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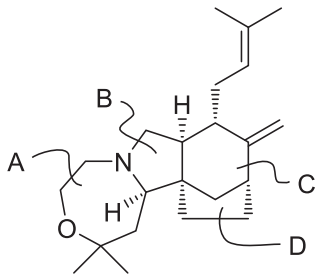
SYNTHETIC STUDIES TOWARD CONCAVINE: SYNTHESIS OF THE BCD RING SYSTEM

Yosuke Komori, Akitoshi Kozen, and Masahiro Toyota*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan, E-mail: toyota@c.s.osakafu-u.ac.jp

Abstract – The BCD ring system of concavine is realized stereoselectively using palladium-catalyzed cycloalkenylation to synthesize the CD ring and an intramolecular aza-Michael reaction to append the third ring.

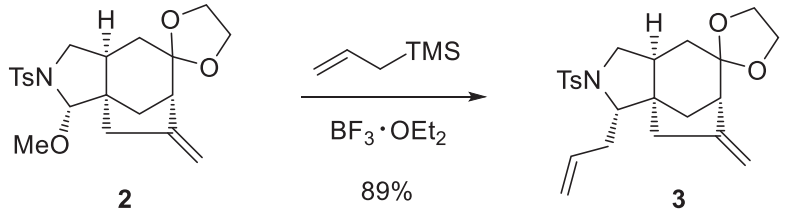
Concavine (**1**), a diterpene alkaloid, was isolated from cultures of *Clitocybe concave* in 2005 by Nasini and coworkers.[1] **1** contains an octahydropyrrolo[1,2-*d*][1,4]oxazepine unit (AB ring part), a bicyclo[3.2.1]octane system (CD ring part), and five stereocenters, four of which are consecutive (Figure 1). Although weak, **1** shows antibacterial activities against on *Bacillus cereus* and *B. subtilis*.[1]



concavine (**1**)

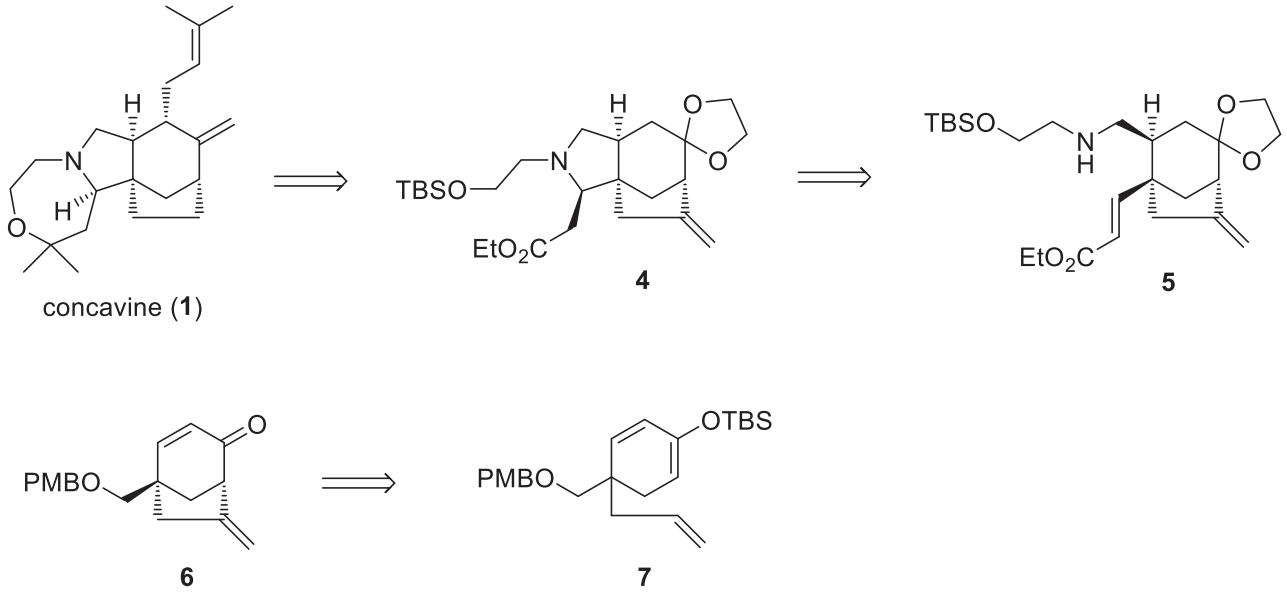
Figure 1

In an effort to demonstrate the utility of our palladium-catalyzed cycloalkenylation,[2] we applied this catalytic cyclization process to the synthesis of **1**. Unfortunately, attempts to stereoselectively introduce various carbon units on amine **2** using a variety of established procedures were unsuccessful; for instance, undesired stereoisomer **3** was produced as a single stereoisomer (Scheme 1).[3]



Scheme 1

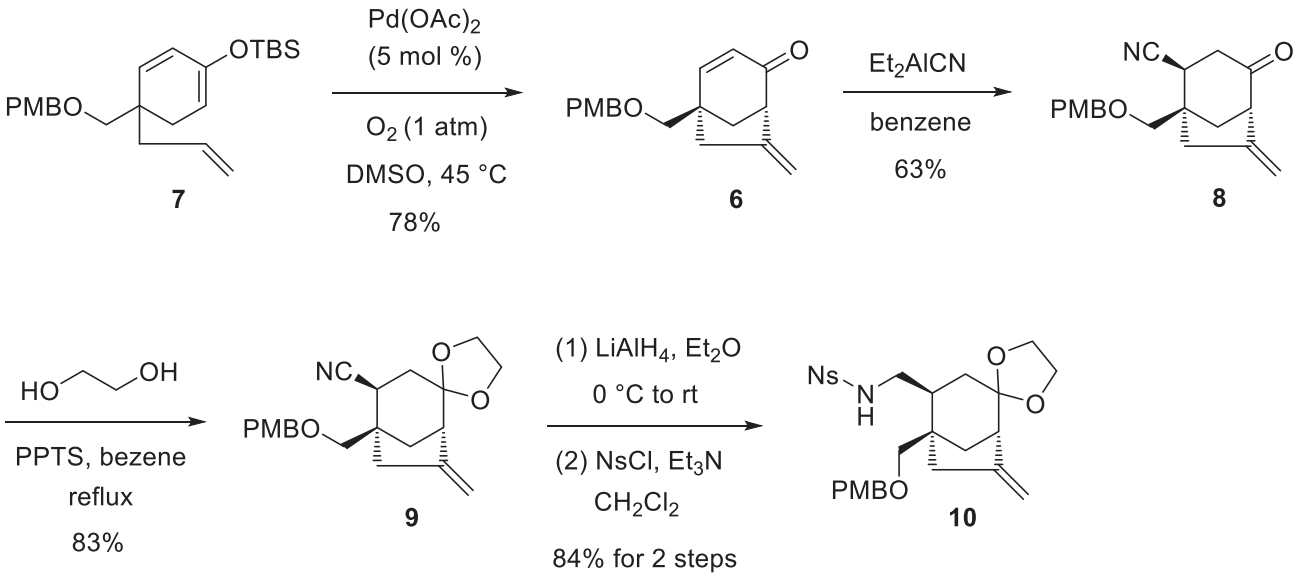
To obtain a potential intermediate of **1**, we focused on an intramolecular aza-Michael reaction[4] as the key step. Scheme 2 shows the retrosynthesis. **1** could be synthesized through a series of functional group interconversions of tricyclic intermediate **4**, which could be prepared from amine **5** by an intramolecular aza-Michael reaction. Requisite substrate **5** could be provided using the structural characteristics of bicyclo[3.2.1]octane **6**, which could be obtained from cross-conjugated silyl enol ether **7** by means of a palladium-catalyzed cycloalkenylation.[2]



Scheme 2

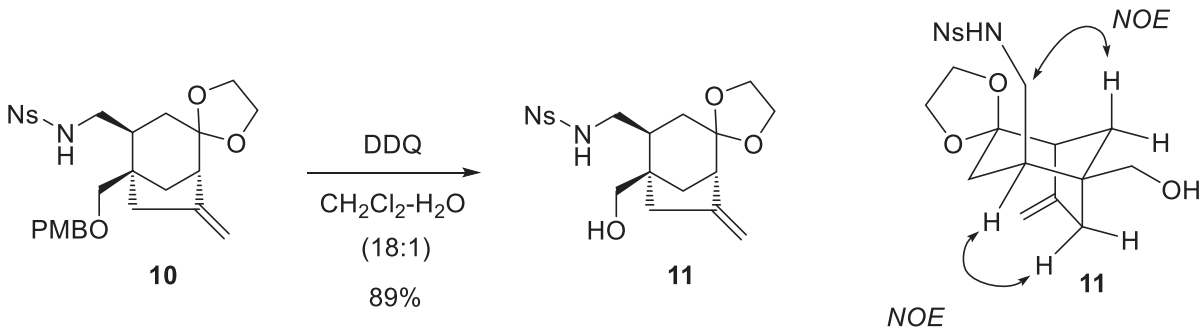
Bicyclo[3.2.1]octane **6**, the CD ring part of **1**, was efficiently constructed in 78% yield using a palladium-catalyzed cycloalkenylation of **7**[5] in the presence of 5 mol % of $Pd(OAc)_2$ under one atmosphere of oxygen.[2] To introduce the methylamine moiety on enone **6** stereoselectively, the Nagata reagent was adopted.[6] Hydrocyanation proceeded from the convex face of bicyclo[3.2.1]octane **6** to give desired cyanide **8** in 63% yield as a single stereoisomer. After protection of the carbonyl moiety of **8**

(83%), the cyanide moiety of **9** was reduced followed by protection of the corresponding primary amine with 2-nitrobenzenesulfonyl chloride (NsCl)[7] and Et_3N furnished sulfonamide **10** in 84% yield over two steps (Scheme 3).



Scheme 3

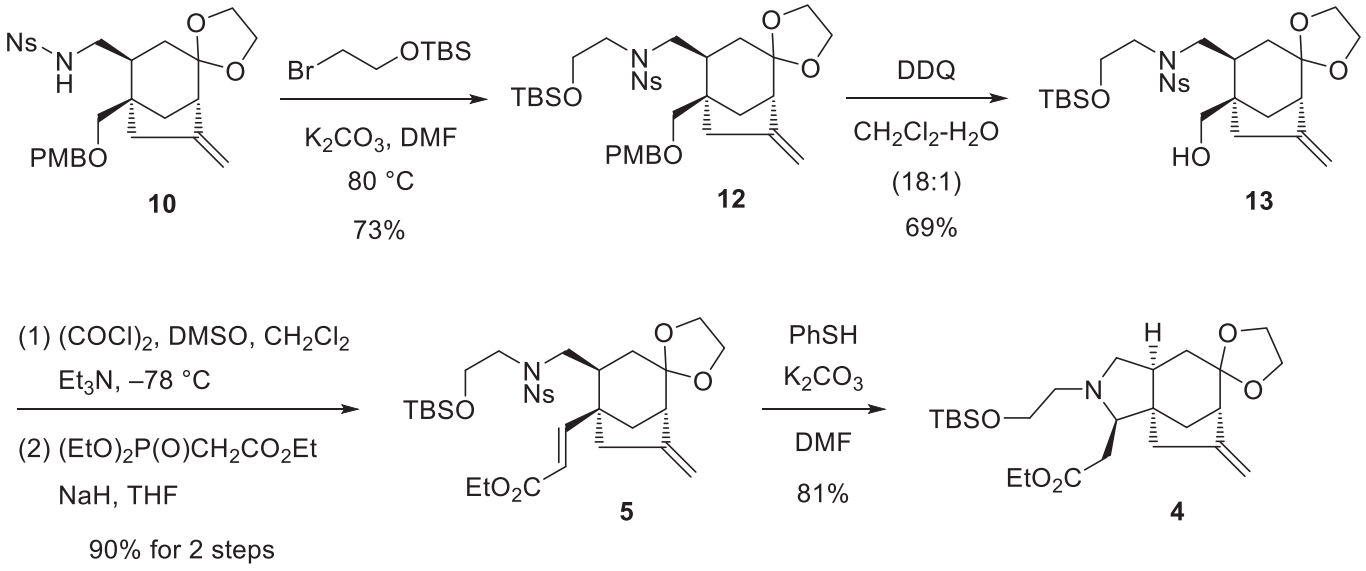
To determine the stereochemistry of **10**, the *p*-methoxybenzyl (PMB) group of the primary alcohol of **10** was removed with DDQ[8] to give alcohol **11** in 89% yield (Scheme 4). The relative stereochemistry of **11** was established by employing NOESY correlations (Figure 2).



Scheme 4 **Figure 2**

N-Alkylation of sulfonamide **10** with TBS-protected 2-bromoethanol afforded TBS ether **12** (73%), which was subjected to deprotection with aqueous DDQ to afford alcohol **13** in 69% yield. Swern

oxidation[9] of the primary alcohol of **13** followed by Emmons olefination[10] of the corresponding aldehyde provided requisite substrate **5** for the second key reaction in the present synthesis. An intramolecular aza-Michael reaction of **5** was performed with PhSH and K_2CO_3, leading to desired tricyclic compound **4** as a 6:1 mixture of diastereoisomers. Each diastereoisomer was easily separated by silica gel flash column chromatography. The relative stereochemistry of major diastereoisomer **4** was determined by NOE experiment (Figure 3).



Scheme 5

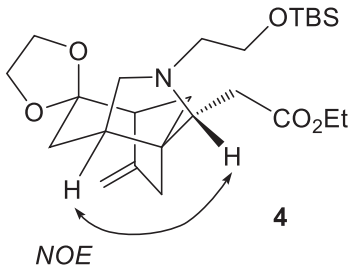


Figure 3

The stereochemical outcome observed in the intramolecular aza-Michael reaction of **5** is attributed to the interaction of the olefinic hydrogen with the equatorial hydrogen in the conformation **B** (Figure 4). This interaction is absent in conformation **A**, producing desired cyclization product **4**.

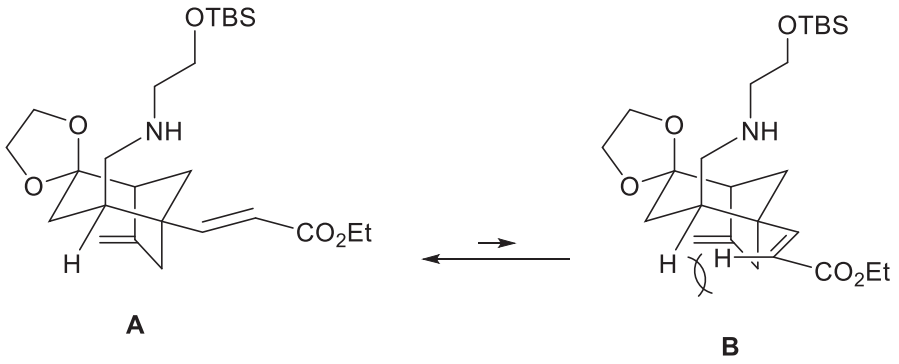


Figure 4

In conclusion, tricyclic compound **4** is available in ten steps from cross-conjugated silyl enol ether **7**. The conversion of **4** into **1** requires the construction of a 1,4-oxazepane ring. Schemes to accomplish this goal are currently under investigation.

EXPERIMENTAL

Unless otherwise noted, all reactions were performed in an oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous THF, CH_2Cl_2 and Et_2O were purchased from Kanto Chemical Co., Inc. Et_3N was distilled from CaH_2 prior to use. DMSO and DMF were distilled from CaH_2 under reduced pressure. Benzene was distilled from P_2O_5. Oxalyl chloride was distilled and immediately used. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried by being stirred over anhydrous $MgSO_4$ or Na_2SO_4, filtered through Celite, and concentrated under reduced pressure with the aid of a rotary evaporator. Flash column chromatography was carried out using Cica 60 (spherical, neutral) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using an ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH) or ammonium molybdate (in 10% H_2SO_4). IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recored on Varian 400 MR (400 MHz) spectrometer with $CHCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometers with $CHCl_3$ (δ 77.16) as an internal standard. Mass spectra were recorded on JEOL JMS-AX 700 spectrometers.

(1*S,5*S**)-5-(4-Methoxybenzyloxymethyl)-7-methylene-bicyclo[3.2.1]oct-3-en-2-one (6).**[5] To a solution of **7** (204.6 mg, 0.511mmol) in DMSO (5.1 mL) was added $Pd(OAc)_2$ (5.9 mg, 0.026 mmol) at rt. The resulting mixture was stirred under one atmosphere of oxygen at 45 °C for 41.5 h. The solution was diluted with EtOAc and filtered through Celite. Water (15 mL) was added and the layers were separated. The aqueous layer was extracted three times with hexane-EtOAc (1:1 v/v). The combined organic layers

were washed with brine and dried over $MgSO_4$. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (4:1 v/v) as an eluent afforded **6** (113.7 mg, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (ddd, *J* = 11.2, 4.8 and 2.0 Hz, 1H), 2.13 (dd, *J* = 10.8 and 2.4 Hz, 1H), 2.12 (d, *J* = 16.0 Hz, 1H), 2.46 (ddd, *J* = 16.0, 2.4 and 2.4 Hz, 1H), 3.46 (d, *J* = 4.8 Hz, 1H), 3.50 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 4.52 (s, 2H), 5.05 (s, 1H), 5.28 (s, 1H), 5.83 (dd, *J* = 9.6 and 1.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 9.6 and 1.6 Hz, 1H) and 7.27 (d, *J* = 8.0 Hz, 2H).

(1*S,2*S**,5*S**)-1-(4-Methoxybenzyloxymethyl)-6-methylene-4-oxobicyclo[3.2.1]octane-2-carbonitrile (8).** To a stirred solution of enone **6** (377.8 mg, 1.33mmol) in benzene (10 mL) was added 1 M solution of Et_2AlCN in toluene (2.0 mL, 2.0 mmol) at rt. After 2 h, the mixture was poured into 15% NaOH solution, the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (2.5:1 v/v) afforded **8** (261.8 mg, 63%) as a colorless oil. IR (neat) 2238.0 and 1722.1 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89 (ddd, *J* = 12.4, 5.2 and 2.8 Hz, 1H), 2.10 (d, *J* = 12.4 Hz, 1H), 2.52 (d, *J* = 16.4 Hz, 1H), 2.64 (s, 2H), 2.77 (dd, *J* = 16.8 and 8.8 Hz, 1H), 3.34 (d, *J* = 5.6 Hz, 1H), 3.40-3.46 (m, 2H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.99 (s, 1H), 5.10 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 2H) and 7.26 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.5, 36.7, 36.8, 40.0, 46.5, 55.4, 59.0, 73.5, 74.4, 110.6, 114.0, 120.1, 129.5, 129.9, 159.5 and 204.1; LRMS *m/z* (M^+) 311; HRMS calcd for $C_{19}H_{21}NO_3$ (M^+) 311.1521, found 311.1520.

(1*S,2*S**,5*S**)-4,4-Ethylenedioxy-1-(4-methoxybenzyloxymethyl)-6-methylene-bicyclo[3.2.1]octane-2-carbonitrile (9).** A solution of **8** (175.9mg, 0.565 mmol), ethylene glycol (0.60 mL, 10.7 mmol) and PPTS (15.4 mg, 0.0613 mmol) in benzene (10 mL) was refluxed under Dean-Stark trap. The solution was cooled to rt and poured into saturated aqueous $NaHCO_3$ solution. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (2:1 v/v) gave **9** (167.5 mg, 83%). IR (neat) 2237.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (ddd, J = 12.0, 5.2 and 2.0 Hz, 1H), 1.88 (d, *J* = 14.4 Hz, 1H), 1.96 (dd, *J* = 14.4 and 6.8 Hz, 1H), 2.19 (d, *J* = 12.0 Hz, 1H), 2.38 (s, 2H), 2.62 (d, *J* = 5.2 Hz, 1H), 3.15 (d, *J* = 7.2 Hz, 1H), 3.33 (d, *J* = 9.2 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.89-4.08 (m, 4H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.92 (s, 1H), 5.06 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 2H) and 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.9, 32.7, 34.8, 40.0, 45.8, 51.2, 55.4, 64.6, 65.1, 73.4, 75.1, 108.9, 113.9, 120.8, 129.3, 130.2, 148.3 and 159.3; LRMS *m/z* (M^+) 355; HRMS calcd for $C_{21}H_{25}NO_4$ (M^+) 355.1784, found 355.1784.

(1*S,4*S**,5*S**)-5-(4-Methoxybenzyloxymethyl)-7-methylene-4-{*N*-(2-nitrobenzenesulfonyl)-aminomethyl}-bicyclo[3.2.1]octan-2-one ethylene acetal (10).** To a suspension of $LiAlH_4$ (18.6 mg,

0.490 mmol) in Et_2O (1 mL) was added dropwise a solution of **9** (50.0 mg, 0.141 mmol) in Et_2O (5 mL) at 0 °C. The mixture was allowed to warm to rt. After 2 h, the reaction was quenched by successive addition of water (0.02 mL), 15% NaOH solution (0.02 mL) and water (0.06 mL) at 0 °C. $MgSO_4$ was added and the mixture was filterd through Celite. Removal of the solvent gave a colorless oil, which was used immediately in the next step.

To a solution of the above crude product in CH_2Cl_2 (5 mL) were added Et_3N (0.10 mL, 0.72 mmol) and a solution of NsCl (31.4 mg, 0.142 mmol) in CH_2Cl_2 (1 mL). After 2 h, water (2 mL) was added. The layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and column chromatography with $CHCl_3$-MeOH (50:1 v/v) afforded **10** (64.6 mg, 84%) as a green oil. IR (neat) 1540.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (dd, *J* = 12.8 and 5.2 Hz, 1H), 1.54 (d, *J* = 14.8 Hz, 1H), 1.86 (dd, *J* = 15.2 and 7.6 Hz, 1H), 2.00-2.10 (m, 2H), 2.24 (d, *J* = 17.2 Hz, 1H), 2.36-2.44 (m, 1H), 2.52 (d, *J* = 5.2, 1H), 3.14-3.32 (m, 3H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.82 (s, 3H), 3.85-4.01 (m, 4H), 4.54 (s, 2H), 4.86 (s, 1H), 5.00 (s, 1H), 6.08 (dd, *J* = 6.8 and 5.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.62-7.7.72 (m, 2H), 7.80-7.83 (m, 1H) and 8.02-8.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.7, 33.5, 39.2, 43.6, 45.0, 45.6, 51.0, 55.4, 64.3, 65.0, 73.0, 75.2, 108.1, 110.2, 113.9, 125.2, 129.4, 130.4, 131.3, 132.7, 133.4, 134.0, 148.2, 149.8 and 159.3; LRMS *m/z* (M^+) 544; HRMS calcd for $C_{27}H_{32}NO_8S$ (M^+) 544.1879, found 544.1876.

(1*S,4*S**,5*S**)-5-(Hydroxymethyl)-7-methylene-4-{*N*-(2-nitrobenzenesulfonyl)-aminomethyl}-bicycle[3.2.1]octan-2-one ethylene acetal (11).** To a solution of **10** (10.1 mg, 0.0185 mmol) in CH_2Cl_2 (1.8 mL) and H_2O (0.1 mL) was added DDQ (11.5 mg, 0.0507 mmol) at rt. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (4 mL). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and column chromatography of the residue with $CHCl_3$-MeOH (25:1 v/v) afforded **11** (7.0 mg, 89%) as a colorless oil. IR (neat) 3499.2, 3284.2, 2249.6 and 1658.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (ddd, *J* = 12.0, 5.6 and 1.6 Hz, 1H), 1.53 (d, *J* = 14.8 Hz, 1H), 1.82-1.88 (m, 2H), 1.92-2.02 (m, 2H), 2.26 (ddd, *J* = 17.2, 2.4 and 2.4 Hz, 1H), 2.43 (s, 3H), 2.52 (d, *J* = 4.8 Hz, 1H), 3.05-3.18 (m, 2H), 3.42 (d, *J* = 11.2 Hz, 1H), 3.73 (d, *J* = 11.2 Hz, 1H), 3.84-3.96 (m, 4H), 4.88 (s, 1H), 5.01 (s, 1H), 5.31 (dd, *J* = 7.2 and 4.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H) and 7.74 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 32.7, 33.0, 39.4, 42.8, 44.2, 46.6, 51.1, 64.1, 64.8, 68.1, 108.3, 110.3, 127.2, 129.8, 137.1, 143.4 and 149.6; LRMS *m/z* (M^+) 393; HRMS calcd for $C_{20}H_{27}NO_5S$ (M+) 393.1610, found 393.1616.

(1*S,4*S**,5*S**)-4-[*N*-{(*tert*-Butyldimethylsilyloxy)ethyl}-*N*-(2-nitrobenzenesulfonyl)aminomethyl]-5-(4-methoxybenzyloxymethyl)-7-methylene-bicyclo[3.2.1]octan-2-one ethylene acetal (12).** A mixture of **10** (38.2 mg 0.0701 mmol), K_2CO_3 (31.6 mg, 0.229 mmol) and (2-bromoethoxy)*tert*-butyldimethylsilane (23 μL, 0.107 mmol) in DMF (1 mL) was stirred at 80 °C for 24

h. Water was added. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (2:1 v/v) afforded **12** (35.8 mg, 73%) as a colorless oil. IR (neat) 1544.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.24-1.32 (m, 1H), 1.54 (dd, *J* = 14.8 and 2.8 Hz, 1H), 1.73 (d, *J* = 14.8 Hz, 1H), 1.79 (d, *J* = 11.6 Hz, 1H), 2.09-2.17 (m, 1H), 2.26 (d, *J* = 17.6 Hz, 1H), 2.42 (d, *J* = 17.2 Hz, 1H), 2.50 (d, *J* = 4.4 Hz, 1H), 3.15 (d, *J* = 9.2 Hz, 1H), 3.23-3.33 (m, 2H), 3.50-3.58 (m, 2H), 3.65-3.95 (m, 11H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.86 (s, 1H), 5.00 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H) and 7.51-7.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.31, −5.28, 18.4, 26.0, 29.6, 33.1, 37.6, 43.6, 45.3, 49.2, 51.0, 51.8, 55.4, 62.0, 64.1, 64.8, 73.1, 75.1, 107.9, 110.2, 113.8, 124.2, 129.4, 130.5, 131.1, 131.5, 133.3, 133.9, 148.4, 150.0 and 159.2; LRMS *m/z* (M^+) 703; HRMS calcd for $C_{19}H_{21}NO_3$ (M^++1) 703.3085, found 703.3087.

(1*S,4*S**,5*S**)-4-[*N*-{2-(*tert*-Butyldimethylsilyloxy)ethyl}-*N*-{(2-nitrobenzenesulfonyl)amino}methyl]-5-(hydroxymethyl)-7-methylene-bicyclo[3.2.1]octan-2-one ethylene acetal (13).** To a solution of **12** (16.2 mg, 0.0230 mmol) in CH_2Cl_2 (1.8 mL) and H_2O (0.1 mL) was added DDQ (7.9 mg, 0.035 mmol) at rt. The mixture was stirred for 1 h and DDQ (5.3 mg, 0.0233 mmol) was added. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (4 mL). The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (1:1 v/v) afforded **13** (9.3 mg, 69%) as a colorless oil. IR (neat) 3555.1, 2248.6 and 1658.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.25 (ddd, *J* =12.0, 5.2 and 1.6 Hz, 1H), 1.65-1.74 (m, 3H), 2.07 (dd, *J* = 6.0 and 6.0 Hz, 1H), 2.18-2.21 (m, 1H), 2.30 (ddd, *J* = 17.2, 2.4 and 2.4 Hz, 1H), 2.43 (dd, *J* = 17.2 and 1.6 Hz, 1H), 2.54 (d, *J* = 5.2 Hz, 1H), 3.34-3.59 (m, 4H), 3.68-3.76 (m, 3H), 3.86-3.95 (m, 5H), 4.89 (s, 1H), 5.01 (s, 1H), 7.60-7.69 (m, 3H) and 8.02-8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.33, -5.31, 18.5, 26.0, 30.5, 32.7, 37.8, 42.9, 46.6, 49.1, 51.3, 51.5, 62.0, 64.0, 64.8, 68.0, 108.2, 110.4, 124.3, 130.9, 131.6, 133.5, 133.8, 148.4 and 149.7; LRMS *m/z* (M^+) 582; HRMS calcd for $C_{27}H_{42}N_2O_8SSi$ (M^+) 582.2431, found 582.2430.

(1*S,4*S**,5*S**)-Ethyl (*E*)-3-[4,4-ethylenedioxy-6-methylene-2-{*N*-[2-(*tert*-butyldimethylsilyloxy)ethyl]-*N*-[(2-nitrobenzenesulfonyl)amino]methyl}-bicyclo[3.2.1]oct-1-yl]propenoate (5).** To a solution of $(COCl)_2$ (0.17 mL, 1.98 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.19 mL, 2.68 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After 10 min, a solution of **13** (391.1 mg, 0.671 mmol) in CH_2Cl_2 (3 mL) was added and the mixture was stirred for 15 min. Et_3N (1.0 mL, 7.17 mmol) was added. The mixture was allowed to warm to rt. The reaction was quenched with 5 mL of water. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of

the solvent and column chromatography of the residue with hexane-EtOAc (1.5:1) afforded the corresponding aldehyde (367.8 mg, 94%) as a colorless oil. Dara for aldehyde; IR (neat) 1719.2 and 1659.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (br s, 9H), 1.67 (ddd, *J* = 14.4, 6.4 and 0.8 Hz, 1H), 1.84 (ddd, *J* = 10.4, 5.2 and 1.6 Hz, 1H), 1.88 (d, *J* = 14.4 Hz, 1H), 2.03 (dd, *J* = 12.0 and 2.4 Hz, 1H), 2.28 (dd, *J* = 16.8 and 1.6 Hz, 1H), 2.45-2.51 (m, 1H), 2.50 (ddd, *J* = 16.8, 2.4 and 2.4 Hz, 1 H), 2.67 (d, *J* = 5.2 Hz, 1H), 3.03 (dd, *J* = 13.6 and 1.6 Hz, 1H), 3.39 (ddd, *J* = 15.2, 6.4 and 6.4 Hz, 1H), 3.55 (ddd, *J* = 15.2, 5.6 and 5.6 Hz, 1H), 3.69-3.80 (m, 2H), 3.82-3.89 (m, 2H), 3.94-4.02 (m, 3H), 5.00 (s, 1H), 5.16 (s, 1H), 7.58-7.60 (m, 1H), 7.65-7.68 (m, 1H), 7.97-7.99 (m, 1H) and 9.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.34, -5.28, 18.4, 26.0, 29.6, 31.3, 37.2, 38.8, 50.0, 51.2, 52.2, 55.6, 62.0, 64.3, 65.0, 109.7, 109.8, 124.2, 130.7, 131.6, 133.1, 133.5, 146.6, 148.6 and 203.2.

To a suspension of NaH (washed three times with hexane, 47.0 mg, 1.96 mmol) in THF (3 mL) was added triethyl phosphonoacetate (0.45 mL, 2.27 mmol) at 0 °C. The solution was allowed to warm to rt and stirred for 30 min. A solution of the above aldehyde (367.8 mg, 0.633 mmol) in THF (4 mL) was added at 0 °C. After an hour, the reaction was quenched with water. The mixture was extracted three times with EtOAc. The combined organic layers were washed brine and dried over Na_2SO_4. Removal of the solvent and column chromatography of the residue with hexane-EtOAc (2:1) as an eluent afforded **5** (395.8 mg, 96%) as a colorless oil. IR (neat) 1716.3 and 1650.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.64 (ddd, *J* =12.0, 5.6 and 1.6 Hz, 1H), 1.73 (dd, *J* = 14.4 and 6.0 Hz, 1H), 1.85 (d, *J* = 14.8 Hz, 1H), 1.96 (dd, *J* = 12.0 and 2.0 Hz, 1H), 2.08-2.12 (m, 1H), 2.27 (ddd, *J* = 16.8, 2.4 and 2.4 Hz, 1H), 2.44 (d, *J* = 16.8 Hz, 1H), 2.59 (d, *J* = 4.8 Hz, 1H), 2.98 (d, *J* = 13.6 Hz, 1H), 3.19 (ddd, *J* =14.8, 6.8 and 6.8 Hz, 1H), 3.54 (ddd, *J* = 15.2, 5.2 and 5.2 Hz, 1H), 3.68-3.71 (m, 2H), 3.79 (dd, *J* = 14.0 and 10.8 Hz, 1H), 3.83-3.89 (m, 1H), 3.92-3.97 (m, 3H), 4.19 (q, *J* =7.2 Hz, 2H), 4.90 (s, 1 H), 5.05 (s, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 7.03 (d, *J* = 16.0 Hz, 1H), 7.57-7.60 (m, 1H), 7.64-7.70 (m, 2H) and 7.96-7.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.35, -5.33, 14.4, 18.4, 26.0, 29.5, 33.0, 41.9, 44.1, 47.1, 50.3, 51.8, 60.6, 61.9, 64.1, 64.9, 76.8, 108.9, 109.5, 120.1, 124.2, 131.0, 131.6, 133.2, 133.5, 148.1, 148.5, 152.9 and 166.6; LRMS *m/z* (M^+) 650; HRMS calcd for; $C_{31}H_{46}N_2O_9Si$ (M^+) 650.2693, found 650.2694.

(1*S,2*R**,5*S**,8*S**)-Ethyl [{3-(2-*tert*-butyldimethylsililoxy)ethyl}-7,7-ethylene-dioxy-9-methylene-3-azatricyclo[6.2.1.0^{1,5}]undec-2-yl]ethanoate (4).** To a solution of **5** (55.0 mg, 0.0845mmol) in DMF (2 mL) was added K_2CO_3 (176.4 mg, 1.28 mmol) and PhSH (0.1 mL) at rt. After 1 h, 5 mL of water was added. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and column chrpmatography of the residue with hexane-EtOAc (1.6:1) as an eluent afforded **4** (31.9 mg, 81%) as a colorless oil and its diastereomer (5.0 mg, 13%) as a colorless oil. Data for **4**; IR (neat) 1733.7 and 1655.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400

MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.30 (t, *J* =4.8 Hz, 3H), 1.47 (ddd, *J* = 12.0, 5.6 and 1.2 Hz, 1H), 1.52 (d, *J* = 14.8 Hz, 1H), 1.88 (dd, *J* = 14.8 and 8.0 Hz, 1H), 1.97 (dd, *J* = 8.0 and 2.8 Hz, 1H), 2.02 (dd, *J* = 8.4 and 1.6 Hz, 1H), 2.07 (d, *J* = 14.8 Hz, 1H), 2.29 (ddd, *J* = 16.0, 2.4 and 2.4 Hz, 1H), 2.34 (dd, *J* = 14.8 and 1.6 Hz, 2H), 2.49-2.60 (m, 3H), 2.77 (ddd, *J* = 12.8, 7.6 and 6.8 Hz, 1H), 3.08 (dd, *J* = 10.4 and 10.4 Hz, 1H), 3.13 (t, *J* = 6.0 Hz, 1H), 3.57-3.66 (m, 2H), 3.86-3.96 (m, 4H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.97 (s, 1H) and 5.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.19, -5.14, 14.3, 18.4, 26.1, 30.7, 31.2, 36.1, 39.7, 43.0, 49.1, 51.1, 56.7, 57.7, 60.5, 62.8, 64.1, 64.6, 65.1, 109.9, 111.3, 148.6 and 173.2; LRMS *m/z* (M^+) 465; HRMS calcd for; $C_{25}H_{43}NO_5Si$ (M^+) 465.2911, found 465.2916. Data for diastereoisomer of **4**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.46 (dd, *J* = 10.8 and 5.6 Hz, 1H), 1.57 (d, *J* = 15.2 Hz, 1H), 1.87 (dd, *J* = 14.8 and 8.4 Hz, 1H), 2.04-2.17 (m, 3H), 2.28-2.34 (m, 3H), 2.53 (d, *J* = 5.6 Hz, 1H), 2.59 (dd, *J* = 12.0 and 8.8 Hz, 1H), 2.71 (ddd, *J* = 12.0, 7.2 and 6.0 Hz, 1H), 2.93 (ddd, *J* = 12.4, 8.0 and 6.0 Hz, 1H), 3.00 (dd, *J* = 8.8 and 6.8 Hz, 1H), 3.06 (t, *J* = 6.8 Hz, 1H), 3.57-3.67 (m, 2H), 3.86-3.97 (m, 4H), 4.09-4.17 (m, 2H), 4.98 (s, 1H), 5.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.17, -5.15, 14.4, 18.5, 26.1, 30.3, 37.4, 38.7, 40.7, 41.9, 46.5, 50.5, 57.1, 59.5, 60.4, 62.8, 64.0, 64.7, 67.7, 109.9, 111.2, 148.5 and 172.7; LRMS *m/z* (M^+) 465; HRMS calcd for; $C_{25}H_{43}NO_5Si$ (M^+) 465.2911, found 465.2908.

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