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SYNTHETIC STUDIES ON MPC1001: A DIPOLAR CYCLOADDITION APPROACH TO THE PYRROLIDINE RING SYSTEM

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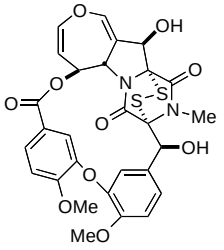
Abstract – A novel [1,3]-dipolar azomethine ylide cycloaddition has been developed in an approach to the synthesis of the MPC1001 family of natural products.

INTRODUCTION

MPC1001 was isolated from the mycelium of the *Cladorrhinum sp.* in 2004 by Hasegawa and coworkers (Figure 1).[1] A biological assay revealed antiproliferative activity against the human prostate cancer cell line DU145 (IC_{50} = 9.3 nM). The biological activity of MPC1001 was shown to be more potent than therapeutic agents etoposide (IC_{50} = 400 nM), adriamycin (IC_{50} = 20 nM), and mitomycin C (IC_{50} = 25 nM).[1] The potent anticancer activity coupled with a synthetically challenging morphology renders MPC1001 an interesting synthetic target. To date, most synthetic approaches to the dihydrooxepin subunit in MPC1001 have only been achieved in very simple model systems.[2,3] Most model systems utilize a Cope rearrangement of *cis*-divinyl epoxides. Until recently, the oxepin ring had not been synthesized in a densely functionalized setting. Clive and coworkers reported the synthesis of a tricyclic model system of MPC1001 starting from commercially available *trans*-4-hydroxy-L-proline.[2] Later, Bräse and coworkers also prepared a synthetic analogue of the tricyclic ring system.[3] Here, we report our own approach based on azomethine ylide dipolar cycloaddition methodology.

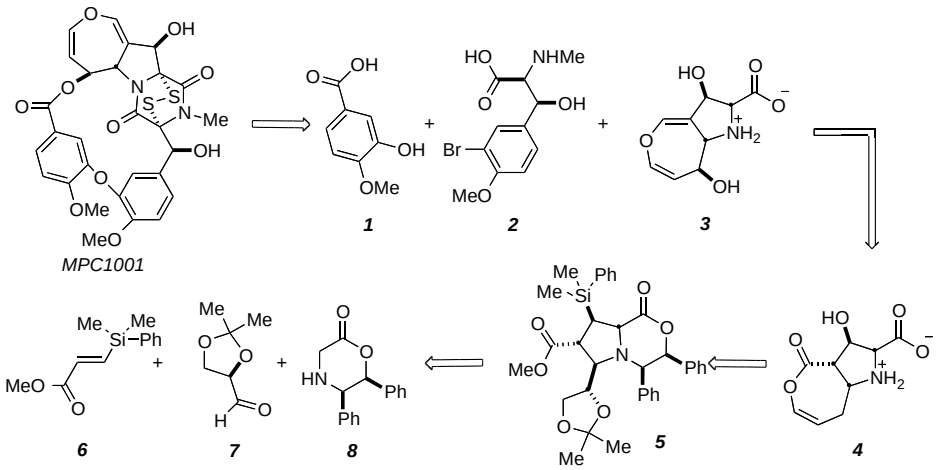


MPC1001

Figure 1. Structure of MPC1001

RESULTS AND DISCUSSION

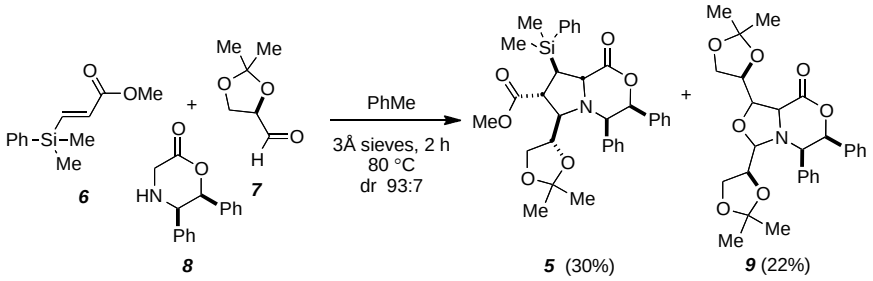
Our approach is based on disconnections across the dioxopiperazine and the diaryl ether subunit of MPC1001 utilizing a commercially available benzoic acid derivative (**1**), an unnatural β-hydroxy-α-amino acid (**2**), and a synthetically challenging 4,5-dihydrooxepin ring (**3**) (Scheme 1). Late-stage construction of the oxepin ring was envisioned from compound **4** *via* an allylic oxidation of the vinyl ester followed by partial reduction of the lactone. Lactone **4** could be elaborated from the highly substituted pyrrolidine (**5**), which in turn could arise from a [1,3]-dipolar cycloaddition involving substrates **6**, **7**, and **8**. The dipolar cycloaddition, if successful, would allow for rapid access to amino acid **4** with the objective of complete stereochemical control of the four contiguous stereogenic centers necessary for the construction of MPC1001.



Scheme 1. Retrosynthetic analysis of **1**

Our laboratory has demonstrated the effectiveness of the [1,3]-dipolar cycloaddition using morpholinone **8** for the synthesis of complex pyrrolidine-containing natural products within the spirotryprostatin family.[4] To expand upon this methodology, we planned to employ vinyl silane **6** to furnish a highly functionalized pyrrolidine ring that would be useful in a planned total synthesis of MPC1001. Our synthesis commenced with coupling partners **6**, **7** and **8** which were prepared by known procedures.[5,6]

Initial attempts at the three-component coupling of **6**, **7**, and **8** were carried out in toluene in the presence of 3 Å molecular sieves (Scheme 2). The desired product (**5**) was obtained in 30% yield (93:7 dr) along with unexpected by-product (**9**) as a single isomer in 22% yield. The regio- and stereochemistry of the desired product were elucidated by extensive NMR studies and corroborated through X-ray crystallography.

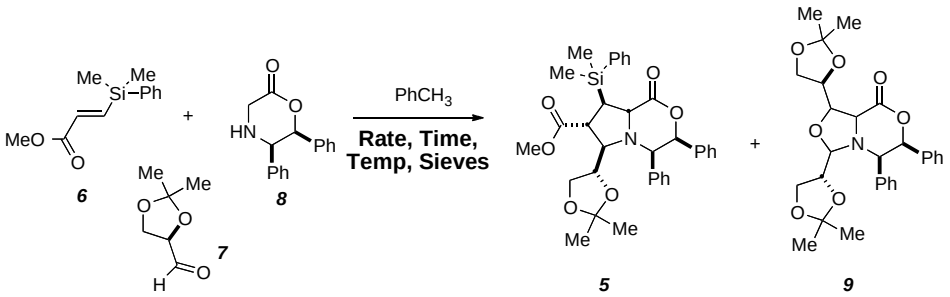


Scheme 2. Three-component dipolar cycloaddition

Our efforts towards optimizing the key cycloaddition reaction are illustrated in Table 1. All the reactions in entries 1 through 7 were done on a 50 mg scale with 1 equivalent of lactone **8**, except for entry 8, which was done with 1 g of lactone **8**. Initial conditions, as seen in entry one, allowed for 30% yield of the desired product **5** and 22% yield of the by-product **9.** Extending the reaction time to 14 h (entry 2) and utilizing a pressure tube at 190 ºC for three days (entry 3) did not have a significant effect upon optimizing the yield of the desired product **5**. Changing from 3Å to 4Å molecular sieves improved the yield to 57% of compound **5** and 18% yield of by-product **9** seen in entry 4. When the equivalents of the dipolarophile **6** (15 equiv.) in entry 5 were increased, the yield of the desired product **5** increased to 63%, and reduced the yield of the undesired by-product **9** to less than 10%. Utilizing a syringe pump with the addition rate of 0.05 mL/h with a total reaction time of fourteen hours increased the yield of the desired product **5** to 75% in entry 6, and lowered the yield of by-product **9** significantly. Extending the total reaction time to three days with fifteen equivalents of dipolarophile **6** and an addition rate of 2 mL/h resulted in a 78% yield of the desired compound **5** and provided only trace amounts of the by-product **9 (**entry 7**)**. Finally, scaling the reaction up to 1 g, as seen in entry 8, allowed for a 78% yield of the desired product **6** and trace amounts of compound **9**. It is important to note that diluting the aldehyde (**7)** in toluene proved to be necessary for the stability of compound **7** and the slow addition rate suppressed the formation of by-product **9**.

Noticing the potential for by-product **9** to undergo a formal retro-[1,3]-dipolar cycloaddition/[1,3]-dipolar cycloaddition cascade to give desired ester **5**, its reactivity was investigated (Table 2). It was found that heating **9** at 160 ºC in a sealed tube in the presence of silane **6** resulted in the formation of a trace amount of **5**. Increasing the temperature to 220 ºC provided **5** in 28% purity as a mixture of diastereomers (Entry 4, Table 2).

Table 1. Optimization of the cycloaddition



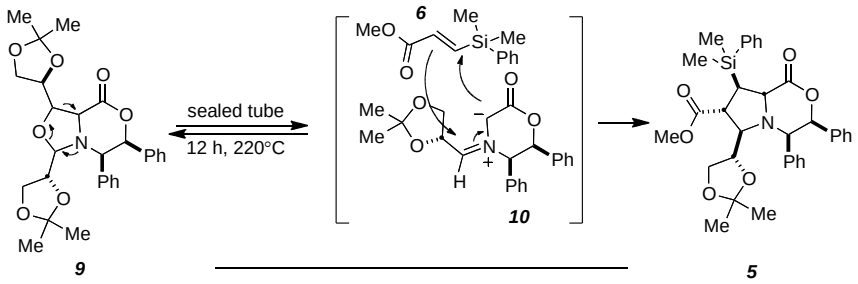
6 7 8 5 9

Entry	7	6	Addition Rate	Total Time	Temp °C	Sieves	Product Yield 5	Byproduct Yield 9
1.	1.25 Eq	3 Eq	NA	3 h	80 °C	3Å MS	~ 30%	~ 22%
2.	1.25 Eq	3 Eq	NA	14 h	80 °C	3Å MS	30% 10 : 1.4 dr	16%
3.	1.25 Eq	3 Eq	NA	3 days	190 °C pressure tube	3Å MS	33 % 10 : 1.6 dr	didn't isolate
4.	1.4 Eq	3 Eq	NA	14 h	1. 80 °C 2. 90 °C	4Å MS	1. 57% 2. 57%	1. 18% 2. NA
5.	2 Eq	15 Eq	NA	14 h	90 °C	4Å MS	63% 10 : 1 dr	> ~10%
6.	1.4 Eq	3 Eq	.05ml/hr	14 h	90 °C	4Å MS	1. 61% 2. 75%	1. NA 2. ~10%
7.	4 Eq in 30 ml	15 Eq	2ml/hr	3 days	90 °C	4Å MS	78%	Trace
8.	4 Eq in 30 ml	5 Eq	2ml/hr	24 h	90 °C	4Å MS	78%	Trace

With the cycloaddition effectively optimized, we turned our attention to forming the dioxopiperazine **13** (Scheme 3). Hydrogenolysis of the oxazinone template with 10% Pd/C in the presence of acetyl chloride (which facilitated the cleaveage of the chiral auxiliary template), followed by coupling the amino acid **11** with sarcosine ethyl ester (**12**), furnished **13**. X-Ray crystallographic analysis of the amino acid **(11)** confirmed the regio- and stereochemistry of the dipolar cycloaddition. Conducting the deprotection and coupling in a rapid one-pot procedure, provided substance **13** in 40% overall yield.

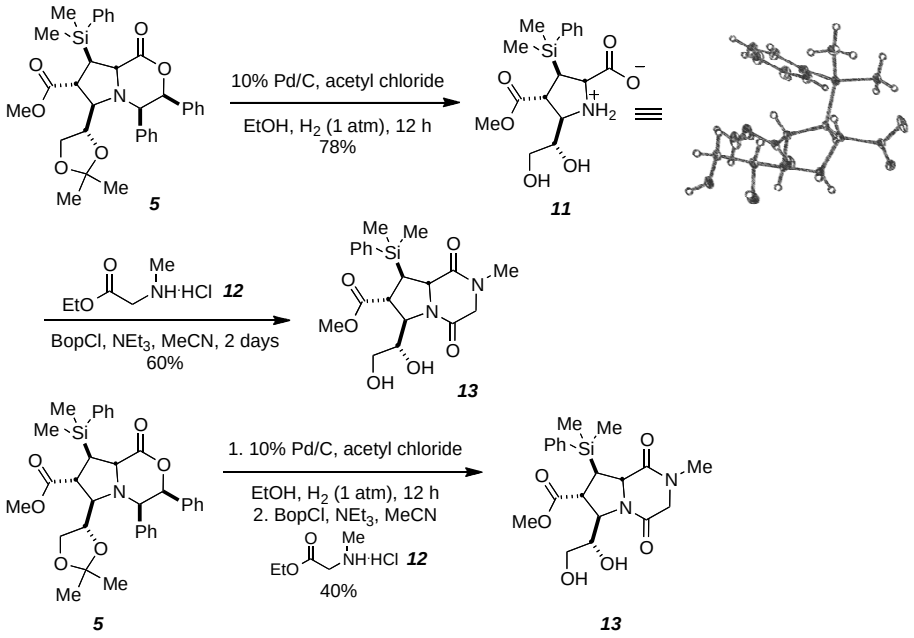
Continuing with the synthesis, diol **13** was transformed to the terminal olefin **14**, which was followed by transesterification with Otera's catalyst[7] (tetrabutyl-1,3-diisothiocyanatodistannoxane) to yield allyl ester **15** (Scheme 4). Exposure of compound **15** with Grubbs 1st and 2nd as well as Hoveyda-Grubbs 2nd generation catalyst provided irreproducible results.

Table 2. Formal retro-[1,3]/[1,3]-dipolar cycloaddition



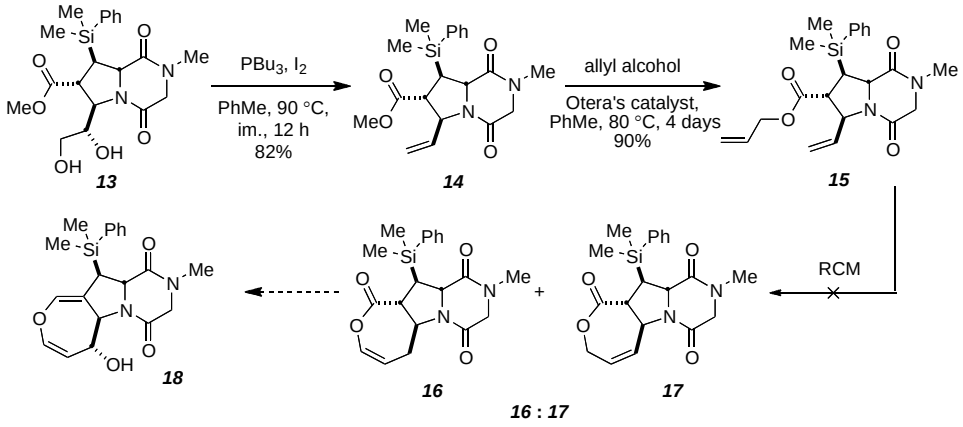
9 ***6*** ***10*** ***5***

Entry	Conditions	Result
1.	**9** + **6**, 90 °C sealed tube 1.5 days	**9** + **5**
2.	**9** + **6**, 160 °C sealed tube 12 h	**9** + trace **5**
3.	**9** + **6**, 190 °C sealed tube 12 h	**9** + **5** 1 : 1
4.	**9** + **6**, 220 °C sealed tube 12 h	28% **5**

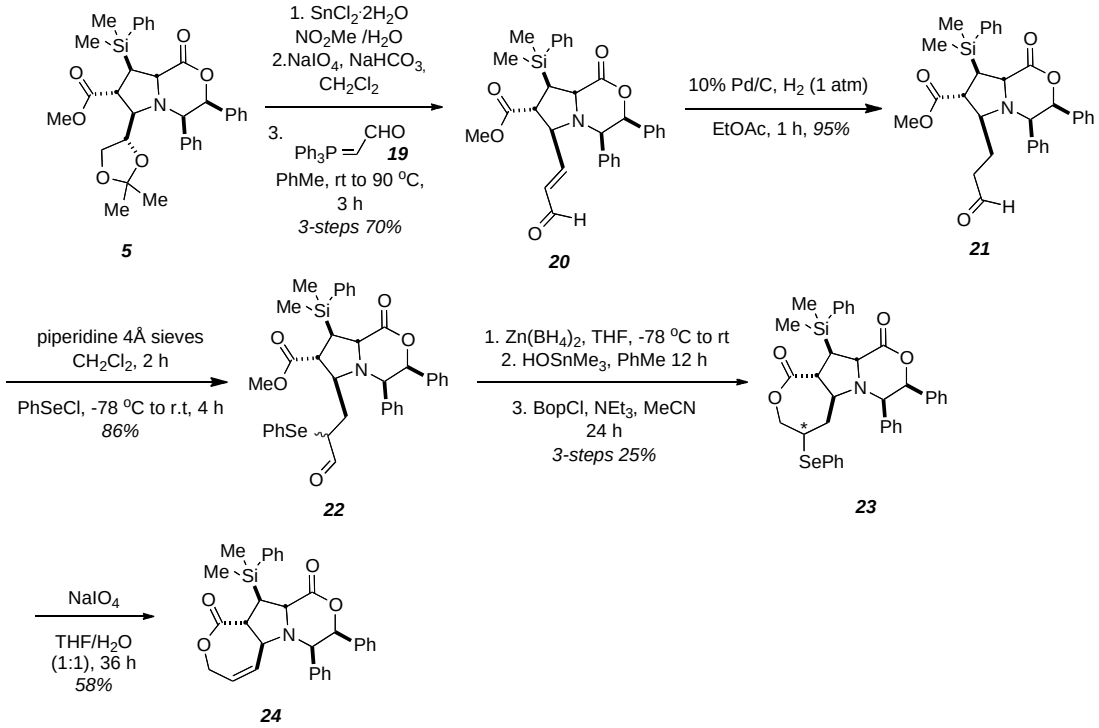


5 ***11*** ***12*** ***13*** ***5*** ***12*** ***13***

Scheme 3. Formation of dioxopiperazine **13**



Scheme 4. Formation of the 7-5-6 ring system

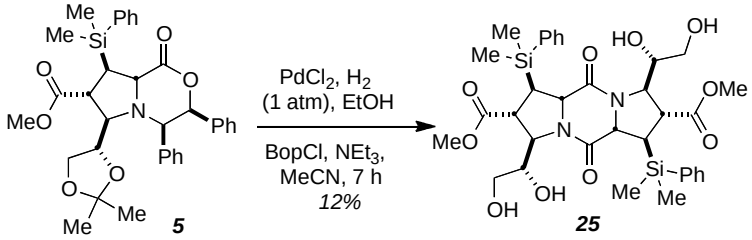


Scheme 5. Alternative construction of lactone **24**

To access a synthetic derivative of lactones **16** and **17** that could be elaborated into the oxepin ring, another approach was attempted (Scheme 5). Dipolar cycloadduct **5** was converted to the α,β-unsaturated aldehyde **20** in 70% overall yield for the three steps without purification. The double bond was reduced with 10% Pd/C at 1 atm of H_2 in EtOAc yielding **21** in 96% yield, which was followed by formation of the enamine and installation of selenium to give aldehyde **22** in 86% yield. Reduction of the aldehyde with $Zn(BH_4)_2$ and exposure to Me_3SnOH in toluene at 90 °C for 24 hours followed by closure of the lactone ring furnished tricycle **23** in 25% overall yield from **22**. Oxidative removal of the selenide with $NaIO_4$ furnished the desired lactone **24** in 58% yield with complete regioselectivity due to conformational

constraints.[8] With access to substrate **24** now realized, current efforts are focused on the elaboration to the oxepin ring which is presently under investigation.

Cycloadduct **5** can potentially serve as a point of divergence to access the symmetrical dimeric aranotin family of natural products (Scheme 6). Towards this end, the lactone template was removed with palladium chloride and the incipient generation of HCl mediated the cleavage of the acetonide as well as the template. The incipient amino acid was dimerized to afford dioxopiperazine **25**. Efforts are being directed at the further elaboration of this highly functionalized species towards the aranotins.



Scheme 6. Dimerization of cycloadduct **5**

CONCLUSION

In summary, a novel asymmetric dipolar cycloaddition was explored with vinyl silane **6**, which allowed for an efficient synthesis of a potential precursor to the pyrrolidine core of MPC 1001. Efforts are currently underway for the elaboration of compound **24** to the oxepin ring.

EXPERIMENTAL SECTION

(3*S*,4*R*,6*R*,7*R*,8*R*,8a*S*)-Methyl 8-(dimethyl(phenyl)silyl)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (5)

To a flame dried 100 mL round-bottomed flask equipped with a stir bar was added amine **8** (1.0 g, 0.00394 mol, 1 equiv.), dipolarophile **6** (13.0 g, 0.0592 mol, 4 equiv.), 4Å powdered molecular sieves (torched dried) and toluene (2.36 mL). The reaction was heated to 90 °C and aldehyde **7**[8] (2.05 g, 0.157 mol, 4 equiv.) was dissolved in toluene (30 mL) followed by syringe pump addition at 2mL/h. The reaction was stirred for 24 h followed by filtration over Celite, and concentrated to afford the crude material. The yellowish material was subjected to flash chromatography (gradient elution, 95:5 hexanes/EtOAc to 90:10 hexanes/EtOAC) to the desired product **5** (1.8 g, 78% yield). R_f=0.32 (80:20 hexanes:EtOAc); $[\alpha]^{25}_D$ -14.6 (*c* 0.3, $CHCl_3$); IR (neat) ν 2924, 2854, 1736, 1638, 1458, 1377, 1259 1159, 1073, cm^{-1}; ^1H NMR ($CDCl_3$ 300MHz) : δ 7.58 – 6.74 (m, 15H), 5.69 (d, J = 3.3, 1H), 4.61, (d, J = 3.6, 1H), 4.28 (d, J = 6.9, 11.1H), 3.76 (m, 1H), 3.63 (dd, J = 6.0, 8.1, 1H), 3.45 (dd, J = 8.1, 15.0, 1H), 3.28 (t, J = 5.1, 5.1, 1H), 2.75 (dd, J = 4.5, 9.3, 1H), 2.53 (dd, J = 9.9, 10.2, 1H), 1.32 (s, 1H), 1.24 (s, 1H), 0.51

(s, 1H), 0.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.47, 170.36, 136.63, 136.00, 135.80, 134.59, 129.71, 12956, 128.43, 128.10, 128.00, 127.91, 127.83, 109.21, 82.10, 78.97, 69.01, 66.43, 64.90, 63.65, 52.33, 49.40, 34.21, 26.42, 25.72, -2.70, -4.39; HRMS Calcd. for $C_{34}H_{40}NO_6Si$. $[M+H]^+$ 586.2. Found 586.2 $[M+H]^+$.

(5*R*,6*S*)-1,3-Bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-diphenyltetrahydrooxazolo[4,3-*c*][1,4]oxazin-8(3*H*)-one (9)

The yield of this product varies depending upon the specific reaction conditions; please refer to Table 1. R_f=0.55 (70:30 hexanes:EtOAc); $[\alpha]^{25}_D$ -106.6 (*c* 0.42, $CHCl_3$); IR (neat) ν 3925, 1736, 1457, 1370, 1220, 1142, 1069; ^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.30 – 6.90 (m, 10 H), 5.43 (d, J = 3.6, 1H), 4.67 (d, J = 9.3, 1H), 4.53 – 4.44 (m, 3H), 4.24 (dd, J = 3.0, 9.3, 1H), 4.17 – 4.07 (m, 2H), 3.99 (dd J = 15.9, 8.7, 1H), 3.91 (dd, J = 7.8, 7.8, 1H), 3.80 (dd, J = 4.8, 9.0, 1H), 1.42 (s, 6H), 1.26 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 177.54, 134.90, 134.22, 129.95, 128.80, 128.72, 128.65, 128.21, 127.92, 110.04, 109.43,97.048, 85.59, 76.64, 74.98, 74.76, 66.64, 66.26, 62.26, 60.91, 26.62, 25.70, 25.26; HRMS Calcd. for $C_{29}H_{34}NO_7$ $[M+H]^+$ 496.2. Found 496.2 $[M+H]^+$.

(2*S*,3*R*,4*R*,5*R*)-5-(1,2-Dihydroxyethyl)-3-(dimethyl(phenyl)silyl)-4-(methoxycarbonyl)pyrrolidin-1-ium-2-carboxylate (11)

To a 100 mL round-bottomed flask was added compound **5** (500 mg, 0.835 mmol, 1 equiv.) in absolute EtOH (5 mL). The reaction was purged with argon and 10% Pd on carbon (250 mg by weight) was added followed by equipping the reaction vessel with a stir bar and a balloon of H_2. Acetyl chloride (181 μL, 2.55 mmol, 3 equiv.) was added to the reaction mixture and stirring continued overnight and monitored by TLC until all starting material was consumed. The reaction was filtered over Celite, and concentrated to reveal a white foam. The foam was dissolved in CH_2Cl_2 (20 mL) and was purified by flash chromatography with C18 reverse phase silica gel 90:10 MeCN/H_2O to provide pure product **11** (240 mg, 78% yield). R_f=0.50 (60:40 MeCN/H_2O.); $[\alpha]^{25}_D$ -10.3 (*c* 1.05, $CHCl_3$); IR (neat) ν 3333, 2955 2349, 1737, 1629, 1428, 1368, 1200, 1052, 778 cm^{-1}; ^{1}H NMR (CD_3OD, 300MHz) : δ 7.57 – 7.64 (m, 2H), 7.39 – 7.33 (m, 2H), 4.35 (t, J = 18, 1H), 3.95 (t, J = 15, 1H), 3.86 (d, J = 9, 1H), 3.79 (dd, J = 2.1, 9.6, 1 H), 3.70 (m, 1H) 3.33 (s, 3H), 3.06 (dd, J = 9.6, 12.3, 1H) 2.19 (dd, J = 8.4, 9.0, 1H) 0.50 (s, 3H), -0.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 177.04, 140.92, 139.53, 139.18, 134.65, 133.13, 132.92, 73.47, 69.93, 69.82, 69.04, 56.81, 54,.45, 38.46, 1.26, -0.95; HRMS Calcd. for $C_{17}H_{25}NO_6Si$ $[M+H]^+$ 368.1. Found 368.1 $[M+H]^+$.

(6*R*,7*R*,8*R*,8a*S*)-Methyl 6-(1,2-dihydroxyethyl)-8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxo octahydro-

pyrrolo[1,2-a]pyrazine-7-carboxylate (13)

To a 100 mL round-bottomed flask was added **11** (281 mg, 0.76 mmol, 1 equiv.), MeCN (10 mL), sarcosine ethyl ester hydrochloride **12** (163 mg, 1.07 mmol, 1.4 equiv.), TEA (692 μL, 4.97 mmol, 6.5 equiv.) and the reaction was stirred for 30 min. followed by the addition of BopCl (272 mg, 1.07 mmol, 1.4 equiv). The reaction was stirred for 2 days and evaporated to dryness. EtOAc (5 mL) and 1N HCl (5 mL) was added and stirring continued for 1 h. The aqueous layer was extracted with EtOAc (2 x 10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 x 10 ml), H_2O (2 x 10 mL) and a saturated aqueous solution of NaCl (2 x 10 mL). The light yellow material was dried over $NaSO_4$ and concentrated. The crude reaction mixture was purified by flash chromatography (gradient elution 98.75:1.25 to 93:7 CH_2Cl_2/MeOH) to afford compound **13** (217 mg, 60% yield). R_f=0.41 (95:5 CH_2Cl_2/MeOH.); $[\alpha]^{25}_D$ +18.5 (*c* 1.78, $CHCl_3$); IR (neat) ν 3406, 2953, 1736, 1652, 1468, 1406, 1340, 1300, 1255, 1212, 1111, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): δ 7.54 – 7.52 (m, 2H), 7.33 – 7.31 (m, 3H), 4.38 (dd, J = 2.7, 4.2, 1H), 4.20 (d, J = 9.3, 1H), 4.14 (dd, 1H), 3.87 (dd, 1H), 3.68 – 3.86 (m, 1H), 3.56 – 3.50 (m, 1H), 3.44 (s, 3H), 3.39 (dd, J = 5.1, 14.4, 1H), 3.00, (dd, J = 3.0, 8.4, 1H), 2.95 (s, 3H), 2.15 (dd, J = 8.4, 9.0, 1H), 1.21 (t, J = 4.8, 1H) 0.50 (s, 3H), 0.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 174.13, 165.34, 163.57, 137,03, 134.70, 129.44, 127.84, 74.44, 63.61, 63.20, 62.13; HRMS Calcd. for $C_{20}H_{28}BrN_2O_6SiNa$ [M+Na] 443.1. Found 443.1 [M+Na].

One-pot procedure (13)

To a flame dried 5mL round-bottomed flask was added compound **5** (102 mg, 0.17 mmol, 1 equiv.) in absolute EtOH (1.5mL). The reaction was purged with argon before adding $PdCl_2$ (25 mg, 0.01 mmol, 0.8 equiv.) to the reaction mixture followed by equipping the reaction vessel with a stir bar and a balloon of H_2 (1 atm). The reaction was stirred 12 h, filtered over Celite, and concentrated under reduced pressure to afford 87 mg of crude product. The crude yellow product was dried under reduced pressure for 2 h. The crude free amino acid was re-dissolved in MeCN (1.5 mL) followed by the addition of sarcosine ethyl ester hydrochloride **12** (126 mg, 0.49 mmol, 2.95 equiv.), and BopCl (60 mg, 0.576 mmol, 2.2 equiv.). The reaction vessel was purged with argon followed by the addition of NEt_3 (104 μL, 0.74 mmol, 4.3 equiv.). The reaction was stirred for 2 days. 1N HCl (10 mL) and EtOAc (10 mL) was added and stirring continued for another h. The two layers were separated and the aqueous layer was extracted EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified by flash chromatography (gradient elution, 98.75:1.25 to 95:5 CH_2Cl_2/MeOH) to give compound **13** (30 mg, 40% yield).

(6*S*,7*R*,8*R*,8a*S*)-Methyl 8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxo-6-vinyloctahydropyrrolo[1,2-*a*]-

pyrazine-7-carboxylate (14)

To a 50 mL round-bottomed flask equipped with a stir bar was added compound **13** (202 mg, 0.483 mmol, 1 equiv.) tributylphosphine (408 μL, 1.92 mmol, 4 equiv), imidazole (131 mg, 1.92 mmol, 4 equiv) in toluene (10 mL). The reaction was heated to 90 °C upon addition of I_2 (731 mg, 2.88 mmol, 6 equiv.) in small portions and the reaction was stirred for 24 h. The reaction mixture was then diluted with EtOAc (25 mL) and the organic layer was washed with 10% aqueous $NaSO_4$ (20 mL), H_2O (2 x 20 mL) and a saturated aqueous solution of NaCl (2 x 20 mL). The reaction was dried, concentrated and purified by flash chromatography in 98.25:1.75 CH_2Cl_2/MeOH to afford pure compound **14** (153 mg, 82% yield). R_f =0.44 (97:3 CH_2Cl_2/MeOH); $[\alpha]^{25}_D$ +28.0 (*c* 0.891, $CHCl_3$); IR (neat) ν 2954, 1736, 1671, 1435, 1256, 1111, 843, 779, 739, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ 7.70 – 7.43 (m, 45H), 5.62 – 5.50 (m, 1H), 5.10 – 5.04 (m, 2H), 4.64 (t, J = 3.9, 3.9, 1H), 4.17 - 4.04 (m, 2H), 3.80 (dd, 1H), 3.49 (s, 3H), 2.98 (s, 3H), 2.69 (dd, J = 6.0, 11.4, 1H), 2.31 (dd, J = 11.1, 10.5, 1H), -0.50 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.33, 166.28, 161.74, 136.39, 135.13, 134.65, 129.64, 128.15, 128.02, 116.30, 63.27, 61.46, 53.47, 52.53, 50.88, 33.90, 33.21, 29.91, -2.60, -3.63; HRMS Calcd. for $C_{20}H_{26}N_2NaO_4Si$ [M+Na] 409.1. Found 409.1 [M+Na].

(6*S*,7*R*,8*R*,8a*S*)-Allyl 8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxo-6-vinyloctahydropyrrolo[1,2-*a*]-pyrazine-7-carboxylate (15)

To a 10 mL pressure vessel equipped with a stir bar was added compound **14** (72 mg, 0.18 mmol, 1 equiv.), allyl alcohol (633 μL, 9.31 mmol, 50 equiv.) and Otera's catalyst[7] (222 mg, 0.18 mmol, 1 equiv.) in toluene (2 mL). The reaction was heated at 80 °C for 4 days and filtered over a pad of silica, and concentrated under reduced pressure overnight. The crude residue was purified by flash chromatography (gradient elution, 98.75:1.25 to 97:3 CH_2Cl_2/MeOH to afford **15** (69 mg, 90% yield). R_f=0.40 (97:3 CH_2Cl_2/MeOH); $[\alpha]^{25}_D$ +26.4 (*c* 0.56, $CHCl_3$); IR (neat) ν 29.25, 2854, 1735, 1670, 1453, 1299, 1257, 1157, 1111 cm^{-1}; ^1H-NMR ($CDCl_3$ 300MHz) : δ 7.57 - 7.51 (m, 2H), 7.36 – 7.34 (m, 3H), 5.70, (ddd, 1H), 6.52 (m, 1H), 5.27 – 5.16 (m, 2H), 5.107 – 5.05 (m, J = , 2H), 4.66 (t, J = 8.13, 1H), 4.49 – 4.26 (m, 1H), 4.33 – 4.26 (m,1H), 4.10 (dd, J = 17.1, 24.0, 2H), 3.83 (d, J =, 1H), 2.98 (s, 3H), 2.72 (dd, J = 6.0, 10.8, 1H), 2.32 (t, J = 11.1, 1H), 0.50 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.04, 169.83, 165.21, 139.93, 138.66, 138.18, 135.26, 133.15, 131.55, 122.62, 119.83, 69.66, 66.76, 64.97, 57.01, 54.447, 37.42, 37.42, 36.64, 0.09, -0.00; HRMS Calcd. for $C_{20}H_{26}N_2NaO_4Si$ [M+Na] 435.1. Found 435.1 [M+Na].

(3*S*,4*R*,6*S*,7*R*,8*R*,8a*S*)-Methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-((E)-3-oxoprop-1-en-1-yl)-3,4-diphenyl-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (20)

To a 250 mL round-bottomed flask equipped with a stir bar was added compound **5** (1.41 g, 2.30 mmol, 1

equiv.), in nitromethane (20 mL) saturated with H_2O. $SnCl_2 \cdot 2H_2O$ (1.65 g, 7.10 mmol, 3 equiv.) was added to the reaction mixture in small portions. The reaction was stirred for 2 h and saturated aqueous solution of $NaHCO_3$ (15 mL) was added followed by the addition EtOAc (20 mL). The crude reaction mixture was then filtered over Celite, separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O (3 X 10 mL) and dried, filtered, and concentrated to afford 1.37 g of pure material that was transferred to a 100 mL round-bottomed flask. The diol (1.37 g, 2.50 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (20 mL) followed by the addition of a saturated aqueous solution of $NaHCO_3$ (250 μL). $NaIO_4$ (850 mg, 3.76 mmol, 1.5 equiv.) was added in portions over a 30 min period. After 48 h of vigorous stirring, anhydrous Na_2SO_4 was added and stirring continued for another 30 min. The reaction mixture was filtered with a fritted funnel, and concentrated to give 1.07 g of pure material. (Note- if the reaction is slow, more $NaIO_4$ can be added to speed the reaction up). The aldehyde (1.07 g, 2.08 mmol, 1 equiv.) was added to a 100 mL round-bottomed flask and azeotroped with toluene (20 mL). Next, (triphenylphosphoranylidene)acetaldehyde (**19**) (760 mg, 2.50 mmol, 1.2 equiv.) was added and the reaction was slowly warmed from rt to 90 °C and stirring continued for 3 h. The reaction was concentrated and purified by flash chromatography 80:20 hexanes:EtOAc to afford compound **20** (750 mg, 70% yield overall for the three steps). R_f=0.41 (70:30 hexanes/EtOAc); $[\alpha]^{25}_D$ -63.1 (*c* 0.63, $CHCl_3$); IR (neat) ν 2924, 2853, 1738, 1691, 1497, 1454, 1428, 1347, 1231, 1172, 1113 cm^{-1}; ^1H NMR ($CDCl_3$ 400MHz) : δ. 9.28 (d, J=7.80, 1H) 7.56 – 6.74 (m, 15H), 6.28 (dd, J = 6.0, 15.6, 1H), 5.66 (d, J = 3.9, 1H), 4.38 (d, J = 3.6, 1H), 4.15 (d, J = 10.5 1H), 3.83 (t, J= 12.3, 1H), 3.43 (s, 3H), 2.72 – 2.54 (m, 2H) 0.52 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 193.21, 173.53, 170.06, 155.527, 135.70, 135.59, 134.99, 134.62, 132.17, 129.87, 129.08, 128.60, 128.48, 128.33, 128.17, 128.10, 127.61, 82.32, 69.867, 63.50, 63.268, 52.59, 52.20, 33.73, -2.99, -4.26; HRMS Calcd. for $C_{32}H_{33}NO_5Si$ $[M+H]^+$ 540.2. Found 540.2 $[M+H]^+$.

(3*S*,4*R*,6*S*,7*R*,8*R*,8a*S*)-Methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-(3-oxopropyl)-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (21)

To a flame-dried 10 mL round-bottomed flask was added compound **20** (310 mg, 0.57 mmol, 1.0 equiv.) in EtOAc (5 mL). The reaction was purged with argon before adding 10 mol% Pd/C (150 mg by weight, 0.24 equiv.) The reaction was stirred under an atmosphere of H_2 (1 atm) for 1 h at which time compound **20** was completely consumed as observed by TLC. The reaction was filtered through Celite with EtOAc (100 mL). The combined filtrates were dried with Na_2SO_4, and concentrated to dryness to give compound **21** (300 mg, 96% yield). The crude reaction mixture was directly used in the next reaction without purification. R_f=0.36 (70:30 Hexanes/EtOAc); $[\alpha]^{25}_D$ -51.3 (*c* 0.33, $CHCl_3$); IR (neat) ν 2925, 2854, 1734, 1455, 1259, 701 cm^{-1}; ^1H NMR ($CDCl_3$ 300MHz): δ. 9.46 (s, 1H), 7.61 – 6.66 (m – 15H) 5.64 (d, J = 2.7,

1H), 4.34 (d, J = 3.6, 1H), 4.07 (d, J = 10.8, 1H), 3.42 (s, 3H), 3.10 (dd, J = 5.4, 11.7, 1H), 2.54 m, 2H), 2.19 (m, 2H), 1.51 (dd, J = 6, 11.4, 2H), 0.56 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 205.49, 179.19, 174.45, 140.47, 140.19, 139.86, 138.95, 138.91, 134.00, 133.74, 132.76, 132.46, 132.40, 132.30, 132.24, 132.15, 132.12, 86.45, 72.40, 67.83, 67.42, 56.64, 56.02, 44.34, 38.18, 31.03, 5.53, 1.41, -0.00.

(3*S*,4*R*,6*S*,7*R*,8*R*,8a*S*)-Methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-(3-oxo-2-(phenylselanyl)propyl)-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (22)

To a flame dried 100 mL recovery flask was added 4 Å powered molecular sieves, compound **21** (298 mg, 0.058 mmol, 1 equiv.), CH_2Cl_2 (10 mL) and piperidine (73 μL, 0.07 mmol, 1.25 equiv.). The reaction was stirred for 3 h and concentrated re-dissolved in THF (10 mL) and evaporated from THF (3 x 10 mL) and dried under reduced pressure for 1 h. THF (5 mL) was added and the reaction was cooled to -78 °C. A solution of PhSeCl (167 mg, 0.08 mmol, 1.5 equiv.) was added in THF (2 mL) to the reaction and stirring continued for 1 h at -78 °C. The reaction was warmed to rt and stirring continued for 3 h. The reaction was filtered over Celite with EtOAc (20 mL), dried over Na_2SO_4 followed by purification purified by flash chromatography (gradient elution, 95:5 to 70:30 hexanes/EtOAc) to afford compound **22** (350 mg, 86% yield). R_f=0.58 (70:30 hexanes/EtOAc); $[\alpha]^{25}_D$ -48.8 (*c* 0.23, $CHCl_3$); IR (neat) ν 2925, 2854, 1736, 1455, 1259, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300MHz): δ 9.20 (d, J = 1.8, 1H), 8.95 (d, J = 3.0, 1H), 7.60 – 6.55 (m, 40H), 5.75 (d, J = 3.3, 1H), 5.67 (d, J = 3, 1H), 4.44 (d, J = 6.0, 1H), 4.24 (d, J = 3.6, 1H), 4.07 (dd, J = 11.1, 16.8, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 2.53 (m, 3H), 0.54 (s, 3H), 0.49 (s, 3H), 0.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 196.15, 195.93, 179.49, 179.25, 174.55, 174.46, 140.86, 140.69. 140.56, 140.46, 140.24, 140.16, 140.11, 140.02, 139.19, 139.12, 139.08, 86.33, 86.14, 72.95, 72.40, 69.06, 68.97, 67.78, 67.75, 57.36, 56.96, 56.88, 56.29, 53.79, 53.08, 39.19, 39.10, 37.92, 37.86, 5.75, 1.65, 1.16, 0.29, -0.00.

(3*S*,4*R*,5a*S*,10a*R*,11*R*,11a*S*)-11-(Dimethyl(phenyl)silyl)-3,4-diphenyl-7-(phenylselanyl)octahydro-1*H*-oxepino[3',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-1,10(10a*H*)-dione (23)

To a flame dried 10 mL round-bottomed flask was added **22** (114 mg, 0.0163 mmol, 1 equiv.) and THF (3 mL). The reaction was cooled to -78 °C and allowed to slowly warm to rt while a 0.083M solution of $Zn(BH_4)_2$ in THF was added dropwise until the reaction was complete by TLC. The organic layer was washed with a saturated aqueous NH_4Cl solution (3 mL), and H_2O (2 mL) and dried with Na_2SO_4, and concentrated to dryness to give 93 mg of pure product that was used directly in the next reaction. The crude reaction mixture was dissolved in toluene (5 mL) and trimethyltin hydroxide (240 mg, 0.13 mmol, 10 equiv.) was added. The reaction was heated at 90 °C and let stir for 24 h. The reaction was evaporated to give 73 mg of crude material that was purified by passage through a plug of silica gel with 97:3

CH_2Cl_2/MeOH to give 73 mg of crude material that was used directly in the next reaction. To a 10 mL round-bottomed flask was added the acid (73 mg, 0.01g mmol, 1 equiv.), MeCN (3 mL), triethylamine (82 μl, 0.06 mmol, 6 equiv.) and BopCl (54 mg. 0.021 mmol, 2.0 equiv.). The reaction was stirred for 24 h and was evaporated to dryness. EtOAc (2 mL) and 1N HCl (2 mL) was added and stirring continued for 15 min. The organic layer was washed with 1N HCl (2 x 2 mL), water (2 x 2 mL) and a saturated aqueous solution of NaCl (2 mL). The crude material was dried over Na_2SO_4 and concentrated. The light yellow material was purified by flash chromatography (gradient elution, 95:5 to 70:30 hexanes:EtOAc) to give **23** (27 mg, 25% yield for the three steps). R_f=0.30 (80:20 hexanes/EtOAc); $[\alpha]^{25}_D$ +21.6 (*c* 0.16, $CHCl_3$); IR (neat) ν 2925, 2854, 1742, 1579, 1463, 1378, 1260, 1111, cm^{-1}; ^1H NMR ($CDCl_3$ 300MHz): δ 7.53 – 6.79 (m, 20H), 5.87 (d, J = 3.9, 1H), 4.01 (m, 2H), 4.09 (d, 8.7, 1H), 3.97 (d, J = 5.4, 1H), 3.64 (m, 1H), 2.87 (t, J = 10.5, 1H), 2.71 (dd, J = 8.7, 10.8, 1H), 2.04 (m, 1H), 1.61 (m, 1H), 0.43 (s, 3H), 0.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.54, 175.14, 141.62, 139.95, 139.72, 139.38, 138.81, 138.87, 138.40, 133.21, 132.78, 132.34, 132.18, 131.97, 131.94, 131.89, 131.78, 131.73, 131.59, 131.54, 131.42, 130.00, 129.04, 81.08, 73.10, 66.98, 66.63, 64.07, 53.49, 44.99, 42.73, 33.86 33.47, 25.22, 0.00, -0.03; HRMS Calcd. for $C_{37}H_{37}NO_4SeSi$ $[M+H]^+$ 668.1. Found 668.1 $[M+H]^+$.

(3*S*,4*R*,5a*S*,10a*R*,11*R*,11a*S*)-11-(Dimethyl(phenyl)silyl)-3,4-diphenyl-3,4,8,10a,11,11a-hexahydro-1H-oxepino[3',4':4,5]pyrrolo[2,1-c][1,4]oxazine-1,10(5aH)-dione (24)

To a 10 mL flask was added **23** (9 mg, 0.0013 mmol, 1 equiv.) and dissolved in a 4:1 THF/H_2O (1 mL). $NaIO_4$ (56 mg, 0.0269 mmol, 20 equiv.) was added over 30 min and let stir for 31 h at rt. Na_2SO_4 was added and the reaction was filtered over Celite, and concentrated to give 11 mg of crude material that was purified by flash chromatography (gradient elution 95:5 to 70:30 hexanes/EtOAc) to give compound **24** (4 mg, 58% yield). R_f = 0.33 (60:40 hexanes:EtOAc); $[\alpha]^{25}_D$ +17.5 (*c* 0.43, $CHCl_3$); IR (neat) ν 2924, 2853, 1744, 1497, 1455, 1427, 1402, 1262, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) : δ 7.55 – 6.89 (m, 15H), 5.85 (d, J = 3.3, 1H), 5.72 (m, 1H), 5.63 – 5.59 (m, 1H), 4.62 (m, 1H), 4.40(m, 1H), 4.26 (d, J = 10.5, 1H), 4.20 (d, J = 3.3, 1H), 3.72 (m, 1H), 3.28 (dd, J = 11.4, 11.4, 1H), 2.53 (dd, J = 12.0, 11.4, 1H), 0.51 (s, 3H), 0.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.98, 174.94, 139.77, 139.72, 139.08, 135.19, 133.31, 132.37, 131.97 131.92, 131.65, 131.63, 130.39, 128.44, 81.95, 70.11, 68.70, 68.14, 64.22, 51.51, 35.68, 34.54, 33.25, 0.35, -0.00; HRMS Calcd. for $C_{31}H_{31}NO_4Si$ $[M+H]^+$ 510.20. Found 510.20 $[M+H]^+$.

(1*R*,2*R*,3*R*,5a*S*,6*R*,7*R*,8*R*,10a*S*)-Dimethyl 3,8-bis(1,2-dihydroxyethyl)-1,6-bis(dimethyl(phenyl)silyl)-5,10-dioxodecahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,7-dicarboxylate (25)

To a flame dried 10mL round-bottomed flask was added compound **5** (253 mg, 0.431 mmol, 1 equiv.) in absolute EtOH (5 mL). The reaction was purged with argon and $PdCl_2$ (61 mg, 0.03 mmol, 0.8 equiv.)

was added to the reaction mixture followed by equipping the reaction vessel with a stir bar and a balloon of H_2 (1 atm). The reaction was stirred overnight, filtered over Celite, and concentrated under reduced pressure to afford the crude product. The reaction was azeotroped with toluene (3 x 20 mL) and concentrated under reduced pressure for 1 h. BopCl (138 mg, 0.10 mmol, 2.1 equiv.) was added and the reaction vessel was purged with argon for 5 min. The two compounds were dissolved in MeCN (5 mL) followed by cooling to -78 °C and dropwise addition of triethylamine (342 µL, 2.64 mol, 6.1 equiv.). The reaction vessel was warmed to rt and stirred for 7 h followed by concentration and dilution by EtOAc (10 mL) and 1 N HCl (10 mL). The organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The reaction was purified by flash chromatography (gradient elution, 98.75:1.25 to 95:5 CH_2Cl_2/MeOH) to afford compound **25** (18 mg, 12% yield). R_f=0.39 (97:3 CH_2Cl_2:MeOH); $[\alpha]^{25}_D$ -129.4 (*c* 0.68, $CHCl_3$); IR (neat) ν 3424, 2925, 1737, 1642, 1429, 1256, 1209, 1111, 1038 cm^{-1}; ^1H NMR ($CDCl_3$ 300MHz): δ 7.25 (m, 2H), 7.34 (m, 3H), 4.53 (dd, J = 3, 6, 1H) 4.27 (d, J = 12, 1H), 3.37 (m, 1H), 3.36 (m, 4H), 3.28 (dd, J = 7.5, 10.8, 1H), 3.11 (dd, J = 6, 11.4, 1H), 0.47 (s, 3H), 0.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.09, 169.09, 14018, 138.01, 132.93, 131.26, 78.2, 68.05, 65.22, 56.06, 50.53, 36.10, 0.77, -0.00; HRMS Calcd. for $C_{34}H_{46}N_2NaO_{10}Si_2$: 721.2 [M+Na]. Found 721.1 [M+Na].

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