 (1H, dd, *J* = 12.4, 4.1 Hz), 1.60 (3H, s), 1.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 145.1, 134.4, 118.7, 115.2, 114.4, 108.5, 105.9, 85.3, 62.9, 55.8, 47.7, 45.7, 33.2, 24.7, 22.5; HRMS (ESI–TOF) calcd for $C_{16}H_{20}O_5Na$ ([M + Na]$^+$) 315.1208, found 315.1207.

*2-(2,5-Dimethylfuran-3-yl)acetic acid (**17**).*

To a stirred solution of **12** (2.99 g, 17.8 mmol) in MeOH (35 mL) were added 3.0 M NaOH aqueous solution (12.5 mL) at room temperature. After stirred for 2 h at same temperature, the reaction was acidified by adding 1.0 M HCl aqueous solution, and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by recrystallization (hexane) to afford **17** (2.70 g, 17.5 mmol, 98%) as colorless needles.

Mp: 52–54 °C (hexane); IR (KBr) 3407, 3104, 2985, 2949, 2924, 2676, 1713, 1586, 1434, 1415, 1229, 1099, 991, 926, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, s), 3.34 (2H, s), 2.22 (3H, s), 2.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 149.7, 147.2, 111.4, 107.7, 30.8, 13.4, 11.3; HRMS (ESI–TOF) calcd for $C_8H_{10}O_3Na$ ([M + Na]$^+$) 177.0528, found 177.0527; Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.20, 6.51.

*(S)-4-Benzyl-3-[2-(2,5-dimethylfuran-3-yl)acetyl]oxazolidin-2-one (**3**).*

To a stirred solution of **17** (1.75 g, 11.4 mmol) and triethylamine (1.75 mL, 1.26 g, 12.6 mmol) in THF (38 mL) was added dropwise pivaloyl chloride (1.54 mL, 1.51 g, 12.5 mmol) at –78 °C, and the reaction mixture was stirred for 1 h at 0 °C. To this mixture was added dropwise a solution of lithium (*S*)-4-benzyl-2-oxooxazolin-3-ide in THF (42 mL), prepared from (*S*)-4-benzyloxazolidin-2-one (2.22 g, 12.5 mmol) and *n*-buthyllithium (1.63 M in hexane, 7.69 mL, 12.5 mmol), at –78 °C. After stirred for 1 h at 0 °C, the reaction was quenched with saturated NH_4Cl aqueous solution (50 mL), and extracted with AcOEt (2 × 120 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 4:1) to afford **3** (3.30 g, 10.5 mmol, 93%) as colorless oil.

$[\alpha]_D^{25}$ +56.4 (*c* 1.00, $CHCl_3$); IR (neat) 3029, 2981, 2921, 1781, 1701, 1584, 1454, 1390, 1356, 1211, 1197, 1111, 1052, 994, 762, 747, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (3H, m), 7.19–7.16 (2H, m), 5.92 (1H, s), 4.70–4.64 (1H, m), 4.22 (1H, B part of ABX, *J* = 9.2, 7.6 Hz), 4.18 (1H, A part of ABX, *J* = 9.2, 3.2 Hz), 3.94 and 4.01 (2H, ABq, *J* = 17.0 Hz), 3.29 (1H, dd, *J* = 13.3, 3.2 Hz), 2.77 (1H, dd, *J* = 13.3, 9.6 Hz), 2.24 (3H, s), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 153.4, 149.6, 147.5, 135.1, 129.4 (2C), 128.9 (2C), 127.3, 111.4, 107.9, 66.1, 55.2, 37.7, 31.9, 13.4, 11.5; HRMS (ESI–TOF) calcd for $C_{18}H_{19}NO_4Na$ ([M + Na]$^+$) 336.1212, found 336.1208.

*(S)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)ethanone (**4**).*

To a stirred solution of **17** (376 mg, 2.39 mmol) in CH_2Cl_2 (6.25 mL) was added (*S*)-4-benzylthiazolidine-2-thione (250 mg, 1.19 mmol), 1-ethyl-3-(3-dimethylamiopropyl)carbodiimide hydrochloride salt (343 mg, 1.79 mmol) and 4-dimethylaminopyridine (7.3 mg, 0.0597 mmol) at 0 °C, and the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with 1.0 M HCl aqueous solution (10 mL), and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with 3.0 M NaOH aqueous solution, brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 4:1) to afford **4** (412 mg, 1.19 mmol, quant.) as colorless oil.

$[\alpha]_D^{25}$ +56.4 (*c* 1.00, $CHCl_3$); IR (neat) 3029, 2981, 2921, 1781, 1701, 1584, 1454, 1390, 1356, 1211, 1197, 1111, 1052, 994, 762, 747, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (3H, m), 7.19–7.16 (2H, m), 5.92 (1H, s), 4.70–4.64 (1H, m), 4.22 (1H, A part of ABX, *J* = 9.2, 7.6 Hz), 4.18 (1H, B part of ABX, *J* = 9.2, 3.2 Hz), 4.01 and 3.94 (2H, ABq, *J* = 17.0 Hz), 3.29 (1H, dd, *J* = 13.3, 3.2 Hz), 2.77 (1H, dd, *J* = 13.3, 9.6 Hz), 2.24 (3H, s), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 153.4, 149.6, 147.5, 135.1, 129.4 (2C), 128.9 (2C), 127.3, 111.4, 107.9, 66.1,

55.2, 37.7, 31.9, 13.4, 11.5; HRMS (ESI–TOF) calcd for $C_{18}H_{19}NO_4Na$ ([M + Na]$^+$) 336.1212, found 336.1208.

*4-[(1S,2S)-3-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-1-hydroxy-3-oxopropyl]-2-methoxyphenyl 2-nitrobenzenesulfonate (**6**).*

To a stirred solution of **4** (1.31 g, 4.18 mmol) in CH_2Cl_2 (14 mL) were added dropwise *N*,*N*-diisopropylethylamine (0.981 mL, 0.728 g, 5.63 mmol), and di-*n*-butylboryl trifluoromethanesulfonate (1.0 M in CH_2Cl_2, 4.74 mL, 4.74 mmol) at 0 °C. After stirred for 45 min at 0 °C, to this mixtre was added dropwise a solution of *O*-*o*-Ns-vanillin **5** (1.00 g, 2.96 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After stirred for 2.5 h at –78 °C, the reaction was quenched with MeOH (40 mL) and saturated NH_4Cl aqueous solution (40 mL) at –78 °C, and extracted with $CHCl_3$ (2 × 200 mL). The combined organic layers were washed with brine, and the washed solution was dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **6** (1.89 g, 2.90 mmol, 98%) as colorless oil.

$[\alpha]_D^{25}$ +4.7 (*c* 1.00, $CHCl_3$); IR (neat) 3502, 3088, 2921, 2850, 1774, 1690, 1604, 1545, 1501, 1385, 1364, 1272, 1199, 1111, 1031, 864, 852, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.00 (1H, m), 7.85–7.76 (2H, m), 7.75–7.68 (1H, m), 7.29–7.22 (3H, m), 7.11 (1H, d, *J* = 8.4 Hz), 7.08–7.01 (2H, m), 6.91–6.84 (2H, m), 6.13 (1H, s), 5.18 (1H, d, *J* = 6.8 Hz), 5.15 (1H, d, *J* = 6.8 Hz), 4.60–4.53 (1H, m), 4.12–4.02 (2H, m), 3.49 (3H, s), 3.09 (1H, dd, *J* = 13.6, 3.2 Hz), 3.06–2.90 (1H, br s), 2.67 (1H, dd, *J* = 13.6, 9.2 Hz), 2.26 (3H, s), 2.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 152.7, 151.2, 150.2, 150.1, 148.3, 141.5, 137.7, 134.9, 134.6, 131.8, 131.6, 129.9, 129.4 (2C), 128.8 (2C), 127.3, 124.5, 123.7, 119.2, 112.1, 111.3, 106.4, 74.2, 65.8, 55.5, 54.7, 47.6, 37.3, 13.5, 11.3; HRMS (ESI–TOF) calcd for $C_{32}H_{30}N_2O_{11}SNa$ ([M + Na]$^+$) 673.1468, found 673.1465.

*(S)-(1S,2S)-3-[(S)-4-Benzyl-2-oxooxazolidin-3-yl]-2-(2,5-dimethylfuran-3-yl)-1-[3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl]-3-oxopropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**18**).*

To a stirred solution of **6** (50.0 mg, 0.0768 mmol) in CH_2Cl_2 (1 mL) was added pyridine (31.0 μL, 30.4 mg, 0.384 mmol), and (*R*)-(–)-α-methoxy-α-trifluoromethylphenylacetyl chloride (28.8 μL, 38.8 mg, 0.154 mmol) in 0 °C. After stirred for 5 h at room temperature, the reaction was quenched with saturated NH_4Cl aqueous solution (3 mL), and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **18** (51.4 mg, 0.0593 mmol, 77%) as colorless amorphous solids.

$[\alpha]_D^{20}$ –12.5 (*c* 0.34, $CHCl_3$); IR (neat) 3430, 3027, 2950, 2922, 2849, 1774, 1752, 1696, 1638, 1606, 1546, 1502, 1452, 1389, 1362, 1271, 1255, 1201, 1182, 1113, 1022, 999, 863, 851, 760, 717 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (1H, d, *J* = 7.9 Hz), 7.84–7.80 (1H, m), 7.79–7.72 (2H, m), 7.39–7.35 (1H, m), 7.29–7.27 (2H, m), 7.23–7.20 (3H, m), 7.19–7.14 (3H, m), 7.07 (1H, dd, *J* = 8.4, 1.8 Hz), 7.02 (1H, d, *J* = 1.9 Hz), 6.97–6.92 (2H, m), 6.49 (1H, d, *J* = 10.0 Hz), 6.10 (1H, s), 5.65 (1H, d, *J* = 10.0 Hz), 4.52–4.46 (1H, m), 4.08 (1H, A part of ABX, *J* = 9.0, 8.4 Hz), 4.02 (1H, B part of ABX, *J* = 9.0, 3.6 Hz), 3.54 (3H, s), 3.26 (3H, m), 2.95 (1H, dd, *J* = 13.6, 3.4 Hz), 2.68 (1H, dd, *J* = 13.6, 8.3 Hz), 2.25 (3H, s), 1.93 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 165.5, 152.9, 151.6, 150.1, 149.9, 148.4, 138.4, 137.7, 135.0, 134.4, 132.0, 131.8, 131.5, 129.9, 129.42 (2C), 129.36, 128.7 (2C), 128.2 (2C), 127.3, 126.9 (2C), 124.4, 124.3, 123.2 (q, *J* = 288.7 Hz), 120.5, 112.64, 112.56, 105.8, 84.3 (q, *J* = 27.5 Hz), 77.04, 65.7, 55.7, 55.3, 54.5, 45.1, 37.1, 13.6, 11.2; HRMS (ESI–TOF) calcd for $C_{42}H_{37}F_3N_2O_{13}SNa$ ([M + Na]$^+$) 889.1866, found 889.1856.

*(R)-(1S,2S)-3-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-1-[3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl]-3-oxopropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**19**).*

To a stirred solution of **6** (50.0 mg, 0.0768 mmol) in CH_2Cl_2 (1 mL) was added pyridine (31.0 μL, 30.4 mg, 0.384 mmol), and (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (28.8 μL, 38.8 mg, 0.154 mmol) in 0 °C. After stirred for 5 h at room temperature, the reaction was quenched with saturated NH_4Cl aqueous solution (3 mL), and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **19** (61.9 mg, 0.0714 mmol, 93%) as colorless amorphous solids.

$[\alpha]_D^{20}$ +16.8 (*c* 0.62, $CHCl_3$); IR (neat) 3432, 3026, 2950, 2923, 2850, 1775, 1753, 1696, 1637, 1606, 1546, 1502, 1452, 1389, 1365, 1270, 1255, 1202, 1182, 1113, 1030, 1000, 864, 851, 760 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11–8.08 (1H, m), 7.84–7.80 (1H, m), 7.77–7.73 (2H, m), 7.37–7.33 (1H, m), 7.27–7.21 (5H, m), 7.12–7.06 (3H, m), 6.99–6.94 (3H, m), 6.82 (1H, d, *J* = 1.9 Hz), 6.34 (1H, d, *J* = 10.2 Hz), 6.20 (1H, s), 5.66 (1H, d, *J* = 10.2 Hz), 4.51–4.46 (1H, m), 4.05 (1H, B part of ABX, *J* = 9.1, 8.3 Hz), 4.00 (1H, A part of ABX, *J* = 9.1, 3.0 Hz), 3.41 (3H, s), 3.26 (3H, m), 2.98 (1H, dd, *J* = 13.6, 3.2 Hz), 2.69 (1H, dd, *J* = 13.6, 8.3 Hz), 2.28 (3H, s), 2.18 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 165.3, 152.8, 151.4, 150.3, 150.1, 148.4, 138.3, 137.5, 134.9, 134.5, 131.84, 131.81, 131.6, 129.9, 129.5, 129.4 (2C), 128.8 (2C), 128.2 (2C), 127.3, 127.1

(2C), 124.4, 124.1, 123.2 (q, *J* = 288.7 Hz), 120.7, 113.4, 112.0, 105.7, 84.5 (q, *J* = 27.5 Hz), 77.9, 65.7, 55.5, 55.1, 54.5, 45.3, 37.1, 13.6, 11.5; HRMS (ESI–TOF) calcd for $C_{42}H_{37}F_3N_2O_{13}SNa$ ([M + Na]$^+$) 889.1866, found 889.1863.

*4-[(1S,2S)-3-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-3-oxo-1-(triethylsilyloxy)propyl]-2-methoxyphenyl 2-nitrobenzenesulfonate (**20**).*

To a stirred solution of **6** (500 mg, 0.768 mmol) in CH_2Cl_2 (4 mL) were added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (0.689 mL, 703 mg, 4.62 mmol), and triethylsilyl trifluoromethanesulfonate (0.434 mL, 508 mg, 1.92 mmol) at –78 °C, and the mixture was stirred for 20 h at –50 °C. The reaction was quenched with saturated NH_4Cl aqueous solution (5 mL), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **20** (527 mg, 0.689 mmol, 90%) as colorless gum.

$[\alpha]_D^{25}$ +10.9 (*c* 1.00, $CHCl_3$); IR (neat) 3028, 2955, 2915, 2876, 2360, 2341, 1776, 1696, 1604, 1548, 1501, 1389, 1281, 1201, 1111, 1004, 891, 859, 655, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 8.2 Hz), 7.84–7.77 (2H, m), 7.75–7.67 (1H, m), 7.30–7.20 (3H, m), 7.11–7.01 (3H, m), 6.99 (1H, d, *J* = 1.4 Hz), 6.88 (1H, dd, *J* = 8.2, 1.8 Hz), 6.20 (1H, s), 5.25 (1H, d, *J* = 8.2 Hz), 5.00 (1H, d, *J* = 8.2 Hz), 4.42–4.36 (1H, m), 4.03–3.92 (2H, m), 3.50 (3H, s), 3.06 (1H, dd, *J* = 13.5, 3.0 Hz), 2.65 (1H, dd, *J* = 13.5, 8.9 Hz), 2.25 (3H, s), 2.21 (3H, s), 0.71 (9H, t, *J* = 7.9 Hz), 0.34 (6H, q, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 152.9, 151.1, 149.3, 149.2, 148.4, 144.0, 137.4, 134.89, 134.87, 131.7, 131.5, 129.8, 129.4 (2C), 128.7 (2C), 127.2, 124.4, 123.4, 119.4, 114.4, 111.3, 106.7, 75.9, 65.6, 55.6, 54.9, 49.0, 37.3, 13.5, 11.6, 6.4 (3C), 4.5 (3C); HRMS (ESI–TOF) calcd for $C_{38}H_{44}N_2O_{11}SSiNa$ ([M + Na]$^+$) 787.2333, found 787.2331.

*4-[(1S,2R)-2-(2,5-Dimethylfuran-3-yl)-3-hydroxy-1-(triethylsilyloxy)propyl]-2-methoxyphenyl 2-nitrobenzenesulfonate [(–)-**21**].*

To a stirred suspension of lithium chloride (55.4 mg, 1.31 mmol) in THF–EtOH (1:1, 2.6 mL) was added sodium borohydride (49.5 mg, 1.31 mmol) at room temperature, and the mixture was stirred for 0.5 h at room temperature. To this mixture was added dropwise a solution of **20** (100 mg, 0.131 mmol) in THF–EtOH (1:1, 1.3 mL) at room temperature, and the mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated NH_4Cl aqueous solution (5 mL), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford (–)-**21** (64.5 mg, 0.109 mmol, 83%) as pale yellow oil.

$[\alpha]_D^{25}$ –27.0 (*c* 0.3, $CHCl_3$); IR (neat) 3582, 3419, 3098, 2955, 2914, 2877, 1732, 1604, 1548, 1500, 1464, 1417, 1387, 1282, 1266, 1200, 1148, 1111, 1007, 866, 851, 761, 741, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.94 (1H, m), 7.86–7.78 (2H, m), 7.70–7.65 (1H, m), 7.07 (1H, dd, *J* = 8.2 Hz), 6.69 (1H, dd, *J* = 8.2, 1.8 Hz), 6.55 (1H, d, *J* = 1.8 Hz), 5.77 (1H, s), 4.93 (1H, d, *J* = 3.7 Hz), 3.84 (1H, dd, *J* = 10.5, 7.3 Hz), 3.70 (1H, dd, *J* = 10.5, 7.3 Hz), 3.38 (3H, s), 2.77 (1H, ddd, *J* = 7.3, 7.3, 3.7 Hz), 2.18 (3H, s), 1.79 (1H, br s), 1.72 (3H, s), 0.87–0.82 (9H, m), 0.41–0.55 (6H, m),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.8, 148.5, 148.0, 144.2, 137.1, 134.7, 131.6 (2C), 130.0, 124.6, 123.3, 118.4, 115.1, 111.3, 106.8, 74.9, 63.7, 55.3, 46.9, 13.4, 10.9, 6.67 (3C), 4.65 (3C); HRMS (ESI–TOF) calcd for $C_{28}H_{37}NO_9SSiNa$ ([M + Na]$^+$) 614.1856, found 614.1860.

*4-((1R,3S,3aR,6S,7aR)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenyl 2-nitrobenzenesulfonate [(+)-**7**].*

The title compound (+)-**7** (30.8 mg, 0.0645 mmol, 76%) was obtained by same procedue to (±)-**7** with (–)-**21** (50.0 mg, 0.0845 mmol) and methanesulfonic acid (8.12 mg, 5.5 μL, 0.0845 mmol) as colorless amorphous solids.

$[\alpha]_D^{25}$ +33.3 (c 0.55, $CHCl_3$); IR (neat) 3502, 3096, 2985, 2936, 2879, 2360, 2341, 1732, 1604, 1546, 1505, 1465, 1453, 1385, 1274, 1200, 1166, 1112, 1059, 1032, 942, 896, 852, 758, 592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 7.8 Hz), 7.88–7.85 (1H, m), 7.84–7.79 (1H, m), 7.74–7.68 (1H, m), 7.15 (1H, d, *J* = 8.7 Hz), 6.86–6.82 (2H, m), 4.98 (1H, d, *J* = 3.7 Hz), 3.78–3.75 (2H, m), 3.57 (3H, s), 2.68 (1H, dd, *J* = 10.1, 3.7 Hz), 2.50–2.45 (1H, m), 2.26 (1H, d, *J* = 12.4 Hz), 1.88 (1H, dd, *J* = 12.4, 4.1 Hz), 1.60 (3H, s), 1.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 148.4, 143.5, 137.5, 134.8, 131.9, 131.6, 130.2, 124.7, 124.3, 117.8, 115.5, 110.2, 106.1, 84.6, 63.0, 55.6, 48.0, 45.5, 33.2, 24.7, 22.5; HRMS (ESI–TOF) calcd for $C_{22}H_{23}NO_9SNa$ ([M + Na]$^+$) 500.0991, found 500.0994.

*4-((1R,3S,3aR,6S,7aR)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenol [(+)-catunaregin (**1**)].*

The title compound (+)-**1** (22.6 mg, 0.0773 mmol, quant.) was obtained by same procedue to (±)-**1** with (+)-**7** (37.0 mg, 0.0775 mmol) and thiophenol (23.8 μL, 25.6 mg, 0.232 mmol) and cesium carbonate (126 mg, 0.387 mmol) as colorless amorphous solids.

$[\alpha]_D^{25}$ +38.5 (*c* 0.350, MeOH); $[\alpha]_D^{24}$ +40.3 (*c* 0.405, $CHCl_3$); IR (neat) 3408, 2984, 2937, 2879, 1608, 1603, 1517, 1460, 1450, 1432, 1385, 1331, 1270, 1238, 1195, 1170, 1113, 1057, 1032, 942, 847, 819, 794, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–6.86 (1H, m), 6.83–6.77 (2H, m), 5.60 (1H, s), 4.95 (1H, d, *J* = 4.1 Hz), 3.91 (3H, s), 3.73–3.78 (2H, m), 2.71 (1H, dd, *J* = 10.1, 3.7 Hz), 2.52–2.46 (1H, m), 2.26 (1H, d, *J* = 12.3 Hz), 1.88 (1H, dd, *J* = 12.3, 3.7 Hz), 1.60 (3H, s), 1.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 145.2, 134.4, 118.8, 115.3, 114.4, 108.6, 105.9, 85.3, 62.9, 55.9, 47.8, 45.7, 33.3, 24.8, 22.6; HRMS (ESI–TOF) calcd for $C_{16}H_{20}O_5Na$ ($[M + Na]^+$) 315.1208, found 315.1201.

*4-((1R,2R)-3-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-1-hydroxy-3-oxopropyl)-2-methoxyphenyl 2-nitrobenzenesulfonate (**8**).*

To a stirred solution of **4** (102.0 mg, 0.296 mmol) in CH_2Cl_2 (1.49 mL) was added dropwise tetramethylethylenediamine (48.6 μL, 37.9 mg, 0.326 mmol) and a solution of titanium chloride (65.0 μL, 112 mg, 0.593 mmol) in CH_2Cl_2 (0.6 mL) at –78 °C. After stirred for 2 h at –78°C, to this reaction mixture was added dropwise a solution of **5** (50.0 mg, 0.148 mmol) in CH_2Cl_2 (0.75 mL) at –78 °C. After stirred for 18 h at –78 °C, the reaction was quenched by adding methanol (1 mL) and saturated NH_4Cl aqueous solution (3 mL), and extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **8** (72.1 mg, 0.106 mmol, 72%) as colorless gum.

$[\alpha]_D^{25}$ +31.9 (*c* 0.17, $CHCl_3$); IR (neat) 3515, 3381, 3087, 3064, 3025, 2960, 2938, 2855, 1766, 1681, 1604, 1546, 1503, 1386, 1263, 1200, 1112, 1032, 861, 853, 755, 703, 590, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.76 (3H, m), 7.64 (1H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 7.40–7.24 (5H, m), 7.09 (1H, ddd, *J* = 8.2, 1.6, 1.6 Hz), 6.87 (1H, d, *J* = 8.2 Hz), 6.81 (2H, m), 6.17 (1H, q, *J* = 1.4 Hz), 5.95 (1H, s), 5.28 (1H, s), 5.27 (1H, s), 3.47 (3H, d, *J* = 1.8 Hz), 3.23 (1H, dd, *J* = 11.3, 7.0 Hz), 3.11 (1H, dd, *J* = 13.3, 2.7 Hz), 2.97 (1H, dd, *J* = 12.3, 11.4 Hz), 2.82 (1H, d, *J* = 11.4 Hz), 2.20 (3H, m), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 174.7, 151.2, 149.9, 149.8, 148.4, 141.4, 137.6, 136.2, 134.7, 131.8, 131.6, 130.1, 129.4 (2C), 128.9 (2C), 127.3, 124.7, 123.6, 119.1, 111.8, 111.5, 106.9, 73.8, 69.1, 55.6, 47.5, 36.6, 31.7, 13.5, 11.5; HRMS (ESI–TOF) calcd for $C_{32}H_{30}N_2O_9S_3Na$ ($[M + Na]^+$) 705.1011, found 705.1024.

*(S)-(1R,2R)-3-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-1-[3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl]-3-oxopropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**22**).*

The title compound **22** (47.0 mg, 0.0523 mmol, 96%) was obtained by same procedue to **18** with **8** (37.1 mg, 0.0543 mmol), pyridine (26.3 μL, 25.8 mg, 0.326 mmol), and (*R*)-(–)-α-methoxy-α-trifluoromethylphenylacetyl chloride (30.5 μL, 41.2 mg, 0.163 mmol) as pale yellow oil.

$[\alpha]_D^{25}$ +41.8 (*c* 1.0, $CHCl_3$); IR (neat) 3088, 3064, 3028, 2980, 2949, 2923, 2851, 1753, 1687, 1605, 1548, 1505, 1465, 1453, 1389, 1343, 1257, 1183, 1167, 1116, 1040, 1018, 1009, 866, 851, 823, 760, 703, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.73 (3H, m), 7.54 (1H, ddd, *J* = 7.7, 7.5, 1.1 Hz), 7.39–7.23 (7H, m), 7.20–7.15 (2H, m), 7.13–7.05 (3H, m), 7.00 (1H, dd, *J* = 8.2, 1.8 Hz), 6.88 (1H, d, *J* = 1.8 Hz), 6.84 (1H, d, *J* = 9.6 Hz), 6.38 (1H, d, *J* = 9.6 Hz), 6.06 (1H, s), 5.19 (1H, ddd, *J* = 10.3, 6.7, 3.6 Hz), 3.43 (3H, s), 3.27 (3H, s), 3.17 (1H, dd, *J* = 11.7, 7.1 Hz), 2.73 (1H, dd, *J* = 11.0, 3.2 Hz), 2.65 (1H, dd, *J* = 13.3, 3.7 Hz), 2.24 (3H, s), 2.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 171.1, 165.4, 151.3, 150.4, 150.0, 148.3, 138.4, 137.1, 136.2, 134.8, 131.9, 131.8, 131.4, 129.9, 129.5, 129.3 (2C), 128.9 (2C), 128.2 (2C), 127.2, 127.1 (2C), 124.7, 123.7, 123.2 (q, *J* = 288.9 Hz), 121.3, 113.5, 112.6, 105.8, 84.5 (q, *J* = 27.3 Hz), 78.4, 69.1, 55.5, 55.1, 45.1, 36.3, 31.1, 13.5, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –7.34 (3F, s); HRMS (ESI–TOF) calcd for $C_{42}H_{37}F_3N_2O_{11}S_3Na$ ($[M + Na]^+$) 921.1409, found 921.1429.

*(R)-(1R,2R)-3-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-1-[3-methoxy-4-(2-nitrophenylsulfonyloxy)phenyl]-3-oxopropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**23**).*

The title compound **23** (46.8 mg, 0.0521 mmol, 95%) was obtained by same procedue to **19** with **8** (37.3 mg, 0.0546 mmol), pyridine (26.5 μL, 25.9 mg, 0.328 mmol), and (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetyl chloride (30.7 μL, 41.4 mg, 0.164 mmol) as pale yellow oil.

$[\alpha]_D^{25}$ +86.4 (*c* 1.0, $CHCl_3$); IR (neat) 3097, 3064, 3028, 2984, 2950, 2923, 2850, 1751, 1688, 1605, 1548, 1505, 1464, 1453, 1389, 1343, 1257, 1187, 1168, 1116, 1040, 1018, 999, 866, 851, 824, 759, 703, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.73 (3H, m), 7.53 (1H, ddd, *J* = 7.7, 7.7, 1.1 Hz), 7.40–7.23 (7H, m), 7.22–7.09 (7H, m), 6.80 (1H, d, *J* = 9.6 Hz), 6.54 (1H, d, *J* = 9.1 Hz), 5.96 (1H, s), 5.15 (1H, ddd, *J* = 10.6, 7.0, 3.6 Hz), 3.55 (3H, s), 3.27 (3H, s), 3.15 (1H, dd, *J* = 11.7, 7.1 Hz), 2.80–2.70 (1H, m), 2.65 (1H, dd, *J* = 13.3, 3.2 Hz), 2.21 (3H, s), 1.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 171.1, 165.5, 151.5, 149.96, 149.94, 148.3, 138.5, 137.4, 136.2, 134.8, 132.1, 131.7, 131.4, 129.9, 129.34, 129.27 (2C), 128.9 (2C), 128.2 (2C), 127.2, 126.9 (2C), 124.7, 124.0, 122.8 (q, *J* = 288.9 Hz), 121.2, 113.0, 112.8, 105.7, 84.3 (q, *J* = 27.3 Hz), 77.6, 69.2, 55.8, 55.4, 44.9, 36.3, 31.1, 13.5, 11.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –7.68 (3F, s); HRMS (ESI–TOF) calcd for $C_{42}H_{37}F_3N_2O_{11}S_3Nas$ ([M + Na]+) 921.1409, found 921.1404.

*4-((1R,2R)-3-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-2-(2,5-dimethylfuran-3-yl)-3-oxo-1-(triethylsilyloxy)propyl)-2-methoxyphenyl 2-nitrobenzenesulfonate (**24**).*

To a stirred solution of **8** (34.5 mg, 0.0505 mmol) in CH_2Cl_2 (0.3 mL) were added dropwise triethylsilyl trifluoromethanesulfonate (28.5 μL, 33.4 mg, 0.126 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (45.2 μL, 46.2 mg, 0.303 mmol) at –78 °C, and the mixture was stirred for 15 h at –78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution (5 mL), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The dried solution was filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford **24** (34.6 mg, 0.0434 mmol, 86%) as yellow needles.

Mp: 131-133 ºC (Et_2O); $[\alpha]_D^{25}$ +93.2 (*c* 1.00, $CHCl_3$); IR (KBr) 3087, 3064, 3027, 2954, 2914, 2876, 1688, 1604, 1548, 1501, 1463, 1389, 1343, 1256, 1200, 1162, 1112, 1099, 1036, 1007, 876, 851, 834, 752, 703, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, dd, *J* = 8.0, 1.1 Hz), 7.78–7.67 (2H, m), 7.48 (1H, ddd, *J* = 7.7, 7.7, 1.1 Hz), 7.36–7.23 (3H, m), 7.22–7.17 (2H, m), 7.07 (1H, d, *J* = 1.8 Hz), 7.02 (1H, d, *J* = 8.2 Hz), 6.95 (1H, dd, *J* = 8.2, 1.8 Hz), 6.48 (1H, d, *J* = 8.2 Hz), 6.07 (1H, s), 5.24 (1H, ddd, *J* = 10.7, 7.2, 3.7 Hz), 5.08 (1H, d, *J* = 8.2 Hz), 3.51 (3H, s), 3.16 (1H, dd, *J* = 11.4, 7.3 Hz), 2.76–2.65 (2H, m), 2.58 (1H, dd, *J* = 13.3, 3.2 Hz), 2.22 (3H, s), 2.18 (3H, s), 0.75–0.66 (9H, m), 0.42–0.26 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 172.4, 151.1, 149.5, 149.4, 148.4, 143.6, 137.6, 136.6, 134.6, 131.6, 131.5, 130.0, 129.3 (2C), 128.9 (2C), 127.1, 124.6, 123.3, 120.2, 114.7, 112.2, 106.5, 76.4, 68.9, 55.7, 48.6, 36.1, 30.8, 13.5, 12.3, 6.4 (3C), 4.5 (3C); HRMS (ESI–TOF) calcd for $C_{38}H_{44}N_2O_9S_3SiNa$ ($[M + Na]^+$) 819.1876, found 819.1878.

*4-[(1R,2S)-2-(2,5-Dimethylfuran-3-yl)-3-hydroxy-1-(triethylsilyloxy)propyl]-2-methoxyphenyl 2-nitrobenzenesulfonate [(+)-**21**].*

The title compound (+)-**21** (120 mg, 0.203 mmol, 95%) was obtained by same procedue to (–)-**21** from **24** (170 mg, 0.222 mmol) with lithium chloride (94.2 mg, 2.22 mmol) and sodium borohydride (84.1 mg, 2.22 mmol) as pale yellow oil.

$[\alpha]_D^{25}$ +30.5 (*c* 1.00, $CHCl_3$); IR (neat) 3582, 3419, 3098, 2955, 2914, 2877, 1732, 1604, 1548, 1500, 1464, 1417, 1387, 1282, 1266, 1200, 1148, 1111, 1007, 866, 851, 761, 741, 591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 7.8, 1.4 Hz), 7.85 (1H, dd, *J* = 8.0, 1.6 Hz), 7.80 (1H, ddd, *J* = 7.7, 7.5, 1.4 Hz), 7.68 (1H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 7.07 (1H, d, *J* = 8.2 Hz), 6.69 (1H, dd, *J* = 8.2, 1.8 Hz), 6.56 (1H, d, *J* = 1.8 Hz), 5.77 (1H, s), 4.93 (1H, d, *J* = 3.7 Hz), 3.84 (1H, dd, *J* = 10.5, 7.3 Hz), 3.70 (1H, dd, *J* = 10.5, 6.9 Hz), 3.37 (3H, d, *J* = 14.2 Hz), 2.78 (1H, ddd, *J* = 7.4, 7.2, 3.8 Hz), 2.18 (3H, s), 1.72 (3H, s), 0.89–0.81 (9H, m), 0.56–0.41 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.9, 148.5, 148.0, 144.2, 137.1, 134.7, 131.6 (2C), 130.0, 124.6, 123.3, 118.5, 115.1, 111.3, 106.8, 74.9, 63.7, 55.4, 46.9, 13.4, 11.0, 6.7 (3C), 4.7 (3C). HRMS (ESI–TOF) calcd for $C_{28}H_{37}NO_9SSiNa$ ($[M + Na]^+$) 614.1856, found 614.1855.

*4-((1S,3R,3aS,6R,7aS)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenyl 2-nitrobenzenesulfonate [(–)-**7**].*

The title compound (–)-**7** (26.6 mg, 0.0557 mmol, 66%) was obtained by same procedue to (+)-**7** from (+)-**21** (50.0 mg, 0.0845 mmol) with methanesulfonic acid (5.5 μl, 8.15 mg, 0.0845 mmol) in CH_2Cl_2 (1 mL) as colorless amorphous solids.

$[\alpha]_D^{25}$ –30.6 (*c* 1.00, $CHCl_3$); IR (neat) 3502, 3096, 2985, 2936, 2879, 2360, 2341, 1732, 1604, 1546, 1505, 1465, 1453, 1385, 1274, 1200, 1166, 1112, 1059, 1032, 942, 896, 852, 758, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, dd, *J* = 8.0, 1.1 Hz), 7.86 (1H, dd, *J* = 8.2, 1.4 Hz), 7.81 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.71 (1H, ddd, *J* = 7.7, 7.5, 1.4 Hz, 1H), 7.15 (1H, d, *J* = 8.7 Hz), 6.87–6.82 (2H, m), 4.98 (1H, d, *J* = 3.7 Hz), 3.77 (2H, d, *J* = 2.3 Hz), 3.57 (3H, d, *J* = 5.5 Hz), 2.68 (1H, dd, *J* = 10.1, 3.7 Hz), 2.47 (1H, dddd, *J* = 10.2, 3.9, 2.0, 2.0 Hz), 2.26 (1H, d, *J* = 12.3 Hz), 1.87 (1H, dd, *J* = 12.6, 3.9 Hz), 1.60 (3H, s), 1.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 148.4, 143.5, 137.5, 134.8, 131.9, 131.6, 130.2, 124.7, 124.3, 117.8, 115.5, 110.2, 106.0, 84.6, 62.9, 55.6, 48.0, 45.5, 33.2, 24.7, 22.5; HRMS (ESI–TOF) calcd for $C_{22}H_{23}NO_9SNa$ ($[M + Na]^+$) 500.0991, found 500.0990.

*4-((1S,3R,3aS,6R,7aS)-1,6-Dimethylhexahydro-1H-1,6-epoxyfuro[3,4-c]pyran-3-yl)-2-methoxyphenol [(–)-catunaregin (**1**)].*

The title compound (–)-**1** (31.6 mg, 0.108 mmol, quant.) was obtained by same procedue to (+)-**1** with (–)-**7** (51.7 mg, 0.108 mmol) and thiophenol (33.2 μL, 35.8 mg, 0.325 mmol) and cesium carbonate (177 mg, 0.542 mmol) as colorless amorphous solids.

$[\alpha]_D^{25}$ –37.5 (*c* 0.30, MeOH); $[\alpha]_D^{25}$ –64.4 (*c* 0.12, $CHCl_3$); IR (neat) 3408, 2984, 2937, 2879, 1608, 1603, 1517, 1460, 1450, 1432, 1385, 1331, 1270, 1238, 1195, 1170, 1113, 1057, 1032, 942, 847, 819, 794, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, d, *J* = 8.7 Hz), 6.83–6.77 (2H, m), 5.64–5.56 (1H, br s), 4.95 (1H, d, *J* = 3.7 Hz), 3.89 (3H, s), 3.76 (2H, d, *J* = 2.3 Hz), 2.71 (1H, dd, *J* = 10.3, 3.9 Hz), 2.49 (1H, dddd, *J* = 10.3, 3.8, 2.0, 2.0 Hz), 2.27 (1H, d, *J* = 12.3 Hz), 1.88 (1H, dd, *J* = 12.3, 4.1 Hz), 1.60 (3H, s), 1.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 145.2, 134.4, 118.8, 115.3, 114.4, 108.6, 105.9, 85.3, 63.0, 55.9, 47.8, 45.8, 33.3, 24.8, 22.6; HRMS (ESI–TOF) calcd for $C_{16}H_{20}O_5Na$ ($[M + Na]^+$) 315.1208, found 315.1204.

Cell culture assays

A549 cells (JCRB 0076) and HL-60 cells (JCRB 0085) were obtained from the Japanese Collection of Research Bioresources (Osaka, Japan). A549 cells or HL-60 cells were cultured in MEM or RPMI 1640 medium containing heat-inactivated 10%(v/v) FBS supplemented with L-glutamine, 100 unit/mL penicillin G sodium salt, and 100 μg/mL streptomycin sulfate in a humidified incubator at 37 °C with 5% CO_2. The cell growth was measured with an MTT reduction assay.[13] They (A549: 1 x 10^4 cells/mL, HL-60: 4 x 10^4 cells/mL) were continuously treated with each compound for 72 h, and cell viability was measured with an MTT reduction assay procedure. Dose–response curves were plotted for (±)-**1**, (+)-**1**, and (–)-**1**, and the concentrations giving 50% inhibition (IC_{50}) were calculated.

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Keywords: catunaregin • norneolignan • Evans aldol reaction • enantioselective synthesis • biological property

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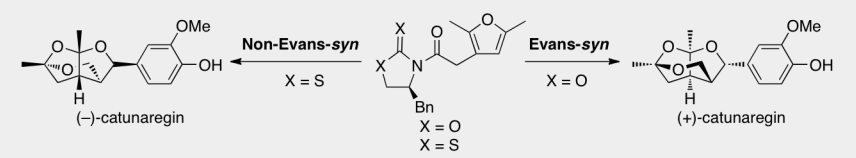

Total synthesis of catunaregin in both racemic and optically active forms was accomplished. This enantioselective synthesis employs Evans aldol methodology using oxazolidinone or thiazolidinethione as the chiral auxiliary. The key features include a *syn* selective aldol reaction to form the Evans-*syn* or Non-Evans-*syn* product, and successive ketalization of a furanyl diol derivative under acidic conditions.

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Total Synthesis of Catunaregin and Preliminary Evaluation of Its Antitumor Activity