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Carbonylation of functionalized diamine diols to cyclic ureas: application to derivatives of DMP 450

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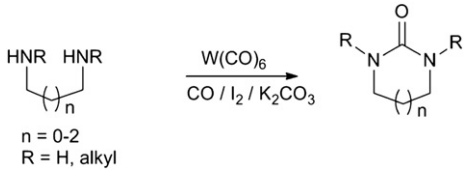
ABSTRACT

Synthesis of the cyclic urea core structure of the HIV protease inhibitor DMP 450 has been achieved via $W(CO)_6/I_2$-catalyzed carbonylation of diamine intermediates. Carbonylations of related functionalized diamines to derivatives of the DMP 450 core structure were also examined. Selected diamine diol substrates could be converted to the cyclic urea core structure by catalytic carbonylation without protection of the diol functionality.

1. Introduction

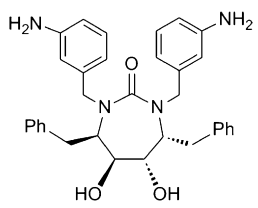
The presence of the urea moiety in various compounds, such as agrochemicals, pharmaceutical candidates, resins, and dyes[1–5] has prompted the development of methods for the synthesis of ureas. Classical methods for the preparation of ureas from amines involve the use of toxic reagents, such as phosgene or isocyanates.[6,7] The use of phosgene or isocyanates poses environmental and health concerns because of the storage and use of large amounts of chlorine during their manufacture. The high toxicity associated with these reagents has led to efforts to develop less hazardous reagents for the synthesis of ureas from amines. Alternatives to phosgene have included, but are not limited to, the utilization of phosgene derivatives or the use of carbon monoxide as the carbonyl source.[8] An area of considerable interest is catalytic oxidative carbonylation, which uses amines, an oxidant, and carbon monoxide as starting materials to afford ureas.[9] The only byproducts are the reduced form of the oxidant and protons, making it appealing by atom economy[10] standards. Various transition-metal catalysts including Pd,[11–16] Co,[17–21] Ni,[22] Ru,[20,23] Mn,[24] and Au,[25–27] have been shown to yield at least some urea. However, it is often a minor product. Additionally, harsh reaction conditions are required, which can result in complex mixtures of ureas, oxamides, and formamides.

Our prior experiences using tungsten hexacarbonyl [$W(CO)_6$] as a catalyst for the catalytic oxidative carbonylation of diamines to ureas with I_2 as the oxidant (Scheme 1)[28,29] included its application to the synthesis of functionalized targets,[30–32] including the core structure of the HIV protease inhibitor DMP 450.[33,34]



Scheme 1. Cyclic ureas previously prepared by catalytic carbonylation.

The practical synthesis of DMP 450[35] involved the use of phosgene or a phosgene derivative to install the urea moiety, which required protection of the diol functionality. In the initial small-scale preparations, a primary diamine was reacted with the phosgene derivative 1,1′-carbonyldiimidazole (CDI), followed by N-alkylation as appropriate.[34–36] A subsequent approach to the synthesis of DMP 450 analogues involved the use of phosphorus tethers in conjunction with ring-closing metathesis to afford the diamine precursors but the urea moiety was also installed by carbonylation with CDI.[37]



DMP 450

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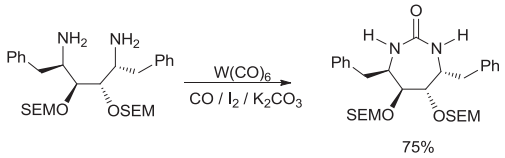
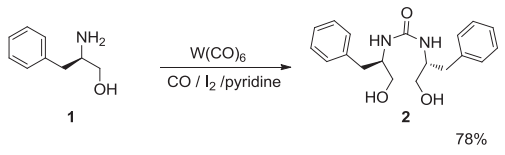
Since the use of phosgene or its derivatives, such as CDI requires protection of the diol, an extensive study of protecting groups was carried out in order to find the best conditions.[35,38] Although protection of the diol functionality was integral to the success of the catalytic carbonylation reaction using our original reaction conditions, as it had been with stoichiometric use of phosgene and its derivatives, yields from the carbonylation reaction were comparable to those obtained using stoichiometric methods (Scheme 2).[30]



Scheme 2. Synthesis of the core DMP450 structure by catalytic carbonylation.

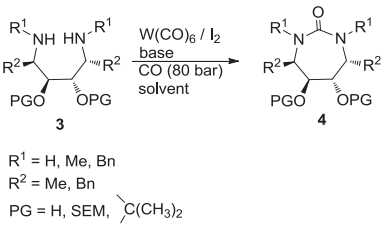
Subsequent modification of our reaction conditions led to the selective catalytic oxidative carbonylation of unprotected amino alcohols to ureas.[31] Using pyridine as the base and changing the work-up allowed for conversion of a series of 1,2-, 1,3-, 1,4-, and 1,5-amino alcohols to ureas in good to excellent yields, in preference to cyclization to the carbamate. Good yields of urea **2** from the 1,2-amino alcohol **1** (Scheme 3)[31] suggested that it could be possible to synthesize the core structure of DMP 450 by catalytic carbonylation without protecting group chemistry. We now report the extension of our original study on the preparation of the core structure of DMP 450 (primary diamine substrates with protected diols) to encompass related substrates with secondary diamines and unprotected diols. Although there are steric limitations to the catalytic oxidative carbonylation reaction, several of these more challenging substrates afford the cyclic urea in good to excellent yields.



Scheme 3. Carbonylation of 1,2-amino alcohol **1**.

2. Results and discussion

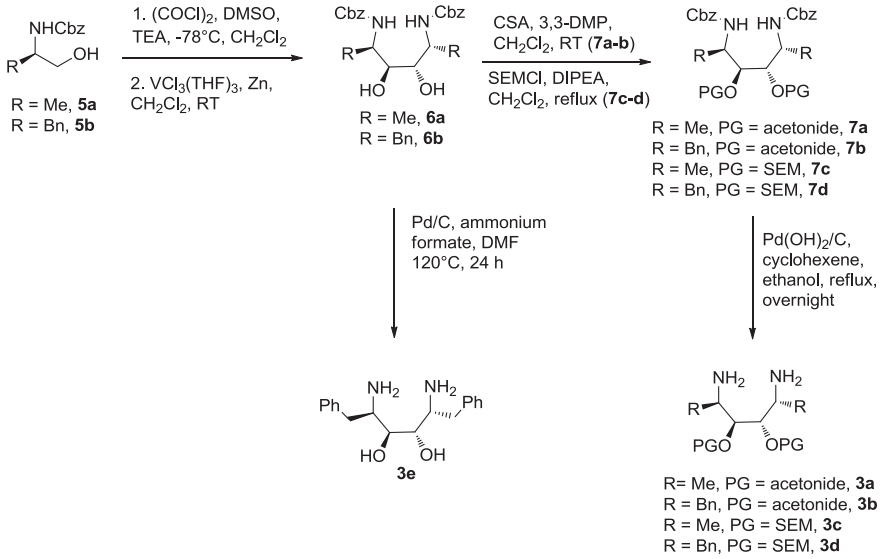
Substrates for the carbonylation study were chosen from a series of primary and secondary diamine diols that would afford the core structure of DMP 450 and its derivatives (Scheme 4). In order to assess the need for protecting group chemistry, the substrates included *O*-protected, as well as unprotected hydroxyl substituents. All substrates were subjected to $W(CO)_6/I_2$ catalyzed oxidative carbonylation. Depending on the substrate, there were two sets of reaction conditions for carbonylation, the main differences being in base and solvent. In one procedure, potassium carbonate was used as the base with a biphasic solvent system (CH_2Cl_2/H_2O), while in a second procedure, the preferred base was pyridine with methylene chloride or dichloroethane (at 80 °C) as the solvent.



Scheme 4. Diamine substrates **3** and their respective cyclic ureas.

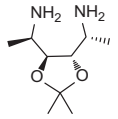
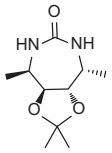
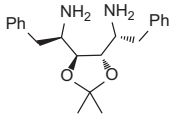
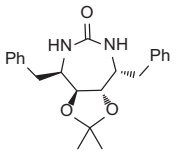
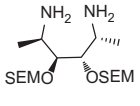
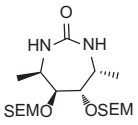
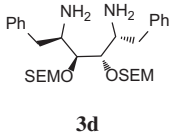
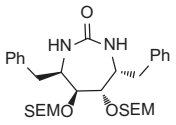
We began our investigation with the synthesis of primary diamines **3a**–**e**, starting from the appropriate chiral amino alcohol (Scheme 5).[34,36,39] Swern oxidation of **5a**,**b** followed by vanadium-mediated coupling affords diols **6a**,**b**. Protection of the diols to produce **7a**–**d**, and hydrogenolysis using cyclohexene as the hydrogen source gives *O*-protected amines **3a**–**d**. Unprotected diol **3e** can be obtained by the direct hydrogenolysis of **6b**.

For α-methyl diamines **3a** and **3c**, ureas were obtained in good yields regardless of whether the protecting group was acetonide or SEM (Table 1, entries 1 and 3). The protecting group preference was more apparent with a benzyl group in the alpha position (Scheme 2, Table 1, entries 2 and 4).[30] In addition, urea **4e**, the core structure of DMP 450, could be obtained from diamine **3e** in low yield without protection of the diol (Scheme 6). Optimization experiments on carbonylation of **3e** indicated that this reaction required increased temperature (80 °C) with dichloroethane as the solvent. However, in contrast to results with 1,2-amino alcohols,[31] formation of the urea

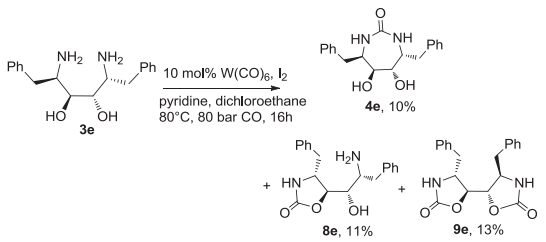


Scheme 5. Synthesis of bis(amino)hexanediols **3a**–**e**.

Table 1
Carbonylation of diamines **3a**–**d**[a]

Entry	Aminohexanediol	Product	Yield[b] (%)
1	 **3a**	 **4a**	83
2	 **3b**	 **4b**	38[30]
3	 **3c**	 **4c**	75
4	 **3d**	 **4d**	75[30]

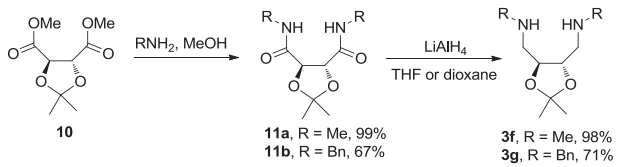
[a] Reagents and conditions: $W(CO)_6$, I_2, K_2CO_3, 80 bar CO, CH_2Cl_2/H_2O, 40 °C, 24 h.
[b] Isolated yields.



Scheme 6. Carbonylation of diamine **3e**.

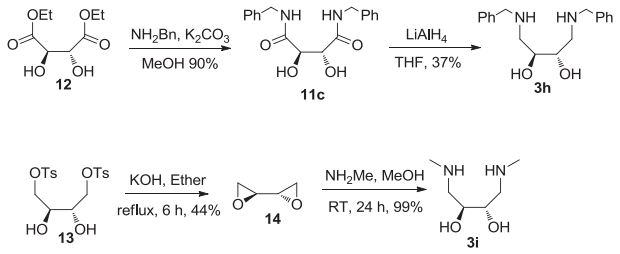
was accompanied by cyclization to oxazolidinones **8e** and **9e** in roughly equimolar quantities. The reaction also suffered from low conversion (54% conversion) due to the formation of the amine hydroiodide from HI generated in the reaction. Although the amine salt could be recovered and recycled, the formation of a mixture of products limits the utility of the reaction in the case of **3e**.

To explore the feasibility of the carbonylation of secondary amines, *N*-substituted diamines **3f**–**i** were synthesized. Amidation of the starting chiral tartrate[40–42] **10** followed by reduction by lithium aluminum hydride[42,43] to afford the bis(amino)butanediols **3f** and **3g** in good yield (Scheme 7). A similar approach can be



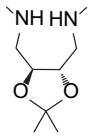
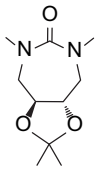
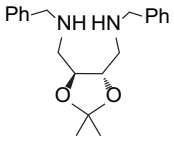
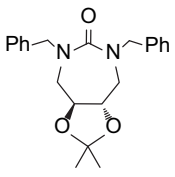
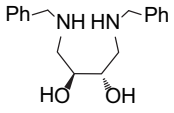
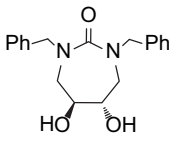
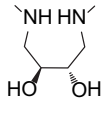
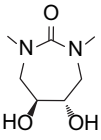
Scheme 7. Synthesis of **3f**–**g**.

applied to obtain **3h**, starting from the appropriate parent tartrate **12**. Due to purification issues, a different route was employed to synthesize compound **3i**. Starting from the ditosylate **13**, aminolytic ring opening of diepoxide **14** provided compound **3i** in quantitative yield (Scheme 8). Results from the carbonylation of aminobutanediols **3f**–**i** are summarized in Table 2.



Scheme 8. Synthesis of **3h**,**i**.

Table 2
Carbonylation of diamines **3f**–**i**[a]

Entry	Aminobutanediol	Product	Yield[b] (%)
1	 **3f**	 **4f**	58
2	 **3g**	 **4g**	99[d]
3	 **3h**	 **4h**	10
4	 **3i**	 **4i**	42[c]

[a] Reagents and conditions: $W(CO)_6$, I_2, pyridine, 80 bar CO, CH_2Cl_2, 40 °C, 24 h.
[b] Isolated yields.
[c] 48 h.
[d] Based on starting material consumed (36%).

From Table 2, it is apparent that the $W(CO)_6/I_2$ catalytic carbonylation method can be applied to secondary diamines bearing the seven-membered ring skeleton. Although yields were generally lower than those from the primary diamines, the tetrasubstituted ureas were obtained in good yields whether or not the diol was protected. Protected *N*-methyl diamine **3f** afforded urea **4f** in 58% yield (Table 2, entry 1) and the unprotected *N*-methyl variant **3i** took 48 h to give a 42% yield of urea (Table 2, entry 4). Urea **4g** was

obtained in excellent yields of urea based on the amount of **3g** consumed in the reaction (36%).

Free diol **3h** produced only 10% of the corresponding urea (Table 1, entries 2 and 3). As was also observed for **3e**, a portion of **3h** (25%) was recovered in salt form, stemming from the inability of the base, pyridine, to deprotonate the resulting hydroiodide salt of the substrate. However, substituting pyridine with DMAP or DBU did not increase the yield. It is possible that because the HI salts of these free diol substrates are insoluble in the reaction media, they cannot be deprotonated by the organic base. The importance of the solubility of the HI salt has been discussed previously.[44] It is important to note that the free diol substrates **3h** and **3i** formed their respective ureas without competitive formation of the oxazolidinone from reaction at a hydroxyl group. This is remarkable given the kinetic preference for the formation of five-membered rings over the desired seven-membered rings and the behavior of primary diamine diol **3e**.

The method was then applied to secondary diamines with alkylation at the alpha position, such as compound **3j** (Scheme 9). N-Methylation of **7c** followed by deprotection of the Cbz group afforded **3j** in good yields. Attempts at the synthesis of urea **4j** by carbonylation of **3j** were met with difficulty. The compound did not react using standard conditions from the synthesis of ureas **3f**–**i** ($W(CO)_6/I_2$, pyridine, 80 bar CO, CH_2Cl_2, 40 °C, 24 h). Increasing the temperature to 80 °C, while using dichloroethane as the solvent, also proved unsuccessful. In addition, using the stronger base DBU resulted in decomposition of the starting material.

It seems that alkylation at both the nitrogen and the α-carbon is a detriment to the success of the reaction, most likely due to steric reasons. Catalytic carbonylation of amines is often considered to involve isocyanate intermediates,[26,45–47] but secondary amines, such as **3f**–**i** yield ureas although they cannot form isocyanates. An alternative route to formation of tetrasubstituted ureas from secondary amines is nucleophilic attack of the amine on a carbonyl ligand to form a carbamoyl complex, followed by a second nucleophilic attack on the carbamoyl.[48] Assuming that the cyclic ureas are formed by intramolecular nucleophilic attack on a carbamoyl complex, we studied the steric implications of *N*-alkyl and α-alkyl substituents computationally using molecular modeling for geometry optimization followed by basic molecular dynamics calculations with a target temperature of 353 K. The optimized structures show the effect of the additional steric bulk introduced at the metal center by *N*-alkyl groups. If there is no substituent in the α-position, the *N*-alkyl substituent can avoid steric problems with the ligand when in a pseudo-equatorial position (Fig. 1A). However, in the presence of both an *N*-alkyl and an α-alkyl group, the *N*-alkyl must be in steric conflict with either the ligands or the α-alkyl (Fig. 1B and B′). It has also been shown the seven-membered rings of the urea products can exist in two pseudo-chair conformations. Related conformational analysis of the urea product reveals that there is a preferred conformation when the nitrogens are substituted due to allylic 1,2-strain.[34] This provides further evidence that the secondary amines with α-substituents may be unable to adopt the necessary conformation to form the urea when bound to the metal.

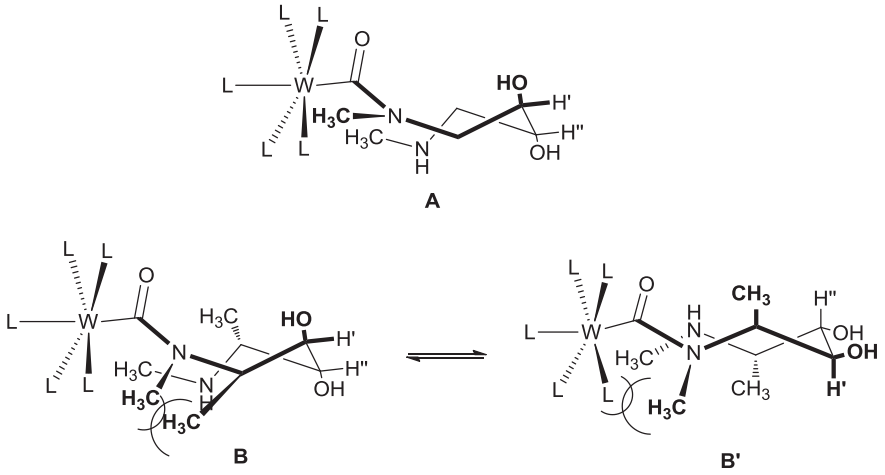
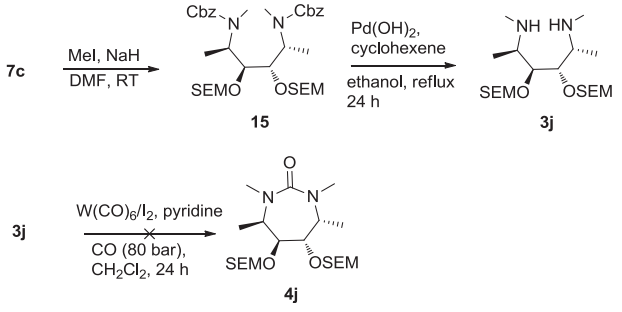


Fig. 1. Conformations of the postulated carbamate intermediates for ring closure to α-disubstituted *N*,*N*′-dialkyl cyclic ureas.



Scheme 9. Attempted synthesis of urea **4j**.

3. Conclusion

Building on our previous success with the synthesis of the *O*-protected core structure of DMP 450, we have shown that oxidative catalytic carbonylation can be used to prepare cyclic ureas from similar functionalized diamine substrates. Furthermore, the cyclic ureas can be obtained without protection of the diol in several cases. The synthesis of tetrasubstituted ureas can also be achieved, although steric constraints tend to lower the yields of the ureas and substitution at the α-carbon was not tolerated. Although there were limitations, the scope of the $W(CO)_6/I_2$-catalyzed carbonylation of amines to ureas has been extended to include the synthesis of derivatives of DMP 450.

4. Experimental

4.1. General

All experimental procedures were carried out under nitrogen in oven-dried glassware unless otherwise indicated. Solvents and

reagents were obtained from commercial sources in the appropriate grade and used without purification unless otherwise noted. Carbonylation reactions were conducted in a 300 mL glass liner in a Parr autoclave behind a blast shield. Carbon monoxide was purchased from Airgas South. Compounds **10**, **12**, **5a**, and **5b** were purchased from Sigma–Aldrich. Compound **13** was prepared as described in the literature.[49] ^{1}H and ^{13}C NMR spectra were obtained on Varian Gemini 300 MHz, VXR 300 MHz, and Mercury 300 MHz spectrometers. ^{1}H spectra were referenced to residual protons in the deuterated NMR solvents. ^{13}C spectra were referenced to carbon signals of the solvent. Infrared spectra were measured using a Perkin–Elmer Spectrum One FTIR. High-resolution mass spectrometry was performed by the University of Florida analytical service. Molecular modeling was carried out using MM2 energy minimization followed by MM2 molecular dynamics.[50]

*4.1.1. (1R,1′R)-1,1′-((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)diethanamine (**3a**).* The procedure was adapted from the literature.[36] Compound **7a** (0.73 g, 1.6 mmol), 45 mL ethanol, $Pd(OH)_2/C$ (108 mg), and cyclohexene (45 mL) were combined and refluxed overnight. After cooling to room temperature, the reaction was filtered through a bed of Celite and the resulting liquor was concentrated into an oil. Column chromatography with 9:1 CH_2Cl_2/CH_3OH provided **3a** as a pale brown oil (0.28 g, 93% yield). The product was identified by comparison with literature data.[51] ^{1}H NMR ($CDCl_3$) δ 3.55 (d, J=5.2 Hz, 2H), 2.86 (quint, J=5.1 Hz, 2H), 2.64 (br s, 4H), 1.34 (s, 6H), 1.04 (d, J=6.6 Hz, 6H).

*4.1.2. (1R,1′R)-1,1′-((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl) bis(2-phenylethanamine) (**3b**).* The procedure for **3a** was used to produce **3b** (730 mg, 99% yield) from **7b** (1.32 g, 2.17 mmol). The product was identified by comparison with literature data.[51] ^{1}H NMR ($CDCl_3$) δ 7.38–7.10 (m, 10H), 4.04 (dd, J=1.4, 2.0 Hz, 2H), 3.08–2.91 (m, 2H), 2.89–2.75 (m, 2H), 2.58 (dd, J=9.6, 13.1 Hz, 2H), 1.46 (s, 6H).

*4.1.3. (2R,3S,4S,5R)-3,4-Bis((2-(trimethylsilyl)ethoxy)methoxy)hexane-2,5-diamine (**3c**).* The procedure for **3a** was used to produce **3c** (1.28 g, 86% yield) from **7c** (2.46 g, 3.63 mmol). The product was identified by comparison with literature data.[36] ^{1}H NMR ($CDCl_3$) δ 4.73 (d, J=7.0 Hz, 2H), 4.62 (d, J=7.0 Hz, 2H), 3.64 (s, 2H), 3.62–3.47 (m, 6H), 1.26 (d, J=6.7 Hz, 6H), 0.85 (ddd, J=3.4, 7.3, 9.7 Hz, 4H), 0.00 (s, 18H).

*4.1.4. (2R,3S,4S,5R)-1,6-Diphenyl-3,4-bis((2-(trimethylsilyl)ethoxy) methoxy)hexane-2,5-diamine (**3d**).* The procedure for **3a** was used to produce **3d** (0.454 g, 95% yield) from **7d** (0.706 g, 0.851 mmol). The product was identified by comparison with literature data.[52] ^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (m, 10H), 4.80–4.62 (m, 4H), 3.84–3.55 (m, 6H), 3.25–3.20 (m, 2H), 2.94–2.68 (m, 4H), 1.01–0.81 (m, 4H), 0.05 (s, 18H).

*4.1.5. (2R,3S,4S,5R)-2,5-Diamino-1,6-diphenyl-3,4-hexanediol (**3e**).* The procedure was adapted from the literature.[39] A mixture of **6b** (1.33 g, 2.34 mmol), ammonium formate (0.88 g, 0.014 mol), and 10% Pd/C (0.80 g) in DMF (20 mL) was heated to 120 °C under an Ar atmosphere for 4 h. The reaction was allowed to cool, exposed to air, and the mixture was filtered through Celite. The filter cake was rinsed with methanol and the combined filtrates were concentrated into a pale yellow oil. The oil was taken up in ethyl acetate and washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to obtain **3e** (0.40 g, 70% yield). The product was identified by comparison with literature data.[39] ^{1}H NMR ($CDCl_3$) δ 7.39–7.02 (m, 10H), 3.67 (s, 2H), 3.02 (dd, J=5.6, 8.9 Hz, 2H), 2.91 (dd, J=5.8, 13.2 Hz, 2H), 2.71 (dd, J=8.9, 13.1 Hz, 2H).

*4.1.6. 1,1′-((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(N-methylmethanamine) (**3f**).* Using a variation of the literature procedure,[42] a solution of diamide tartrate **11a** (3.51 g, 0.0162 mol) in dioxane (50 mL) was added slowly to a vigorously stirring suspension of lithium aluminum hydride (1.85 g, 0.0487 mol) in dioxane (160 mL) under inert atmosphere. The reaction was refluxed overnight after addition was complete. After the reaction mixture cooled, it was quenched by careful addition of 3 mL water, 3 mL 15% NaOH, and 3 mL water. The solution was opened to air, filtered, and the filtrate concentrated to afford crude **3f** as a pale red oil (3.01 g, 98% yield). The product was identified by comparison with literature data.[53] ^{1}H NMR ($CDCl_3$) δ 3.93–3.88 (m, 2H), 2.76–2.72 (m, 4H), 2.46 (s, 6H), 1.40 (s, 6H).

*4.1.7. N,N′-(((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(-methylene))bis(1-phenylmethanamine) (**3g**).* The procedure used to prepare **3f** was used with **11b** (4.00 g, 0.0109 mol) to obtain **3g** in 71% yield (2.62 g) as a pale brown oil after purification by column chromatography with 99:1 CH_2Cl_2/CH_3OH as eluent. The product was identified by comparison with literature data.[42] ^{1}H NMR ($CDCl_3$) δ 7.31–7.19 (m, 10H), 3.97–3.90 (m, 2H), 3.79 (s, 4H), 2.77 (dd, J=2.1, 3.4 Hz, 4H), 1.66 (br s, 2H), 1.38 (s, 6H).

*4.1.8. (2S,3S)-1,4-Bis(benzylamino)butane-2,3-diol (**3h**).* Under nitrogen, diamide **11c** (4.00 g, 0.0122 mol) was placed in a Soxhlet thimble and extracted into a refluxing suspension of lithium aluminum hydride (1.20 g, 0.0316 mol) in 200 mL of tetrahydrofuran. Refluxing was continued for 72 h and the suspension stirred at room temperature overnight. Water (3 mL) was then added dropwise to the mixture followed by 15% NaOH (3 mL), and additional water (3 mL). The mixture was opened to air, filtered, and the solids washed with tetrahydrofuran. The filtrate was concentrated and the resulting residue was purified by column chromatography with 44:1 CH_2Cl_2/CH_3OH as the eluent to afford **3h** (1.36 g, 37% yield) as a white solid. The product was identified by comparison with literature data.[54] Mp 82–85 °C. ^{1}H NMR ($CDCl_3$) δ 7.34–7.17 (m, 10H), 3.85–3.69 (m, 6H), 3.10 (dd, J=3.8, 12.0 Hz, 2H), 2.72 (dd, J=2.1, 12.0 Hz, 2H), 1.54 (br s, 2H).

*4.1.9. (2S,3S)-1,4-Bis(methylamino)butane-2,3-diol (**3i**).* Diepoxide **14** (0.232 g, 2.69 mmol) was added to methylamine (11.6 mL of a 2.0 M solution in methanol, 0.0232 mol) at 0 °C and then stirred at room temperature overnight under nitrogen. The reaction was then exposed to air and concentrated to yield **3i** as a white solid (0.40 g, 99%). The product was identified by comparison with literature data.[54] ^{1}H NMR ($CDCl_3$) δ 3.83 (t, J=2.5 Hz, 2H), 3.05 (dd, J=3.3, 12.0 Hz, 2H), 2.65 (dd, J=2.5, 12.0 Hz, 2H), 2.42 (s, 6H).

*4.1.10. (2R,3S,4S,5R)-N2,N5-Dimethyl-3,4-bis((2-(trimethylsilyl)ethoxy)methoxy)hexane-2,5-diamine (**3j**).* The procedure for **3a** was used to produce **3j** (450 mg, 75% yield) from **15** (970 mg, 1.38 mmol). ^{1}H NMR ($CDCl_3$) δ 4.77 (d, J=1.1 Hz, 4H), 3.72–3.56 (m, 6H), 2.83 (br s, 2H), 2.41 (s, 6H), 1.13 (d, J=6.5 Hz, 6H), 0.93 (t, J=8.6 Hz, 4H), 0.01 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 96.8, 82.9, 66.1, 55.6, 34.1, 18.3, 16.5, –1.2. HRMS calcd for $C_{20}H_{48}N_2O_4Si_2$ $[M+H]^+$ 437.3225, found 437.3241.

*4.1.11. General procedure A for catalytic oxidative carbonylation of diamines with $W(CO)_6/I_2$: (3aS,4R,8R,8aS)-2,2,4,8-tetramethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3]diazepin-6(7H)-one (**4a**).* In air, a glass-lined 300 mL Parr high-pressure vessel equipped with a stir bar and containing 40 mL of CH_2Cl_2 and 10 mL of water was loaded with diamine **3a** (200 mg, 1.06 mmol), $W(CO)_6$ (18.6 mg, 0.0531 mmol), I_2 (270 mg, 1.06 mmol), and K_2CO_3 (587 mg, 4.25 mmol). The vessel was then charged with 80 bar of CO and heated on a hotplate at 80 °C for 24 h. After cooling to room

temperature, the pressure was released and 10 mL of water was added. The organics were separated and washed with a saturated solution of Na_2SO_3 followed by 0.1 M HCl. Each of the collected aqueous layers was extracted with 3:1 $CHCl_3$/EtOH. The organic layers were combined, dried over $MgSO_4$, and filtered. The solvents were removed by evaporation and the residue was purified by column chromatography using 9:1 CH_2Cl_2/CH_3OH as the eluent to yield **4a** as a pale yellow solid. IR (neat) ν_{CO} 1639 cm^{-1}. ^1H NMR ($CDCl_3$, CD_3OD) δ 3.97 (d, J=8.3 Hz, 2H), 3.70 (s, 2H), 1.39 (s, 6H), 1.19 (d, J=6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, CD_3OD) δ 158.2, 108.0, 80.3, 44.1, 25.9, 18.5. HRMS calcd for $C_{10}H_{18}N_2O_3$ $[M+H]^+$ 215.1390, found 215.1387.

*4.1.12. (3aS,4R,8R,8aS)-4,8-Dibenzyl-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3]diazepin-6(7H)-one (**4b**).* Following procedure A, compound **4b** was obtained in 36% yield (46.9 mg) from **3b** (120 mg, 0.352 mmol). The product was purified by column chromatography using 7:3 hexanes/ethyl acetate as the eluent. The product was identified by comparison with literature data.[38] IR (neat) ν_{CO} 1674 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.42–7.16 (m, 10H), 4.97 (d, J=6.1 Hz, 2H), 4.26 (s, 2H), 3.62–3.48 (m, 2H), 3.07 (dd, J=1.2, 13.3 Hz, 2H), 2.91–2.74 (m, 2H), 1.54 (s, 6H). HRMS calcd for $C_{22}H_{26}N_2O_3$ $[M+H]^+$ 503.2752, found 503.2797.

*4.1.13. (4R,5S,6S,7R)-4,7-Dimethyl-5,6-bis((2-(trimethylsilyl)ethoxy)methoxy)-1,3-diazepan-2-one (**4c**).* Following procedure A, **3c** (400 mg, 0.979 mmol) was converted to **4c** (320 mg, 75% yield). The product was identified by comparison with literature data.[36] IR (neat) ν_{CO} 1683 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.81 (d, J=7.2 Hz, 2H), 4.70 (d, J=7.0 Hz, 2H), 4.36 (s, 2H), 3.75 (q, J=6.6 Hz, 2H), 3.65 (dd, J=7.3, 9.6 Hz, 4H), 3.53 (s, 2H), 1.27 (d, J=6.9 Hz, 6H), 0.93 (dd, J=7.6, 9.6 Hz, 4H), 0.02 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 164.3, 95.7, 78.1, 65.9, 46.9, 19.4, 18.2, −1.3. HRMS calcd for $C_{19}H_{42}N_2O_5Si_2$ $[M+Na]^+$ 457.2525, found 457.2536.

*4.1.14. (4R,5S,6S,7R)-4,7-Dibenzyl-5,6-bis((2-(trimethylsilyl)ethoxy)methoxy)-1,3-diazepan-2-one (**4d**).* Following procedure A, compound **4d** was obtained in 75% yield (72.2 mg) from **3d** (92.9 mg, 0.164 mmol). The product was identified by comparison with literature data.[34] IR (neat) ν_{CO} 1679 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37–7.23 (m, 10H), 4.81 (d, J=7.0 Hz, 2H), 4.73 (d, J=7.0 Hz, 2H), 4.21 (s, 2H), 3.95 (t, J=7.5 Hz, 2H), 3.71–3.59 (m, 6H), 2.93–2.92 (m, 4H), 0.93–0.91 (m, 4H), 0.05 (s, 18H). HRMS calcd for $C_{31}H_{50}N_2O_5Si_2$ $[M+H]^+$ 587.3336, found 587.3355.

*4.1.15. (4R,5S,6S,7R)-4,7-Dibenzyl-5,6-dihydroxy-1,3-diazepan-2-one (**4e**), (4R,5S)-5-((1S,2R)-2-amino-1-hydroxy-3-phenylpropyl)-4-benzyloxazolidin-2-one (**8e**), and (4R,4′R,5S,5′S)-4,4′-dibenzyl-[5,5′-bioxazolidine]-2,2′-dione (**9e**).* In air, a glass-lined 300 mL Parr high-pressure vessel equipped with a stir bar and containing 1,2-dichloroethane (60 mL) was loaded with diamine **3e** (610 mg, 2.03 mmol), $W(CO)_6$ (71.0 mg, 0.203 mmol), I_2 (515 mg, 2.03 mmol), and pyridine (642 mg, 8.12 mmol). The vessel was then charged with 80 bar of CO and heated on a hotplate at 80 °C for 16 h. After cooling to room temperature, the pressure was released and 10 mL of CH_2Cl_2 was added to further dissolve any crude material. The solution was washed with a saturated solution of Na_2SO_3 followed by 0.1 M HCl, then dried over $MgSO_4$, and filtered. The solvent was removed by evaporation and the resulting residue was purified by column chromatography using 9:1 CH_2Cl_2/CH_3OH as the eluent to yield **4e** (30 mg, 10% yield), **8e** (32 mg, 11% yield), and **9e** (42 mg, 13%) based on 54% conversion of **3e**. Urea **4e** was identified by comparison with literature data.[38] IR (neat) ν_{CO} 1662 cm^{-1}. ^1H NMR ($CDCl_3$ with sufficient CD_3OD to dissolve the sample) δ 7.29–7.08 (m, 10H), 3.82 (t, J=7.6 Hz, 2H), 3.50 (s, 2H), 3.01–2.78 (m, 4H). Carbamate **8e**: IR (neat) ν_{CO} 1736 cm^{-1}. Mp 70–74 °C. ^1H NMR ($CDCl_3$ with sufficient CD_3OD to dissolve the sample) δ 7.47–6.92 (m, 10H), 4.37 (d, J=5.5 Hz, 1H), 4.26 (dd, J=12.9, 6.9 Hz, 1H), 3.86–3.68 (m, 1H), 3.15–2.89 (m, 4H), 2.79 (dd, J=13.5, 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$ with sufficient CD_3OD to dissolve the sample) δ 159.4, 135.3, 134.6, 129.7, 129.5, 129.4, 129.0, 127.8, 127.4, 82.6, 67.8, 55.6, 55.3, 40.9, 36.1. HRMS calcd for $C_{19}H_{23}N_3O_2$ $[M+H]^+$ 327.1708, found 327.1714. Carbamate **9e** was identified by comparison with literature data.[55] Mp 159–162 °C. ^1H NMR ($CDCl_3$) δ 7.38–7.18 (m, 7H), 7.06 (dd, J=1.9, 7.5 Hz, 4H), 5.80 (s, 2H), 4.04 (q, J=6.5 Hz, 2H), 3.93 (d, J=5.3 Hz, 2H), 2.86 (dd, J=6.7, 13.5 Hz, 2H), 2.70 (dd, J=7.3, 13.5 Hz, 2H).

*4.1.16. General procedure B for catalytic oxidative carbonylation of diamines with $W(CO)_6$/I_2: (3aS,8aS)-2,2,5,7-tetramethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3]diazepin-6(7H)-one (**4f**).* In air, a glass-lined 300 mL Parr high-pressure vessel equipped with a stir bar and containing CH_2Cl_2 (40 mL) was loaded with diamine **3f** (200 mg, 1.06 mmol), $W(CO)_6$ (18.6 mg, 0.0531 mmol), I_2 (270 mg, 1.06 mmol), and pyridine (336 mg, 4.25 mmol). The vessel was then charged with 80 bar of CO and heated on a hotplate at 40 °C for 24 h. After cooling to room temperature, the pressure was released and 10 mL of CH_2Cl_2 was added to further dissolve any crude material. The solution was washed with a saturated solution of Na_2SO_3 followed by 0.1 M HCl, then dried over $MgSO_4$, and filtered. The solvent was removed by evaporation and the resulting residue was purified by column chromatography using 9:1 CH_2Cl_2/CH_3OH as the eluent to yield **4f** as a pale brown oil (133 mg, 58% yield). IR (neat) ν_{CO} 1637 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.65–3.54 (m, 2H), 3.32–3.17 (m, 4H), 2.91 (s, 6H), 1.45 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 165.0, 111.5, 79.5, 51.2, 40.3, 26.9. HRMS calcd for $C_{10}H_{18}N_2O_3$ $[M+Na]^+$ 237.1210, found 237.1226.

*4.1.17. (3aS,8aS)-5,7-Dibenzyl-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-e][1,3]diazepin-6(7H)-one (**4g**).* Following procedure B, urea **4g** was obtained in 99% yield (53.2 mg) from **3g** (50.0 mg, 0.147 mmol reacted) after column chromatography on silica using 95:5 CH_2Cl_2/CH_2Cl_2/ethyl acetate as the eluent. IR (neat) ν_{CO} 1638 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.43–7.12 (m, 10H), 4.52 (s, 4H), 3.41 (dd, J=5.7, 2.8 Hz, 2H), 3.33 (dd, J=13.1, 2.7 Hz, 2H), 3.23–3.09 (m, 2H), 1.33 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 165.1, 138.3, 128.7, 128.7, 127.6, 111.5, 79.9, 55.5, 48.6, 26.8. HRMS calcd for $C_{22}H_{26}N_2O_3$ $[M+Na]^+$ 389.1836, found 389.1853.

*4.1.18. (5S,6S)-1,3-Dibenzyl-5,6-dihydroxy-1,3-diazepan-2-one (**4h**).* Following procedure B, urea **4h** was obtained as a clear oil in 10% yield (40.1 mg) from **3h** (370 mg, 1.23 mmol) after column chromatography using 1:1 CH_2Cl_2/ethyl acetate as the eluent. IR (neat) ν_{CO} 1622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 10H), 4.54, 4.32 (AB, J=14.7 Hz, 4H), 3.38–3.21 (m, 2H), 3.22–3.02 (m, 4H), 2.39 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 165.9, 138.2, 128.9, 128.7, 127.8, 73.1, 54.3, 51.2. HRMS calcd for $C_{19}H_{22}N_2O_3$ $[M+Na]^+$ 349.1523, found 349.1540.

*4.1.19. (5S,6S)-5,6-Dihydroxy-1,3-dimethyl-1,3-diazepan-2-one (**4i**).* Following procedure B, **4i** (53.2 mg, 45% yield) was obtained from **3i** (100 mg, 0.675 mmol) after 48 h. IR (neat) ν_{CO} 1625 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.55 (d, J=7.0 Hz, 2H), 3.40–3.16 (m, 2H), 3.11 (dd, J=13.9, 7.9 Hz, 2H), 2.86 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 166.2, 72.7, 53.8, 39.1. HRMS calcd for $C_7H_{14}N_2O_3$ $[M+H]^+$ 175.1077, found 175.1074.

*4.1.20. Dibenzyl ((2R,3S,4S,5R)-3,4-dihydroxyhexane-2,5-diyl)dicarbamate (**6a**).* Preparation of **6a** was adapted from a literature procedure.[56] In a two-necked round-bottom flask equipped with a stir bar and an addition funnel, a solution of oxalyl chloride (18.0 mL of 2.0 M solution in CH_2Cl_2, 0.036 mol) in CH_2Cl_2 (30 mL) was cooled to −78 °C, and anhydrous dimethylsulfoxide (3.40 mL, 0.0478 mol) in CH_2Cl_2 (53 mL) was added over 20 min while the temperature was kept near −78 °C. Immediately thereafter,

a solution of *N*-*Z*-D-alaninol **5a** (5.00 g, 0.0239 mol) in CH_2Cl_2 (70 mL) was added over 30 min, followed by stirring at −78 °C for 40 min. Triethylamine (9.67 g, 0.0956 mol) was added over 15 min, followed by stirring for 2 h at −78 °C to ensure completion of the reaction. After 20% aqueous $KHSO_4$ (50 mL) was added, the reaction mixture was allowed to warm to room temperature and water (45 mL) was added. The aqueous phase was separated and washed twice with CH_2Cl_2 (20 mL). The organic layers were combined and washed with saturated sodium bicarbonate (50 mL×2), water (50 mL×3), and saturated sodium chloride (50 mL×2), dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the resulting aldehyde in quantitative yield as an oil (4.95 g, 99% yield). The crude aldehyde was used without further purification to prevent possible racemization. Under an inert atmosphere, Zn dust (0.937 g, 0.0143 mol) was added to a solution of $VCl_3(THF)_3$ (9.83 g, 0.0263 mol) in dry CH_2Cl_2 (55 mL), resulting in a color change from reddish-brown to green after stirring for 20–30 min. A solution of the aldehyde (4.95 g, 0.0239 mol) in CH_2Cl_2 (55 mL) was added via cannula, causing a color change from green to brown. After being stirred at room temperature overnight, the reaction was opened to air and poured into 1 M HCl (125 mL). The two phases were stirred together overnight resulting in a blue aqueous layer and the precipitated coupling product in the organic layer. Adding CH_2Cl_2 and tetrahydrofuran dissolved all solids. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (85 mL). The combined organic layers were washed with saturated sodium bicarbonate (20 mL) and saturated sodium chloride (20 mL), and then dried, filtered, and evaporated to yield a white solid. Recrystallization from THF and hexanes afforded diol **6a** (3.92 g, 84% yield). The product was identified by comparison with literature data.[36] Mp 170–173 °C. ^{1}H NMR (DMSO-d_6) δ 7.38–7.26 (m, 10H), 6.83 (d, J=8.8 Hz, 2H), 5.08–4.93 (m, 4H), 4.37 (d, J=5.7 Hz, 2H), 3.84–3.70 (m, 2H), 3.25–3.14 (m, 2H), 1.00 (d, J=6.4 Hz, 6H).

*4.1.21. (2R,3S,4S,5R)-Bis[N-(benzyloxycarbonyl)amino]-1,6-diphenyl-3,4-hexanediol (**6b**).* Using the same procedure as for **6a**, diol **6b** (3.08 g, 63% yield) was produced from **5b** (5.00 g, 0.0175 mol). The product was identified by comparison with literature data.[38] ^{1}H NMR (DMSO-d_6) δ 7.38–7.09 (m, 20H), 6.83 (d, J=9.6 Hz, 2H), 5.05–4.86 (m, 4H), 4.55 (br s, 2H), 4.29–4.10 (m, 2H), 3.26 (br s, 2H), 2.83–2.66 (m, 2H), 2.59 (dd, J=5.0, 13.3 Hz, 2H).

*4.1.22. Dibenzyl ((1R,1′R)-((4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(ethane-1,1-diyl))dicarbamate (**7a**).* The procedure was adapted from the literature.[57] To a suspension of diol **6a** (1.14 g, 2.74 mmol) in 70 mL CH_2Cl_2 was added 2,2-dimethoxypropane (1.99 g, 0.0192 mol) at 0 °C. A catalytic amount of (±)-camphor-10-sulfonic acid (50.0 mg) was added and the mixture was stirred overnight at room temperature under nitrogen. The reaction was then exposed to air and concentrated into a dark oil. Column chromatography (7:3 hexanesethyl acetate) afforded **7a** as a white solid (1.18 g, 94% yield). The product was identified by comparison with literature data.[51] ^{1}H NMR ($CDCl_3$) δ 7.44–7.27 (m, 10H), 5.19–5.01 (m, 4H), 4.95 (d, J=9.5 Hz, 2H), 4.00–3.82 (m, 2H), 3.61 (s, 2H), 1.35 (s, 6H), 1.22 (d, J=6.1 Hz, 6H).

*4.1.23. Dibenzyl ((1R,1′R)-((4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(2-phenylethane-1,1-diyl))dicarbamate (**7b**).* Using the same procedure as for **7a**, **7b** (1.88 g, 84% yield,) was obtained from **6b** (2.09 g, 3.68 mmol). The product was identified by comparison with literature data.[51] ^{1}H NMR ($CDCl_3$) δ 7.49–6.97 (m, 20H), 5.07–4.63 (m, 6H), 3.68 (s, 2H), 2.92–2.63 (m, 4H), 1.36 (s, 6H).

*4.1.24. Dibenzyl ((2R,3S,4S,5R)-3,4-bis((2-(trimethylsilyl)ethoxy)methoxy)hexane-2,5-diyl)dicarbamate (**7c**).* The procedure was adapted from the literature.[36] To a suspension of diol **6a** (1.58 g, 3.79 mmol) in 65 mL CH_2Cl_2 was added DIPEA (2.94 g, 0.0228 mol) and cooled to 0 °C. SEM chloride (2.78 g, 0.0167 mmol) was then added dropwise until gas evolution ceased. The mixture was then refluxed overnight under nitrogen. After cooling to room temperature, cold water was added and the layers separated. The aqueous layer was extracted with methylene chloride. The organic layers were combined and washed with water, dried over magnesium sulfate, and concentrated into a yellow oil. Column chromatography using 7:3 hexanes/ethyl acetate afforded pure **7c** as a pale yellow oil (2.52 g, 98% yield). The product was identified by comparison with literature data.[36] ^{1}H NMR ($CDCl_3$) δ 7.47–7.28 (m, 10H), 5.22–4.97 (m, 6H), 4.80–4.62 (m, 4H), 4.09–3.95 (m, 2H), 3.83–3.67 (m, 2H), 3.58–3.39 (m, 4H), 1.21 (d, J=6.6 Hz, 6H), 1.01–0.84 (m, 4H), 0.01 (s, 18H).

*4.1.25. Dibenzyl ((2R,3S,4S,5R)-1,6-diphenyl-3,4-bis((2-(trimethylsilyl)ethoxy)methoxy)-hexane-2,5-diyl)dicarbamate (**7d**).* Using the same procedure as for **7c**, **7d** (1.63 g, 77% yield,) was obtained from **6b** (1.45 g, 2.55 mmol). The product was identified by comparison with literature data.[52] ^{1}H NMR ($CDCl_3$) δ 7.43–7.06 (m, 20H), 5.17–4.55 (m, 10H), 4.29–3.60 (m, 4H), 3.55 (s, 4H), 2.79 (d, J=7.3 Hz, 4H), 1.09–0.86 (m, 4H), 0.05 (s, 18H).

*4.1.26. (4R,5R)-4N,5N,2,2-Tetramethyl-1,3-dioxolane-4,5-dicarboxamide (**11a**).* Methylamine (46 mL, 2.0 M in methanol) was added to dimethyl 2,3-*O*-isopropylidene-L-tartrate **10** (4.20 mL, 22.9 mmol) in methanol (15 mL) and stirred at room temperature for 3 days under nitrogen. The solution was then concentrated to afford **11a** as a white solid (4.93 g, 99% yield). The compound was identified by comparison with literature data.[53] Mp 130–132 °C. ^{1}H NMR ($CDCl_3$) δ 7.06 (br s, 2H), 4.51 (s, 2H), 2.89 (d, J=4.9 Hz, 6H), 1.49 (s, 6H).

*4.1.27. (4R,5R)-4N,5N-Dibenzyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide (**11b**).* A mixture of **10** (10.78 g, 49.40 mol), benzylamine (10.32 g, 96.30 mmol), potassium carbonate (0.172 g, 1.24 mmol), and methanol (35 mL) was refluxed overnight under nitrogen. It was then cooled to room temperature, exposed to air and the solvent evaporated to afford an orange oil. The oil was purified by column chromatography (1:1 ethyl acetate/CH_2Cl_2) to afford **11b** as a pale yellow solid (10.73 g, 67% yield). The compound was identified by comparison with literature data.[42] Mp 82–84 °C. ^{1}H NMR ($CDCl_3$) δ 7.38–7.24 (m, 10H), 4.63 (s, 2H), 4.50 (d, J=6.0 Hz, 4H), 1.46 (s, 6H).

*4.1.28. (2R,3R)-1,4-N,N-Dibenzylamino-2,3-dihydroxysuccinamide (**11c**).* Using the same procedure as for **11b**, diethyl-L-tartrate **12** (7.00g, 0.0339 mol) was employed to afford **11c** as a white solid. The crude product was filtered, washed with water, and recrystallized from 50% ethanol in water to obtain pure **11c** (10.0 g, 90% yield). The compound was identified by comparison with literature data.[58] Mp 197–199 °C. ^{1}H NMR (DMSO-d_6) δ 8.25 (t, J=6.3 Hz, 2H), 7.39–7.13 (m, 10H), 5.74 (d, J=7.2 Hz, 2H), 4.48–4.17 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 172.1, 139.4, 127.5, 126.5, 72.7, 41.9.

*4.1.29. (2S,2′S)-2,2′-Bioxirane (**14**).* In air, compound **13**[49] (2.62 g, 6.09 mmol) was suspended in 30 mL ether. Pulverized potassium hydroxide (0.72 g, 0.013 mol) was then added and the mixture refluxed for 6 h under nitrogen. The reaction was exposed to air, filtered, and the filtrate concentrated into a colorless oil. The residue was purified by fractional distillation to obtain **14** as an oil (0.231 g, 44% yield). The product was identified by comparison with literature data.[59] ^{1}H NMR ($CDCl_3$) δ 2.94–2.88 (m, 2H), 2.87–2.82 (m, 2H), 2.77–2.73 (m, 2H).

*4.1.30. Dibenzyl ((2R,3S,4S,5R)-3,4-bis((2-(trimethylsilyl)ethoxy)methoxy)hexane-2,5-diyl)bis(methylcarbamate) (**15**).* Sodium hydride (0.472 g, 0.0197 mmol, 60% dispersion in mineral oil) was washed

with dry hexanes. DMF (10 mL) was added, followed by the *N*-protected diamine diol **7c** (2.22 g, 3.28 mmol) in DMF (10 mL) via cannula. After 1 h, methyl iodide (2.79 g, 0.0197 mmol) was added and the reaction was left to stir overnight at room temperature. The reaction was exposed to air, poured into cold water, and extracted three times with ethyl acetate. The combined organic layers were then washed with water three times, dried, and evaporated to obtain a crude residue. Flash chromatography using 9:1 hexanes/ethyl acetate afforded *N*-methylated compound **15**. ^{1}H NMR (DMSO-d_6, 98 °C) δ 7.41–7.22 (m, 10H), 5.09 (s, 4H), 4.68–4.50 (m, 4H), 4.49–4.29 (m, 2H), 3.60 (t, J=8.1 Hz, 4H), 3.52 (d, J=4.4 Hz, 2H), 2.82 (s, 6H), 1.11 (d, J=6.7 Hz, 6H), 0.96–0.75 (m, 4H), 0.00 (s, 18H). ^{13}C NMR (DMSO-d_6, 98 °C) δ 155.3, 136.7, 127.7, 127.0, 126.8, 95.4, 79.0, 65.7, 64.8, 51.0, 29.4, 17.2, 14.5, −2.0. HRMS calcd for $C_{36}H_{60}N_2O_8Si_2$ $[M+H]^+$ 705.3961, found 705.3947.

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **3j**, **4a**,**f**–**i**, **8e**, and **15**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.015.

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