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CHEMOSELECTIVITY-TUNABLE [5 + 2] CYCLOADDITIONS OF ALLENAMIDES AND OXIDOPYRYLIUMS

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Abstract – [5 + 2] Cycloadditions between allenamides and oxidopyryliums are described. A series of substituted cycloheptanones were synthesized by this method with moderate to good yields. Interestingly, the chemoselectivity of this reaction could be tuned by changing the electron-withdrawing groups on the allenamide nitrogen atom. When oxazolidinone chiral auxiliaries were introduced in the allenamide substrate, [5 + 2] cycloadducts could be obtained with high diastereoselectivities. This reaction provides a useful synthetic protocol for the construction of highly substituted seven-membered rings.

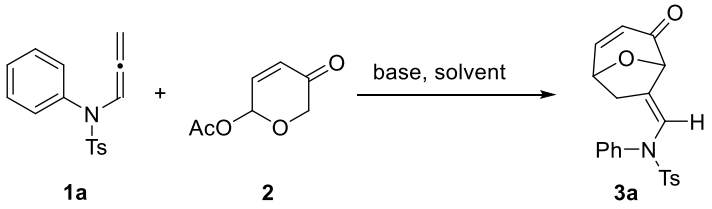
Allenamide represents a powerful synthetic building block for the access of a diverse array of useful structures.[1,2] The nitrogen atom substituted at the allene terminal carbon not only expands the reaction patterns of the allenic moiety but also generates an electronic bias that can lead to high chemo- and regioselectivities. In addition, this nitrogen atom can also provide an opportunity for controlling the stereochemical outcomes of chemical reactions via the introduction of nitrogen-based chiral auxiliaries.

Cycloaddition reactions have been demonstrated as one of the most powerful method in organic synthesis. Although [2 + 1],[3] [2 + 2],[4] [3 + 2],[5] [4 + 2],[6] and [4 + 3] cycloadditions[7] of allenamides have been reported, [5 + 2] cycloaddition of allenamides remain unexplored.[8] Considering the prevailing of seven-membered ring structures in natural products and related biological active compounds,[9] the [5 + 2] cycloaddition of allenamides may provide a useful method towards the synthesis of highly substituted seven-membered carbocycles. We herein report our success in developing a chemo-, regio-, and diastereoselective [5 + 2] cycloaddtion reaction between allenamides and oxidopyryliums.

Our investigation on the allenamide [5 + 2] cycloaddition commenced with submitting *N*-sulfonyl-allenamide **1a** to the known [5 + 2] conditions (Et_3N in CH_2Cl_2) with an equimolar amount of oxidopyrylium precursor **2** (Table1, entry 1).[10] However, while compound **2** consumed quickly to form

dimeric products, **1a** remain intact during the reaction process. Considering the stability of *N*-sulfonyl-allenamides, we tried to promote the reaction by adding excess amount of compound **2**. As a result, when 6 equivalents of **2** was added slowly to the reaction mixture, [5 + 2] cycloadduct **3a** was obtained as the only isomer in 39% yield. Although the reaction yield is moderate, the high chemo- and regioselectivities of the cycloaddition encouraged us to continue investigating the reaction conditions. Further screening indicated that diisopropylethylamine (DIPEA), $CHCl_3$ and 10 equivalents of **2** constituted the optimized conditions of this reaction (Table 1, entry 5), which provided cycloadduct **3a** in 60% yield (or 80% yield based on the recovery of **1a**).

Table 1. Optimization of the [5 + 2] condition between **1a** and **2**



1a **2** **3a**

entry	base	equiv of **2**	solvent	temp	yield (%)[a]	yield brsm (%)
1	Et_3N	1	CH_2Cl_2	rt	-	-
2	Et_3N	6	CH_2Cl_2	rt	39	63
3	Et_3N	10	CH_2Cl_2	rt	48	64
4	DIPEA	10	CH_2Cl_2	rt	55	73
5	DIPEA	10	$CHCl_3$	rt	60	80
6	DIPEA	10	$CHCl_3$	40 °C	52	68
7	DIPEA	15	$CHCl_3$	rt	58	77

[a] isolated yields

With the optimized conditions in hand, we explored the scope of allenamide [5 + 2] cycloaddition. As shown in Figure 1, several *N*-sulfonyl-allenamides reacted well in this reaction to give corresponding cycloadducts in moderate to good yields. Besides the *N*-aryl-allenamides, *N*-alkyl-allenamides (see **3b** and **3c**) also worked well under these reaction conditions. It is noteworthy that all the reactions exhibited high chemo- and regioselectivities. The structure of **3d** was unambiguously characterized by its X-ray single-crystal structure.[11]

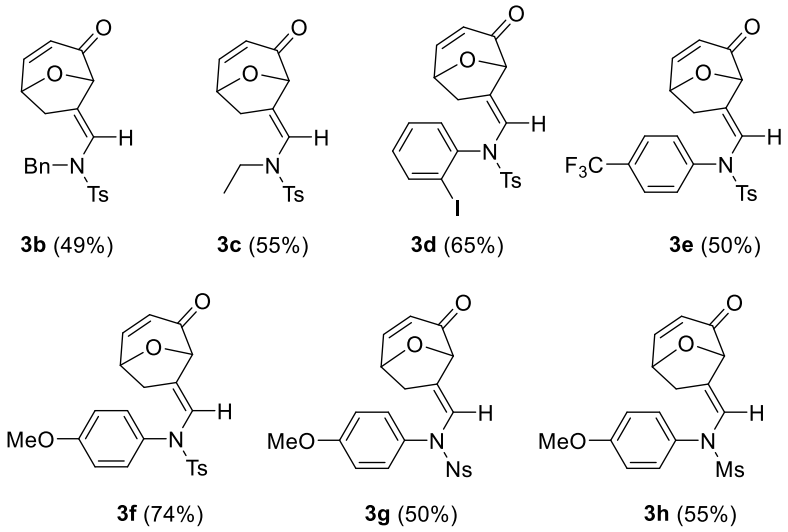
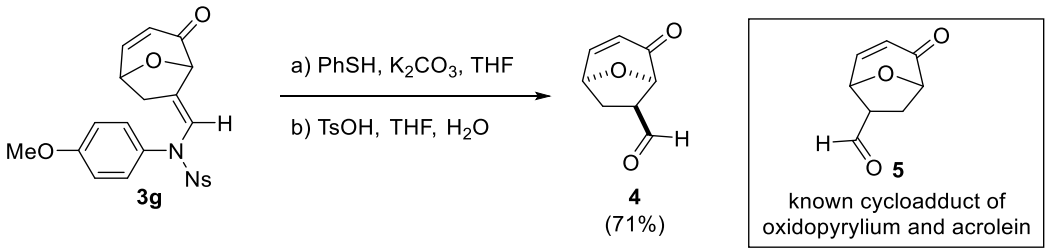


Figure 1. Scope of [5 + 2] cycloadditions with *N*-sulfonyl-allenamides

To demonstrate the synthetic potential of the above cycloaddcuts, a derivation reaction was carried out. As shown in Scheme 1, after a deprotection-hydrolysis reaction sequence, cycloadduct **3g** was converted to aldehyde **4**, which represents a useful intermediate in the synthesis of natural products. The relative stereochemistry of **4** could be clearly assigned by NOESY. It is also noteworthy that aldehyde **4** cannot be obtained directly from a [5 + 2] cycloaddition of oxidopyrylium and acrolein, because of the opposite regioselectivity of this known reaction (see compound **5**).[12]

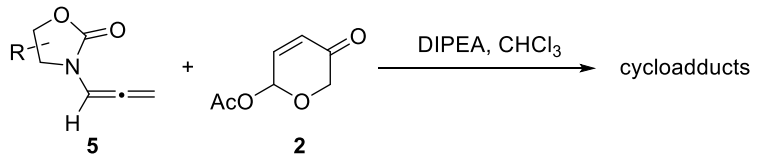


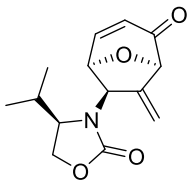
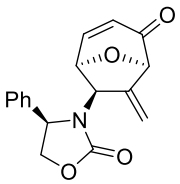
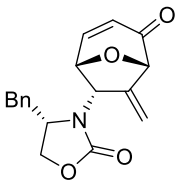
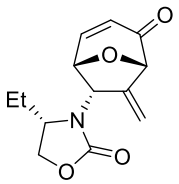
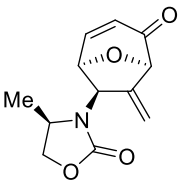
Scheme 1. Derivation of cycloadduct **3g**

In order to further explore the synthetic potential of the allenamide [5 + 2] cycloaddition, we tried to use oxazolidinone-based chiral auxiliaries to control the stereochemical outcomes of this reaction. These chiral oxazolidinone-attached allenes are known to be able to manipulate the stereochemistry of [4 + 3] cycloadditions.[7] As shown in Table 2, when *N*-oxazolidinone-allenamides were submitted to the optimized conditions of allenamides [5 + 2] cycloaddition, corresponding cycloadducts **7a – 7e** was obtained with good isolated yields, which indicates the higher reactivities of *N*-acyl-allenamides than

those of *N*-sulfonyl-allenamides. While these reactions all provided excellent regio- and diastereoselectivities as we have expected, the most surprising part is their chemoselectivities. All the [5 + 2] cycloadditions occurred at the enamide double bond of the *N*-acyl-allenamides. These results are completely different from the observed selectivities in the reactions of *N*-sulfonyl-allenamides. The structure of **7a** was unambiguously characterized by its X-ray single-crystal structure.[13]

Table 2. [5 + 2] Cycloadditions of *N*-acyl-allenamides



				
6a	**6b**	**6c**	**6d**	**6e**
(90%)[a]	(81%)[a]	(94%)[a]	(92%)[a]	(87%)[a]
dr[b] = 17:1	dr[b] = 25:1	dr[b] = 13:1	dr[b] = 17:1	single diastereomer

[a] isolated yield; [b] ratio determined by ^{1}H NMR

Assuming that all the allenamide [5 + 2] cycloadditions go through a concerted mechanism, a reaction model was proposed to rationalize the observed selectivities. As depicted in Figure 2A, for the chemoselectivity issue, **TS1** is favored by steric effect since the reaction occurs on the less hindered double bond. In contrast, **TS2** is favoured by electronic effect because of the electrophilic nature of oxidopyryliums. When *N*-sulfonyl-allenamides are the substrates, the extremely strong electron-withdrawing effect of sulfonyl group can greatly reduce the resonance effect between the nitrogen atom and the enamide double bond. So, in these cases, steric effect is dominating and the reaction go through **TS1**. When *N*-acyl-allenamides are used, the acyl group, while also electron-withdrawing, can still allow an effective level of delocalization from the nitrogen lone pair to the enamide alkene. As a result, electronic effect is more important in these reactions and the cycloadducts come from **TS2**. In both transition states, regioselectivities can be explained by the electronic effect.

Moreover, the diastereoselectivities found in cycloadducts **7a – 7e** can be rationalized by the reaction model shown in Figure 2B. For oxazolidinone-based allenamides, it is known that conformation A is more stable than conformation B because of the 1,3-allylic effect.[3b] As a result, the oxidopyrylium approaches the allenamide in conformation A from the open face and undergoes an *endo* transition state to give the observed cycloadducts.[14]

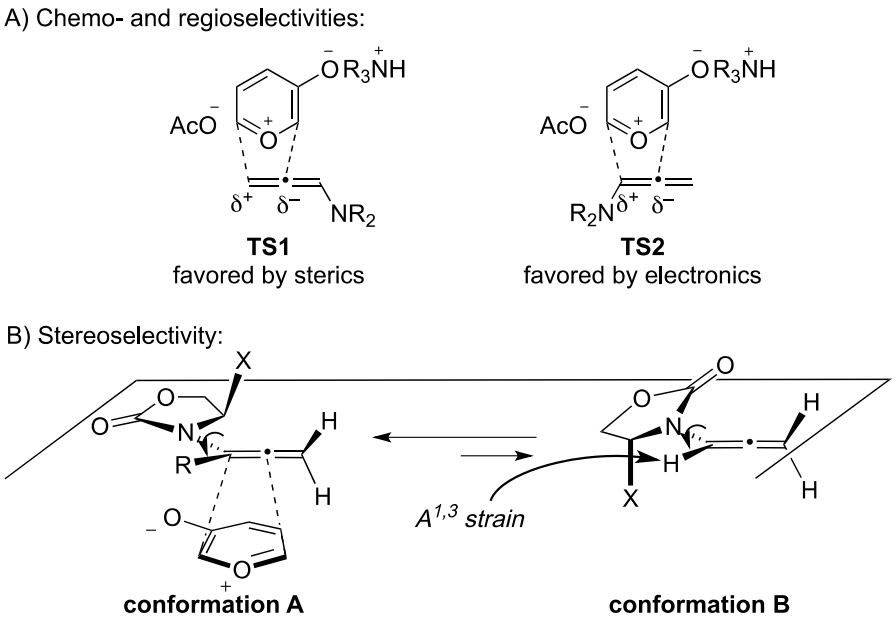


Figure 2. Rationalization of the selectivities

In summary, we have developed a chemo-, regio- and diastereoselective [5 + 2] cycloaddition reaction of allenamides and oxidopyryliums. This method can be used for the synthesis of highly functionalized seven-membered rings. The chemoselectivity of this reaction can be dramatically changed by switching the electron-withdrawing groups on the nitrogen atom of allenamides. Further mechanistic studies and efforts in applying this method in synthesis are underway.

EXPERIMENTAL

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aladdin, Macklin, Innochen, or TCI unless otherwise noted. Chromatographic separations were performed using Silica Gel, AR, 200-300 mesh. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-400, VI-500 and VI-600 spectrometers using $CDCl_3$ as the solvent. Infrared spectra were obtained on Thermo Scientific Nicolet iS 50. TLC analysis was visualized using UV, p-anisoladehyde and phosphomolybdic acid stains. High-resolution mass spectra were obtained using AB SCIEX X500R QTOF. All spectral data obtained for new compounds are reported here.

Starting Materials. Oxidopyryliums (**2**)[15] and allenamides[16] were prepared by previously reported procedures. All other chemicals used in this study were commercially available.

Generall Procedure for [5 + 2] Cycloaddition Using 3a As an Example.

To a solution of allene **1a** (142 mg, 0.5 mmol) in dry $CHCl_3$ (2 mL) was added DIPEA (1.6 g, 12.5 mmol, 25.0 equiv) at rt. A solution of compound **2** (780 mg, 5.0 mmol, 10.0 equiv) in dry $CHCl_3$ (4 mL) was

added to the above solution via syringe pump over 8 h. The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified using silica gel flash column chromatography to give **3a** (114 mg, 60%).

4-Methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)-*N*-phenylbenzenesulfonamide (3a). yellow viscous oil; IR (KBr) 2918, 2253, 1744, 1686, 1491, 1354, 1166, 949, 803, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.28 (m, 3H), 7.25 (t, *J* = 5.5 Hz, 2H), 7.06 (s, 1H), 7.02 – 6.98 (m, 2H), 6.98 – 6.92 (m, 1H), 5.87 (dd, *J* = 9.9, 1.2 Hz, 1H), 4.82 (s, 1H), 4.64 (dd, *J* = 6.8, 4.5 Hz, 1H), 2.42 (s, 3H), 1.97 (ddd, *J* = 15.8, 6.9, 2.6 Hz, 1H), 1.42 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 151.2, 144.3, 138.0, 134.6, 129.7, 129.7, 129.0, 128.5, 127.6, 125.8, 125.2, 119.1, 84.5, 73.8, 31.6, 21.6; HRMS (ESI) Calculated for $C_{21}H_{19}NO_4S$ $[M+H]^+$: 382.1108, found 382.1096.

***N*-Benzyl-4-methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)benzenesulfonamide (3b).** yellow viscous oil; IR (KBr) 2969, 1697, 1597, 1456, 1341, 1163, 1086, 942, 881, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.20 – 7.13 (m, 2H), 6.94 (dd, *J* = 9.9, 4.5 Hz, 1H), 5.75 (dd, *J* = 9.9, 1.2 Hz, 1H), 5.64 (s, 1H), 4.79 – 4.70 (m, 2H), 4.28 (d, *J* = 13.8 Hz, 1H), 4.12 (d, *J* = 13.8 Hz, 1H), 2.60 (ddd, *J* = 15.9, 6.8, 2.7 Hz, 1H), 2.48 – 2.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 151.1, 144.1, 139.3, 135.5, 134.3, 129.94, 128.6, 128.5, 127.8, 127.4, 125.6, 123.1, 83.6, 73.7, 54.1, 33.1, 21.5; HRMS (ESI) Calculated for $C_{22}H_{21}NO_4S$ $[M+H]^+$: 396.1264, found 396.1262.

***N*-Ethyl-4-methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)benzenesulfonamide (3c).** yellow viscous oil; IR (KBr) 2985, 2922, 1699, 1595, 1447, 1340, 1198, 1163, 1041, 855 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.24 (dd, *J* = 9.9, 4.5 Hz, 1H), 6.00 (dd, *J* = 9.9, 1.2 Hz, 1H), 5.71 (s, 1H), 5.02 – 4.92 (m, 1H), 4.87 (s, 1H), 3.25 – 3.19 (m, 1H), 3.12 – 3.03 (m, 1H), 2.90 (ddd, *J* = 15.9, 6.5, 2.6 Hz, 1H), 2.82 (dd, *J* = 15.9, 0.9 Hz, 1H), 2.42 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 192.6, 151.7, 143.8, 136.6, 134.4, 129.8, 127.2, 125.8, 123.2, 84.0, 73.9, 44.5, 33.2, 21.54, 13.8; HRMS (ESI) Calculated for $C_{17}H_{19}NO_4S$ $[M+H]^+$: 334.1108, found 334.1100.

***N*-(2-Iodophenyl)-4-methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)benzenesulfonamide (3d).** white solid; mp 190-192 °C; IR (KBr) 2971, 2920s, 1683, 1595, 1467, 1360, 1173, 1146, 815, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.77 (m, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 4H), 7.14 – 7.02 (m, 2H), 6.96 (s, 1H), 5.92 (d, *J* = 9.2 Hz, 1H), 4.84 (s, 1H), 4.64 (dd, *J* = 6.7, 4.5 Hz, 1H), 2.44 (s, 3H), 1.92 (d, *J* = 13.7 Hz, 1H), 1.22 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

192.6, 150.8, 144.6, 140.2, 135.5, 132.2, 130.4, 129.9, 128.7, 128.0, 126.2, 123.7, 115.9, 84.9, 73.9, 31.2, 21.6; HRMS (ESI) Calculated for $C_{21}H_{18}INO_4S$ $[M+H]^+$: 508.0074, found 508.0094.

4-Methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)-*N*-(4-(trifluoromethyl)phenyl)-benzenesulfonamide (3e). brown viscous oil; IR (KBr) 2919, 2657, 1698, 1606, 1359, 1330, 1177, 1127, 944, 806 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 9.9, 4.5 Hz, 1H), 6.90 (s, 1H), 5.81 (d, *J* = 9.9 Hz, 1H), 4.78 (s, 1H), 4.64 (dd, *J* = 6.8, 4.5 Hz, 1H), 2.35 (s, 3H), 1.99 (ddd, *J* = 15.7, 6.9, 2.5 Hz, 1H), 1.52 (d, *J* = 15.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 151.4, 144.8, 141.8, 134.1, 132.5, 129.9, 129.1, 127.4, 126.2, 125.7, 124.6, 123.5, 84.2, 73.7, 32.2, 21.5; HRMS (ESI) Calculated for $C_{22}H_{18}F_3NO_4S$ $[M+H]^+$: 450.0987, found 450.0987.

***N*-(4-Methoxyphenyl)-4-methyl-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)benzene-sulfonamide (3f).** yellow viscous oil; IR (KBr) 2919, 2840, 1686, 1598, 1500, 1341, 1244, 1162, 1085, 1024, 797 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 6.97 (dd, *J* = 9.9, 4.5 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.81 – 6.77 (m, 2H), 5.87 (dd, *J* = 9.9, 1.3 Hz, 1H), 4.80 (s, 1H), 4.64 (dd, *J* = 6.8, 4.5 Hz, 1H), 3.81 (s, 3H), 2.42 (s, 3H), 1.98 (ddd, *J* = 15.8, 7.0, 2.6 Hz, 1H), 1.49 – 1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 159.5, 151.1, 144.2, 134.7, 131.2, 130.1, 129.6, 127.6, 125.8, 125.4, 117.0, 114.1, 84.6, 73.8, 55.4, 31.6, 21.6; HRMS (ESI) Calculated for $C_{22}H_{21}NO_5S$ $[M+H]^+$: 412.1213, found 412.1209.

***N*-(4-Methoxyphenyl)-4-nitro-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)benzene-sulfonamide (3g).** yellow viscous oil; IR (KBr) 2931, 1695, 1515, 1344, 1250, 1156, 1035, 973, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 7.06 (s, 1H), 7.02 (dd, *J* = 9.9, 4.5 Hz, 1H), 6.94 – 6.89 (m, 2H), 5.92 (dd, *J* = 9.9, 1.3 Hz, 1H), 4.85 – 4.78 (m, 1H), 4.69 (dd, *J* = 6.6, 4.5 Hz, 1H), 3.84 (s, 3H), 2.95 (s, 3H), 2.07 – 2.00 (m, 1H), 1.44 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.91, 159.82, 151.20, 130.99, 129.91, 125.91, 124.99, 116.62, 114.69, 84.73, 73.89, 55.56, 38.17, 31.55; HRMS (ESI) Calculated for $C_{16}H_{17}NO_5S$ $[M+H]^+$: 336.0900, found 336.0907.

***N*-(4-Methoxyphenyl)-*N*-((4-oxo-8-oxabicyclo[3.2.1]oct-2-en-6-ylidene)methyl)methanesulfonamide (3h).** brown viscous oil; IR (KBr) 2916, 2578, 1698, 1545, 1515, 1374, 1250, 1174, 1035, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 1H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.56 - 7.51 (m, 2H), 7.18 (s, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 7.00 (dd, *J* = 9.9, 4.5 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.90 (dd, *J* = 9.9, 1.0 Hz, 1H), 4.88 (s, 1H), 4.67 (dd, *J* = 6.8, 4.5 Hz, 1H), 3.81 (s, 3H), 1.99 (ddd, *J* = 15.7, 6.9, 2.5 Hz, 1H), 1.45 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.7, 160.0, 151.0, 147.9, 134.4, 132.2, 131.7, 131.4, 130.6, 128.5, 125.8, 125.2, 124.2, 114.4, 84.7, 73.9, 55.5, 31.4; HRMS (ESI) Calculated for $C_{21}H_{18}N_2O_7S$ $[M+H]^+$: 443.0907, found 3443.0900.

(*R*)-4-Isopropyl-3-((1*R*,5*R*,6*R*)-7-methylene-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)oxazolidin-2-one

(7a). white solid; mp 150-151 °C; $[\alpha]_D^{25}$ -19.3 (c 0.1, MeOH); IR (KBr) 2952, 2929, 1741, 1688, 1484, 1421, 1240, 1046 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 10.0, 4.5 Hz, 1H), 6.12 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.61 (s, 1H), 5.39 (s, 1H), 5.21 – 5.16 (m, 1H), 4.87 – 4.80 (m, 2H), 4.20 – 4.17 (m, 1H), 4.17 – 4.15 (m, 1H), 3.84 – 3.79 (m, 1H), 2.19 – 2.13 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 157.6, 149.3, 139.8, 128.1, 113.7, 85.2, 74.7, 62.7, 61.36, 58.7, 28.0, 18.1, 14.0; HRMS (ESI) Calculated for $C_{14}H_{17}NO_4$ $[M+H]^+$: 264.1230, found 264.1218.

(*R*)-3-((1*R*,5*R*,6*R*)-7-Methylene-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)-4-phenyloxazolidin-2-one

(7b). yellow viscous oil; $[\alpha]_D^{25}$ +63.1 (c 0.28, MeOH); IR (KBr) 2982, 2936, 1748, 1691, 1473, 1413, 1215, 1040, 829, 704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 3H), 7.30 (dd, *J* = 10.0, 4.6 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.20 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.42 (s, 1H), 5.05 (dd, *J* = 5.9, 4.8 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.81 (d, *J* = 1.0 Hz, 1H), 4.79 (dd, *J* = 8.3, 3.2 Hz, 1H), 4.71 (s, 1H), 4.57 (t, *J* = 8.5 Hz, 1H), 4.18 (dd, *J* = 8.7, 3.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.7, 157.5, 149.9, 139.6, 138.0, 129.6, 129.3, 128.7, 126.1, 116.2, 85.6, 74.9, 70.8, 60.8, 58.4; HRMS (ESI) Calculated for $C_{17}H_{15}NO_4$ $[M+H]^+$: 298.1074, found 298.1068.

(*S*)-4-Benzyl-3-((1*S*,5*S*,6*S*)-7-methylene-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)oxazolidin-2-one (7c). yellow viscous oil; $[\alpha]_D^{25}$ -285.5 (c 0.48, MeOH); IR (KBr) 2974, 2249, 1741, 1691, 1411, 1348, 1090, 891 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 10.0, 4.6 Hz, 1H), 7.29 (t, *J* = 3.7 Hz, 2H), 7.26 (dd, *J* = 4.9, 3.6 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.24 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.64 (d, *J* = 0.5 Hz, 1H), 5.53 (s, 1H), 5.28 – 5.21 (m, 1H), 4.99 (dd, *J* = 6.3, 4.7 Hz, 1H), 4.88 (d, *J* = 1.0 Hz, 1H), 4.04 – 3.98 (m, 3H), 3.24 – 3.16 (m, 1H), 2.54 – 2.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 158.2, 149.1, 139.8, 135.2, 129.0, 128.7, 128.5, 114.1, 85.0, 73.9, 66.6, 59.2, 57.8, 38.9; HRMS (ESI) Calculated for $C_{18}H_{17}NO_4$ $[M+H]^+$: 312.1230, found 312.1219.

(*S*)-4-Ethyl-3-((1*S*,5*S*,6*S*)-7-methylene-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)oxazolidin-2-one (7d). yellow solid; mp 146-147 °C; $[\alpha]_D^{25}$ -45.1 (c 0.14, MeOH); IR (KBr) 2972, 1731, 1692, 1420, 1228, 1107, 1017 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 10.0, 4.5 Hz, 1H), 6.13 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.61 (s, 1H), 5.42 (d, *J* = 0.7 Hz, 1H), 5.11 – 5.05 (m, 2H), 4.86 (d, *J* = 1.2 Hz, 1H), 4.34 (t, *J* = 8.3 Hz, 1H), 4.03 (dd, *J* = 8.6, 4.9 Hz, 1H), 3.75 – 3.69 (m, 1H), 1.83 – 1.75 (m, 1H), 1.49 – 1.41 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8, 158.1, 148.9, 139.8, 128.4, 114.0, 85.2, 74.2, 67.1, 58.7, 58.0, 25.5, 8.7; HRMS (ESI) Calculated for $C_{13}H_{15}NO_4$ $[M+H]^+$: 250.1074, found 250.1069.

(*R*)-4-Methyl-3-((1*R*,5*R*,6*R*)-7-methylene-2-oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl)oxazolidin-2-one

(7e). white solid; mp 143-144 °C; $[\alpha]_D^{25}$ -52.3 (c 0.12, MeOH); IR (KBr) 2999, 2947, 1719, 1691, 1487, 1417, 1254, 1131, 1037 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 10.0, 4.6 Hz, 1H), 6.15 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.62 (s, 1H), 5.45 (s, 1H), 5.21 – 5.14 (m, 1H), 5.05 – 4.99 (m, 1H), 4.87 (s, 1H), 4.36

(t, J = 7.7 Hz, 1H), 3.91 (ddt, J = 13.5, 7.9, 5.8 Hz, 2H), 1.22 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8, 158.3, 148.8, 139.6, 128.6, 114.3, 85.1, 74.0, 69.1, 58.8, 52.7, 19.5; HRMS (ESI) Calculated for $C_{12}H_{13}NO_4$ $[M+H]^+$: 236.0917, found 236.0910.

4-Oxo-8-oxabicyclo[3.2.1]oct-2-ene-6-carbaldehyde (4). To a solution of **3g** (50 mg, 0.11 mmol) in THF (1 mL) was added K_2CO_3 (30.40 mg, 0.22 mmol, 2 equiv), and then PhSH (24.23 mg, 0.22 mmol, 2 equiv) was added at rt. The reaction was stirred at rt for 3 h and monitored by TLC before being filtered though CeliteTM. Subsequently, the filtrate was added TsOH (9.50 mg, 0.05 mmol, 0.5 equiv), H_2O (0.1 mL). The reaction was stirred at rt for 8 h before being quenched with aq $NaHCO_3$ and extracted with Et_2O, dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified using silica gel flash column chromatography to give **4** (11 mg, 71%). colourless oil; IR (KBr) 2950, 2750, 1669, 1075, 1037 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.79 (d, J = 1.6 Hz, 1H), 7.34 (dd, J = 9.9, 4.6 Hz, 1H), 6.05 (dd, J = 9.9, 1.0 Hz, 1H), 4.95 (dd, J = 6.9, 4.6 Hz, 1H), 4.83 (s, 1H), 2.98 – 2.89 (m, 1H), 2.54 – 2.49 (m, 1H), 2.09 (dd, J = 12.5, 9.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 194.5, 153.1, 126.0, 81.6, 73.7, 50.8, 29.8; HRMS (ESI) Calculated for $C_8H_8O_3$ $[M+H]^+$: 153.0546, found 153.0555.

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