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Synthesis of the Tetracyclic Core (ABCE Rings) of Daphenylline

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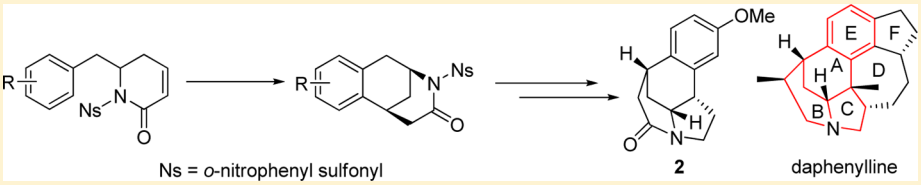
Supporting Information



ABSTRACT: A concise synthesis of the tetracyclic core (ABCE rings) of daphenylline has been accomplished involving a benzobicyclo[3.3.1] lactam as the key intermediate. This bridged bicyclic intermediate was efficiently constructed via a Brønsted acid promoted intramolecular Friedel–Crafts type Michael addition of a δ-benzyl α,β-unsaturated δ-lactam.

The daphniphyllum alkaloids, originated from plants of the genus *Daphniphyllum* (daphniphyllaceae), is a large and fast growing family of natural products with diverse structures.[1,2] These fused-heteropolycyclic structures have received broad interest for both total synthesis and biosynthesis due to their unique complexity.[3] Daphenylline (**1**), a novel member of the daphniphyllum alkaloids, was isolated from the fruits of the *Daphniphyllum longeracemosum Rosenth* by Hao and co-workers in 2009 (Figure 1).[4] The structural features of

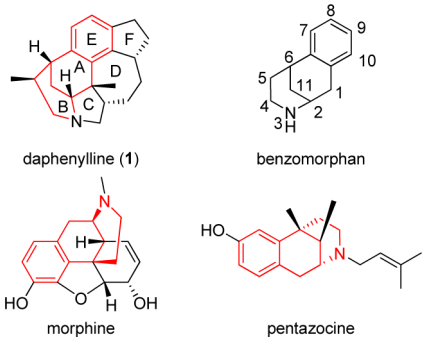


Figure 1. Daphenylline (**1**) and selected natural products bearing the benzomorphan core.

daphenylline (**1**) include a polycyclic skeleton with four carbocycles and two N-heterocycles, on which are embedded with one full-carbon quaternary and five tertiary stereogenic centers. More importantly, the daphenylline (**1**) skeleton incorporates benzomorphan (benzobicyclo[3.3.1] core) as the subunit.[5] Such a scaffold has been widely recognized in many biologically active natural products such as sinomenine,[6] morphine,[7] codeine,[8] pentazocine[9] along with various artificial analgesics[10] (Figure 1). Deriving from our previous study on Friedel–Crafts type Michael addition to α,β-unsaturated carbonyl compounds,[11] we intended to apply our methodology to synthesize natural products bearing such a benzomorphan backbone. Herein, we describe a concise synthesis of the tetracyclic core (**2**) (ABCE rings) of daphenylline by employing a benzobicyclo[3.3.1] lactam (**3**) as the key intermediate, which was efficiently constructed by a Brønsted acid (CF_3SO_3H) promoted intramolecular Friedel–Crafts type Michael addition of a δ-benzyl α,β-unsaturated δ-lactam (**4**).

The retrosynthetic pathway of the tetracyclic (ABCE rings) core **2** was depicted in Scheme 1. The C ring of the polycyclic core **2** could be readily constructed from the benzomorphan analogue **3** by an intramolecular N-alkylation. On the basis of our previous study regarding the formation of the benzobicyclo[3.3.1] lactone via an intramolecular Friedel–Crafts type Michael addition of the corresponding α,β-unsaturated lactone,[11] we envisioned that the key benzomorphan analogue **3** (benzobicyclo[3.3.1] lactam) could be obtained from δ-benzyl α,β-unsaturated δ-lactam **4** via a similar pathway. The δ-lactam **4** could be synthesized from *anti*-sulfonamide **5**, which in turn could be converted from *syn*-homoallylic alcohol **6** by the S_N2 reaction. The Barbier-type allylation reaction readily established the relative configuration (*syn*) of **6**, which could be easily accessed from commercially available (3-methoxyphenyl) acetonitrile **7**.

The synthesis of the tetracyclic core (ABCE rings) of daphenylline (**2**) was initiated from (3-methoxyphenyl) acetonitrile **7** (Scheme 2). Monoalkylation of **7** with the known iodide **8**[12] afforded nitrile **9** in 85% yield followed by

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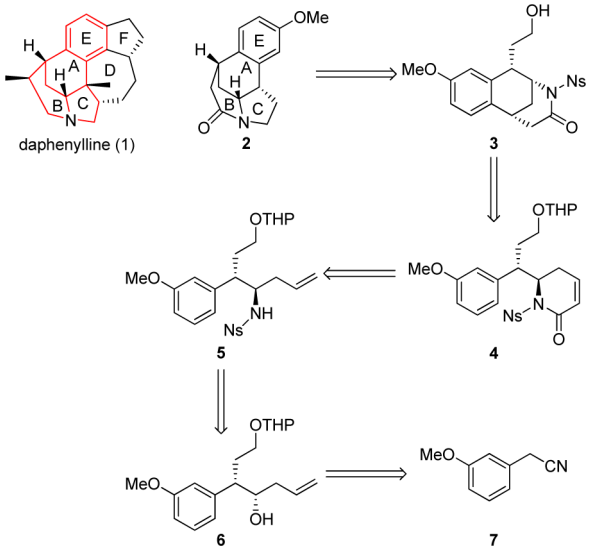
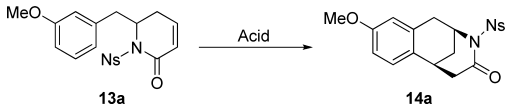
Scheme 1. Retrosynthetic Plan for Symthesis of the ABCE Rings of Dapherylline



DIBAL-H reduction of the cyano functionality into the corresponding aldehyde **10**. It was found that aldehyde **10** reacted smoothly with allyl bromide in the presence of activated zinc powder in a mixed solvent of saturated aqueous ammonium chloride and THF,[13] giving the homoallylic alcohols in high yield. Although the diastereoselectivity remained moderate (d.r. = 6/1), the desired alcohol **6** could be easily isolated by silica-based column chromatography. Activation of *syn*-secondary alcohol **6** as its mesylate and subsequent S_N2 reaction generated *anti*-homoallylic azide **11** in 86% yield. Subsequent treatment of azide **11** with $LiAlH_4$, followed by N-nosylation to smoothly furnish the *anti*-sulfonamide **5** in 85% yield for two consecutive steps. Amidation between **5** and acryloyl chloride afforded olefinic-amide **12** as the ring closing metathesis precursor in 76% yield. Ring closure of **12** employing the second generation Grubbs' catalyst (GII)[14] under high dilution gave the key intermediate, δ-benzyl α,β-unsaturated δ-lactam **4**, in 74% yield.

With the key lactam **4** in hand, we set out to investigate the one-step construction of the benzomorphan analogue **3**. Different lactam substrates were tested in parallel regarding the postulated intramolecular Friedel–Crafts type Michael addition. Optimization of the reaction conditions started with using *m*-methoxy-substituted lactam **13a** as the model substrate, which closely resembled the key lactam **4**. A series of both Lewis and Brønsted acids were examined (Table 1). It

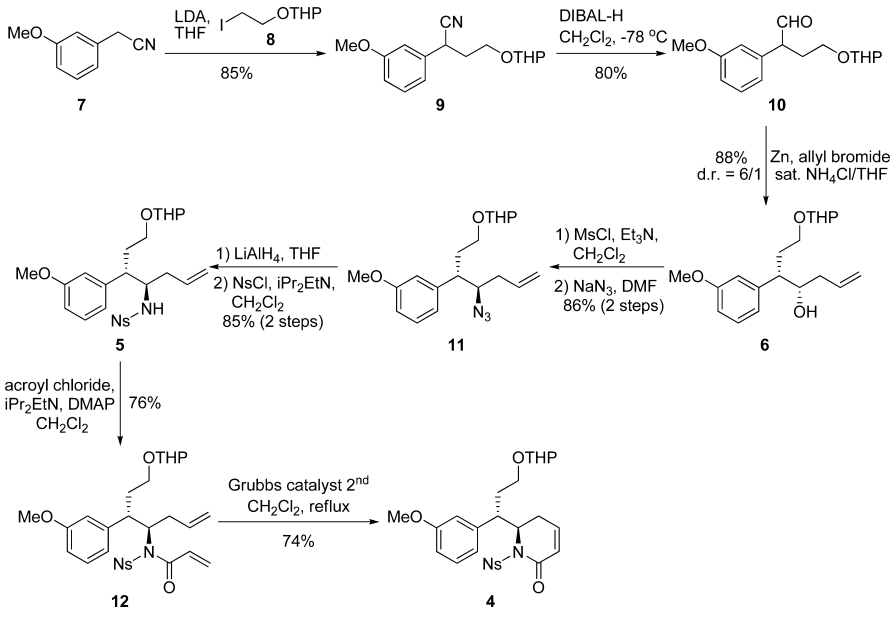
Table 1. Optimization of Reaction Conditions[a]



entry	acid	solvent	temp (°C)	time (h)	yield (%)[b]
1	$SnBr_4$	CH_2Cl_2	rt	24	0[c]
2	$TiCl_4$	CH_2Cl_2	rt	24	trace[d]
3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	rt	24	0[c]
4	$FeCl_3$	CH_2Cl_2	rt	24	0[c]
5	TMSOTf	CH_2Cl_2	rt	24	43
6	$AlCl_3$	CH_2Cl_2	rt	24	trace[d]
7	$AlBr_3$	CH_2Cl_2	rt	24	35
8	BCl_3	CH_2Cl_2	rt	24	0[c]
9	BBr_3	CH_2Cl_2	rt	24	trace[e]
10	TfOH	CH_2Cl_2	rt	24	81[f]
11	*p*-TsOH	CH_2Cl_2	rt	24	0[c]
12	CF_3COOH	CH_2Cl_2	rt	24	0[c]
13	TfOH (1.0 equiv)	$ClCH_2CH_2Cl$	50	12	18[g]
14	TfOH (2.0 equiv)	$ClCH_2CH_2Cl$	50	8	90

[a]**13a** (0.1 mmol), acid (0.25 mmol, 2.5 equiv otherwise indicated in parentheses), and 1 mL of solvent were mixed. [b]Isolated yield. [c]Quantitative recovery of the starting material. [d]Recovery of most of the starting material. [e]Starting material decomposition. [f]Recovery of 10% of the starting material. [g]Recovery of 75% of the starting matetial.

Scheme 2. Synthesis of Lactam 4



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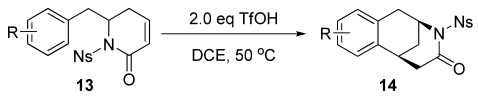
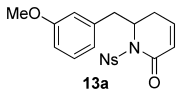
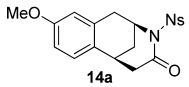
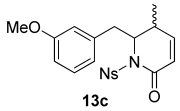
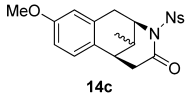
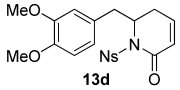
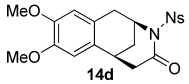
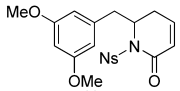
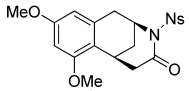
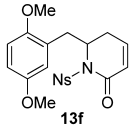
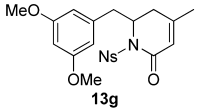
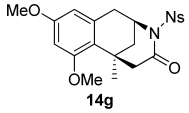
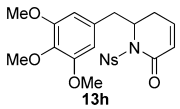
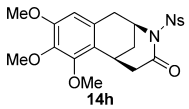
was found that triflic acid promoted the desired intramolecular Friedel–Crafts type Michael addition with great efficiency in dichloromethane (DCM), giving the corresponding benzomorphan derivative **14a** in 81% yield (Table 1, entry 10). Among all the other tested acids, only $AlBr_3$ and TMSOTf could successfully render the desired cyclization, however in much lower yields (Table 1, entries 5 and 7). Treatment of lactam **13a** with BBr_3 led to a complex mixture with decomposition of the starting material (Table 1, entry 9). The rest of the Lewis acids ($SnBr_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $FeCl_3$, $AlCl_3$ and BCl_3) or protic acids (*p*-TsOH and CF_3COOH) resulted in no observable reaction or trace amount in conversion (Table 1, entries 1–4, 6, 8, 11 and 12). When dichloromethane was replaced with 1,2-dichloroethane (DCE), the desired benzobicyclo[3.3.1] lactam **14a** was obtained in excellent yield (90%) using 2 equiv of triflic acid at 50 °C in 8 h, which was set as the optimized conditions (Table 1, entry 14).[15]

Further investigation was focused on the substrate scope of the intramolecular Michael addition of lactams possessing electron-rich aryl groups along with the limitation of this reaction (Table 2). 3,5-Dimethoxy and 3,4,5-trimethoxy substituted lactams (Table 2 entries 5 and 8) proceeded smoothly under the optimized reaction conditions, while 4-methoxy and 2,5-dimethoxy substitution failed to give any desired cyclization products (Table 2 entries 2 and 6). This indicated that the methoxy group locating at the *meta*-position to the reaction site significantly lowered the overall activity, giving no desired products. To our delight, substrates **13c** and **13g** could also react well to give the corresponding benzobicyclo[3.3.1] products **14c** and **14g**, which contained a bridged methyl group and a quaternary bridgehead carbon, respectively (Table 2 entries 3 and 7). The structure of **14g** was characterized by X-ray diffraction analysis confirming the relative stereochemistry of formed bridged lactams.[16]

Table 2. Synthesis of Benzobicyclo[3.3.1] Lactam 14[a]



entry	substrate	product	yield (%)[b]
1	 **13a**	 **14a**	90
2	 **13b**	-	0[c]
3[d]	 **13c**	 **14c**	84[e]
4	 **13d**	 **14d**	89
5	 **13e**	 **14e**	88
6	 **13f**	-	0[c]
7	 **13g**	 **14g**	78
8	 **13h**	 **14h**	81

[a]All reactions were performed on a 0.1 mmol scale at 0.1 M in $ClCH_2CH_2Cl$ for 8 h at 50 °C. [b]Isolated yield. [c]Quantitative recovery of the starting material. [d]A 1:1 diastereomeric mixture of **13c** was illustrated. [e]A 2:1 diastereomeric mixture of **14c** was illustrated.

Encouraged by the optimized conditions of the intramolecular Friedel–Crafts type Michael addition, we continued to complete the synthesis of the tetracyclic core (ABCE rings) of daphenylline (**2**) (Scheme 3). Gratifyingly, subjection of the key lactam **4** to the optimized conditions successfully afforded the bridged lactam **3** in 71% yield, while O-THP protection was removed in the same pot as well because of the overall acidic condition. Removal of the nosyl group was readily accomplished using thiophenol and potassium carbonate in DMF to give alcohol lactam **15**.[17] The primary hydroxyl group was converted to its mesylate **16** in excellent yield, followed by N-cyclization in DMF at 0 °C to furnish the targeted tetracyclic lactam **2** in 77% yield (ABCE rings of daphenylline). The structure of lactam **2** was unambiguously illustrated by X-ray crystallography analysis.[18]

In summary, we have achieved a concise synthesis of the tetracyclic core (ABCE rings) of daphenylline with overall yield of 7.5% over 13 steps. The key feature of the synthesis involves a Brønsted acid promoted intramolecular Friedel–Crafts type Michael addition reaction of a δ-benzyl α,β-unsaturated lactam, which efficiently constructed the benzomorphan (benzobicyclo[3.3.1] lactam) backbone.

EXPERIMENTAL SECTION

Synthesis of Nitrile 9. To a solution of acetonitrile **7** (2.74 g, 18.6 mmol) in dry THF (60 mL) was added LDA (10 mL, 20 mmol, 2.0 M in THF) at −78 °C under Ar. The reaction mixture was stirred for 0.5 h, and iodide **8**[12] (5.24 g, 20.5 mmol) in dry THF (10 mL) was added dropwise. After 2 h, saturated aqueous NH_4Cl (15 mL) was added at −78 °C, and the mixture was warmed to room temperature, followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 20:1) gave nitrile **9** (4.35 g, 85% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.9 Hz, 1H), 6.97–6.85 (m, 3H), 4.62–4.57 (m, 1H), 4.05 (t, J = 7.9 Hz, 1H), 3.93–3.84 (m, 2H), 3.82 (s, 3H), 3.60–3.38 (m, 2H), 2.20–2.12 (m, 2H), 1.87–1.70 (m, 2H), 1.64–1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 160.0, 137.0, 136.9, 130.0, 120.7, 120.6, 119.6, 119.5, 113.5, 113.4, 113.2, 113.1, 99.4, 98.7, 63.9, 63.3, 62.6, 62.1, 55.2, 35.9, 35.7, 33.9, 33.8, 30.5, 30.4, 25.3, 19.6, 19.3; HRMS (ESI) Calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1594, found 276.1587.

Synthesis of Aldehyde 10. To a solution of nitrile **9** (4.32 g, 15.7 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAL-H (13.5 mL, 16 mmol, 1.2 M in toluene) at −78 °C under Ar. The mixture was stirred for 4 h until **9** was completely consumed. Saturated aqueous $NaHCO_3$ was added slowly at −78 °C to quench the excessive DIBAL-H. After warming to room temperature, the mixture was filtered, and the filtration residue was washed with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 15:1) gave aldehyde **10** (3.19 g, 87%

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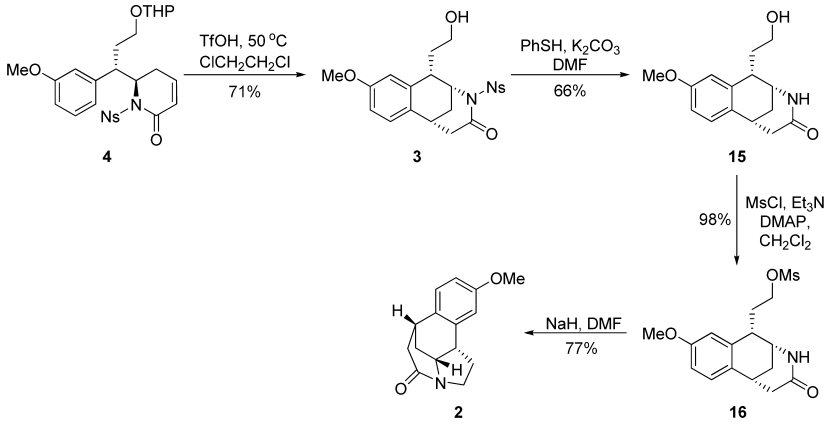
Scheme 3. Synthesis of the Tetracyclic Core of Daphenylline (2)



yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, J = 1.7 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 6.85−6.73 (m, 3H), 4.52 (dt, J = 30.8, 3.6 Hz, 1H), 3.84−3.82 (m, 1H), 3.81 (s, 3H), 3.79−3.66 (m, 2H), 3.49−3.28 (m, 2H), 2.46−2.40 (m, 1H), 2.00−1.95 (m, 1H), 1.82−1.80 (m, 1H), 1.72−1.66 (m, 1H), 1.59−1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 200.2, 200.1, 160.0, 137.4, 137.3, 130.0, 129.9, 121.1, 114.6, 114.5, 112.8, 99.0, 98.5, 64.6, 64.5, 62.3, 61.9, 56.0, 55.9, 55.1, 30.5, 29.8, 25.4, 25.3, 19.5, 19.2; HRMS (ESI) Calcd. for $C_{16}H_{26}NO_4$ $[M + NH_4]^+$ 296.1856, found 296.1850.

Synthesis of *syn*-Alcohol 6. To a solution of aldehyde **10** (2.28 g, 8.2 mmol) in saturated aqueous NH_4Cl (25 mL) and THF (5 mL) were added allyl bromide (3 g, 2.1 mL, 24.6 mmol) and activated zinc dust (1.6 g, 24.6 mmol). The mixture was stirred at room temperature for 3 h, followed by extraction with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc, 7:1) yielded 2.00 g (76%) of *syn*-alcohol **6** and 313 mg (12%) *anti*-alcohol **17** as colorless oils. *syn*-product **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, J = 7.8 Hz, 1H), 6.78−6.72 (m, 3H), 5.88−5.71 (m, 1H), 5.12−4.97 (m, 2H), 4.48 (dt, J = 29.2, 3.6 Hz, 1H), 3.78 (s, 3H), 3.77−3.57 (m, 3H), 3.43−3.38 (m, 1H), 3.23 (dddd, J = 14.6, 9.6, 7.9, 5.5 Hz, 1H), 2.72 (ddt, J = 9.9, 8.1, 4.0 Hz, 1H), 2.41 (dd, J = 4.4, 2.7 Hz, 1H), 2.36−2.23 (m, 1H), 2.19−2.08 (m, 1H), 2.03−1.85 (m, 2H), 1.84−1.73 (m, 1H), 1.72−1.61 (m, 1H), 1.59−1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 159.5, 143.9, 143.8, 135.0, 129.4, 129.3, 120.6, 120.5, 117.7, 114.3, 114.2, 111.3, 99.0, 98.3, 74.1, 74.0, 65.8, 65.6, 62.1, 61.8, 55.0, 49.2, 49.1, 39.6, 39.5, 32.0, 31.7, 30.6, 30.5, 25.3, 25.3, 19.4, 19.2; HRMS (ESI) Calcd. for $C_{19}H_{32}NO_4$ $[M + NH_4]^+$ 338.2326, found 338.2321.

anti-alcohol **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 1H), 6.92−6.71 (m, 3H), 5.91−5.78 (m, 1H), 5.13−5.02 (m, 2H), 4.53−4.41 (m, 1H), 3.85 (dt, J = 12.9, 4.2 Hz, 1H), 3.79 (s, 3H), 3.77−3.55 (m, 2H), 3.47−3.37 (m, 1H), 3.24 (dddd, J = 14.4, 9.7, 7.8, 5.5 Hz, 1H), 2.85−2.76 (m, 1H), 2.29 (ddd, J = 8.3, 6.5, 4.9 Hz, 1H), 2.16−1.92 (m, 3H), 1.90−1.75 (m, 2H), 1.72−1.63 (m, 1H), 1.60−1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 159.5, 142.4, 142.3, 135.1, 135.1, 129.2, 121.3, 117.4, 117.4, 114.9, 114.8, 111.8, 111.7, 99.1, 98.4, 73.6, 73.5, 65.8, 65.5, 62.3, 61.9, 55.0, 48.2, 48.1, 39.4, 39.3, 32.2, 32.1, 30.6, 30.5, 25.3, 25.3, 19.6, 19.3; HRMS (ESI) Calcd. for $C_{19}H_{32}NO_4$ $[M + NH_4]^+$ 338.2326, found 338.2317.

Synthesis of Azide 11. To a solution of *syn*-alcohol **6** (950 mg, 3 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added Et_3N (0.75 mL, 5.4 mmol) and mesyl chloride (0.35 mL, 4.5 mmol). The mixture was stirred for 1 h at room temperature and quenched with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude product as oil, which was used immediately without further purification. The crude product was dissolved in anhydrous DMF (10 mL) and sodium azide (453 mg, 6.6 mmol) was added. The mixture was stirred at 80 °C for 12 h before quenching with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 40:1) gave azide **11** (875 mg, 86% yield for two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 1H), 6.88−6.77 (m, 3H), 5.93−5.73 (m, 1H), 5.17−5.13 (m, 2H), 4.45 (dt, J = 45.6, 3.6 Hz, 1H), 3.81 (s, 3H), 3.76−3.51 (m, 3H), 3.48−3.37 (m, 1H), δ 3.31−3.11 (m, 1H)., 2.99−2.87 (m, 1H), 2.37−2.25 (m, 1H), 2.24−2.14 (m, 1H), 2.12−1.96 (m, 2H), 1.85−1.77 (m, 1H), 1.72−1.62 (m, 1H), 1.60−1.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 159.4, 141.4, 134.0, 129.2, 129.1, 121.4, 118.2, 114.9, 114.9, 112.0, 112.0, 99.2, 98.5, 66.3, 66.2, 65.2, 65.2, 62.4, 61.9, 55.1, 46.3, 46.0, 37.0, 36.9, 32.8, 32.7, 30.6, 30.6, 25.3, 19.6, 19.4; HRMS (ESI) Calcd. for $C_{19}H_{28}N_3O_3$ $[M + H]^+$ 346.2125, found 346.2122.

Synthesis of *anti*-Sulfonamide 5. To a solution of azide **11** (875 mg, 2.5 mmol) in dry THF (25 mL) was added $LiAlH_4$ (200 mg, 5 mmol) at 0 °C. After being stirred for 1 h at room temperature, the mixture was quenched with 15% NaOH solution at 0 °C and filtered through Celite. The filtration residue was washed with ethyl acetate (3 × 10 mL). Concentration in vacuo gave the crude product as oil, which was used immediately without further purification. The crude product was dissolved in dry CH_2Cl_2 (20 mL) at 0 °C, and then diisopropylethylamine (647 mg, 0.83 mL, 5 mmol) and 2-nitrobenzenesulfonyl chloride (1 g, 4.5 mmol) were added. The mixture was stirred at room temperature for 2 h and quenched with H_2O (15 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 2:1) gave *anti*-sulfonamide **5** (1.08 g, 76% yield for two steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 6.8 Hz, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.72−7.63 (m, 2H), 7.10 (t, J = 7.7 Hz, 1H), 6.71 (t, J = 7.4 Hz, 1H), 6.68−6.63 (m, 2H), 5.64−5.51 (m, 1H), 5.26 (dd, J = 11.9, 8.6 Hz, 1H), 4.96 (d, J = 17.1 Hz, 1H), 4.88 (dd, J = 9.8, 4.9 Hz, 1H), 4.41 (dd, J = 48.8, 3.6 Hz, 1H), 3.82−3.77 (m, 2H), 3.75 (s, 3H), 3.69−3.33 (m, 2H), 3.26−3.05 (m, 1H), 3.02−2.95 (m, 1H), 2.40−2.28 (m, 1H), 2.14−2.01 (m, 2H), 2.00−1.86 (m, 1H), 1.83−1.75 (m, 1H), 1.70−1.60 (m, 1H), 1.56−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 159.6, 159.5, 147.2, 141.0, 140.8, 135.2, 133.4, 133.4, 132.9, 132.8, 130.2, 130.1, 129.5, 129.4, 125.3, 120.9, 120.9, 118.5, 118.4, 114.4, 114.3, 112.4, 112.3, 99.0, 98.3, 65.1, 64.9, 62.3, 61.7, 59.1, 59.0, 55.0, 45.6, 45.6, 38.3, 31.9, 31.8, 30.6, 30.5, 25.3, 19.5, 19.2; HRMS (ESI) Calcd. for $C_{25}H_{33}N2O_7S$ $[M + H]^+$ 505.2003, found 505.1995.

Synthesis of Olefinic Amide 12. To a solution of *anti*-sulfonamide **5** (1.08 g, 2.15 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added diisopropylethylamine (556 mg, 0.71 mL, 4.3 mmol),

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acryloyl chloride (350 mg, 0.31 mL, 3.9 mmol) and DMAP (5 mg, 0.02 mmol); the mixture was stirred at room temperature for 6 h and quenched with H_2O (15 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 4:1) gave olefinic amide **12** (906 mg, 76% yield) as a thick brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.54 (m, 2H), 7.31 (s, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.83−6.64 (m, 4H), 6.31 (ddd, J = 16.4, 10.2, 2.8 Hz, 1H), 6.23−6.12 (m, 1H), 5.81 (tt, J = 24.5, 12.4 Hz, 1H), 5.58−5.46 (m, 1H), 5.07−5.00 (m, 1H), 4.38 (dd, J = 50.0, 3.8 Hz, 1H), 3.81−3.61 (m, 5H), 3.70 (s, 3H), 3.55−3.36 (m, 2H), 3.12−2.97 (m, 1H), 2.86 (t, J = 6.5 Hz, 2H), 2.30−2.18 (m, 1H), 1.92−1.75 (m, 2H), 1.70−1.59 (m, 1H), 1.56−1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 166.6, 159.7, 159.7, 148.1, 142.7, 135.3, 133.8, 133.1, 131.9, 130.1, 129.5, 124.5, 121.2, 117.8, 113.9, 113.8, 113.2, 113.2, 99.2, 98.4, 65.4, 65.2, 65.2, 62.3, 61.8, 55.0, 46.0, 45.9, 37.8, 34.1, 33.9, 30.6, 30.5, 25.3, 25.3, 19.5, 19.3; HRMS (ESI) Calcd. for $C_{28}H_{35}N_2O_8S$ $[M + H]^+$ 559.2109, found 559.2113.

Synthesis of Lactam 4. To a solution of the second generation Grubbs catalyst (40 mg, 0.05 mmol) in dry CH_2Cl_2 (90 mL) was added a solution of olefinic amide **12** (491 mg, 0.88 mmol) in dry CH_2Cl_2 (2 mL) under argon atmosphere. The mixture was refluxed for 12 h and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 2:1) gave lactam **4** (345 mg, 74% yield) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52−8.48 (m, 1H), 7.74−7.73 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 6.86−6.77 (m, 3H), 6.49−6.43 (m, 1H), 5.50−5.44 (m, 1H), 4.85 (dd, J = 7.4, 4.4 Hz, 1H), 4.52−4.35 (m, 1H), 3.80 (s, 3H), 3.79−3.69 (m, 1H), 3.68−3.47 (m, 1H), 3.45−3.30 (m, 2H), 3.27−3.09 (m, 2H), 2.62 (dd, J = 19.3, 6.2 Hz, 1H), 2.20 (dd, J = 13.2, 6.3 Hz, 2H), 1.85−1.75 (m, 1H), 1.70−1.62 (m, 1H), 1.57−1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ most of peaks double due to the presence of OTHP group) δ 162.3, 162.3, 159.9, 159.9, 147.9, 142.5, 140.8, 140.8, 135.8, 134.3, 132.7, 131.7, 129.6, 129.6, 124.3, 122.5, 122.5, 121.4, 121.3, 114.2, 114.1, 113.0, 112.9, 99.2, 98.2, 65.4, 64.9, 62.3, 61.7, 59.9, 59.9, 55.1, 48.7, 48.6, 31.5, 31.1, 30.6, 30.5, 27.3, 27.2, 25.3, 19.6, 19.2; HRMS (ESI) Calcd. for $C_{26}H_{31}N_2O_8S$ $[M + H]^+$ 531.1796, found 531.1790.

Following the typical procedure described for the preparation of **4**, lactams **13a**−**13h** were obtained from corresponding acetaldehyde in 7 steps.

13a: a pale yellow solid (233 mg, 29% yield); mp 191−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.55 (m, 1H), 7.80−7.75 (m, 3H), 7.24 (t, J = 7.9 Hz, 1H), 6.84−6.77 (m, 3H), 6.69−6.64 (m, 1H), 5.86 (dd, J = 9.9, 2.8 Hz, 1H), 4.91−4.82 (m, 1H), 3.82 (s, 3H), 3.13 (ddd, J = 23.7, 13.3, 7.3 Hz, 2H), 2.88 (ddd, J = 9.3, 6.7, 3.2 Hz, 1H), 2.42 (dd, J = 18.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 159.8, 148.0, 142.7, 138.3, 135.1, 134.5, 132.6, 131.9, 129.7, 124.3, 123.6, 121.6, 115.0, 112.4, 56.6, 55.2, 40.6, 26.2; HRMS (ESI) Calcd. for $C_{19}H_{22}N_3O_6S$ $[M + NH_4]^+$ 420.1224, found 420.1217.

13b: a pale yellow solid (250 mg, 31% yield); mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.53 (m, 1H), 7.80−7.74 (m, 3H), 7.15 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.67 (t, J = 8 Hz, 1H), 5.87 (dd, J = 9.9, 2.9 Hz, 1H), 4.85−4.77 (m, 1H), 3.80 (s, 3H), 3.09 (ddd, J = 23.9, 13.5, 7.3 Hz, 2H), 2.92−2.83 (m, 1H), 2.41 (dd, J = 18.9, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 158.6, 148.0, 142.8, 135.1, 134.5, 132.6, 131.8, 130.3, 128.7, 124.3, 123.7, 114.1, 56.9, 55.2, 39.7, 26.1; HRMS (ESI) Calcd. for $C_{19}H_{22}N_3O_6S$ $[M + NH_4]^+$ 420.1224, found 420.1213.

13c: a pale yellow solid (216 mg, 26% yield as a 1:1 diastereomeric mixture); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66−8.60 (m, 1H), 8.53−8.48 (m, 1H), 7.81−7.72 (m, 6H), 7.22 (dd, J = 15.3, 7.6 Hz, 2H), 6.93−6.76 (m, 6H), 6.69 (ddd, J = 9.7, 6.2, 1.2 Hz, 1H), 6.36 (dd, J = 9.9, 1.6 Hz, 1H), 5.82 (d, J = 9.8 Hz, 1H), 5.62 (dd, J = 9.8, 3.1 Hz, 1H), 4.93−4.84 (m, 1H), 4.65 (dd, J = 10.7, 3.2 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.59−3.49 (m, 1H), 3.30 (dd, J = 13.4, 3.4 Hz, 1H), 3.28−3.02 (m, 2H), 2.99 (dd, J = 13.4, 10.8 Hz, 1H), 2.61 (p, J = 6.9 Hz, 1H), 1.29 (d, J = 7.7 Hz, 3H), 1.22 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 162.0, 159.8, 159.6, 148.9, 148.4, 148.0, 147.8, 138.5, 138.3, 135.3, 135.1, 134.7, 134.4, 132.7, 132.5, 131.7, 129.7, 129.3, 124.2, 124.1, 122.3, 122.2, 122.0, 121.5, 115.3, 114.9, 112.6, 112.2, 62.4, 61.8, 55.1, 41.0, 36.1, 33.6, 32.1, 19.1, 16.2; HRMS (ESI) Calcd. for $C_{20}H_{24}N_3O_6S$ $[M + NH_4]^+$ 434.1380, found 434.1371.

13d: a pale yellow solid (251 mg, 29% yield); mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.52 (m, 1H), 7.80−7.74 (m, 3H), 6.80 (t, J = 7.9 Hz, 1H), 6.72 (dd, J = 8.1, 1.8 Hz, 1H), 6.63 (t, J = 7.9 Hz, 1H), 5.81 (dd, J = 9.9, 2.8 Hz, 1H), 4.87−4.78 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.07 (qd, J = 13.5, 7.1 Hz, 2H), 2.94−2.83 (m, 1H), 2.42 (dd, J = 18.9, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 149.0, 148.0, 147.9, 142.7, 135.1, 134.5, 132.5, 131.8, 129.2, 124.3, 123.5, 121.3, 112.2, 111.1, 56.6, 55.8, 55.7, 40.4, 26.3; HRMS (ESI) Calcd. for $C_{20}H_{24}N_3O_7S$ $[M + NH_4]^+$ 450.1329, found 450.1329.

13e: a pale yellow solid (285 mg, 33% yield); mp 177−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61−8.55 (m, 1H), 7.81−7.75 (m, 3H), 6.66 (t, J = 7.9 Hz, 1H), 6.42−6.35 (m, 3H), 5.85 (dd, J = 9.9, 2.8 Hz, 1H), 4.88 (ddd, J = 6.9, 6.2, 4.9 Hz, 1H), 3.81 (s, 6H), 3.09 (ddd, J = 23.5, 13.3, 7.3 Hz, 2H), 2.95−2.85 (m, 1H), 2.44 (dd, J = 18.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 161.0, 148.0, 142.7, 139.0, 135.2, 134.6, 132.6, 131.9, 124.4, 123.6, 107.3, 98.8, 56.5, 55.3, 40.9, 26.3; HRMS (ESI) Calcd. for $C_{20}H_{24}N_3O_7S$ $[M + NH_4]^+$ 450.1329, found 450.1320.

13f: a pale yellow solid (257 mg, 30% yield); mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.51 (m, 1H), 7.80−7.71 (m, 3H), 6.81−6.79 (m, 3H), 6.67 (t, J = 7.9 Hz, 1H), 5.84 (dd, J = 9.9, 2.8 Hz, 1H), 4.98−4.87 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.16 (ddd, J = 18.0, 13.1, 7.3 Hz, 2H), 2.95−2.82 (m, 1H), 2.40 (dd, J = 18.6, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 153.5, 152.0, 148.0, 143.4, 135.2, 134.4, 132.7, 131.8, 126.2, 124.3, 123.1, 117.1, 112.8, 111.4, 56.0, 55.7, 55.7, 34.9, 27.0; HRMS (ESI) Calcd. for $C_{20}H_{24}N_3O_7S$ $[M + NH_4]^+$ 450.1329, found 450.1316.

13g: a pale yellow solid (143 mg, 16% yield); mp 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.52 (m, 1H), 7.79−7.73 (m, 3H), 6.36 (s, 3H), 5.62 (d, J = 0.8 Hz, 1H), 4.82 (ddd, J = 10.3, 6.2, 4.3 Hz, 1H), 3.80 (s, 6H), 3.05 (ddd, J = 23.5, 13.2, 7.2 Hz, 2H), 2.90 (dd, J = 18.2, 6.8 Hz, 1H), 2.24 (d, J = 18.2 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 161.0, 155.0, 147.9, 139.1, 135.1, 134.4, 132.7, 131.8, 124.3, 118.9, 107.3, 98.9, 56.2, 55.3, 41.1, 31.4, 23.3; HRMS (ESI) Calcd. for $C_{21}H_{26}N_3O_7S$ $[M + NH_4]^+$ 464.1486, found 464.1480.

13h: a pale yellow solid (314 mg, 34% yield); mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.50 (m, 1H), 7.81−7.74 (m, 3H), 6.63 (t, J = 7.9 Hz, 1H), 6.43 (s, 2H), 5.79 (dd, J = 9.9, 2.7 Hz, 1H), 4.85 (t, J = 10.3 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 3.12−2.99 (m, 2H), 2.97−2.87 (m, 1H), 2.43 (dd, J = 18.9, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 153.3, 147.9, 142.5, 136.9, 135.1, 134.6, 132.4, 132.4, 131.9, 124.3, 123.4, 106.1, 60.7, 56.5, 56.1, 41.2, 26.6; HRMS (ESI) Calcd. for $C_{21}H_{26}N_3O_8S$ $[M + NH_4]^+$ 480.1435, found 480.1425.

Synthesis of Bridged Lactam 14a. To a solution of lactam **13a** (40 mg, 0.1 mmol) in dry $ClCH_2CH_2Cl$ (1 mL) was added triflic acid (18 μL, 0.2 mmol, 2.0 equiv) at room temperature under Ar. The mixture was stirred at 50 °C for 8 h and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 1:1) gave bridged lactam **14a** (36 mg, 90% yield) as a white solid: mp 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 5.8, 3.0 Hz, 1H), 7.78−7.72 (m, 3H), 7.03 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.3 Hz, 1H), 6.68 (d, J = 1.9 Hz, 1H), 4.96 (s, 1H), 3.79 (s, 3H), 3.24 (s, 3H), 2.74 (dd, J = 17.9, 5.4 Hz, 1H), 2.56 (d, J = 17.9 Hz, 1H), 2.42 (d, J = 13.3 Hz, 1H), 2.27 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 158.7, 147.9, 135.0, 134.4, 133.1, 132.3, 131.8, 130.0, 129.6, 124.2, 113.9, 55.2, 52.5, 43.4, 37.4, 30.5, 28.7; HRMS (ESI) Calcd. for $C_{19}H_{19}N_2O_6S$ $[M + H]^+$ 403.0958, found 403.0950.

Following the typical procedure described for the preparation of **14a**, lactams **14c**−**14e**, **14g**, **14h** and **3** were obtained in one step.

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14c: a white solid (34 mg, 84% yield as a 2:1 diastereomeric mixture); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48−8.39 (m, 1H), 7.79−7.71 (m, 3H), 7.00 (dd, J = 8.4, 3.2 Hz, 1H), 6.81−6.75 (m, 1H), 6.69 (d, J = 2.8 Hz, 1H), 4.74 (d, J = 1.8 Hz, 0.65H), 4.65 (s, 0.35H), 3.79 (s, 3H), 3.39−3.12 (m, 2H), 2.99−2.91 (m, 1H), 2.89−2.71 (m, 1H), 2.60−2.43 (m, 2H), 1.36 (d, J = 7.0 Hz, 2H), 1.16 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 158.7, 158.6, 148.2, 147.8, 135.5, 135.1, 134.5, 134.4, 133.2, 132.0, 131.8, 131.7, 131.6, 131.4, 130.6, 129.4, 128.4, 124.2, 114.2, 113.8, 113.7, 57.7, 56.5, 55.1, 43.8, 38.5, 38.3, 36.5, 36.2, 32.6, 32.4, 32.2, 29.6, 16.4, 16.3; HRMS (ESI) Calcd. for $C_{20}H_{21}N_2O_6S$ $[M + H]^+$ 417.1115, found 417.1109.

14d: a white solid (38 mg, 89% yield); mp 199−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 7.78−7.73 (m, 3H), 6.63 (s, 1H), 6.58 (s, 1H), 4.97 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.19 (d, J = 2.7 Hz, 3H), 2.74 (dd, J = 17.8, 5.4 Hz, 1H), 2.60 (d, J = 17.9 Hz, 1H), 2.41 (dd, J = 13.4, 2.1 Hz, 1H), 2.33−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 148.5, 148.1, 147.9, 135.1, 134.4, 133.2, 131.8, 129.7, 124.2, 123.0, 112.1, 110.9, 55.9, 55.8, 52.6, 43.1, 36.8, 30.9, 28.6; HRMS (ESI) Calcd. for $C_{20}H_{21}N_2O_7S$ $[M + H]^+$ 433.1064, found 433.1058.

14e: a white solid (37 mg, 88% yield); mp 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46−8.35 (m, 1H), 7.78−7.72 (m, 3H), 6.33 (s, 1H), 6.28 (s, 1H), 4.93 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.49 (s, 1H), 3.21 (s, 2H), 2.62 (d, J = 3.7 Hz, 2H), 2.38 (d, J = 11.9 Hz, 1H), 2.19 (d, J = 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 159.6, 157.5, 148.0, 135.1, 134.3, 133.4, 133.0, 131.8, 124.2, 119.0, 104.5, 97.1, 55.3, 52.7, 40.9, 37.5, 28.8, 24.4; HRMS (ESI) Calcd. for $C_{20}H_{21}N_2O_7S$ $[M + H]^+$ 433.1064, found 433.1060.

14g: a white solid (35 mg, 78% yield); mp 242−243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39−8.34 (m, 1H), 7.77−7.71 (m, 3H), 6.33 (d, J = 2.3 Hz, 1H), 6.26 (d, J = 2.2 Hz, 1H), 4.84 (t, J = 3.0 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.25 (dd, J = 17.7, 3.5 Hz, 1H), 3.17 (d, J = 17.6 Hz, 1H), 3.00 (d, J = 17.7 Hz, 1H), 2.27 (d, J = 17.7 Hz, 1H), 2.15 (s, 2H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 159.4, 159.4, 148.0, 135.0, 134.2, 133.9, 133.5, 131.8, 124.1, 121.3, 105.0, 98.2, 55.2, 55.0, 53.0, 46.5, 39.8, 38.7, 32.1, 27.1; HRMS (ESI) Calcd. for $C_{21}H_{23}N_2O_7S$ $[M + H]^+$ 447.1220, found 447.1214.

14h: a white solid (37 mg, 81% yield); mp 217−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43−8.37 (m, 1H), 7.79−7.73 (m, 3H), 6.43 (s, 1H), 4.92 (s, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.47 (s, 1H), 3.18 (s, 2H), 2.68 (dd, J = 18.1, 5.3 Hz, 1H), 2.58 (d, J = 18.1 Hz, 1H), 2.38 (d, J = 13.0 Hz, 1H), 2.19 (dd, J = 11.5, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 152.9, 150.6, 147.9, 140.4, 135.0, 134.4, 133.2, 131.8, 126.6, 124.2, 123.5, 107.6, 60.8, 60.6, 55.8, 52.6, 41.7, 37.1, 28.6, 25.0; HRMS (ESI) Calcd. for $C_{21}H_{23}N_2O_8S$ $[M + H]^+$ 463.1170, found 463.1170.

Bridged Lactam 3. 182 mg of **3** was obtained from lactam **4** (305 mg, 0.57 mmol) in 71% yield as a white solid: mp 198−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45−8.39 (m, 1H), 7.81−7.73 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 6.76 (dd, J = 8.3, 2.2 Hz, 1H), 4.98 (s, 1H), 3.99 (t, J = 6.3 Hz, 2H), 3.80 (s, 3H), 3.32−3.29 (m, 1H), 3.25 (s, 1H), 2.73 (dd, J = 17.8, 5.5 Hz, 1H), 2.67 (ddd, J = 13.4, 4.5, 2.3 Hz, 1H), 2.53 (d, J = 17.8 Hz, 1H), 2.41−2.36 (m, 3H), 1.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.0, 147.8, 136.6, 136.3, 134.5, 132.8, 131.8, 130.9, 129.5, 124.4, 113.0, 112.5, 61.3, 55.9, 55.3, 44.1, 41.4, 32.9, 31.6, 29.6; HRMS (ESI) Calcd. for $C_{21}H_{23}N_2O_7S$ $[M + H]^+$ 447.1220, found 447.1215.

Synthesis of Alcohol Lactam 15. To a solution of bridged lactam **3** (152 mg, 0.34 mmol) in DMF (2 mL) were added anhydrous K_2CO_3 (150 mg, 1.09 mmol) and PhSH (80 μL, 0.78 mmol) at room temperature. After stirring for 1 h at 40 °C, the reaction was quenched with H_2O (1 mL), and the mixture was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/CH_3OH, 20:1) gave amide **15** (58 mg, 66% yield) as a white solid: mp 192−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.79−6.73 (m, 2H), 4.16 (d, J = 3.5 Hz, 1H), 3.98−3.93 (m, 1H), 3.78 (s, 3H), 3.80−3.74 (m, 4H), 3.18 (s, 1H), 2.91 (dt, J = 11.3, 3.8 Hz, 1H), 2.69 (dd, J = 17.6, 5.5 Hz, 1H), 2.38 (d, J = 17.6 Hz, 1H), 2.28−2.23 (m, 1H), 2.16 (ddd, J = 12.7, 4.5, 2.0 Hz, 1H), 2.05 (d, J = 12.8 Hz, 1H), 1.82−1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 158.6, 137.4, 131.6, 129.9, 112.8, 112.3, 61.1, 55.2, 47.7, 43.7, 40.7, 33.3, 31.2, 28.6; HRMS (ESI) Calcd. for $C_{15}H_{20}NO_3$ $[M + H]^+$ 262.1438, found 262.1435.

Synthesis of Mesylate 16. To a solution of alcohol lactam **15** (33 mg, 0.13 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C were added Et_3N (36 μL, 0.26 mmol), mesyl chloride (18 μL, 0.23 mmol) and DMAP (1 mg). The mixture was stirred at room temperature for 1 h and quenched with H_2O (2 mL). The mixture was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/CH_3OH, 20:1) gave mesylate **16** (42 mg, 98% yield) as a white solid: mp 171−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.3 Hz, 1H), 6.81−6.74 (m, 3H), 4.44 (d, J = 4.5 Hz, 2H), 3.97 (s, 1H), 3.80 (s, 2H), 3.23 (s, 1H), 3.08 (s, 3H), 3.08 −3.05 (m, 4H), 2.72 (dd, J = 17.5, 5.4 Hz, 1H), 2.50−2.47 (m, 1H), 2.41 (d, J = 17.6 Hz, 1H), 2.23 (d, J = 10.5 Hz, 1H), 2.10 (d, J = 12.5 Hz, 1H), 2.04−1.94 (m, 1H), 1.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 135.8, 131.6, 130.2, 112.7, 112.5, 68.0, 55.3, 47.5, 41.6, 37.5, 31.2, 30.0, 28.8; HRMS (ESI) Calcd. for $C_{16}H_{22}NO_5S$ $[M + H]^+$ 340.1213, found 340.1209.

Synthesis of Tetracyclic Lactam 2. To a solution of mesylate **16** (42 mg, 0.13 mmol) in anhydrous DMF (2 mL) at 0 °C was added NaH (8 mg of 60% oil dispersion, 0.2 mmol). After stirring for 12 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), and the mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 1:1) gave lactam **2** (23 mg, 77% yield) as a white solid: mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.4 Hz, 1H), 6.69 (dd, J = 8.4, 2.3 Hz, 1H), 6.66 (s, 1H), 4.23−4.16 (m, 1H), 3.77 (s, 4H), 3.30 (dd, J = 7.5, 4.5 Hz, 1H), 3.16 (s, 1H), 2.98 (td, J = 11.1, 5.5 Hz, 1H), 2.66 (dd, J = 16.6, 4.1 Hz, 1H), 2.48−2.37 (m, 2H), 2.35−2.29 (m, 1H), 2.24 (d, J = 13.2 Hz, 1H), 2.16−2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 158.9, 139.1, 130.3, 130.1, 114.5, 112.4, 57.1, 55.2, 43.1, 41.7, 40.3, 32.4, 31.8, 26.5; HRMS (ESI) Calcd. for $C_{15}H_{18}NO_2$ $[M + H]^+$ 244.1332, found 244.1325.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and crystallographic information in CIF format for compounds **2** and **14g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For a comprehensive review, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936−962.

(2) For recent isolations see: (a) Li, C.-S; Di, Y.-T.; Zhang, Q.; Zhang, Y.; Tan, C.-J.; Hao, X.-J. *Helv. Chim. Acta* **2009**, *92*, 653−659. (b) Zhang, Y.; Di, Y.; He, H.; Li, S.; Lu, Y.; Gong, N.; Hao, X. *Eur. J. Org. Chem.* **2011**, *74*, 4103−4107. (c) Zhang, C.-R.; Fan, C.-Q.; Dong, S.-H.; Liu, H.-B.; Zhou, W.-B.; Wu, Y.; Yue, J.-M. *Org. Lett.* **2011**, *13*,

2440−2443. (d) Yang, T.-Q.; Di, Y.-T.; He, H.-P.; Zhang, Q.; Zhang, Y.; Hao, X.-J. *Helv. Chim. Acta* **2011**, *94*, 397−403. (e) Cao, M.; Zhang, Y.; He, H.; Li, S.; Huang, S.; Chen, D.; Tang, G.; Li, S.; Di, Y.; Hao, X. *J. Nat. Prod.* **2012**, *75*, 1076−1082.

(3) For recent synthetic approaches to daphniphyllum alkaloids, see: (a) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575−2585. (b) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120−1130. (c) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461−5464. (d) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593−605. (e) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833−1836. (f) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658−5661. (g) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267−1269. (h) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812−1815. (i) Bélanger, G.; Boudreault, J.; Lévesque, F. *Org. Lett.* **2011**, *13*, 6204−6207. (j) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360−2366. (k) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501−11505. (l) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684−1687. (m) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. *J. Org. Chem.* **2012**, *77*, 6307−6313.

(4) Zhang, Q.; Di, Y.-T.; Li, C.-S.; Fang, X.; Tan, C.-J.; Zhang, Z.; Zhang, Y.; He, H.-P.; Li, S.-L.; Hao, X.-J. *Org. Lett.* **2009**, *11*, 2357−2359.

(5) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1−36.

(6) Knorr, L.; Horlein, H. *Chem. Ber.* **1907**, *40*, 4883−4889.

(7) Hudlicky, T.; Rinner, U. Synthesis of Morphine Alkaloids and Derivatives. In *Alkaloid Synthesis*; Knölker, H. J., Ed.; Springer-Verlag: Berlin, 2012; Topics in Current Chemistry Series 309, pp 33−66.

(8) (a) Rice, K. C.; In *The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H.; Eds.; Springer-Verlag: Berlin, 1985; pp 191−203. (b) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R. *Stud. Nat. Prod. Chem.* **1995**, *18*, 43−154. (c) Novak, B. H.; Hudlicky, T.; Reed, J. W.; Mulzer, J.; Trauner, D. *Curr. Org. Chem.* **2000**, *4*, 343−362. (d) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159−1168.

(9) (a) Archer, S.; Albertson, N. F.; Harris, L. S.; Pierson, A. K.; Bird, J. G. *J. Med. Chem.* **1964**, *7*, 123−127. (b) Tullar, B. F.; Harris, L. S.; Perry, R. L.; Pierson, A. K.; Soria, A. E.; Wetterau, W. F.; Albertson, N. F. *J. Med. Chem.* **1967**, *10*, 383−386. (c) Rice, K. C.; Jacobson, A. E. *J. Med. Chem.* **1976**, *19*, 430−432.

(10) For selected examples, see: (a) Grauert, M.; Bechtel, W. D.; Weiser, T.; Stransky, W.; Nar, H.; Carter, A. J. *J. Med. Chem.* **2002**, *45*, 3755−3764. (b) Wentland, M. P.; Ye, Y.; Cioffi, C. L.; L, R.; Zhou, Q.; Xu, G.; Duan, W.; Dehnhardt, C. M.; Sun, X.; Cohen, D. L.; Bidlack, J. M. *J. Med. Chem.* **2003**, *46*, 838−849. (c) Zhang, A.; Xiong, W.; Bidlack, J. M.; Hilbert, J. E; Knapp, B. I.; Wentland, M. P.; Neumeyer, J. L. *J. Med. Chem.* **2004**, *47*, 165−174. (d) Wentland, M. P.; VanAlstine, M.; Kucejko, R.; Luo, R.; Cohen, D. L.; Parkhill, A. L.; Bidlack, J. M. *J. Med. Chem.* **2006**, *49*, 5635−5639.

(11) Sun, Y.; Yu, B.; Wang, X.; Tang, S.; She, X; Pan, X. *J. Org. Chem.* **2010**, *75*, 4224−4229.

(12) (a) Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438−1447. (b) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573−576.

(13) (a) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910−912. (b) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087−3091.

(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(15) For Friedel-Crafts alkylation with α,β-unsaturated amides using Lewis acid, see: Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2004**, *45*, 3547−3549.

(16) CCDC number: 891316; see the Supporting Information.

(17) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

(18) CCDC number: 891317; see the Supporting Information.