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Stereoselective Olefination with Sterically Demanding Julia–Kocienski Reagents: Total Synthesis of Oxo-prothracarcin, Oxo-tomaymycin, and Boseongazepine B

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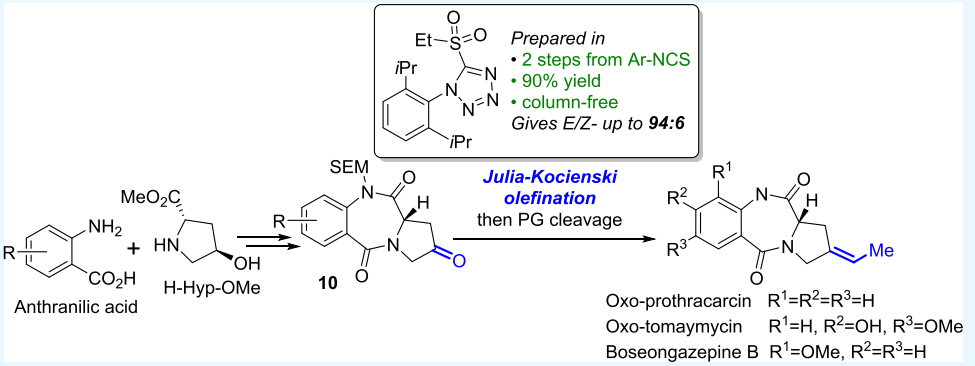

ABSTRACT: Total syntheses of three pyrrolo[1,4]benzodiazepine anticancer antibiotic family members oxo-prothracarcin, oxo-tomaymycin, and boseongazepine B are described. The total syntheses feature late-stage stereoselective olefination employing modified Julia–Kocienski reagents that can be conveniently prepared in only two steps and allows for a significant reduction in the number of linear steps. Detailed density functional theory (DFT) studies explain the stereochemical outcome of the key step.

INTRODUCTION

Pyrrolo[1,4]benzodiazepines (PBD) are a class of naturally occurring anticancer antibiotics.[1,2] A characteristic structural feature of PBDs is the right-hand twisted three-ring system possessing electrophilic imine functionality at N10-C11 (Figure 1) known to bind covalently to the minor groove of DNA *via* an exocyclic amino group of the guanine base.[3−5] As a consequence, interference with DNA repair, replication, transcription, and thus cell division is observed. Also, the N10-C11 amide group-possessing PBDs exhibit considerable cytotoxicity in various cancer cell lines acting as noncovalent binders.[6] A number of naturally occurring and synthetic PBDs have been studied in clinical trials, and nowadays, the PBDs are considered a privileged warhead scaffold in the development of antibody–drug conjugates (ADCs).[7−9] Structurally, several naturally occurring PBDs possess an exocyclic alkylidene group at the C2 position. Studies in synthetic PBD series also reveal that this alkylidene substituent is crucial for the superior cytotoxicity of these compounds.[10]

RESULTS AND DISCUSSION

Recently, a scalable route toward ethylidene group-containing oxo-tomaymycin has been reported by Sanofi, revealing an important role of alkylidene PBDs in the ADC development process.[11] Although several total syntheses of alkylidene PBDs have been reported, a stereoselective introduction of the C2 exocyclic double bond remains a considerable challenge. For example, direct carbonyl olefination methods (Wittig and Julia–Kocienski) on PBDs or closely related proline scaffolds mainly give the undesired *Z*-isomer predominantly or lack *E*/*Z* selectivity at all.[11−15] As an alternative, strategies based on Ireland–Claisen rearrangement[16−18] or asymmetric enolate *α*-alkylation[19] for the stereoselective introduction of an alkylidene substituent have been developed. However, the desired 3-ethylideneproline building block is typically obtained in a 9–12 step linear sequence and a low overall yield. In 2018, our group reported a formal total synthesis of limazepine E (**3**) based on late-stage Julia–Kocienski olefination with sterically demanding phenyltetrazole sulfones.[20] Herein, we report a further extension of this methodology, resulting in the total synthesis of oxo-prothracarcin (**4**), oxo-tomaymycin (**5**), and boseongazepine B (**6**).

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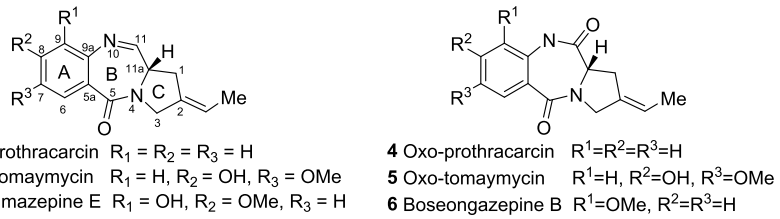
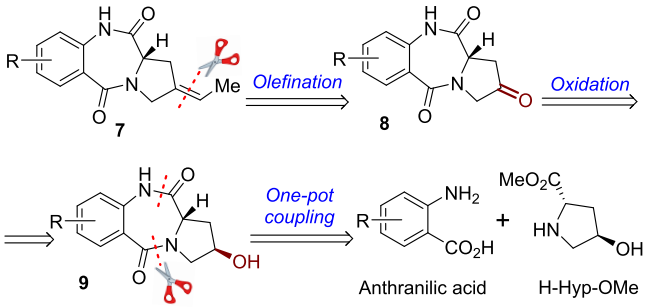


Figure 1. Representative examples of the C2 ethylidene group-possessing PBD natural products.

Our retrosynthetic analysis (Scheme 1) was based on late-stage Julia–Kocienski olefination of trione **8**. The tricyclic

Scheme 1. Retrosynthetic Analysis of Ethylidene PBD Natural Products



PBD scaffold can in turn be constructed from readily available anthranilic acids and *trans*-4-hydroxy-L-proline ester (H-Hyp-OMe) *via* a one-pot coupling-cyclization sequence[21] followed by oxidation of the C2 hydroxy group.

We started our synthetic studies on simple A-ring unsubstituted PBD trione **10a** and studied the key Julia–Kocienski olefination step (Table 1). During our previous studies on olefination in the PBD series, the phenyltetrazole-based sulfones turned out to give the best results in terms of *E*/*Z* selectivity and yield;[14,20] therefore, further studies in this direction were conducted. After the initial assessment of reaction conditions (see the Supporting Information, Table S1), a series of new and known phenyltetrazole sulfones were examined in Julia–Kocienski olefination of A-ring unsubstituted PBD trione **10a** (Table 1).

First, the electronic effects of substituents in the phenyl ring of phenyltetrazole sulfones **11** were studied (Table 1, entries 1–5). In general, good selectivity (up to 88:12) toward the desired *E* double-bond isomer of **12a** was observed in all cases. The electron-donating methoxy group in the phenyl ring (entry 2) gave a comparable *E*/*Z* ratio compared to simple phenyl (entry 1) but a slightly lower yield (72 vs 86%). In contrast, the electron-withdrawing cyano group (entry 3) completely shut down reactivity and most of trione **10a** was recovered. Similarly, for 2,5-dimethoxy substitution (entry 5), the formation of **12a** was not observed. Interestingly, the electron-withdrawing fluorine substituent in the phenyl ring (entry 4) gave an even higher *E*/*Z* ratio compared to simple phenyl (entry 1) but a slightly lower yield (66 vs 86%). Next, the steric effects of substituents in the phenyl ring of phenyltetrazole sulfones **11** were studied. As known from our previous studies,[20] the introduction of ortho-substituents in the phenyl ring of the Julia–Kocienski reagent increases the *E*/*Z* selectivity of the olefination. The introduction of two *ortho*-methyl groups (entry 6) only slightly increased the olefination stereoselectivity; however, sterically demanding isopropyl (entry 7) or cyclohexyl (entry 8) groups allowed for an increase in the *E*/*Z* ratio up to 88:12 compared to 72:28 measured in the case of the classical Julia–Kocienski reagent **11a** (entry 1). Due to the concise synthesis (*vide infra*), the comparably high *E*/*Z* selectivity and higher olefination yield of 2,6-di-isopropylphenyl-substituted phenyltetrazole sulfone **11g** (entry 7) was selected for further studies. With the optimal sulfone substitution pattern in hand, olefination solvent screening was performed; however, the initially used THF turned out to be superior to others (see the Supporting Information, Table S2). The next task was to develop a high-yielding and scalable preparation procedure for the synthesis of sulfone **11g** (Scheme 2).

In analogy with the literature known procedures,[22] sulfone **11g** was successfully synthesized in decagram quantities starting from readily available thiocyanate **13g** (Scheme 2). The developed method allowed obtaining sulfone **11g** in 90% yield over two steps with only one isolated intermediate **14g**. It is important to note that sulfone **11g** was successfully prepared without any chromatographic purification and the final crystallization gave **11g** in 99% purity (according to HPLC).

After finding the optimal Julia–Kocienski reagent structure and optimized reaction conditions, we turned our attention toward the scope of our developed methodology in the PBD series (Scheme 3).

Olefination of triones **10** typically proceeds with good *E*-selectivity in all cases, and the *E*/*Z* ratio can be significantly improved by our optimized Julia–Kocienski reagent **11g** (Scheme 2). Employing sulfone **11g**, the reaction yields are moderate, ranging from 48 to 70%, which is caused mostly by partial deprotonation of α protons of the keto group of **10**, resulting in a ketone enolate not being able to participate in the olefination reaction. This hypothesis was confirmed by quenching of the crude reaction mixture with D_2O, which resulted in partial deuteration of unreacted substrate **10**. Additives like $CeCl_3$[23] or $LaCl_3$*2LiCl,[24] known to suppress α-deprotonation of carbonyl compounds with organometallic reagents, unfortunately, did not increase the reaction yield. Fortunately, unreacted trione **10** in all cases could be easily recovered during the chromatographic purification step. Besides the chloro-, trifluoromethyl-, and dimethoxy-substituted PBDs **12b**, **12c**, and **12e**, four natural product precursors **12a**, **12d**, **12f**, and **12g**[20] were successfully prepared by employing our developed methodology with *E*/*Z* selectivity up to 94:6. Intermediates **12a**, **12d**, and **12f** were further converted into the corresponding natural products by a simple protecting group cleavage (Scheme 4), and **12g** is a common intermediate from the total synthesis of limazepine E (**3**).[17]

The trimethylsilylethoxymethyl (SEM)-protecting group of intermediates **12a** and **12d** were successfully cleaved using aqueous HCl in the THF mixture at elevated temperatures, furnishing oxo-prothracarcin (**4**) and boseongazepine B (**6**) in 55 and 62% yields, respectively. In the case of **12f**, both SEM-

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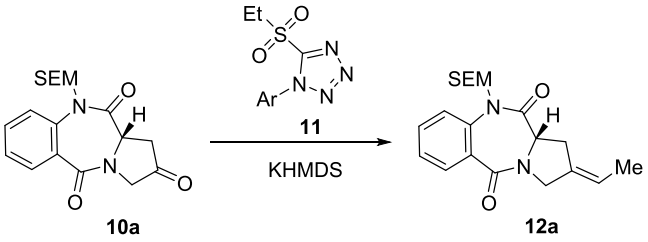
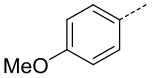
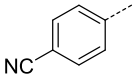
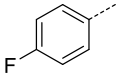
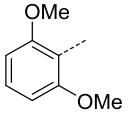
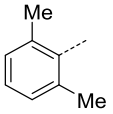
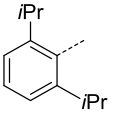
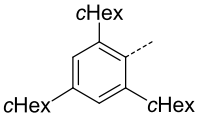
Table 1. Phenyltetrazole-Based Julia–Kocienski Reagent Screening for the Olefination of Trione 10[abc]



Entry	Sulfone	Yield (brsm)[b]	E/Z-[c]
1	**11a** 	86% (96%)	72:28
2	**11b** 	72% (81%)	69:31
3	**11c** 	<5%	-
4	**11d** 	66% (78%)	78:22
5	**11e** 	<5%	nm
6	**11f** 	45% (63%)	79:21
7	**11g** 	70% (86%)	87:13
8	**11h** 	51% (77%)	88:12

[a]0.150 mmol **10**, 0.450 mmol **11**, 0.450 mmol **KHMDS**, tetrahydrofuran (THF) (4.2 mL), −78 °C to room temperature (rt). [b]Determined by QNMR; brsm, based on recovered starting material. [c]Determined by high-performance liquid chromatography (HPLC).

and Bn-protecting groups were cleaved simultaneously in one step using methanesulfonic acid and anisole.[11] The spectroscopic data of the synthetic samples of all three natural products were in good agreement with the literature. The developed methodology also allows for a significant decrease in the number of linear steps (LLS) of the total syntheses of PBD

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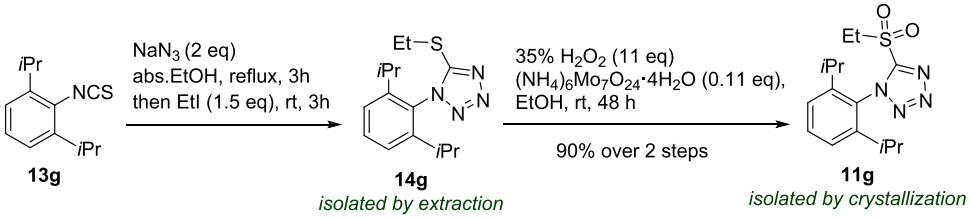
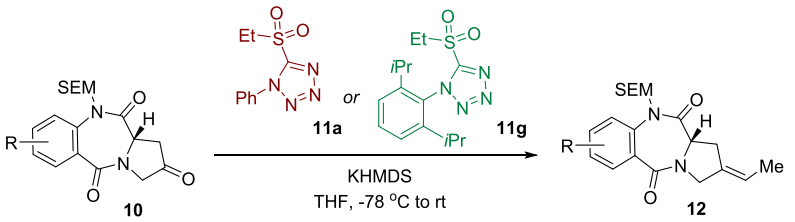
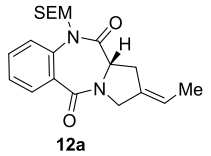
Scheme 2. Optimized Synthesis of Sulfone 11g

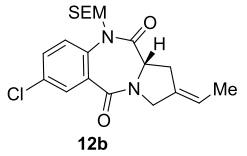


Scheme 3. Substrate Scope of the Julia–Kocienski Olefination of Triones 10

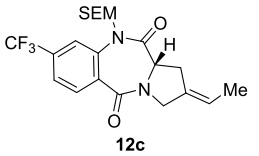




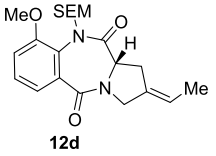
With **11a**
86% QNMR Yield (96% brsm), *E*/*Z*- 72:28
With **11g**
70% QNMR Yield (86% brsm), *E*/*Z*- 87:13
62% Isolated Yield



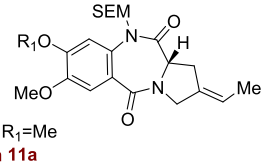
With **11a**
71% QNMR Yield (85% brsm), *E*/*Z*- 78:22
With **11g**
48% QNMR Yield (64% brsm), *E*/*Z*- 86:14
40% Isolated Yield



With **11a**
77% QNMR Yield (96% brsm), *E*/*Z*- 77:23
With **11g**
50% QNMR Yield (61% brsm), *E*/*Z*- 86:14
41% Isolated Yield

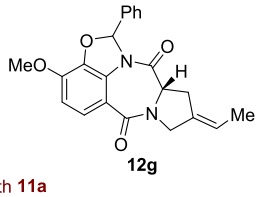


With **11a**
66% QNMR Yield (72% brsm), *E*/*Z*- 72:28
With **11g**
64% QNMR Yield (75% brsm), *E*/*Z*- 85:15
57% Isolated Yield



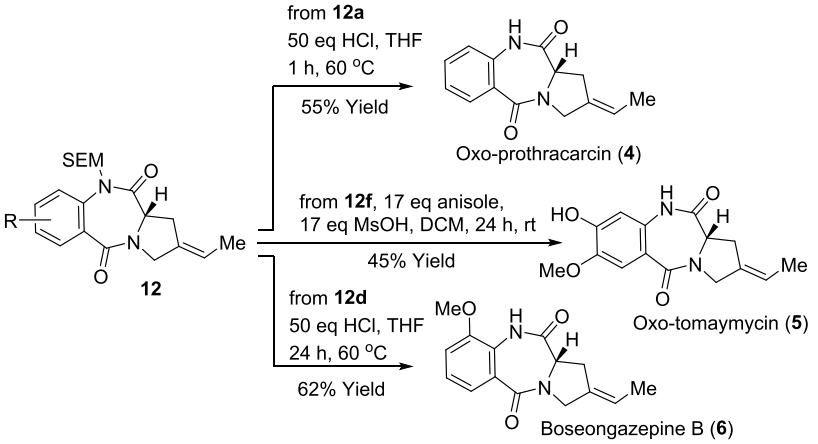
12e R_1=Me
With **11a**
83% QNMR Yield (98% brsm), *E*/*Z*- 82:18
With **11g**
62% QNMR Yield (99% brsm), *E*/*Z*- 92:8
56% Isolated yield

12f R_1=Bn
With **11a**
75% QNMR Yield (93% brsm), *E*/*Z*- 79:21
With **11g**
60% QNMR Yield (89% brsm), *E*/*Z*- 88:12
53% Isolated yield



With **11a**
75% QNMR Yield (90% brsm), *E*/*Z*- 89:11
With **11g**
67% QNMR Yield (75% brsm), *E*/*Z*- 94:6
63% Isolated yield

Scheme 4. Total Synthesis of Oxo-prothracarcin (4), Oxo-tomaymycin (5), and Boseongazepine B (6)



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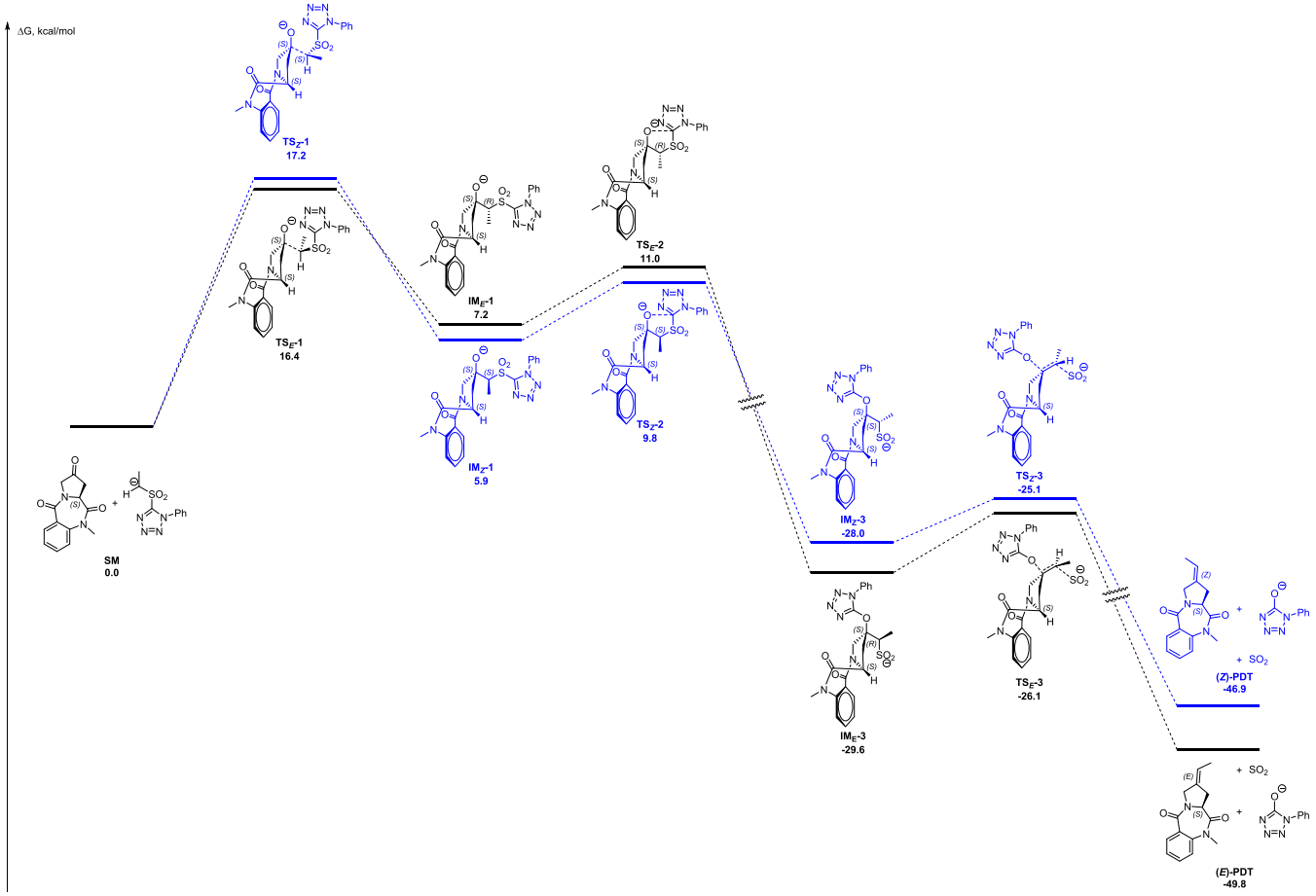
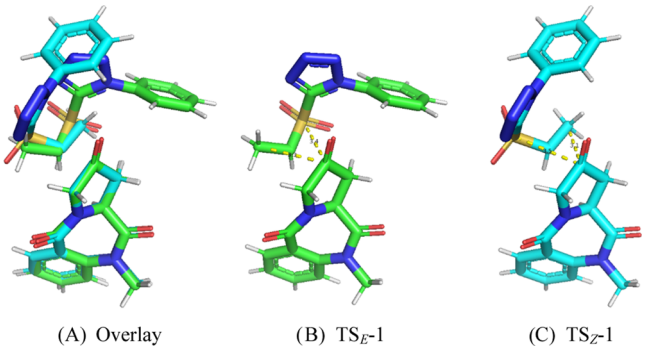
Scheme 5. Potential Energy Surface of the Julia−Kocienski Olefination of PBDs



natural products. For example, oxo-prothracarcin (**4**) and boseongazepine B (**6**) were obtained in seven steps compared to ten steps reported earlier.[17,21]

Although a remarkably high *E*/*Z* ratio of the olefination in the PBD series was observed, the origin of this selectivity remained unclear since the steric discrimination between both sides of the keto group in **1** was not obvious. To understand the observed selectivity, density functional theory (DFT) calculations were performed using the b3lyp/6-311++g-(df,p)//b3lyp/6-31+g(d) method. To simplify the computational model, two approximations were made: (a) *N*-phenyltetrazole sulfone was used instead of *N*-(2,6-diisopropylphenyl) sulfone and (b) *N*-Me substituted ketone **10** was used instead of *N*-SEM ketone **10** (Scheme 5; for computational details, see the Supporting Information). Three distinct transformations of the olefination pathway were elaborated by the calculations: first, nucleophilic addition of the carbanion (TS-1) to the ketone to give an alkoxide; the second is the Smiles rearrangement (TS-2) during which the tetrazole subunit is transferred from the sulfinate to the alkoxide; and third, the formation of the olefine *via* elimination of sulfur dioxide and the tetrazololate leaving group (TS-3). The proposed pathway is in agreement with a previous study by Legnani and Vidari.[25] According to the calculations, the rate-limiting and selectivity-determining step is the first step—the nucleophilic addition of the carbanion to the ketone (TS-1). The Gibbs free energy difference between TS$_E$-1 and TS$_Z$-1 was determined to be 0.8 kcal/mol in favor of the *E* pathway. This is in good agreement with experimental observations that the formation of (*E*)-olefin is favored over (*Z*)-olefin. The energy difference between TS-1 geometries for both *E* and *Z* pathways can be explained by a slight change in the orientation of the approaching carbanion species (Figure 2). The distance



(A) Overlay (B) TS$_E$-1 (C) TS$_Z$-1

Figure 2. Overlay of transition-state geometries (for a detailed view, see the Supporting Information); (A) overlay of TS$_E$-1 (green) and TS$_Z$-1 (cyan), (B) geometry of TS$_E$-1, and (C) geometry of TS$_Z$-1.

from the C atom of the ketone carbonyl group to the S atom (SO_2 subunit) and the C atom (methyl group) of the carbanion in TS$_E$-1 is equidistant (3.4 and 3.3 Å, respectively), whereas in TS$_Z$-1, the carbanion is slightly skewed—the corresponding distances between the C atom of the ketone carbonyl group to the S atom (SO_2 subunit) and the C atom (methyl group) are 3.5 and 3.1 Å, respectively. The change in carbanion orientation increases steric interactions between the

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Me group of the carbanion and the CH_2 group of the ketone in TS_Z-1 compared to that in TS_E-1. The origin of the orientation change can be attributed to the repulsive interactions of the dipoles of the SO_2 subunit of the approaching carbanion and the benzylic amide subunit of the ketone. Indeed, the overall dipole moment of the TS_E-1 (13.4 Debye) is 11% lower than that of the less favored TS_Z-1 (15.1 Debye).

In summary, we have developed a stereoselective Julia–Kocienski olefination approach for the late-stage introduction of an ethylidene substituent in the PBD series. The utility of our developed method is showcased in concise total syntheses of three PBD natural products, namely, oxo-prothracarcin (**4**), oxo-tomaymycin (**5**), and boseongazepine B (**6**). The modified Julia–Kocienski reagent can be conveniently prepared in a two-step sequence starting from commercial isothiocyanate in a column-free fashion.

EXPERIMENTAL SECTION

General Experimental Details. Commercially available reagents and starting materials were used as received. Sulfones **11a** and **11h** and trione **10g** were prepared according to the literature.[20] All reactions in anhydrous solvents were performed under an atmosphere of argon. THF was dried over Na and benzophenone and distilled prior to use, and other solvents were purchased from commercial sources labeled as anhydrous over molecular sieves. For analytical thin-layer chromatography, Merck TLC Silica gel 60 F_{254} plates were used. Flash chromatography was carried out using Zeochem silica gel ZEOprep 60 (40–63 μm) for the direct phase and Biotage KP-C18-HS for the reverse phase. NMR spectra were recorded on Varian Mercury (600 and 400 MHz) and Bruker (300 MHz) spectrometers. Chemical shift values were referenced against residual protons in the deuterated solvents. Cross-peak multiplicity was marked as (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, h = sextet, hept = heptet, m = multiplet, br = broad). Infrared spectra were recorded in the range of 4000–500 cm^{-1} as a film. HRMS spectra were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer (TOF). Optical rotations were measured on a Rudolph Research Analytical Autopol VI polarimeter. Melting points were determined using a Stanford Research System MPA100 apparatus and are uncorrected. Chromatographic analyses for determination of *E*/*Z* isomers were performed on Apollo $C_{18\text{-}12}$ 5 μm (4.6 × 150 mm, isocratic 70% ACN/10% (0.1% H_3PO_4), 1 mL/min flow rate at 40 °C) or ZirChrom CARB 5 μm (4.6 × 150 mm, isocratic 90% ACN/10% (0.1% H_3PO_4), 1.2 mL/min flow rate at 40 °C) columns. Crystallographic data have been registered in the Cambridge Crystallographic Data Centre and assigned the following deposition numbers for the sulfone (2152438) and PBD (2155056).

General Procedure for the Preparation of PBD Triones 10—Step 1. To a stirred solution of the corresponding anthranilic acid (110.1 mmol, 2.0 equiv) and PyBOP (57.3 g, 110.0 mmol, 2.0 equiv) in anhydrous dimethylformamide (DMF) (50 mL) was added triethylamine (TEA) (77.0 mL, 550.6 mmol, 10.0 equiv) at room temperature, and the resulting mixture was stirred for 15 min. Then, methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (10.0 g, 55.0 mmol, 1.0 equiv) was added and stirring was continued for 16 h. After that, the suspension was filtered, and the filtrate was concentrated to ∼1/2 of its original volume and subjected to reverse-phase flash column chromatography (full gradient; water/MeCN 100:0 → 0:100). The product-containing fractions were combined and evaporated *in vacuo* to give the title compound **SI-1**.

*(2R,11aS)-2-Hydroxy-1,2,3,11a-tetrahydro-5H-benzo[e]-pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-1a**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with anthranilic acid (15.10 g, 110.122 mmol, 2 equiv). The title compound was obtained in 11.10 g (87%) as a white solid. $\mathbf{R}_f$ = 0.34 (DCM 1: MeOH 0.1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 10.53 (1H, br.s), 7.79 (1H, dd, J = 7.9, 1.7 Hz), 7.52 (1H, ddd, J = 8.1, 7.3, 1.7 Hz), 7.23 (1H, ddd, J = 7.9, 7.3, 1.2 Hz), 7.13 (1H, dd, J = 8.1, 1.2 Hz), 5.16 (1H, d, J = 4.2 Hz), 4.31 (1H, h, J = 4.4 Hz), 4.19 (1H, dd, J = 8.1, 5.8 Hz), 3.61 (1H, ddd, J = 12.1, 3.8, 1.2 Hz), 3.47 (1H, dd, J = 12.1, 4.8 Hz), 2.62 (1H, dt, J = 13.1, 5.5 Hz), 1.93 (1H, dddd, J = 13.0, 8.2, 4.6, 1.5 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6): δ 170.4, 165.1, 136.3, 132.2, 130.4, 126.0, 124.0, 121.3, 67.4, 55.2, 54.02 34.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{12}H_{13}N_2O_3$, 233.0926; found 233.0934. **IR** (ν_{max}, film): 3383, 3235, 2941, 1691, 1622, 1480, 1445, 1415, 1090, 760 cm^{-1}. $[\alpha]_D^{20}$ = 469° (c = 0.1, MeOH). **MP** = 225–226 °C (water/MeCN).

*(2R,11aS)-7-Chloro-2-hydroxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-1b**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with 2-amino-5-chlorobenzoic acid (3.77 g, 22.024 mmol, 2 equiv). The title compound was obtained in 1.76 g (60%) as a white solid. $\mathbf{R}_f$ = 0.40 (DCM 1: MeOH 0.1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 10.64 (1H, br.s), 7.74 (1H, d, J = 2.6 Hz), 7.59 (1H, dd, J = 8.7, 2.6 Hz), 7.15 (1H, d, J = 8.7 Hz), 5.16 (1H, d, J = 4.3 Hz), 4.31 (1H, h, J = 4.3 Hz), 4.25 (1H, dd, J = 8.1, 5.8 Hz), 3.61 (1H, ddd, J = 12.2, 3.8, 1.5 Hz), 3.48 (1H, dd, J = 12.2, 4.8 Hz), 2.62 (1H, dt, J = 13.1, 5.5 Hz), 1.94 (1H, dddd, J = 12.9, 8.0, 4.5, 1.4 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6): δ 170.2, 163.9, 135.3, 132.0, 129.6, 128.0, 127.4, 123.4, 67.4, 55.2, 54.1, 34.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{12}H_{12}N_2O_3Cl$, 267.0536; found 267.0545. **IR** (ν_{max}, film): 3365, 3212, 3138, 2943, 1622, 1449, 1086, 813 cm^{-1}. $[\alpha]_D^{20}$ = 440° (c = 0.1, MeOH). **MP** = 192–193 °C (water/MeCN).

*(2R,11aS)-2-Hydroxy-8-(trifluoromethyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-1c**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with 2-amino-4-trifluoromethylbenzoic acid (2.93 g, 14.315 mmol, 2 equiv). The title compound was obtained in 0.93 g (43%) as a white solid. $\mathbf{R}_f$ = 0.42 (DCM 9: MeOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 10.75 (1H, br.s), 8.00 (1H, d, J = 8.2 Hz), 7.57 (1H, d, J = 8.2 Hz), 7.48 (1H, br.s), 5.20 (1H, br.s), 4.36–4.26 (2H, m), 3.63 (1H, dd, J = 12.2, 3.8 Hz), 3.50 (1H, dd, J = 12.2, 4.8 Hz), 2.62 (1H, dt, J = 13.1, 5.5 Hz), 1.95 (1H, m). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6) δ 170.4, 164.1, 137.0, 132.1, 132.0 (q, J = 32.1 Hz), 129.2, 123.5 (q, J = 273.0 Hz), 120.1 (q, J = 3.8 Hz), 118.2 (q, J = 3.8 Hz), 67.4, 55.2, 54.2, 34.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{13}H_{12}N_2O_3F_3$, 301.0800; found 301.0811. **IR** (ν_{max}, film): 3458, 3370, 3291, 2963, 2179, 1700, 1635, 1436, 1336, 1141, 667 cm^{-1}. $[\alpha]_D^{20}$ = 369° (c = 0.1, MeOH). **MP** = 213–214 °C (water/MeCN).

*(2R,11aS)-2-Hydroxy-9-methoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-1d**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with 2-amino-3-

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methoxybenzoic acid (7.00 g, 41.846 mmol, 2 equiv). The title compound was obtained in 4.12 g (75%) as a white solid. R_f = 0.42 (DCM 9: MeOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 9.53 (1H, s), 7.38−7.31 (1H, m), 7.26−7.20 (2H, m), 5.14 (1H, d, J = 4.1 Hz), 4.32 (1H, h, J = 4.6 Hz), 4.17 (1H, dd, J = 8.1, 5.7 Hz), 3.85 (3H, s), 3.58 (1H, ddd, J = 12.2, 3.8, 1.5 Hz), 2.62 (1H, dt, J = 13.0, 5.5 Hz), 1.92 (1H, dddd, J = 13.0, 8.1, 4.6, 1.5 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6) δ 169.7, 164.8, 149.8, 127.6, 125.4, 124.8, 121.3, 113.7, 67.4, 56.2, 55.3, 53.9, 34.3. **HRMS-ESI** (m/z): [M + H] calculated for $C_{13}H_{15}N_2O_4$, 263.1032; found 263.1035. **IR** (ν_{max}, film): 3406, 2961, 2840, 1684, 1442, 1260, 1071, 747, 600 cm^{-1}. $[\alpha]_D^{20}$ = 500° (c = 0.1, MeOH). **MP** = 236−238 °C (water/MeCN).

*(2R,11aS)-2-hydroxy-7,8-dimethoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-1e**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with 2-amino-4,5-dimethoxybenzoic acid (5.21 g, 26.429 mmol, 2 equiv). The title compound was obtained in 1.73 g (45%) as a white solid. R_f = 0.21 (DCM 9: MeOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 10.28 (1H, br.s), 7.25 (1H, s), 6.69 (1H, s), 5.12 (1H, d, J = 4.1 Hz), 4.30 (1H, h, J = 4.5 Hz), 4.15 (1H, dd, J = 8.1, 6.0 Hz), 3.78 (3H, s), 3.77 (3H, s), 3.62 (1H, ddd, J = 12.0, 3.7, 1.4 Hz), 3.43 (1H, dd, J = 12.0, 4.8 Hz), 2.60 (1H, dt, J = 13.1, 5.5 Hz), 1.92 (1H, dddd, J = 12.9, 8.0, 4.5, 1.5 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6) δ 170.0, 165.0, 151.7, 145.3, 130.7, 117.8, 111.9, 104.4, 67.4, 55.6 (2 × C), 55.3, 54.0, 34.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{14}H_{17}N_2O_5$, 293.1137; found 293.1151. **IR** (ν_{max}, film): 3429, 3245, 2990, 2836, 1677, 1609, 1519, 1434, 1264, 1011, 868, 624. $[\alpha]_D^{20}$ = 376° (c = 0.1, MeOH). **MP** = 170 °C (dec; water/MeCN).

*(2R,11aS)-8-(Benzyloxy)-2-hydroxy-7-methoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11-(10H)-dione (**SI-1f**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 1 started with 2-amino-4-benzyloxy-5-methoxybenzoic acid (14.15 g, 51.785 mmol, 2 equiv). The title compound was obtained in 6.64 g (38%) as a beige solid. R_f = 0.34 (DCM 10: MeOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 10.31 (1H, s), 7.51−7.32 (5H, m), 7.27 (1H, s), 6.81 (1H, s), 5.15−5.02 (3H, m), 4.30 (1H, h, J = 4.5 Hz), 4.18−4.10 (1H, m), 3.79 (3H, s), 3.62 (1H, ddd, J = 12.0, 3.8, 1.4 Hz), 3.43 (1H, dd, J = 12.0, 4.8 Hz), 2.60 (1H, dt, J = 13.0, 5.5 Hz), 1.92 (1H, dddd, J = 13.0, 8.1, 4.5, 1.4 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6) δ 170.0, 164.9, 150.7, 145.5, 136.2, 130.6, 128.5, 128.2, 128.1, 118.1, 112.1, 105.7, 70.0, 67.4, 55.7, 55.3, 54.0, 34.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{20}H_{21}N_2O_5$, 369.1450; found 369.1455. **IR** (ν_{max}, film): 3399, 3239, 2934, 1627, 1609, 1436, 1270, 1019, 730, 633 cm^{-1}. $[\alpha]_D^{20}$ = 298° (c = 0.1, MeOH). **MP** = 158−159 °C (water/MeCN).

General Procedure for the Preparation of PBD Triones 10—Step 2. To a solution containing **SI-1** (0.86 mmol, 1.0 equiv) and imidazole (175.9 mg, 2.58 mmol, 3.0 equiv) in anhydrous DMF (4 mL) at 0 °C was added TBSCl (389 mg, 2.58 mmol, 3.0 equiv). The mixture was warmed to rt and stirred for 16 h. Then, the reaction mixture was diluted with EtOAc (40 mL) and washed with water (4×30 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated, furnishing the title compound.

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-2a**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1a** (200 mg, 0.860 mmol, 1 equiv). The title compound was obtained in 267 mg (89%) as a white solid. R_f = 0.32 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.12 (1H, br.s), 8.01 (1H, dd, J = 8.0, 1.6 Hz), 7.48 (1H, ddd, J = 8.0, 7.3, 1.6 Hz), 7.29 (1H, ddd, J = 8.0, 7.3, 1.1 Hz), 6.99 (1H, dd, J = 8.0, 1.1 Hz), 4.54 (1H, p, J = 5.4 Hz), 4.22 (1H, dd, J = 8.2, 4.6 Hz), 3.72 (2H, qd, J = 12.0, 5.4 Hz), 2.85 (1H, dtd, J = 13.0, 5.4, 0.8 Hz), 2.08 (1H, dddd, J = 12.9, 8.1, 5.9, 0.8 Hz), 0.87 (9H, s), 0.10 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 171.0, 165.9, 135.1, 132.7, 131.6, 126.8, 125.5, 121.0, 69.4, 55.7, 54.4, 35.4, 25.9, 18.2, −4.6, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{18}H_{27}N_2O_3Si$, 347.1791; found 347.1800. **IR** (ν_{max}, film): 3235, 2954, 2928, 2857, 1695, 1623, 1481, 1251, 1131, 837, 759 cm^{-1}. $[\alpha]_D^{20}$ = 328° (c = 0.1, $CHCl_3$). **MP** = 194-195 °C (EtOAc).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-7-chloro-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H)-dione (**SI-2b**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1b** (1.50 g, 5.624 mmol, 1 equiv). The title compound was obtained in 1.87 g (87%) as a white solid. R_f = 0.42 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.71 (1H, br.s), 7.98 (1H, d, J = 2.5 Hz), 7.43 (1H, dd, J = 8.5, 2.5 Hz), 6.97 (1H, d, J = 8.5 Hz), 4.52 (1H, p, J = 5.0 Hz), 4.21 (1H, dd, J = 8.1, 5.0 Hz), 3.71 (2H, d, J = 5.0 Hz), 2.84 (1H, dt, J = 13.1, 5.0 Hz), 2.08 (1H, ddd, J = 13.2, 8.1, 5.6 Hz), 0.87 (9H, s), 0.09 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.9, 164.7, 133.7, 132.7, 131.2, 131.1, 128.0, 122.6, 69.3, 55.7, 54.6, 35.4, 25.9, 18.2, −4.6, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{18}H_{26}N_2O_3ClSi$, 381.1401; found 381.1414. **IR** (ν_{max}, film): 3227, 2954, 2857, 1700, 1644, 1481, 1438, 1252, 1128, 838, 776 cm^{-1}. $[\alpha]_D^{20}$ = 327° (c = 0.1, $CHCl_3$). **MP** = 177−178 °C (EtOAc).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-8-(trifluoro-methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11(10H)-dione (**SI-2c**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1c** (0.878 g, 2.924 mmol, 1 equiv). The title compound was obtained in 915 mg (75%) as a white solid. R_f = 0.37 (PE 3: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.58 (1H, br.s), 8.15 (1H, d, J = 9.2 Hz), 7.53 (1H, dd, J = 8.6, 1.4 Hz), 7.29 (1H, br.s), 4.54 (1H, p, J = 5.0 Hz), 4.23 (1H, dd, J = 8.1, 5.0 Hz), 3.73 (2H, d, J = 5.0 Hz), 2.86 (1H, dt, J = 13.1, 5.0 Hz), 2.11 (1H, ddd, J = 13.5, 8.1, 5.5 Hz), 0.87 (9H, s), 0.10 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 171.2, 164.8, 135.7, 134.5 (q, J = 33.2 Hz), 132.6, 129.5, 123.0 (q, J = 271.8 Hz), 121.8 (q, J = 3.5 Hz), 118.4 (q, J = 3.7 Hz), 69.3, 55.7, 54.6, 35.4, 25.8, 18.1, −4.8. **HRMS-ESI** (m/z): [M + H] calculated for $C_{19}H_{26}N_2O_3F_3Si$, 415.1665; found 415.1661. **IR** (ν_{max}, film): 3213, 2954, 2931, 2859, 1707, 1647, 1439, 1341, 1135, 838, 776 cm^{-1}. $[\alpha]_D^{20}$ = 280° (c = 0.1, $CHCl_3$). **MP** = 218−219 °C (EtOAc).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-9-methoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H)-dione (**SI-2d**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1d** (3.40 g, 12.964 mmol, 1 equiv). The title compound was obtained in 4.85 g (99%) as a white solid. R_f = 0.43 (PE 1: EA 2). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.91 (1H, br.s), 7.57 (1H, dd, J = 8.0, 1.4 Hz), 7.20 (1H, t, J = 8.0 Hz), 7.02 (1H, dd, J = 8.0, 1.4 Hz), 4.53 (1H, p, J = 5.4 Hz), 4.19

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(1H, dd, J = 8.2, 4.5 Hz), 3.90 (3H, s), 3.74 (1H, dd, J = 12.0, 5.4 Hz), 3.68 (1H, dd, J = 12.0, 5.4 Hz), 2.85 (1H, dddd, J = 13.0, 5.4, 4.5, 1.0 Hz), 2.06 (1H, dddd, J = 13.0, 8.2, 6.0, 1.0 Hz), 0.87 (9H, s), 0.09 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 170.4, 165.8, 148.6, 126.8, 125.2, 125.0, 122.7, 112.9, 69.3, 56.2, 55.9, 54.4, 35.4, 25.9, 18.1, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{19}H_{29}N_2O_4Si$, 377.1897; found 377.1895. **IR** (ν_{max}, film): 3385, 3237, 2953, 2857, 1702, 1636, 1413, 1260, 1130, 754 cm^{-1}. $[\alpha]_D^{20}$ = 312° (c = 0.1, $CHCl_3$).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-7,8-dimethoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H)-dione (**SI-2e**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1e** (1.70 g, 5.816 mmol, 1 equiv). The title compound was obtained in 2.09 g (88%) as a white solid. R_f = 0.25 (PE 1: EA 2). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.46 (1H, br.s), 7.44 (1H, s), 6.47 (1H, s), 4.52 (1H, p, J = 5.6 Hz), 4.20 (1H, dd, J = 8.2, 4.3 Hz), 3.93 (3H, s), 3.90 (3H, s), 3.73 (1H, dd, J = 11.9, 5.5 Hz), 3.65 (1H, dd, J = 11.9, 5.5 Hz), 2.83 (1H, dt, J = 12.8, 5.0 Hz), 2.05 (1H, m), 0.87 (9H, s), 0.09 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 170.9, 165.8, 152.5, 146.7, 129.5, 118.9, 112.5, 103.9, 69.4, 56.4, 56.3, 55.8, 54.3, 35.3, 25.9, 18.2, −4.7 (2 × C). **HRMS-ESI** (m/z): [M + H] calculated for $C_{20}H_{31}N_2O_5Si$, 407.2002; found 407.2009. **IR** (ν_{max}, film): 3273, 2928, 2856, 1699, 1606, 1495, 1258, 1121, 838, 776, 651 cm^{-1}. $[\alpha]_D^{20}$ = 273° (c = 0.1, $CHCl_3$). **MP** = 268−269 °C (EtOAc).

*(2R,11aS)-8-(Benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-7-methoxy-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11(10H)-dione (**SI-2f**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 2 started with **SI-1f** (6.39 g, 17.346 mmol, 1 equiv). The title compound was obtained in 6.42 g (76%) as a white solid. R_f = 0.46 (PE 1: EA 2). **^{1}H NMR** (600MHz; $CDCl_3$): δ 8.36 (1H, br.s), 7.47−7.28 (6H, m), 6.48 (1H, s), 5.16 (2H, dd, J = 19.2, 12.3 Hz), 4.51 (1H, p, J = 5.4 Hz), 4.17 (1H, dd, J = 8.2, 4.5 Hz), 3.92 (3H, s), 3.68 (2H, qd, J = 12.0, 5.4 Hz), 2.81 (1H, dt, J = 12.9, 5.0 Hz), 2.04 (1H, m), 0.87 (9H, s), 0.09 (6H, s). **^{13}C{1H} NMR** (150 MHz, $CDCl_3$) δ 170.8, 165.8, 151.5, 147.2, 136.0, 129.3, 128.9, 128.4, 127.4, 119.2, 112.8, 106.0, 71.2, 69.4, 56.4, 55.8, 54.3, 35.3, 25.9, 18.1, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{26}H_{35}N_2O_5Si$, 483.2315; found 483.2321. **IR** (ν_{max}, film): 3220, 2953, 1700, 1609, 1517, 1430, 1254, 1121, 1005, 836, 778 cm^{-1}. $[\alpha]_D^{20}$ = 189° (c = 0.1, $CHCl_3$).

General Procedure for the Preparation of PBD Triones 10—Step 3. To a stirred suspension of NaH (60% in mineral oil, 101.6 mg, 2.54 mmol, 1.1 equiv; washed twice with dry THF before the reaction) in THF (5 mL, freshly distilled over Na/Ph_2CO) was added a solution of **SI-2** (2.308 mmol, 1.0 equiv) in dry THF (15 mL) at 0 °C, and the mixture was stirred until hydrogen evolution ceased (approx. 15 min). Then, to the reaction mixture was added a solution of SEMCl (1.1 mL, 5.771 mmol, 2.5 equiv) in dry THF (5 mL), and stirring was continued for 16 h at rt. Next, the suspension was cooled (ice bath), quenched with water (50 mL), extracted with DCM (2 × 50 mL), and dried (Na_2SO_4). Volatiles were evaporated, and the residue was purified on silica gel (PE/EtOAc). The product-containing fractions were combined and evaporated *in vacuo*, furnishing the title compound.

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-3a**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2a** (800 mg, 2.308 mmol, 1 equiv). The title compound was obtained in 920 mg (83%) as colorless oil. R_f = 0.41 (PE 2: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.91 (1H, dd, J = 7.8, 1.7 Hz), 7.67 (1H, dd, J = 8.2, 0.9 Hz), 7.52 (1H, ddd, J = 8.2, 7.3, 1.7 Hz), 7.34 (1H, ddd, J = 7.8, 7.3, 1.1 Hz), 5.50 (1H, d, J = 9.9 Hz), 4.73 (1H, d, J = 9.9 Hz), 4.59 (1H, p, J = 5.8 Hz), 4.22 (1H, dd, J = 8.1, 3.9 Hz), 3.80−3.70 (2H, m), 3.65 (1H, ddd, J = 9.6, 8.7, 7.8 Hz), 3.56 (1H, dd, J = 11.7, 5.5 Hz), 2.86 (1H, ddd, J = 12.2, 5.0, 3.9 Hz), 2.03 (1H, dddd, J = 13.0, 8.2, 6.4, 0.9 Hz), 0.98 (2H, dd, J = 8.8, 7.9 Hz), 0.87 (9H, s), 0.09 (6H, s), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.1, 165.9, 139.8, 132.5, 130.3, 129.3, 126.5, 122.7, 78.1, 69.7, 67.1, 56.5, 53.8, 35.7, 25.9, 18.4, 18.1, −1.3, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{24}H_{41}N_2O_4Si_2$, 477.2605; found 477.2614. **IR** (ν_{max}, film): 2953, 2857, 1690, 1652, 1461, 1411, 1250, 1129, 1072, 861, 837, 777, 762, 709 cm^{-1}. $[\alpha]_D^{20}$ = 237° (c = 0.1, $CHCl_3$).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-7-chloro-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-3b**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2b** (1.80 g, 4.725 mmol, 1 equiv). The title compound was obtained in 1.60 g (66%) as a colorless oil. R_f = 0.48 (PE 3: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.88 (1H, d, J = 2.6 Hz), 7.64 (1H, d, J = 8.8 Hz), 7.47 (1H, dd, J = 8.8, 2.6 Hz), 5.50 (1H, d, J = 9.9 Hz), 4.66 (1H, d, J = 9.9 Hz), 4.57 (1H, p, J = 5.5 Hz), 4.21 (1H, dd, J = 8.1, 4.1 Hz), 3.77−3.61 (3H, m), 3.57 (1H, dd, J = 11.9, 5.0 Hz), 2.86 (1H, m), 2.04 (1H, m), 0.98 (2H, m), 0.87 (9H, s), 0.09 (6H, s), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.7, 164.6, 138.31, 132.5, 132.3, 130.6, 130.1, 124.2, 78.1, 69.6, 67.2, 56.5, 54.0, 35.7, 25.9, 18.4, 18.1, −1.3, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{24}H_{40}N_2O_4ClSi_2$, 511.2215; found 511.2227. **IR** (ν_{max}, film): 2953, 2858, 1695, 1652, 1441, 1363, 1250, 1071, 836, 776 cm^{-1}. $[\alpha]_D^{20}$ = 230° (c = 0.1, $CHCl_3$).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-8-(trifluoromethyl)-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-3c**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2c** (900 mg, 2.171 mmol, 1 equiv). The title compound was obtained in 623 g (52%) as colorless oil. R_f = 0.53 (PE 3: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.03 (1H, d, J = 8.2 Hz), 8.01 (1H, br.s), 7.58 (1H, ddd, J = 8.2, 1.8, 0.7 Hz), 5.55 (1H, d, J = 10.0 Hz), 4.70 (1H, d, J = 10.0 Hz), 4.58 (1H, p, J = 5.4 Hz), 4.22 (1H, dd, J = 8.1, 4.3 Hz), 3.82−3.64 (3H, m), 3.61 (1H, ddd, J = 12.3, 5.0, 1.0 Hz), 2.87 (1H, dt, J = 13.0, 4.9 Hz), 2.10−2.01 (1H, m), 0.98 (2H, m), 0.86 (9H, s), 0.09 (6H, s), 0.03 (9, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.7, 164.7, 140.2, 134.4 (q, J = 33.0 Hz), 132.1, 131.3, 123.2 (q, J = 274.5 Hz), 123.1 (q, J = 3.6 Hz), 120.0 (q, J = 3.6 Hz), 78.0, 69.6, 67.5, 56.5, 54.1, 35.8, 25.8, 18.3, 18.1, −1.3, −4.7 (2 × C). **HRMS-ESI** (m/z): [M + H] calculated for $C_{25}H_{40}N_2O_4F_3Si_2$, 545.2479; found 545.2476. **IR** (ν_{max}, film): 2954, 2930, 2896, 2859, 1699, 1656, 1447, 1319, 1251, 1133, 1070, 838 cm^{-1}. $[\alpha]_D^{20}$ = 219° (c = 0.1, $CHCl_3$).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-9-methoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-**

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3d). Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2d** (5.09 g, 13.518 mmol, 1 equiv). The title compound was obtained in 6.70 g (97%) as colorless oil. R_f = 0.45 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.48 (1H, dd, J = 7.9, 1.4 Hz), 7.35 (1H, t, J = 7.9 Hz), 7.07 (1H, dd, J = 7.9, 1.4 Hz), 5.72 (1H, d, J = 10.5 Hz), 4.96 (1H, d, J = 10.5 Hz), 4.62 (1H, p, J = 5.7 Hz), 4.16 (1H, dd, J = 8.0, 3.8 Hz), 3.88 (3H, s), 3.78 (1H, dd, J = 12.0, 6.0 Hz), 3.50 (1H, dd, J = 12.0, 5.5 Hz), 3.39−3.27 (2H, m), 2.84 (1H, ddd, J = 12.3, 5.7, 3.5 Hz), 2.01−1.92 (1H, m), 0.86 (9H, s), 0.83−0.65 (2H, m), 0.08 (6H, s), −0.07 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.9, 165.4, 152.8, 133.6, 128.2, 126.7, 121.6, 114.4, 75.2, 69.8, 66.3, 56.9, 56.0, 53.5, 35.4, 25.9, 18.1, 17.9, −1.4, −4.7. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{25}H_{42}N_2O_5Si_2Na$, 529.2530; found 529.2541. **IR** (ν_{max}, film): 2952, 1652, 1410, 1258, 1075, 837 cm^{-1}. $[\alpha]_D^{20}$ = 116° (c = 0.1, $CHCl_3$).

*(2R,11aS)-2-((tert-Butyldimethylsilyl)oxy)-7,8-dimethoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-3e**)*. Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2e** (100 mg, 0.246 mmol, 1 equiv). The title compound was obtained in 126 mg (95%) as colorless oil. R_f = 0.52 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34 (1H, s), 7.23 (1H, s), 5.52 (1H, d, J = 9.9 Hz), 4.64 (1H, d, J = 9.9 Hz), 4.58 (1H, p, J = 5.7 Hz), 4.23 (1H, dd, J = 7.9, 3.9 Hz), 3.94 (3H, s), 3.91 (3H, s), 3.83−3.63 (3H, m), 3.55 (1H, dd, J = 11.8, 5.7 Hz), 2.85 (1H, ddd, J = 12.2, 5.2, 3.8 Hz), 2.06−1.98 (1H, m), 0.98 (2H, m), 0.87 (9H, s), 0.10 (6H, s), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.1, 165.8, 152.0, 147.3, 134.1, 121.6, 111.4, 105.6, 78.2, 69.7, 67.2, 56.7, 56.3 (2 × C), 53.8, 35.6, 25.9, 18.5, 18.2, −1.2, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{26}H_{45}N_2O_6Si_2$, 537.2816; found 537.2838. **IR** (ν_{max}, film): 2952, 2857, 1684, 1652, 1517, 1456, 1434, 1361, 1249, 1130, 1069, 836, 777 cm^{-1}. $[\alpha]_D^{20}$ = 209° (c = 0.1, $CHCl_3$).

*(2R,11aS)-8-(Benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-7-methoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-3f**)*. Prepared according to the general procedure for the preparation of PBD triones **10**. Step 3 started with **SI-2f** (6.40 g, 13.260 mmol, 1 equiv). The title compound was obtained in 7.62 g (93%) as colorless oil. R_f = 0.39 (PE 2: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.46−7.40 (2H, m), 7.40−7.28 (4H, m), 7.24 (1H, br.s), 5.42 (1H, d, J = 9.8 Hz), 5.20 (2H, m), 4.56 (1H, p, J = 5.8 Hz), 4.47 (1H, d, J = 9.8 Hz), 4.20 (1H, dd, J = 8.2, 3.9 Hz), 3.94 (3H, s), 3.77−3.63 (2H, m), 3.64−3.49 (2H, m), 2.83 (1H, m), 2.00 (1H, m), 0.95 (2H, m), 0.86 (9H, s), 0.09 (6H, s), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.0, 165.7, 150.9, 147.7, 136.1, 133.8, 128.8, 128.3, 127.5, 121.8, 111.7, 107.8, 78.1, 71.0, 69.7, 67.0, 56.6, 56.4, 53.7, 35.6, 25.9, 18.5, 18.1, −1.2, −4.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{32}H_{49}N_2O_6Si_2$, 613.3129; found 613.3140. **IR** (ν_{max}, film): 3447, 2953, 2894, 1689, 1641, 1463, 1361, 1249, 1129, 1069, 836, 776 cm^{-1}. $[\alpha]_D^{20}$ = 189° (c = 0.1, $CHCl_3$).

General Procedure for the Preparation of PBD Triones 10—Step 4. To a stirred solution of **SI-3** (2.936 mmol, 1.0 equiv) in THF (60 mL) was added TBAF trihydrate (1.43 g, 4.404 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred for 3 h at room temperature. Then, volatiles were evaporated *in vacuo* and the residual oil was purified on silica gel (EtOAc:EtOH). The product-containing fractions were combined and evaporated *in vacuo* furnishing the title compound.

*(2R,11aS)-2-Hydroxy-10-((2-(trimethylsilyl)ethoxy)-methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11(10H)-dione (**SI-4a**)*. Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 started with **SI-3a** (1.40 g, 2.936 mmol, 1.0 equiv). The title compound was obtained in 893 mg (84%) as colorless oil. R_f = 0.43 (EA 1: EtOH 0.05). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.87 (1H, dd, J = 7.8, 1.7 Hz), 7.68 (1H, dd, J = 8.2, 1.2 Hz), 7.52 (1H, ddd, J = 8.2, 7.3, 1.7 Hz), 7.32 (1H, td, J = 7.8, 1.2 Hz), 5.50 (1H, d, J = 9.8 Hz), 4.74 (1H, d, J = 9.8 Hz), 4.67 (1H, m), 4.30 (1H, dd, J = 8.1, 5.6 Hz), 3.87 (1H, ddd, J = 12.7, 3.5, 1.6 Hz), 3.79−3.61 (3H, m), 2.99 (1H, dt, J = 13.6, 5.5 Hz), 2.18 (1H, d, J = 3.7 Hz), 2.13 (1H, dddd, J = 13.6, 8.1, 4.2, 1.6 Hz), 0.99 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.8, 166.0, 139.8, 132.6, 130.4, 129.1, 126.6, 122.8, 78.2, 69.5, 67.1, 56.4, 54.1, 35.2, 18.4, −1.3. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{18}H_{26}N_2O_4SiNa$, 385.1560; found 385.1558. **IR** (ν_{max}, film): 3393, 2952, 2895, 1694, 1634, 1463, 1249, 1076, 763 cm^{-1}. $[\alpha]_D^{20}$ = 275° (c = 0.1, $CHCl_3$).

*(2R,11aS)-7-Chloro-2-hydroxy-10-((2-(trimethylsilyl)-ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-4b**)*. Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 starting from **SI-3b** (1.60 g, 3.130 mmol, 1.0 equiv). The title compound was obtained in 1.15 g (93%) as colorless foam. R_f = 0.47 (EA 100: EtOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.81 (1H, d, J = 2.5 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.47 (1H, dd, J = 8.7, 2.5 Hz), 5.51 (1H, d, J = 9.9 Hz), 4.68 (1H, d, J = 9.9 Hz), 4.66 (1H, m), 4.31 (1H, dd, J = 8.1, 6.0 Hz), 3.89 (1H, ddd, J = 12.8, 3.1, 1.7 Hz), 3.78−3.61 (3H, m), 2.98 (1H, dt, J = 13.7, 5.6 Hz), 2.24 (1H, br.s), 2.16 (1H, dddd, J = 13.7, 8.1, 3.8, 1.8 Hz), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.4, 164.8, 138.3, 132.6, 132.4, 130.4, 130.1, 124.3, 78.2, 69.4, 67.3, 56.4, 54.3, 35.2, 18.4, −1.3. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{18}H_{25}N_2O_4SiClNa$, 419.1170; found 419.1165. **IR** (ν_{max}, film): 3404, 2953, 2894, 1694, 1639, 1444, 1362, 1249, 1075, 836 cm^{-1}. $[\alpha]_D^{20}$ = 274° (c = 0.1, $CHCl_3$). **MP** = 60−61 °C (EtOAc:EtOH).

*(2R,11aS)-2-Hydroxy-8-(trifluoromethyl)-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-4c**)*. Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 started with **SI-3c** (620 mg, 1.138 mmol, 1.0 equiv). The title compound was obtained in 325 mg (66%) as colorless foam. R_f = 0.37 (EA 100: EtOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.01 (1H, br.s), 7.99 (1H, d, J = 8.2 Hz), 7.57 (1H, dd, J = 8.2, 1.1 Hz), 5.56 (1H, d, J = 10.0 Hz), 4.71 (1H, d, J = 10.0 Hz), 4.67 (1H, m), 4.29 (1H, dd, J = 8.0, 5.9 Hz), 3.89 (1H, ddd, J = 12.7, 3.2, 1.6 Hz), 3.84−3.73 (1H, m), 3.72−3.62 (2H, m), 2.99 (1H, dt, J = 13.7, 5.5 Hz), 2.35 (1H, d, J = 3.7 Hz), 2.16 (1H, dddd, J = 13.7, 8.1, 3.9, 1.7 Hz), 1.04−0.94 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.4, 164.9, 140.2, 134.5 (q, J = 33.0 Hz), 131.9, 131.3, 123.2 (q, J = 275.1 Hz), 123.1 (q, J = 3.6 Hz), 120.0 (q, J = 3.6 Hz), 78.1, 69.3, 67.5, 56.4, 54.3, 35.2, 18.3, −1.3. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{19}H_{25}N_2O_4SiF_3Na$, 453.1433; found 453.1429.

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IR (ν_{max}, film): 3392, 2954, 1702, 1639, 1321, 1174, 1133, 1083, 860, 838 cm^{-1}. $[\alpha]_D^{20}$ = 256° (*c* = 0.1, $CHCl_3$).

*(2R,11aS)-2-Hydroxy-9-methoxy-10-((2-(trimethylsilyl)-ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-4d**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 started with **SI-3d** (6.70 g, 13.220 mmol, 1.0 equiv). The title compound was obtained in 3.41 g (65%) as colorless foam. R_f = 0.38 (EA 20: EtOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.41 (1H, dd, *J* = 7.9, 1.5 Hz), 7.31 (1H, t, *J* = 8.0 Hz), 7.06 (1H, dd, *J* = 8.0, 1.5 Hz), 5.70 (1H, d, *J* = 10.4 Hz), 4.95 (1H, d, *J* = 10.4 Hz), 4.63 (1H, h, *J* = 4.6 Hz), 4.22 (1H, dd, *J* = 8.2, 5.5 Hz), 3.87 (3H, s), 3.81 (1H, ddd, *J* = 12.6, 3.5, 1.6 Hz), 3.63 (1H, dd, *J* = 12.6, 4.8 Hz), 3.38−3.24 (2H, m), 3.08 (1H, d, *J* = 3.8 Hz), 2.93 (1H, dt, *J* = 13.5, 5.4 Hz), 2.04 (1H, dddd, *J* = 13.7, 8.2, 4.2, 1.6 Hz), 0.81−0.61 (2H, m), −0.10 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.6, 165.6, 152.7, 133.3, 128.2, 126.7, 121.6, 114.5, 75.3, 69.4, 66.3, 56.8, 56.0, 53.8, 34.7, 17.9, −1.4. **HRMS-ESI** (*m*/*z*): [M + Na] calculated for $C_{19}H_{28}N_2O_5SiNa$, 415.1665; found 415.1663. $[\alpha]_D^{20}$ = 133° (*c* = 0.1, $CHCl_3$). **MP** = 159−160 °C (EtOAc:EtOH).

*(2R,11aS)-2-Hydroxy-7,8-dimethoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-4e**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 started with **SI-3e** (573 mg, 1.067 mmol, 1.0 equiv). The title compound was obtained in 305 mg (68%) as colorless foam. R_f = 0.31 (EA 20: EtOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32 (1H, s), 7.23 (1H, s), 5.52 (1H, d, *J* = 9.9 Hz), 4.64 (1H, d, *J* = 9.9 Hz overlapping with 1H, m), 4.30 (1H, dd, *J* = 8.1, 5.6 Hz), 3.90 (6H, br.s), 3.87 (1H, ddd, *J* = 12.5, 3.6, 1.6 Hz), 3.79 (1H, m), 3.71−3.60 (2H, m), 2.96 (1H, dt, *J* = 13.5, 5.5 Hz), 2.52 (1H, br.s), 2.12 (1H, m), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.8, 166.0, 152.1, 147.2, 134.1, 121.3, 111.4, 105.6, 78.3, 69.4, 67.2, 56.6, 56.3, 56.2, 54.0, 35.1, 18.5, −1.2. **HRMS-ESI** (*m*/*z*): [M + H] calculated for $C_{20}H_{31}N_2O_6Si$, 423.1951; found 423.1956. **IR** (ν_{max}, film): 3379, 2954, 1683, 1634, 1519, 1456, 1436, 1360, 1249, 1062, 861, 837, 756 cm^{-1}. $[\alpha]_D^{20}$ = 258° (*c* = 0.1, $CHCl_3$).

*(2R,11aS)-8-(Benzyloxy)-2-hydroxy-7-methoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**SI-4f**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 4 started with **SI-3e** (7.60 g, 12.400 mmol, 1.0 equiv). The title compound was obtained in 5.22 g (84%) as a white solid. R_f = 0.41 (EA 20: EtOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.43 (2H, m), 7.38−7.28 (4H, m), 7.24 (1H, s), 5.42 (1H, d, *J* = 9.8 Hz), 1.98 (2H, s), 4.62 (1H, m), 4.49 (1H, d, *J* = 9.8 Hz), 4.27 (1H, dd, *J* = 8.1, 5.6 Hz), 3.91 (3H, s), 3.86 (1H, ddd, *J* = 12.5, 3.6, 1.5 Hz), 3.75−3.54 (3H, m), 2.94 (1H, dt, *J* = 13.6, 5.4 Hz), 2.47 (1H, d, *J* = 3.6 Hz), 2.10 (1H, dddd, *J* = 13.8, 8.1, 4.4, 1.6 Hz), 0.96 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.7, 165.9, 151.0, 147.7, 136.1, 133.9, 128.8, 128.3, 127.5, 121.5, 111.7, 107.8, 78.2, 71.0, 69.4, 67.1, 56.5, 56.3, 54.0, 35.1, 18.5, −1.2. **IR** (ν_{max}, film): 3378, 2952, 1683, 1626, 1466, 1361, 1248, 1060, 836, 755 cm^{-1}. **HRMS-ESI** (*m*/*z*): [M + H] calculated for $C_{26}H_{35}N_2O_6Si$, 499.2264; found 499.2286. $[\alpha]_D^{20}$ = 245° (*c* = 0.1, $CHCl_3$). **MP** = 69−70 °C (EtOAc:EtOH).

General Procedure for the Preparation of PBD Triones 10—Step 5. To a solution of **SI-4** (16.827 mmol, 1.0 equiv) in anhydrous DCM (200 mL) was added DMP (11.0, 25.241 mmol, 1.5 equiv) at room temperature, and the reaction was stirred for 16 h. Then, sat. aqueous $Na_2S_2O_3$ solution (100 mL) was added, the organic layer was separated and the aqueous phase was extracted with DCM (2 × 100 mL). Combined organic extracts were washed with sat. $NaHCO_3$ (200 mL) and brine (100 mL) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was purified on silica gel (PE/EtOAc). The product-containing fractions were combined and evaporated *in vacuo*, furnishing the title compound.

*(S)-10-((2-(Trimethylsilyl)ethoxy)methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-2,5,11(3H,10H)-trione (**10a**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4a** (6.10 g, 16.827 mmol, 1.0 equiv). The title compound was obtained in 5.30 g (87%) as colorless foam. R_f = 0.45 (PE 1: EA 2). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.91 (1H, dd, *J* = 7.8, 1.7 Hz), 7.72 (1H, dd, *J* = 8.3, 1.2 Hz), 7.59 (1H, ddd, *J* = 8.3, 7.3, 1.7 Hz), 7.40 (1H, ddd, *J* = 8.7, 7.8, 1.2 Hz), 5.53 (1H, d, *J* = 9.9 Hz), 4.79 (1H, d, *J* = 9.9 Hz), 4.63 (1H, dd, *J* = 9.9, 3.0 Hz), 4.22 (1H, br.d, *J* = 19.9 Hz), 3.92 (1H, br.d, *J* = 19.9 Hz), 3.78−3.61 (2H, m), 3.61−3.54 (1H, m), 2.79 (1H, ddd, *J* = 9.9, 1.5, 0.5 Hz), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.7, 168.9, 166.2, 139.8, 133.1, 130.3, 128.4, 127.1, 123.0, 78.3, 67.3, 54.8, 52.3, 37.5, 18.4, −1.3. **HRMS-ESI** (*m*/*z*): [M − H] calculated for $C_{18}H_{23}N_2O_4Si$, 359.1427; found 359.1436. **IR** (ν_{max}, film): 3463, 2950, 1765, 1688, 1648, 1462, 1410, 1248, 1075, 837 cm^{-1}. $[\alpha]_D^{20}$ = 361° (*c* = 0.1, $CHCl_3$).

*(S)-7-Chloro-10-((2-(trimethylsilyl)ethoxy)methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-2,5,11-(3H,10H)-trione (**10b**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4b** (1.10 g, 2.771 mmol, 1.0 equiv). The title compound was obtained in 933 mg (85%) as colorless foam. R_f = 0.58 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.89 (1H, d, *J* = 2.4 Hz), 7.70 (1H, d, *J* = 8.8 Hz), 7.54 (1H, dd, *J* = 8.8, 2.4 Hz), 5.54 (1H, d, *J* = 10.0 Hz), 4.73 (1H, d, *J* = 10.0 Hz), 4.62 (1H, dd, *J* = 10.0, 3.0 Hz), 4.22 (1H, br.d, *J* = 20.0 Hz), 3.92 (1H, br.d, *J* = 20.0 Hz), 3.78−3.62 (2H, m), 3.58 (1H, m), 2.80 (1H, ddd, *J* = 10.8, 10.0, 1.2 Hz), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.2, 168.6, 164.9, 138.3, 133.1, 132.9, 130.1, 129.7, 124.5, 78.2, 67.5, 54.8, 52.4, 37.4, 18.4, −1.3. **HRMS-ESI** (*m*/*z*): [M + Na] calculated for $C_{18}H_{23}N_2O_4ClSiNa$, 417.1013; found 417.1024. **IR** (ν_{max}, film): 2953, 2897, 1768, 1694, 1653, 1448, 1367, 1248,1071, 835, 754 cm^{-1}. $[\alpha]_D^{20}$ = 377° (*c* = 0.1, $CHCl_3$). **MP** = 58−59 °C (PE/EtOAc).

*(S)-8-(Trifluoromethyl)-10-((2-(trimethylsilyl)ethoxy)-methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-2,5,11(3H,10H)-trione (**10c**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4c** (308 mg, 0.715 mmol, 1.0 equiv). The title compound was obtained in 165 mg (53%) as colorless foam. R_f = 0.24 (PE 2: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.04 (2H, m), 7.65 (1H, dd, *J* = 8.1, 1.2 Hz), 5.60 (1H, d, *J* = 10.0 Hz), 4.77 (1H, d, *J* = 10.0 Hz), 4.62 (1H, dd, *J* = 9.9, 3.1 Hz), 4.24 (1H, m), 3.94 (1H, m), 3.84−3.55 (3H, m), 2.82 (1H, ddd, *J* = 11.0, 9.5, 1.2 Hz), 0.99 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.0, 168.5,

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165.0, 140.3, 135.0 (q, J = 34.0 Hz), 131.4, 131.2, 123.6 (q, J = 3.5 Hz), 123.0 (q, J = 273.0 Hz), 120.2 (q, J = 3.5 Hz), 78.2, 67.7, 54.8, 52.4, 37.4, 18.3, −1.3. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{19}H_{23}N_2O_4SiF_3Na$, 451.1277; found 451.1288. **IR** (ν_{max}, film): 2954, 2898, 1768, 1697, 1651, 1446, 1321, 1132, 839 cm^{-1}. $[\alpha]_D^{20}$ = 280° (c = 0.1, $CHCl_3$).

*(S)-9-Methoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-2,5,11(3H,10H)-trione (**10d**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4d** (3.41 g, 8.687 mmol, 1.0 equiv). The title compound was obtained in 3.21 g (94%) as colorless foam. R_f = 0.31 (ether). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.47 (1H, dd, J = 7.9, 1.5 Hz), 7.40 (1H, dd, J = 8.2, 7.9 Hz), 7.13 (1H, dd, J = 8.2, 1.5 Hz), 5.72 (1H, d, J = 10.5 Hz), 5.02 (1H, d, J = 10.5 Hz), 4.57 (1H, dd, J = 9.7, 2.8 Hz), 4.17 (1H, d, J = 19.6 Hz), 3.91 (3H, s), 3.88 (1H, d, J = 19.6 Hz, overlapping with 3H of MeO), 3.55−3.46 (1H, m), 3.40−3.28 (2H, m), 2.71 (1H, ddd, J = 10.9, 9.7, 1.2 Hz), 0.84−0.64 (2H, m), −0.09 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.9, 169.6, 165.8, 152.9, 132.6, 128.8, 126.6, 121.5, 114.9, 75.4, 66.6, 56.1, 55.2, 52.1, 37.3, 18.0, −1.3. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{19}H_{26}N_2O_5SiNa$, 413.1509; found 413.1522. **IR** (ν_{max}, film): 3395, 2952, 1627, 1444, 1248, 1074, 836, 754 cm^{-1}. $[\alpha]_D^{20}$ = 182° (c = 0.1, $CHCl_3$).

*(S)-7,8-Dimethoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-2,5,11(3H,10H)-trione (**10e**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4e** (205 mg, 0.674 mmol, 1.0 equiv). The title compound was obtained in 208 mg (73%) as colorless foam. R_f = 0.25 (PE 1: EA 2). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33 (1H, br.s), 7.26 (1H, br.s), 5.55 (1H, d, J = 9.9 Hz), 4.70 (1H, d, J = 9.9 Hz), 4.64 (1H, dd, J = 9.9, 3.1 Hz), 4.24 (1H, d, J = 20.1 Hz), 3.95 (3H, s), 3.92 (3H, s), 3.90 (1H, d, J = 20.1 Hz), 3.79 (1H, td, J = 9.7, 6.8 Hz), 3.68 (1H, td, J = 9.7, 6.8 Hz), 3.58 (1H, m), 2.79 (1H, ddd, J = 11.3, 9.9, 1.2 Hz), 0.98 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.9, 168.9, 166.1, 152.5, 147.7, 134.1, 120.6, 111.2, 105.7, 78.4, 67.4, 56.4, 56.4, 54.9, 52.4, 37.5, 18.5, −1.2. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{20}H_{28}N_2O_6SiNa$, 443.1614; found 443.1606. **IR** (ν_{max}, film): 2953, 1766, 1687, 1645, 1608, 1519, 1436, 1360, 1251, 1069, 1014, 838, 761 cm^{-1}. $[\alpha]_D^{20}$ = 344° (c = 0.1, $CHCl_3$).

*(S)-8-(Benzyloxy)-7-methoxy-10-((2-(trimethylsilyl)-ethoxy)methyl)-1,11a-dihydro-5H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-2,5,11(3H,10H)-trione (**10f**).* Prepared according to the general procedure for the preparation of PBD triones **10**. Step 5 started with **SI-4f** (5.20 g, 10.428 mmol, 1.0 equiv). The title compound was obtained in 3.08 g (59%) as colorless foam. R_f = 0.39 (PE 1: EA 2). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.46−7.42 (2H, m), 7.41−7.32 (4H, m), 7.28 (1H, s), 5.46 (1H, d, J = 9.9 Hz), 5.22 (2H, dd, J = 14.3, 12.6 Hz), 4.61 (1H, dd, J = 9.9, 3.2 Hz), 4.54 (1H, d, J = 9.9 Hz), 4.23 (1H, m), 3.95 (3H, s), 3.88 (1H, m), 3.74−3.51 (3H, m), 2.77 (1H, ddd, J = 11.0, 9.9, 1.2 Hz), 0.87−0.81 (2H, m), 0.04 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 206.9, 168.8, 166.0, 151.4, 148.2, 135.9, 133.9, 128.9, 128.5, 127.6, 120.7, 111.6, 107.9, 78.3, 71.1, 67.3, 56.4, 54.9, 52.4, 37.4, 18.5, −1.2. **HRMS-ESI** (m/z): [M + H] calculated for $C_{26}H_{33}N_2O_6Si$, 497.2108; found 497.2090. **IR** (ν_{max}, film): 2952, 1766, 1688, 1646, 1435, 1249, 1068, 837, 754 cm^{-1}. $[\alpha]_D^{20}$ = 290° (c = 0.1, $CHCl_3$).

General Procedure for the Preparation of Julia−Kocienski Reagents 11—Step 1. To a solution of isothiocyanate (39.845 mmol, 1.0 equiv) in *i*PrOH (40 mL), sodium azide (5.2 g, 79.691 mmol, 2.0 equiv) and water (65 mL) were added subsequentially, and the resulting mixture was heated in a sealed tube at 100 °C for 5 h. Then, the reaction was cooled to ambient temperature, quenched with 3N HCl (60 mL), partially evaporated (∼1/2 of the initial volume), and extracted with DCM (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo*, furnishing the title compound. The obtained material was used in the next step without further purification.

*1-(4-Methoxyphenyl)-1H-tetrazole-5-thiol (**SI-5b**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 1 started with 1-isothiocyanato-4-methoxybenzene (9.56 g, 57.913 mmol, 1.0 equiv). The product was used in the next step without further purification.

*1-(4-Cyanophenyl)-1H-tetrazole-5-thiol (**SI-5c**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 1 started with 4-isothiocyanatobenzonitrile (1.00 g, 6.242 mmol, 1.0 equiv). The product was purified by silica pad filtration (EtOAc). The title compound was obtained in 345 mg (27%) as a beige solid. R_f = 0.23 (EtOAc 10: EtOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 8.24 (2H, m), 8.11 (2H, m). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6): δ 163.9, 137.7, 133.5, 124.4, 118.0, 111.9. **HRMS-ESI** (m/z): [M − H] calculated for $C_8H_4N_5S$, 202.0187; found 202.0190. **IR** (ν_{max}, film): 3076, 2937, 2239, 1607, 1476, 1352, 1272, 1045, 842, 578 cm^{-1}. **MP** = 168−169 °C (EtOAc).

*1-(4-Fluorophenyl)-1H-tetrazole-5-thiol (**SI-5d**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 1 started with 1-fluoro-4-isothiocyanatobenzene (2.00 g, 13.056 mmol, 1.0 equiv). The product was purified by silica pad filtration (EtOAc). The title compound was obtained in 728 mg (28%) as a beige solid. R_f = 0.48 (EtOAc 10: EtOH 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 7.91 (2H, m), 7.46 (2H, m). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6): δ 164.1, 162.1 (d, J = 247.6 Hz), 130.3 (d, J = 3.1 Hz), 127.2 (d, J = 9.2 Hz), 116.3 (d, J = 23.3 Hz). **HRMS-ESI** (m/z): [M − H] calculated for $C_7H_4N_4FS$, 195.0141; found 195.0149. **IR** (ν_{max}, film): 3062, 2913, 2764, 1505, 1358, 1234, 1049, 834, 787, 570 cm^{-1}. **MP** = 150−151 °C (EtOAc).

*1-(2,6-Dimethoxyphenyl)-1H-tetrazole-5-thiol (**SI-5e**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 1 started with 2-isothiocyanato-1,3-dimethoxybenzene (1.81 g, 9.270 mmol, 1.0 equiv). The product was purified by silica pad filtration (EtOAc). The title compound was obtained in 1.84 g (84%) as a beige solid. R_f = 0.32 (ethylacetate). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 10.90 (1H, br.s), 7.48 (1H, t, J = 8.5 Hz), 6.71 (2H, d, J = 8.5 Hz), 3.83 (6H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 165.9, 156.8, 133.0, 110.6, 104.6, 56.4. **HRMS-ESI** (m/z): [M + Na] calculated for $C_9H_{10}N_4O_2SNa$, 261.0422; found 261.0415. **IR** (ν_{max}, film): 3436, 2942, 2738, 2534, 1602, 1262, 1113, 776 cm^{-1}. **MP** = 153−154 °C (EtOAc).

*1-(2,6-Diisopropylphenyl)-1H-tetrazole-5-thiol (**SI-5g**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 1 started with 1,3-diisopropyl-2-isothiocyanatobenzene (9.50 g, 39.845 mmol, 1.0 equiv). The title compound was obtained in 9.50 g (90%) as a beige solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 15.09

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(1H, br.s), 7.58 (1H, t, J = 7.8 Hz), 7.37 (2H, d, J = 7.8 Hz), 2.40 (2H, hept, J = 6.9 Hz), 1.29 (6H, d, J = 6.9 Hz), 1.16 (6H, d, J = 6.9 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 166.0, 147.1, 132.1, 128.7, 124.6, 29.1, 24.4, 23.4. **HRMS-ESI** (m/z): [M + H] calculated for $C_{13}H_{19}N_4S$, 263.1330; found 263.1336. **IR** (ν_{max}, film): 3040, 2967, 2928, 2761, 2576, 1500, 1353, 1052, 802, 757 cm^{-1}. **MP** = 135−136 °C (DCM).

General Procedure for the Preparation of Julia−Kocienski Reagents 11—Step 2. A suspension containing **SI-5** (28.056 mmol, 1.0 equiv) and KOH (1.70 g, 30.862 mmol, 1.1 equiv) in ab. ethanol (50 mL) was stirred at room temperature for 15 min (until all solids dissolved). Then, ethyl iodide (2.5 mL, 30.862 mmol, 1.1 equiv) was added and stirring was continued for 4 h, during which a precipitate formed. Next, the suspension was evaporated, water (50 mL) was added, and the mixture was extracted with DCM (2 × 40 mL) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was purified on silica gel (PE/DCM). The product-containing fractions were combined and evaporated *in vacuo*, furnishing the title compound.

*5-(Ethylthio)-1-(4-methoxyphenyl)-1H-tetrazole (**SI-6b**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 2 started with **SI-5b** (9.56 g, 57.913 mmol, 1.0 equiv). The title compound was purified by crystallization from EtOAc. The title compound was obtained in 6.39 g (46% in two steps) as a beige solid. R_f = 0.41 (PE 3: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.45 (2H, m), 7.03 (2H, m), 3.87 (3H, s), 3.38 (2H, q, J = 7.4 Hz), 1.48 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 160.9, 154.5, 126.5, 125.7, 115.0, 55.8, 27.8, 14.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{10}H_{13}N_4OS$, 237.0810; found 237.0820. **IR** (ν_{max}, film): 3467, 2971, 2845, 1607, 1515, 1453, 1251, 1170, 1089, 1021, 830, 625, 555 cm^{-1}. **MP** = 92−93 °C (EtOAc).

*5-(Ethylthio)-1-(4-cyanophenyl)-1H-tetrazole (**SI-6c**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 2 started with **SI-5c** (345 mg, 1.697 mmol, 1.0 equiv). The title compound was precipitated from the reaction mixture and collected by filtration and washing of the filter cake with EtOH (2 mL). The title compound was obtained in 343 mg (87%) as a beige solid. R_f = 0.45 (PE 1: EtOAc 1). **^{1}H NMR** (400 MHz; DMSO-d_6): δ 8.17 (2H, m), 7.92 (2H, m), 3.36 (2H, q, J = 7.3 Hz), 1.39 (3H, t, J = 7.3 Hz). **^{13}C{1H} NMR** (100 MHz, DMSO-d_6): δ 154.6, 136.6, 134.2, 125.3, 117.8, 113.1, 27.6, 14.6. **HRMS-ESI** (m/z): [M − H] calculated for $C_{10}H_{10}N_5S$, 232.0657; found 232.0666. **IR** (ν_{max}, film): 3100, 2969, 2232, 1922, 1602, 1506, 1384, 1244, 1082, 839, 565 cm^{-1}. **MP** >250 °C (dec; EtOH).

*5-(Ethylthio)-1-(4-fluorophenyl)-1H-tetrazole (**SI-6d**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 2 started with **SI-5d** (2.00 g, 13.056 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/EtOAc 6:1 as an eluent. The title compound was obtained in 723 mg (87%) as a beige solid. R_f = 0.45 (PE 1: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.56 (2H, m), 7.26 (2H, m), 3.41 (2H, q, J = 7.4 Hz), 1.50 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 163.3 (d, J = 251.8 Hz), 154.6, 129.9 (d, J = 3.4 Hz), 126.2 (d, J = 8.8 Hz), 117.1 (d, J = 23.7 Hz), 27.9, 14.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_9H_{10}N_4SF$, 225.0610; found 225.0618. **IR** (ν_{max}, film): 3080, 2975, 2933, 1514, 1387, 1236, 1083, 840, 623, 552 cm^{-1}. **MP** = 58−59 °C (PE/EtOAc.)

*1-(2,6-Dimethoxyphenyl)-5-(ethylthio)-1H-tetrazole (**SI-6e**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 2 started from **SI-5e** (1.86 g, 7.806 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/EtOAc 1:1 as an eluent. The title compound was obtained in 1.49 g (71%) as a white solid. R_f = 0.50 (PE 1: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.45 (1H, t, J = 8.6 Hz), 6.67 (2H, d, J = 8.6 Hz), 3.77 (6H, s), 3.30 (2H, q, J = 7.4 Hz), 1.42 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 156.8, 156.3, 132.8, 110.6, 104.4, 56.4, 27.5, 14.8. **HRMS-ESI** (m/z): [M + H] calculated for $C_{11}H_{15}N_4O_2S$, 267.0916; found 267.0916. **IR** (ν_{max}, film): 2977, 2845, 1601, 1486, 1399, 1297, 1262, 1110, 775, 731, 650 cm^{-1}. **MP** = 132−133 °C (PE/EtOAc).

*1-(2,6-Dimethylphenyl)-5-(ethylthio)-1H-tetrazole (**SI-6f**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. The procedure started with step 1 (2,6-dimethylphenyl isothiocyanate (6.24 g, 35.168 mmol, 1.0 equiv)) and step 2 (**SI-5f**). The title compound was collected by filtration and used in the next step as it was. The title compound was obtained in 8.10 g (90% in two steps) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35 (1H, m), 7.19 (2H, m), 3.36 (2H, q, J = 7.3 Hz), 1.96 (6H, s), 1.46 (3H, t, J = 7.3 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 155.8, 136.1, 131.4, 131.2, 128.9, 27.2, 17.5, 14.8. **HRMS-ESI** (m/z): [M + H] calculated for $C_{11}H_{15}N_4S$, 235.1017; found 235.1017. **IR** (ν_{max}, film): 2975, 2931, 2871, 1476, 1387, 1265, 1234, 1092, 976, 790 cm^{-1}. **MP** > 180 °C (dec; EtOH).

*1-(2,6-Diisopropylphenyl)-5-(ethylthio)-1H-tetrazole (**SI-6g**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 2 started with **SI-5g** (5.00 g, 19.056 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/DCM 3:1 as an eluent. The title compound was obtained in 3.24 g (58%) as a white solid. R_f = 0.21 (PE 3: DCM 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.53 (1H, t, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 3.37 (2H, q, J = 7.3 Hz), 2.13 (2H, hept, J = 6.9 Hz), 1.46 (3H, t, J = 7.3 Hz), 1.18 (6H, d, J = 6.9 Hz), 1.10 (6H, d, J = 6.9 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 156.9, 146.7, 131.9, 128.5, 124.5, 28.7, 27.4, 24.5, 23.2, 14.8. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{23}N_4S$, 291.1643; found 291.1651. **IR** (ν_{max}, film): 3459, 2967, 2931, 2872, 1465, 1390, 1266, 1086, 759 cm^{-1}. **MP** = 71−72 °C (PE/DCM).

General Procedure for the Preparation of Julia−Kocienski Reagents 11—Step 3. To a solution of **SI-6** (11.018 mmol, 1.0 equiv) in DCM (120 mL), $NaHCO_3$ (4.62 g, 55.091 mmol, 5.0 equiv) and 70% *m*CPBA (6.17 g, 27.545 mmol, 2.5 equiv) were added subsequently and stirring was continued at rt for 16 h. After reaction completion, it was quenched with sat. $Na_2S_2O_3$ (30 mL), then sat. $NaHCO_3$ (30 mL) was added, and the mixture was extracted with DCM (2 × 100 mL). Combined organic extracts were washed with sat. $NaHCO_3$ (200 mL) and brine (100 mL) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was purified on silica gel or by crystallization.

*5-(Ethylsulfonyl)-1-(4-methoxyphenyl)-1H-tetrazole (**11b**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 3 started with **SI-6b** (4.10 g, 17.315 mmol, 1.0 equiv). The title compound was purified by crystallization from Et_2O. The title compound was obtained in 3.66 g (78%) as a white solid. R_f = 0.48 (PE 1: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.59 (2H, m), 7.06

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(2H, m), 3.89 (3H, s), 3.75 (2H, q, J = 7.4 Hz), 1.54 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 161.8, 153.2, 126.7, 125.8, 114.9, 55.8, 50.9, 7.1. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{10}H_{12}N_4O_3SNa$, 291.0528; found 291.0540. **IR** (ν_{max}, film): 3458, 3083, 2942, 1607, 1515, 1339, 1260, 1151, 1023, 836, 731, 612, 544 cm^{-1}. **MP** = 58−59 °C (Et_2O).

*5-(Ethylsulfonyl)-1-(4-cyanophenyl)-1H-tetrazole (**11c**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 3 started **SI-6c** (340 mg, 1.470 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/EtOAc 1:1 as an eluent. The title compound was obtained in 140 mg (36%) as a white solid. R_f = 0.35 (PE 3: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.92 (4H, br.s), 3.82 (2H, q, J = 7.4 Hz), 1.57 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 153.3, 136.3, 133.8, 125.9, 117.2, 115.7, 51.1, 7.1. **HRMS-ESI** (m/z): [M − H] calculated for $C_{10}H_8N_5O_2S$, 262.0399; found 262.0407. **IR** (ν_{max}, film): 3649, 3107, 3022, 2946, 2235, 1766, 1609, 1505, 1335, 1152, 1052, 845, 731, 545 cm^{-1}.

*5-(Ethylsulfonyl)-1-(4-fluorophenyl)-1H-tetrazole (**11d**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 3 started with **SI-6d** (714 mg, 3.183 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/EtOAc 3:1 as an eluent. The title compound was obtained in 625 mg (76%) as a white solid. R_f = 0.30 (PE 3: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.70 (2H, m), 7.29 (2H, m), 3.78 (2H, q, J = 7.4 Hz), 1.55 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 164.2 (d, J = 253.3 Hz), 153.3, 129.1 (d, J = 3.4 Hz), 127.4 (d, J = 9.2 Hz), 117.1 (d, J = 23.7 Hz), 51.0, 7.1. **HRMS-ESI** (m/z): [M + H] calculated for $C_9H_{10}N_4O_2FS$, 257.0508; found 257.0502. **IR** (ν_{max}, film): 3086, 2988, 2946, 1514, 1341, 1234, 1151, 842, 730, 620, 543, 509 cm^{-1}. **MP** = 44−45 °C (PE/EtOAc).

*1-(2,6-Dimethoxyphenyl)-5-(ethylsulfonyl)-1H-tetrazole (**11e**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 3 started with **SI-6e** (1.49 g, 5.594 mmol, 1.0 equiv). The title compound was purified by crystallization from PE/EtOAc. The title compound was obtained in 920 mg (55%) as a white solid. R_f = 0.38 (PE 1: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.50 (1H, t, J = 8.6 Hz), 6.70 (2H, d, J = 8.6 Hz), 3.79 (6H, s), 3.52 (2H, q, J = 7.4 Hz), 1.41 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 155.9, 154.1, 133.4, 111.0, 104.4, 56.4, 50.9, 6.7. **HRMS-ESI** (m/z): [M + H] calculated for $C_{11}H_{15}N_4O_4S$, 299.0814; found 299.0811. **IR** (ν_{max}, film): 2950, 2846, 1605, 1487, 1345, 1266, 1113, 1014, 782, 732, 618, 500 cm^{-1}. **MP** = 124−125 °C (PE/EtOAc).

*1-(2,6-Diisopropylphenyl)-5-(ethylsulfonyl)-1H-tetrazole (**11g**).* Prepared according to the general procedure for the preparation of Julia−Kocienski reagents **11**. Step 3 started with **SI-6g** (4.37 g, 15.046 mmol, 1.0 equiv). The title compound was purified on silica gel with PE/DCM 1:2 as an eluent. The title compound was obtained in 3.38 g (80%) as a white solid. R_f = 0.35 (PE 10: EtOAc 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.57 (1H, t, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz), 3.71 (2H, q, J = 7.5 Hz), 2.02 (2H, hept, J = 6.8 Hz), 1.52 (3H, t, J = 7.5 Hz), 1.24 (6H, d, J = 6.8 Hz), 1.08 (6H, d, J = 6.8 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 154.3, 146.2, 132.4, 128.6, 124.3, 50.6, 29.2, 25.3, 22.2, 6.9. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{23}N_4O_2S$, 323.1542; found 323.1542. **IR** (ν_{max}, film): 2974, 2929, 2871, 1457, 1339, 1150, 1059, 808, 760, 737, 548, 501 cm^{-1}. **MP** = 93−94 °C (PE/DCM).

Optimized Synthesis of 11g. A suspension of 2,6-diisopropylphenyl isothiocyanate (10.00 g, 41.942 mmol, 1.0 equiv) and NaN_3 (5.45 g, 83.885 mmol, 2.0 equiv) in abs. EtOH (100 mL) was heated under reflux for 3 h. Then, the reaction mixture was cooled to room temperature, iodoethane (5.0 mL, 62.913 mmol, 1.5 equiv) was added, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of H_2O (100 mL) and extracted once with DCM (100 mL). The organic extract was dried over Na_2SO_4 and filtered, and the solvents were removed *in vacuo*. The crude product (13.14 g) was dissolved in EtOH (150 mL) and cooled (ice bath), and $(NH_4)_6Mo_7O_{24} \times 4H_2O$ (5.23 g, 4.194 mmol, 0.1 equiv) was added followed by 35% aq H_2O_2 (36 mL, 419.432 mmol, 10.0 equiv). The resulting mixture was stirred at room temperature in a sealed tube for 24 h. Then, the suspension was poured into H_2O (150 mL) and the precipitate was collected by filtration. The filter cake was washed with H_2O (100 mL) and dried under vacuum (at 50 °C over P_2O_5 for 2 days) to obtain 12.28 g (90% in three steps) of **11f** as a white solid.

*1-(2,6-Dimethylphenyl)-5-(ethylsulfonyl)-1H-tetrazole (**11f**).* Prepared according to the optimized procedure for the preparation of Julia−Kocienski reagents **11**. The procedure started with 2,6-dimethylphenyl isothiocyanate (6.24 g, 35.168 mmol, 1.0 equiv). The title compound was obtained in 7.05 g (75%) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.41 (1H, m), 7.23 (2H, m), 3.73 (2H, q, J = 7.5 Hz), 2.00 (6H, s), 1.54 (3H, t, J = 7.4 Hz). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 154.0, 135.9, 131.8, 131.6, 128.9, 50.6, 17.4, 7.1. **HRMS-ESI** (m/z): [M + H] calculated for $C_{11}H_{15}N_4O_2S$, 267.0916; found 267.0925. **IR** (ν_{max}, film): 2984, 2928, 1477, 1456, 1400, 1342, 1336, 1151, 777, 622, 542, 506 cm^{-1}. **MP** > 180 °C (dec; EtOH, H_2O).

General Procedure for Olefination of 10. To a solution of sulfone (0.374 mmol, 3.0 equiv) in THF (2 mL; freshly distilled over Na/Ph_2CO) at −78 °C was added 1 M KHMDS (made prior to use: 78.5 mg, 0.374 mmol, 3.0 equiv dissolved in 0.37 mL of THF), and the mixture was stirred at the same temperature for 15 min. Next, a solution of **10** (0.124 mmol, 1.0 equiv) in THF (1.5 mL) was added, and the resulting mixture was stirred for 15 min at −78 °C before being quenched with sat. NH_4Cl (4 mL). Then, brine (4 mL) was added, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), and volatiles were evaporated *in vacuo*. At this point, the qNMR spectrum was measured. The analytically pure sample was obtained by purification of the crude product by flash column chromatography.

*(S,E)-2-Ethylidene-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H)-dione (**12a**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10a**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with PE/EtOAc 2:1 as an eluent. The title compound was obtained as colorless oil. R_f = 0.45 (PE 1: EA 1). For the *E*-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.89 (1H, dd, J = 7.8, 1.7 Hz), 7, 68 (1H, m), 7.52 (1H, m), 7.33 (1H, m), 5.54 (1H, m), 5.51 (1H, d, J = 9.9 Hz), 4.71 (1H, d, J = 9.9 Hz), 4.37−4.13 (3H, m), 3.75 (1H, m), 3.65 (1H, m), 3.47 (1H, m), 2.62 (1H, m), 1.74 (3H, m),

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0.98 (2H, m), 0.02 (9H, s). For the Z-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.90 (1H, dd, J = 7.8, 1.7 Hz), 7,68 (1H, m), 7.52 (1H, m), 7.33 (1H, m), 5.54 (1H, m), 5.50 (1H, d, J = 9.9 Hz), 4.72 (1H, d, J = 9.9 Hz), 4.37−4.13 (3H, m), 3.75 (1H, m), 3.65 (1H, m), 3.37 (1H, m), 2.77 (1H, m), 1.81 (1H, m), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.10 and 170.04 (isomers), 165.58 and 165.37 (isomers), 139.97, 133.15 and 133.11 (isomers), 132.47, 130.03, 129.63 and 129.58 (isomers), 126.47, 122.70, 118.87 and 118.55 (isomers), 78.18 and 78.12 (isomers), 67.18 and 67.10 (isomers), 57.63 and 57.14 (isomers), 51.14 and 48.14 (isomers), 32.18 and 28.23 (isomers), 18.43, 15.02 and 14.64 (isomers), −1.25. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{20}H_{28}N_2O_3SiNa$, 395.1767; found 395.1765. **IR** (ν_{max}, film): 3272, 2952, 1644, 1461, 1420, 1377, 1248, 1071, 836, 762 cm^{-1}. $[\alpha]_D^{20}$ = 252° (c = 0.1, $CHCl_3$).

*(S,E)-7-Chloro-2-ethylidene-10-((2-(trimethylsilyl)ethoxy)-methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11(10H)-dione (**12b**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10b**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with DCM/MeOH 50:1 as an eluent. The title compound was obtained as colorless oil. **R$_f$** = 0.45 (DCM 50: MeOH 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.88 (1H, d, J = 2.6 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.47 (1H, dd, J = 8.7, 2.6 Hz), 5.54 (1H, m), 5.51 (1H, d, J = 9.9 Hz), 4.66 (1H, d, J = 9.9 Hz), 4.36−4.23 (2H, m), 4.21−4.11 (1H, m), 3.81−3.61 (2H, m), 3.52−3.33 (1H, m), 2.85−2.57 (1H, m), 1.78−1.63 (3H, m), 0.98 (2H, m), 0.02 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.7, 164.1, 138.5, 132.8, 132.5, 132.3, 130.9, 129.8, 124.2, 118.8, 78.1, 67.3, 57.6, 51.3, 28.2, 18.4, 14.7, −1.2. **HRMS-ESI** (m/z): [M − H] calculated for $C_{20}H_{27}ClN_2O_3SiNa$, 405.1401; found 405.1385. **IR** (ν_{max}, film): 2924, 2857, 1694, 1649, 1443, 1365, 1248, 1073, 837 cm^{-1}. $[\alpha]_D^{20}$ = 214° (c = 0.1, $CHCl_3$).

*(S,E)-2-Ethylidene-8-(trifluoromethyl)-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**12c**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10c**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with DCM/MeOH 50:1 as an eluent. The title compound was obtained as colorless oil. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.05−8.00 (2H, m), 7.59 (1H, m), 5.56 (2H, m), 4.70 (1H, d, J = 10.0 Hz), 4.34 (1H, m), 4.28 (1H, dd, J = 9.1, 2.3 Hz), 4.18 (1H, m), 3.79 (1H, m), 3.69 (1H, m), 3.53−3.35 (1H, m), 2.84−2.60 (1H, m), 1.78−1.64 (3H, m), 0.99 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 169.7, 164.2, 140.4, 134.4 (q, J = 32.5 Hz), 132.6, 132.4, 131.1, 123.2 (q, J = 273.8 Hz), 123.0 (q, J = 3.7 Hz), 120.0 (q, J = 3.7 Hz), 119.0, 78.1, 67.5, 57.6, 51.3, 28.3, 18.3, 14.7, −1.3. **HRMS-ESI** (m/z): [M − H] calculated for $C_{21}H_{27}F_3N_2O_3Si$, 439.1665; found 439.1669. **IR** (ν_{max}, film): 2924, 2855, 1698, 1655, 1449, 1180, 1134, 1085, 835, 627 cm^{-1}. $[\alpha]_D^{20}$ = 60° (c = 0.1, $CHCl_3$).

*(S,E)-2-Ethylidene-9-methoxy-10-((2-(trimethylsilyl)-ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine-5,11(10H)-dione (**12d**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10d**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with PE/EtOAc 1:1 as an eluent. The title compound was obtained as colorless oil. **R$_f$** = 0.26 (PE 1: EA 1). For the E-isomer, **^{1}H NMR** (600MHz; $CDCl_3$): δ 7.47 (1H, m), 7.34 (1H, m), 7.07 (1H, m), 5.72 (1H, m), 5.56−5.47 (1H, m), 5.01 (1H, m), 4.33−4.10 (3H, m), 3.89 (3H, m), 3.44−3.27 (3H, m), 2.57 (1H, m), 1.72 (3H, m), 0.81−0.65 (2H, m), 0.08 (9H, s). For the Z-isomer, **^{1}H NMR** (600MHz; $CDCl_3$): δ 7.47 (1H, m), 7.34 (1H, m), 7.07 (1H, m), 5.72 (1H, m), 5.56−5.47 (1H, m), 5.01 (1H, m), 4.33−4.10 (3H, m), 3.89 (3H, m), 3.44−3.27 (3H, m), 2.71 (1H, m), 1.64 (3H, m), 0.81−0.65 (2H, m), 0.08 (9H, s). **^{13}C{1H} NMR** (150 MHz, $CDCl_3$): δ 170.85 and 170.78 (isomers), 165.26 and 165.02 (isomers), 152.80, 134.00 and 133.96 (isomers), 133.42 and 133.34 (isomers), 128.13, 126.73, 121.36, 118.68 and 118.31 (isomers), 114.34, 75.10 and 74.97 (isomers), 66.26, 58.02 and 57.54 (isomers), 55.99, 50.83 and 47.95 (isomers), 31.79 and 27.94 (isomers), 17.96 and 17.92 (isomers), 15.00 and 14.65 (isomers), −1.35. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{21}H_{30}N_2O_4SiNa$, 425.1873; found 425.1876. **IR** (ν_{max}, film): 2951, 1689, 1651, 1410, 1247, 1066, 836, 755 cm^{-1}. $[\alpha]_D^{20}$ = 167° (c = 0.1, $CHCl_3$).

*(S,E)-2-Ethylidene-7,8-dimethoxy-10-((2-(trimethylsilyl)-ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine-5,11(10H)-dione (**12e**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10e**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with PE/EtOAc 2:1 as an eluent. The title compound was obtained as colorless oil. For the E-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34 (1H, d, J = 2.0 Hz), 7.24 (1H, d, J = 2.0 Hz), 5.52 (1H, d, J = 9.9 Hz), 5.52 (1H, m), 4.63 (1H, d, J = 9.9 Hz), 4.37−4.08 (3H, m), 3.94 (3H, s), 3.92 (3H, s), 3.79 (1H, m), 3.68 (1H, m), 3.47 (1H, m), 2.62 (1H, m), 1.74 (3H, m), 0.98 (2H, m), 0.03 (9H, s). For the Z-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34 (1H, d, J = 2.0 Hz), 7.24 (1H, d, J = 2.0 Hz), 5.52 (1H, d, J = 9.9 Hz), 5.52 (1H, m), 4.64 (1H, d, J = 9.9 Hz), 4.37−4.08 (3H, m), 3.94 (3H, s), 3.92 (3H, s), 3.79 (1H, m), 3.68 (1H, m), 3.36 (1H, m), 2.76 (1H, m), 1.65 (3H, m), 0.98 (2H, m), 0.03 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.1, 165.3, 152.0, 147.2, 134.3, 133.3, 121.9, 118.5, 111.1, 105.6, 78.3, 67.2, 57.8, 56.3, 56.3, 51.2, 28.2, 18.5, 14.6, −1.2. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{22}H_{32}N_2O_5SiNa$, 455.1978; found 455.1977. **IR** (ν_{max}, film): 3431, 2955, 2925, 2854, 1700, 1652, 1520, 1456, 1248, 1075, 837 cm^{-1}. $[\alpha]_D^{20}$ = 287° (c = 0.1, $CHCl_3$).

*(S,E)-8-(Benzyloxy)-2-ethylidene-7-methoxy-10-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione (**12f**).* Prepared according to the general procedure for the olefination of **10** starting from trione **10f**. An analytically pure sample was obtained by purification of the crude reaction mixture on silica gel with PE/EtOAc 1:1 as an eluent. The title compound was obtained as colorless oil. **R$_f$** = 0.30 (PE 1: EA 1). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.46−7.41 (2H, m), 7.39−7.28 (4H, m), 7.25 (1H, s), 5.52 (1H, m), 5.43 (1H, d, J = 9.8 Hz), 5.20 (2H, s), 4.47 (1H, d, J = 9.8 Hz), 4.32 (1H, m), 4.27 (1H, dd, J = 9.2, 2.4 Hz), 4.12 (1H, m), 3.94 (3H, s), 3.70 (1H, td, J = 9.5, 7.2 Hz), 3.60 (1H, td, J = 9.5, 7.2 Hz), 3.45 (1H, br.d, J = 16.2 Hz), 2.60 (1H, m), 1.73 (3H, m), 0.97 (2H, m), 0.04 (9H, s). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$): δ 170.0, 165.2, 150.9, 147.7, 136.1, 134.0, 133.3, 128.8, 128.3, 127.6, 122.0, 118.4, 111.4, 107.8, 78.2, 71.0, 67.1, 57.7, 56.4, 51.2, 28.2, 18.5, 14.6, −1.2. **HRMS-ESI** (m/z): [M + H] calculated for $C_{28}H_{37}N_2O_5Si$, 509.2472; found 509.2448. **IR** (ν_{max}, film): 2951, 1689, 1639, 1516, 1436, 1362, 1248, 1069, 836, 751, 696 cm^{-1}. $[\alpha]_D^{20}$ = 272° (c = 0.1, $CHCl_3$).

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Oxo-prothracarcin (4). To a stirred solution of **12a** (22 mg, 0.059 mmol, 1.0 equiv) in THF (1 mL) was added concn HCl (246 μL, 2.95 mmol, 50.0 equiv), and the resulting mixture was heated for 1 h at 60 °C. The volatiles were evaporated *in vacuo*, and the oily residue was purified on silica gel (DCM/MeOH 20:1) to furnish 8 mg (55%) of oxo-prothracarcin (**4**) as colorless wax. R_f = 0.35 (DCM 20: MeOH 1). For the *E*-isomer, **^{1}H NMR** (400 MHz; CD_3OD): δ 7.87 (1H, ddd, *J* = 7.9, 1.6, 0.3 Hz), 7.55 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz), 7.29 (1H, m), 7.14 (1H, m), 5.57 (1H, m), 4.37 (1H, dd, *J* = 9.2, 2.4 Hz), 4.31 (1H, m), 4.13 (1H, dq, *J* = 16.0, 1.8 Hz), 3.45 (1H, br.d, *J* = 16.2 Hz), 2.69 (1H, m), 1.75 (3H, m). For the *Z*-isomer, **^{1}H NMR** (400 MHz; CD_3OD): δ 7.88 (1H, ddd, *J* = 7.9, 1.6, 0.3 Hz), 7.55 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz), 7.29 (1H, m), 7.14 (1H, m), 5.57 (1H, m), 4.37−4.19 (3H, m), 3.35−3.28 (1H, m (partially overlapping with CD_3OD)), 2.83 (1H, m), 1.68 (3H, m). **^{13}C{1H} NMR** (100 MHz, CD_3OD): δ 172.2, 167.8, 137.8, 134.5 and 134.4 (isomers), 133.9, 131.4 and 127.4 (isomers), 125.8, 122.6, 119.4 and 119.1 (isomers), 58.4 and 57.8 (isomers), 52.5, 32.4 and 28.2 (isomers), 14.8 and 14.5 (isomers). **HRMS-ESI** (*m*/*z*): [M + H] calculated for $C_{14}H_{15}N_2O_2$, 243.1134; found 243.1140. **IR** (ν_{max}, film): 3218, 2920, 2854, 1694, 1622, 1446, 1257, 760 cm^{-1}. $[\alpha]_D^{20}$ = 481.0° (*c* = 0.1, MeOH).

Oxo-tomaymycin (5). To a solution of **12f** (211 mg, 0.414 mmol, 1.0 equiv) in DCM (4 mL), anisole (0.77 mL, 7.051 mmol, 17 equiv) and methanesulfonic acid (0.46 mL, 7.051 mmol, 17 equiv) were added sequentially at room temperature, and the mixture was stirred for 16 h. The volatiles were evaporated *in vacuo*, and the oily residue was purified on a reverse-phase column (eluent: MeCN/water 5:95% → 95:5%) to furnish 54 mg (45%) of oxo-tomaymycin (**5**) as a white powder. R_f = 0.41 (DCM 10: MeOH 1). For the *E*-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 10.28−10.21 (1H, m), 9.94 (1H, br.s), 7.26−7.18 (1H, m), 6.60−6.54 (1H, m), 5.47 (1H, m), 4.36−4.08 (2H, m), 4.08−3.91 (1H, m), 3.78 (3H, s), 3.25 (1H, br.d, *J* = 16.2 Hz), 2.77−2.53 (1H, m), 1.66 (3H, m). For the *Z*-isomer, **^{1}H NMR** (400 MHz; $CDCl_3$): δ 10.28−10.21 (1H, m), 9.94 (1H, br.s), 7.26−7.18 (1H, m), 6.60−6.54 (1H, m), 5.52 (1H, m), 4.36−4.08 (2H, m), 4.08−3.91 (1H, m), 3.78 (3H, s), 3.15 (1H, br.d, *J* = 16.2 Hz), 2.77−2.53 (1H, m), 1.60 (3H, m). **^{13}C{1H} NMR** (100 MHz, CD_3OD): δ 172.0, 167.8, 152.4, 146.6, 134.7, 132.6, 118.9, 118.7, 112.9, 108.9, 58.5, 56.6, 52.5, 28.2 and 22.8 (isomers), 14.5 and 12.1 (isomers). **HRMS-ESI** (*m*/*z*): [M + H] calculated for $C_{15}H_{17}N_2O_4$, 289.1188; found 289.1202. **IR** (ν_{max}, film): 3529, 3403, 2919, 2610, 2417, 1677, 1611, 1482, 1268, 878, 759 cm^{-1}. $[\alpha]_D^{20}$ = 391° (*c* = 0.1, MeOH).

Boseongazepine B (6). To a stirred solution of **12d** (100 mg, 0.248 mmol, 1.0 equiv) in THF (3 mL) was added concn HCl (300 μL, 3.600 mmol, 15.0 equiv), and the resulting mixture was heated for 16 h at 60 °C. The volatiles were evaporated *in vacuo*, and the oily residue was purified on silica gel (DCM/MeOH 40: 1) to furnish 42 mg (62%) of boseongazepine B (**5**) as colorless wax. R_f = 0.45 (DCM 40: MeOH 1). For the *E*-isomer, **^{1}H NMR** (400 MHz; CD_3OD): δ 7.47−7.39 (1H, m), 7.31−7.19 (2H, m), 5.57 (1H, m), 4.39−4.22 (2H, m), 4.12 (1H, m), 3.94 (3H, s), 3.44 (1H, br.d, *J* = 16.2 Hz), 2.69 (1H, m), 1.74 (3H, m). For the *Z*-isomer, **^{1}H NMR** (400 MHz; CD_3OD): δ 7.47−7.39 (1H, m), 7.31−7.19 (2H, m), 5.57 (1H, m), 4.39−4.22 (2H, m), 4.12 (1H, m), 3.94 (3H, s), 3.44 (1H, br.d, *J* = 16.2 Hz), 2.82 (1H, m), 1.67 (3H, m). **^{13}C{1H} NMR** (100 MHz, CD_3OD): δ 171.9, 167.5, 151.3, 134.5 and 134.4 (isomers), 128.6, 127.1, 126.3, 122.4, 119.4 and 119.1 (isomers), 114.8, 58.5 and 58.0 (isomers), 56.8, 52.5, 32.3 and 28.2 (isomers), 14.8 and 14.5 (isomers). **HRMS-ESI** (*m*/*z*): [M + H] calculated for $C_{15}H_{17}N_2O_3$, 273.1239; found 273.1252. **IR** (ν_{max}, film): 3257, 2982, 2920, 2860, 1693, 1413, 1261, 1068, 750 cm^{-1}. $[\alpha]_D^{20}$ = 571° (*c* = 0.1, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03732.

Reaction optimization tables, synthetic schemes for the synthesis of olefination reagents and substrates, copies of NMR spectra, and NMR spectra comparison for natural and synthetic PBD natural products (PDF)

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Notes

The authors declare no competing financial interest.

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