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Propellane as a conformational device for the stabilization of the β-lactone of salinosporamide A

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ABSTRACT

The synthesis of a propellane derivative of salinosporamide A having increased stability under physiological-like conditions is reported. The synthesis took advantage of a substrate-controlled stereoselective Ugi 4-center 3-component reaction to construct the required *syn*-bicyclic pyroglutamic acid framework.

1. Introduction

Naturally occurring salinosporamide A exhibits potent and selective inhibition of proteasome activity similar to that of the clinically used pharmaceutical Velcade®.[1] Despite its efficacy as an irreversible inhibitor of the 20S proteasome and possible clinical utility in the treatment of certain types of cancer, salinosporamide A still suffers from a lack of stability that could limit its viability or shelf life.[2] Degradation of the β-lactone through nucleophilic ring-opening of the strained four-membered ring is an issue, especially if it is to be viable in vivo.[3] We were interested in designing an analog which preserves the main structural feature of salinosporamide A, the fused β-lactone-γ-lactam, and thus its biological activity, while enhancing its stability (Fig. 1).

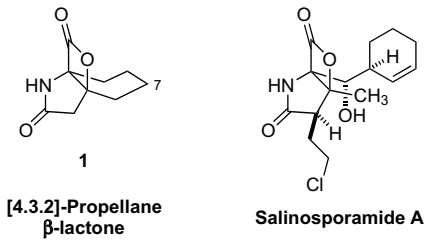
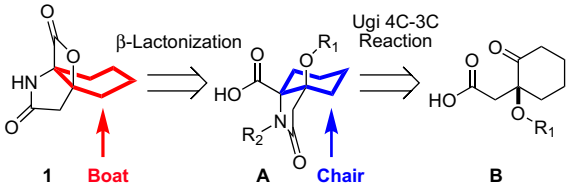


Figure 1. Structures of propellane **1** and salinosporamide A.

The salinosporamide A analog that interested us, [4.3.2]-propellane β-lactone **1**, did so for two reasons. First, we anticipated that introduction of the fused six-membered ring to give the propellane structure could make nucleophilic attack to the lactone more difficult, except for when the necessary orientation is achieved in the protein complex.[4] Second, the conformational change of the cyclohexane ring in going from the boat to chair conformation[5] upon β-lactone opening could be a means to render the proteasomal binding irreversible, similar to the chloroethyl trapping of the resulting alkoxide of salinosporamide A.[6] By these two structural designs, it is expected that we should see increased β-lactone stability, hopefully coinciding with retention of irreversible proteasome complexation.

2. Results and discussion

We were also interested in designing a substrate-controlled stereoselective Ugi 4-center 3-component reaction (4C-3CR) for the synthesis of pyroglutamic acid derivatives (Scheme 1, **B**→**A**). γ-Ketoacid **B** seemed like a logical choice to fit these qualifications; the restricted conformational freedom imposed by the ring could allow for stereoselective kinetic attack of the isocyanide to the putative iminium ion, thus a diastereoselective Ugi reaction.



Scheme 1. Retrosynthetic analysis of propellane **1**.

We envisioned that access to the pyroglutamic acid portion of [4.3.2]-propellane β-lactone **1** could come through the Ugi 4C-3CR with γ-ketoacid **B** and a convertible isocyanide, as shown in Scheme 1. Usage of an appropriate convertible isocyanide would allow for selective hydrolysis of the desired amide to the

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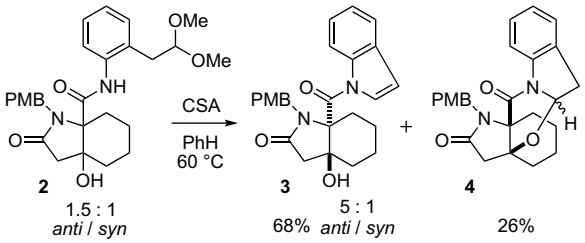
pyroglutamic acid **A**. In order to eventually form the β-lactone, it was necessary that the *syn*-diastereomer be formed as the major product in the Ugi 4C-3CR. Besides the use of the Ugi 4C-3CR as a means to build up the pyroglutamic acid core, it also proved to be a useful method to access the functionalized [4.3.2]-propellane structure.[7]

During our studies on the racemic synthesis of pyroglutamic acid **A** (R_1=H, R_2=PMB), we encountered two limitations in using the synthetic route for the synthesis of **1**.[8] First, negligible (1.5:1 *anti*/*syn*) stereoselectivity was observed in the Ugi 4C-3CR, in favor of the undesired *anti*-isomer of **2** (Scheme 2). Second, we observed loss of the required *syn*-isomer of **2** as the *N*,*O*-acetal **4** during formation of *N*-acylindole **3**. As a solution to both problems, we sought an *O*-protected γ-ketoacid **B**.

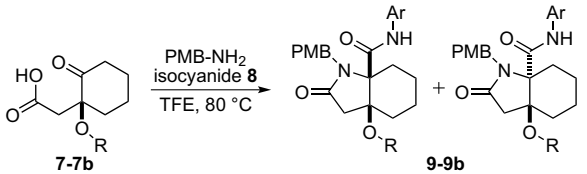


Scheme 2. Loss of *syn*-Ugi product **2** as *N*,*O*-acetal **4**.

Due to the steric congestion around the tertiary alcohol of **B**, our options for protecting groups were limited. However, the methylthiomethyl (MTM) protecting group was feasible due to its previous usage in this realm.[9] It was expected that this protecting group would be stable under acidic conditions, preventing formation of the undesired *N*,*O*-acetal **4**.

The Ugi precursor, γ-ketoacid **7**, was synthesized as described in Scheme 3. The starting ketone **5** was prepared enantioselectively as described previously.[10] Introduction of the MTM protecting group to the tertiary alcohol was efficiently accomplished using DMSO and acetic anhydride. Hydrogenation of the benzyl ester **6** proved difficult; palladium poisoning from the MTM-sulfur greatly diminished the reaction rate. However, a simple alkaline hydrolysis with sodium hydroxide posed no problem and **7** was obtained in quantitative yield.[11]

With γ-ketoacid **7** in hand, the Ugi 4C-3CR was used with *para*-methoxybenzylamine and convertible isocyanide **8**[12] to give the pyroglutamic acid amide **9** in 80% yield as a 7:1 ratio of diastereomers with *syn* as the major isomer.[13] The MTM protecting group was essential for diastereoselectivity in the Ugi 4C-3CR with convertible isocyanide **8** and *para*-methoxybenzylamine (Scheme 4). When protected with the methoxymethyl (MOM) group (**7a**), the diastereoselectivity dropped to 3.5:1 *syn*/*anti*. Without protection (**7b**) there was a 1.5:1 ratio in favor of the *anti*-isomer.



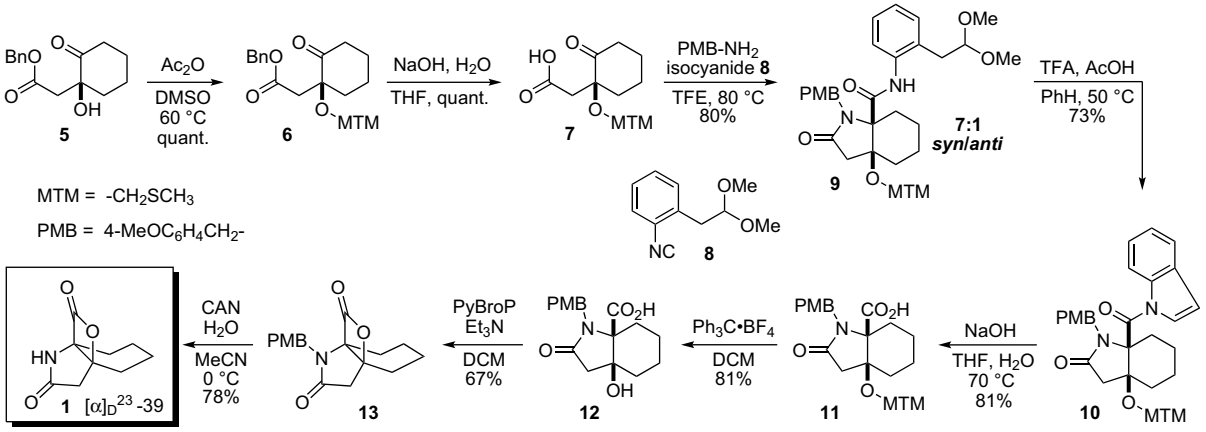
γ-Ketoacid		Yield (%)	Syn		Anti
7	R = -CH_2SCH_3	80	**7.0**	:	**1.0**
7a	R = -CH_2OCH_3	66	**3.5**	:	**1.0**
7b	R = -H	83	**1.0**	:	**1.5**

Scheme 4. Stereocontrolled Ugi 4C-3CR of cyclic levulinic acid derivatives.

The anilide **9** was converted to *N*-acylindole **10** in 73% yield by treatment with a 5:1 mixture of acetic acid and trifluoroacetic acid. The conditions for indole formation were important as it was found that stronger acids like CSA induced deprotection of the MTM group and formation of the aforementioned *N*,*O*-acetal **4** from the major *syn*-isomer. Attempts to convert **4** to the desired unprotected *N*-acylindole were unsuccessful.[14] Alkaline hydrolysis of **10** occurs readily to afford acid **11** in 81% yield under relatively mild conditions due to the lower bond order of the C–N amide bond.

This special *N*-acylindole reactivity is important because strongly basic conditions caused elimination of the protected β-alcohol. Deprotection of the MTM group with trityl tetrafluoroborate occurred in 81% yield, followed by β-lactone formation of hydroxyacid **12** with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) and triethylamine to give **13** in 67% yield.[15] Subsequent oxidative deprotection of the PMB group with ceric ammonium nitrate (CAN) furnished the propellane β-lactone **1** in 78% yield. The relative stereochemistry of the final compound was unambiguously confirmed by single crystal X-ray analysis as shown below (Fig. 2).[16] As anticipated, the cyclohexane ring adopts the boat conformation, causing the pseudo-axial C(7)-H bond to cover the corresponding side of the β-lactone carbonyl (as seen in the space-filling diagrams).

Shown in Scheme 5 is our proposed rationale for the observed trend of stereoselectivity in the Ugi 4C-3CR with the three γ-ketoacids **7**, **7a**, and **7b**. The direction of attack of the isocyanide to the two possible chair conformations **C** and **D** of the iminium salt (*E*-geometry) is what determines the *syn*/*anti* diastereoselectivity. As the size of the R-group increases (H→MOM→MTM), this should shift the



Scheme 3. Stereocontrolled asymmetric synthesis of [4.3.2]-propellane β-lactone **1**.

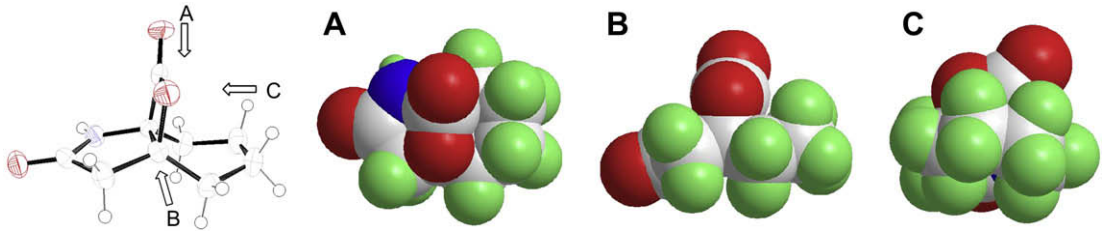
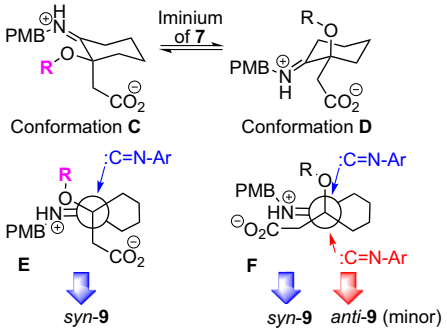


Figure 2. X-ray crystal structure of propellane β-lactone **1** and the space-filling models (gray: carbon; green: hydrogen; red: oxygen; blue: nitrogen) from an aerial view (A), from an anterior view (B) and from a right lateral view (C).



Scheme 5. Analysis of Ugi 4C-3CR stereochemical output.

conformational equilibrium towards **C**, which places the ether in the less encumbered equatorial position. Attack of the isocyanide to **C** for **7** and **7a** should occur from the axial direction (in blue) so as to avoid the eclipsing interaction between the PMB-amine and R-group that occurs upon movement of the PMB-amine to the axial position after equatorial attack (see structure **E** of conformation **C**). The torsional strain incurred in the transition state resulting from equatorial approach and leading to the *anti* diastereomer should become more prominent as the size of the R-group increases.[17] Thus, attack of the isocyanide from the axial direction is favored and the *syn* product is obtained as the major diastereomer for **9** and **9a**. For unprotected γ-ketoacid **7b** (R=H) the amount of conformational bias (**C** vs **D**), as well as the eclipsing interaction, is diminished, leading to a 1.0:1.5 mixture of diastereomers **9b**.[8] Attack of the isocyanide to conformation **D** (structure **F**) requires the seemingly more hindered equatorial approach (in blue) to give the *syn* product. Therefore, more *anti* product may result from this minor conformer. However, the coulombic attraction between the iminium and carboxylate ions present in both conformations could be important and would tend to give the *syn* product for each.

Propellane β-lactone **1** was subjected to buffered alkaline conditions identical to those previously reported in the salinosporamide A stability study by Stella et al.[3,18] Treatment of a 25 mM acetonitrile solution of **1** to pH 7.5 phosphate buffer for the reported salinosporamide A half-life time of 87 min gave no detectable decomposition by TLC (thin-layer chromatography) and ^{1}H NMR analysis of the crude product. At pH 8.07 the reported half-life time of salinosporamide A is 50 min, and treatment of **1** to this higher pH under the same reaction conditions resulted in less than 5% decomposition. As anticipated, the β-lactone showed improved stability under physiological-like conditions.

3. Conclusions

We have demonstrated the feasibility and applicability of the Ugi 4C-3CR to the synthesis of an interesting structural analog of the proteasome inhibitor salinosporamide A by preparation of [4.3.2]-propellane β-lactone **1** in enantiomerically pure form. The protection of the tertiary alcohol in ketoacid **7** led to good diastereocontrol in the Ugi 4C-3CR, as well as a successful transformation to *N*-acylindole without formation of *N*,*O*-acetal side product. The synthesis took advantage of mild hydrolysis of the sterically hindered *N*-acylindole amide **9**. The boat conformation of propellane **1** is important for its enhanced stability compared to salinosporamide A, which could allow for better viability in vivo as a therapeutic agent. Biological testing of [4.3.2]-propellane β-lactone **1** as a potential selective and irreversible proteasome inhibitor will be reported in due course.

4. Experimental section

4.1. General

All solvents were used as purchased from commercial sources or dried over 4 Å molecular sieves prior to use in the case of moisture sensitive reactions. Thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash chromatography was performed using silica gel (32–63 mm particle size). All products were purified to homogeneity by TLC analysis (single spot), using a UV lamp and/or iodine and/or CAM or basic $KMnO_4$ for detection purposes. NMR spectra were recorded on 300 MHz, 400 MHz, and 500 MHz spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard.

4.2. Benzyl (1*S*)-{1-[(methylsulfanyl)methoxy]-2-oxocyclohexyl}acetate (6)

To a solution of **5** (86 mg, 0.328 mmol, 1.0 equiv) in DMSO (1.5 mL) was added Ac_2O (1.5 mL). Heated to 50 °C and periodically added 1 equiv DMSO and Ac_2O until TLC showed completion. After 2 h of heating the reaction was partitioned between 1 M NaOH (25 mL) and EtOAc (20 mL), washed with saturated aqueous sodium chloride (15 mL), dried over sodium sulfate, filtered and concentrated in vacuo. Prior to chromatography, any sulfide byproducts were removed by heating under hi-vacuum. The resultant oil was purified by flash chromatography on silica gel (7:1 hexanes/EtOAc) to yield **6** as a colorless oil (105 mg, 99%). R_f=0.42 (3:1 hexanes/EtOAc); $[\alpha]_D^{23}$ −55.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.30 (m, 5H), 5.12 (s, 2H), 4.64 (d, 1H, *J*=11.0 Hz), 4.30 (d, 1H, *J*=11.0 Hz), 2.91 (d, 1H, *J*=16.0 Hz), 2.78 (td, 1H, *J*=13.0, 6.0 Hz), 2.68 (d, 1H, *J*=16.0 Hz), 2.42–2.32 (m, 2H), 2.18 (s, 3H), 2.08–1.95 (m, 2H), 1.89–1.79 (m, 1H), 1.74–1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.0, 170.4, 135.9, 128.8, 128.5, 81.9, 69.0, 66.8, 39.6, 38.4, 37.5, 27.8, 20.7, 15.2; HRMS calcd for $C_{17}H_{22}O_4S$: 322.1233, found: 322.1241.

4.3. (1*S*)-[1-[(Methylsulfanyl)methoxy]-2-oxocyclohexyl]acetic acid (7)

To a solution of **6** (289 mg, 0.896 mmol, 1.0 equiv) in THF (5 mL) was added NaOH (36 mg, 0.896 mmol, 1.0 equiv) in H_2O (1 mL). After

stirring for 1 h, EtOAc (10 mL) was added and the organic layer removed. The aqueous layer was acidified with concd HCl to pH≤2 and then extracted with EtOAc (3×10 mL), dried over sodium sulfate, filtered and concentrated in vacuo to yield **7** as a colorless oil (205 mg, 98%). $[\alpha]_D^{23}$ −16.1 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.69 (d, 1H, *J*=11.2 Hz), 4.63 (d, 1H, *J*=11.2 Hz), 2.98 (d, 1H, *J*=17.2 Hz), 2.72 (d, 1H, *J*=17.6 Hz), 2.38–2.28 (m, 1H), 2.20 (s, 3H), 2.03–1.96 (m, 1H), 1.90–1.76 (m, 2H), 1.75–1.61 (m, 2H), 1.60–1.49 (m, 1H), 1.43–1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 106.6, 81.4, 68.4, 37.4, 34.5, 29.1, 21.7, 21.5, 14.4; HRMS calcd for $C_{10}H_{16}O_4S$: 232.0764, found: 232.0767.

4.4. (3a*S*,7a*R*)-*N*-[2-(2,2-Dimethoxyethyl)phenyl]-1-(4-methoxybenzyl)-3a-[(methylsulfanyl)methoxy]-2-oxooctahydro-7a*H*-indole-7a-carboxamide (9)

To a solution of **7** (111 mg, 0.478 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (8 mL) was added 4-methoxybenzylamine (62 mL, 0.478 mmol, 1.0 equiv) and isocyanide **8** (91 mg, 0.478 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (2 mL). Reaction progress can be monitored by TLC using isocyanide **8** as a reference. The mixture was heated to 70 °C for 3 h, then saturated aqueous sodium chloride (20 mL) was added and the organics extracted with EtOAc (25 mL). The organics were dried over sodium sulfate, filtered and concentrated in vacuo. The resultant viscous oil was purified by flash chromatography on silica gel (3:1→2:1 hexanes/EtOAc) to yield **9** as an off-white solid (206 mg, 80%, 7:1 *syn*/*anti*). A small amount of **9** already may have converted to the aldehyde (from dimethyl acetal deprotection) during the reaction and/or during chromatography and can be taken into the next reaction. R_f=0.32 (1:1 hexanes/EtOAc); $[\alpha]_D^{23}$ +7.5 (*c* 1.6, $CHCl_3$). Data for the major *syn*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.60 (d, 1H, *J*=8.0 Hz), 7.27 (d, 2H, *J*=8.4 Hz), 7.24–7.18 (m, 1H), 7.18–7.14 (m, 1H), 7.10–7.04 (m, 1H), 6.80 (d, 2H, *J*=8.8 Hz), 4.81 (d, 1H, *J*=15.6 Hz), 4.58 (d, 1H, *J*=10.8 Hz), 4.46 (t, 1H, *J*=5.2 Hz), 4.45 (d, 1H, *J*=10.8 Hz), 3.99 (d, 1H, *J*=15.6 Hz), 3.76 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 3.08 (dd, 1H, *J*=14.0, 6.0 Hz), 3.04 (d, 1H, *J*=14.8 Hz), 2.82 (dd, 1H, *J*=14.0, 4.8 Hz), 2.34 (d, 1H, *J*=15.2 Hz), 2.24–2.08 (m, 2H), 2.04–1.96 (m, 1H), 1.96 (s, 3H), 1.52–1.41 (m, 4H), 0.89–0.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 169.2, 158.7, 136.7, 130.8, 129.9, 128.3, 127.3, 124.9, 124.2, 113.6, 106.7, 79.4, 77.3, 77.0, 76.7, 73.5, 69.2, 44.3, 41.5, 36.8, 31.7, 26.8, 20.7, 20.2, 14.2; HRMS calcd for $C_{29}H_{38}N_2O_6S$: 542.2445, found: 542.2444.

4.5. (3a*S*,7a*R*)-1-(4-Methoxybenzyl)-3a-[(methylsulfanyl)-methoxy]-7a-(1*H*-indol-1-ylcarbonyl)octahydro-2*H*-indol-2-one (10)

To a solution of **9** (572 mg, 1.05 mmol, 1.0 equiv) in benzene (20 mL) was added AcOH (1.51 mL, 26.4 mmol, 25.0 equiv) and trifluoroacetic acid (390 mL, 5.27 mmol, 5.0 equiv). The mixture was heated to 50 °C for 4 h, then saturated aqueous sodium bicarbonate (50 mL) was added and the mixture extracted with EtOAc (30 mL). The organics were dried over sodium sulfate, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (3:1→2:1→1:1 hexanes/EtOAc) to yield **10** as a yellow solid (370 mg, 73%, single diastereomer). R_f=0.41 (1:1 hexanes/EtOAc); mp=102–105 °C; $[\alpha]_D^{23}$ +6.4 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, 1H, *J*=5.6 Hz), 7.95 (s, 1H), 7.55 (d, 1H, *J*=8.4 Hz), 7.36–7.23 (m, 2H), 7.17 (d, 2H, *J*=8.4 Hz), 6.75 (d, 2H, *J*=8.8 Hz), 6.56 (d, 1H, *J*=4.0 Hz), 5.00 (d, 1H, *J*=14.8 Hz), 4.56 (d, 1H, *J*=11.2 Hz), 4.48 (d, 1H, *J*=10.8 Hz), 3.76 (s, 3H), 3.66 (d, 1H, *J*=15.6 Hz), 2.87 (d, 1H, *J*=16.0 Hz), 2.60–2.47 (m, 1H), 2.52 (d, 1H, *J*=15.2 Hz), 2.15–2.03 (m, 1H), 1.83 (s, 3H), 1.78–1.55 (m, 4H), 1.47–1.35 (m, 1H), 1.08–0.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.2, 171.6, 159.1, 137.1, 130.3, 129.9, 129.8, 128.4, 125.0, 124.0, 120.8, 116.7, 114.0, 108.2, 80.9, 76.8, 68.9, 55.4, 45.3, 40.0, 30.7, 21.4, 21.0, 20.4, 14.9; HRMS calcd for $C_{27}H_{30}N_2O_4S$: 478.1921, found: 478.1925.

4.6. (3a*S*,7a*R*)-1-(4-Methoxybenzyl)-3a-[(methylsulfanyl)-methoxy]-2-oxooctahydro-7a*H*-indole-7a-carboxylic acid (11)

To a solution of **10** (355 mg, 0.742 mmol, 1.0 equiv) in 3:1 THF/H_2O (12 mL) was added 1 M NaOH (1.19 mL, 1.19 mmol, 1.6 equiv). The mixture was heated to 70 °C for 5 h, then EtOAc (10 mL) and 1 M NaOH (10 mL) were added and the layers separated. The aqueous layer was acidified with concd HCl to a pH≤2, then extracted with EtOAc (3×10 mL), dried over sodium sulfate, filtered and concentrated in vacuo to yield **11** as an orange solid (215 mg, 77%). R_f=0.13 (100% EtOAc); mp=70–72 °C; $[\alpha]_D^{23}$ −28.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, 2H, *J*=8.8 Hz), 6.79 (d, 2H, *J*=8.8 Hz), 4.57 (d, 1H, *J*=11.2 Hz), 4.49 (d, 1H, *J*=15.2 Hz), 4.47 (d, 1H, *J*=11.2 Hz), 4.18 (d, 1H, *J*=15.2 Hz), 3.76 (s, 3H), 3.17 (d, 1H, *J*=15.2 Hz), 2.36 (d, 1H, *J*=15.6 Hz), 2.24 (td, 1H, *J*=12.8, 4.4 Hz), 2.10 (m, 1H), 2.06 (s, 3H), 1.91 (m, 1H), 1.40 (m, 4H), 0.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 175.6, 159.1, 130.3, 129.1, 113.9, 79.7, 72.3, 69.4, 55.4, 46.3, 44.0, 42.0, 32.1, 25.9, 20.9, 20.3, 20.0, 14.4, 8.9; HRMS calcd for $C_{19}H_{25}NO_5S$: 379.1448, found: 379.1455.

4.7. (3a*S*,7a*R*)-3a-Hydroxy-1-(4-methoxybenzyl)-2-oxooctahydro-7a*H*-indole-7a-carboxylic acid (12)

To a solution of **11** (70 mg, 0.184 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) under N_2 gas was added trityl tetrafluoroborate (73 mg, 0.221 mmol, 1.2 equiv). The mixture was stirred for 14 h, then 1 M NaOH (8 mL) was added and the layers separated. The aqueous layer was acidified with concd HCl to pH≤2 and then extracted with EtOAc (3×5 mL). The organics were dried over sodium sulfate, filtered and concentrated in vacuo to yield **12** as an off-white solid (50 mg, 85%). R_f=0.14 (4:1 EtOAc/methanol); mp=62–64 °C; $[\alpha]_D^{23}$ −30.3 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.23 (d, 2H, *J*=8.5 Hz), 6.80 (d, 2H, *J*=8.0 Hz), 4.66 (d, 1H, *J*=15.5 Hz), 4.24 (d, 2H, *J*=15.5 Hz), 3.78 (s, 3H), 2.77 (d, 1H, *J*=16.0 Hz), 2.46 (d, 1H, *J*=16.5 Hz), 2.14 (m, 2H), 1.81 (m, 2H), 1.67 (td, 1H, *J*=14.5, 4.0 Hz), 1.53 (m, 1H), 1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.7, 175.4, 158.8, 130.0, 129.2, 113.8, 74.1, 72.1, 55.2, 44.3, 44.2, 35.8, 27.7, 20.3, 20.1; HRMS calcd for $C_{17}H_{21}NO_5$: 319.1414, found: 319.1417.

4.8. (3a*S*,7a*R*)-1-(4-Methoxybenzyl)-2-methylenehexahydro-1*H*-3a,7a-(epoxymethano)indol-8-one (13)

To a solution of **12** (127 mg, 0.398 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) (278 mg, 0.597 mmol, 1.5 equiv) and Et_3N (83 mL, 0.597 mmol, 1.5 equiv). The mixture was stirred for 2 h, then water (20 mL) was added and it was extracted with CH_2Cl_2 (2×15 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The resultant oil was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to yield **13** (80 mg, 67%) as a colorless oil. R_f=0.29 (1:1 hexanes/EtOAc); $[\alpha]_D^{23}$ −30.5 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, 2H, *J*=8.8 Hz), 6.83 (d, 2H, *J*=8.8 Hz), 4.70 (d, 1H, *J*=15.2 Hz), 4.33 (d, 2H, *J*=15.2 Hz), 3.79 (s, 3H), 3.07 (d, 1H, *J*=18.8 Hz), 2.67 (d, 1H, *J*=19.2 Hz), 2.26–2.14 (m, 2H), 1.98–1.92 (m, 1H), 1.78–1.72 (m, 1H), 1.68–1.62 (m, 1H), 1.60–1.44 (m, 2H), 1.42–1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 168.9, 159.3, 129.7, 129.0, 114.1, 79.3, 55.4, 44.4, 41.0, 29.9, 24.2, 17.7, 17.5; HRMS calcd for $C_{17}H_{19}NO_4$: 301.1309, found: 301.1311.

4.9. (3a*S*,7a*R*)-Tetrahydro-1*H*-3a,7a-(epoxymethano)indole-2,8-dione (1)

To a solution of **13** (15 mg, 0.05 mmol, 1.0 equiv) in CH_3CN (0.8 mL), and H_2O (0.2 mL) was added cerium ammonium nitrate (109 mg, 0.199 mmol, 4.0 equiv). The mixture stirred for 1 h, then saturated sodium chloride was added and it was extracted with EtOAc (3×5 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel (1:1→1:2 hexanes/EtOAc) to yield **1** as a colorless solid (7 mg, 78%). R_f=0.12 (1:1 hexanes/EtOAc); mp=106–108 °C; $[\alpha]_D^{23}$ −38.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (br s, 1H), 3.00 (d, 1H, *J*=19.2 Hz), 2.60 (d, 1H, *J*=18.8 Hz), 2.31–2.25 (m, 2H), 1.99–1.91 (m, 1H), 1.78–1.53 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 170.2, 81.5, 72.3, 41.0, 30.3, 25.2, 18.1, 17.9; HRMS calcd for $C_9H_{11}NO_3$ ($M+H^+$): 182.0812, found: 182.0814.

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Supplementary data

Experimental procedures for stability tests of **1** and copies of ^{1}H NMR and ^{13}C NMR spectra for **6**–**7**, **9**–**13** and **1** (20 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.085.

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