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Hydroxylamine as an ammonia equivalent in microwave-enhanced aminocarbonylations

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Abstract—A novel palladium-catalyzed and $Mo(CO)_6$ promoted aminocarbonylation protocol was developed for rapid generation of primary aromatic amides from aryl bromides and iodides. Employing controlled microwave heating, hydroxylamine was first reduced in situ to ammonia, which thereafter reacted with carbon monoxide and the aryl halide substrate, delivering the benzamide product in less than 20 min. Based on this in situ carbonylation, a facile preparation of a novel HIV-1 protease inhibitor was achieved.

1. Introduction

Microwave heating has now been used in organic chemistry for 20 years with a steadily increasing number of reported examples every year.[1] In particular, applications in early stages of drug discovery have increased dramatically during the last 5-year period. It is the highly controlled, facile, and rapid in situ heating that makes controlled high-density microwave heating ideal, not only for promoting traditional laboratory-scale reactions, but also for automated organic and medicinal syntheses.[2,3] Despite the impressive advantages, additional robust and selective microwave protocols must be identified to accelerate lead identification and optimization work in the pharmaceutical industry.[4]

The greatest advantage of carbonylative reactions mediated by solid or liquid carbon monoxide sources is that they can be performed without equipment for introduction of gaseous carbon monoxide.[5] Handling in small-scale experiments is also more straightforward and much safer compared to protocols using free carbon monoxide gas. We have previously reported the exploitation of formamides or $Mo(CO)_6$ as robust carbon monoxide releasing reagents in palladium-catalyzed amino-,[6–8] alkoxy-,[9] sulfonamido-[10] and hydrazidocarbonylations.[11] Other research groups have presented alternative methods for carbon monoxide-free carbonylative chemistry.[5] One of our initial forays into $Mo(CO)_6$ promoted aminocarbonylations included the investigation of intermolecular reactions to form secondary and tertiary aromatic amides, and subsequent work has allowed for the extension of this chemistry into intramolecular examples.[12] However, the preparation of primary benzamides by aminocarbonylation of aryl halides with ammonia as the nucleophile is recognized as considerably more troublesome, since the reaction requires two toxic gaseous reactants, ammonia and carbon monoxide. In addition, the nucleophilicity of ammonia is limited and the Pd(II) coordination strength is high.[13] Thus, Indolese's recently reported synthesis of primary benzamides under pressurized carbon monoxide (5 bar) using a nucleophilic Lewis base (imidazole or 4-(dimethylamino)pyridine) as promoter, represented a major improvement.[14] In order to avoid using free carbon monoxide and to speed up the reaction rate, we further developed the protocol from Indolese by applying high-density microwave radiation. Under these high temperature conditions and in the presence of KO*t*-Bu, formamide served not only as the solvent, but also as a combined ammonia and carbon monoxide source.[15] Unfortunately, the strong basic reaction medium prevented utilization of the methodology for preparation of easily racemized and sensitive target structures. Therefore, a mild and rapid method for carbonylative preparation of primary benzamides appeared attractive and of high value for demanding medicinal chemistry applications. Stimulated by reports on $Mo(CO)_6$ mediated reductive cleavage of N–O bonds,[16] we decided to investigate hydroxylamine hydrochloride (**1**) as a convenient solid ammonia equivalent. Herein, we report the development of a rapid palladium-catalyzed procedure for benzamide (**3**) synthesis from hydroxylamine and aryl bromides (**2**) or iodides (**4**) by the reductive and carbon monoxide releasing actions of $Mo(CO)_6$. The methodology was further applied to the synthesis of a complex HIV-1 protease inhibitor.

Keywords: Carbonylation; Microwave; Palladium catalysis; Inhibitors.
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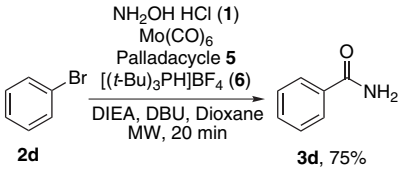
2. Results and discussion

2.1. Aryl bromides as coupling partners

To establish the viability of the carbonylation, we first undertook a small screening of a variety of palladium sources, ligands, solvents, and reaction variables (temperature and irradiation time) employing bromobenzene (**2d**) as substrate and **1** as pronucleophile (Eq. 1). The reactions were performed with 0.5 equiv of $Mo(CO)_6$ in sealed microwave transparent vessels under air. An excess of DBU was used in all attempts both to release free hydroxylamine and to serve as an efficient base in the reaction along with diisopropylethylamine (DIEA). We quickly found that using 5% Herrmann's palladacycle (**5**), 10% $[(t\text{-Bu})_3PH]BF_4$ (**6**) as an additional ligand source, and with 1,4-dioxane as solvent, microwave heating at 150 °C for 20 min furnished a generally successful reaction protocol (Eq. 1). Product **3d** was obtained in 75% isolated yield and importantly, no phenylhydroxamic acid product from a direct carbonylation with **1** was observed. Based on this result, the method was tested on seven additional model aryl bromides.



(1)

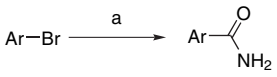
The results are summarized in Table 1. It was quickly proven that both electron-rich and electron-poor aryl bromides worked for this transformation, providing 71–81% yield of **3a–g** without traces of potentially competing hydroxamic acid. In addition, the heterocyclic 3-thiophene amide **3h** was isolated in 70% yield (entry 8). To compare **1** with the perhaps more obvious ammonia source ammonium chloride, two additional carbonylations were performed. Interestingly, ammonium chloride delivered lower yields compared with **1** in both reactions due to the formation of nitriles as side products, indicating a true advantage of hydroxylamine hydrochloride (Table 1, entries 4 and 7).

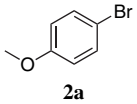
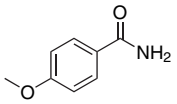
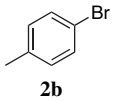
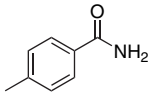
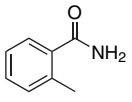
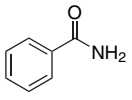
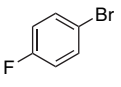
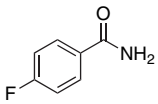
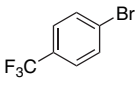
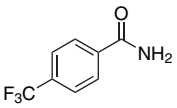
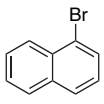
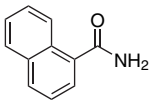
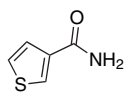
2.2. Aryl iodides as coupling partners

We chose the aminocarbonylation of *o*-tolyl iodide (**4c**) with hydroxylamine hydrochloride as the standard reaction to investigate suitable reaction conditions for both the amidation of electronically diverse model aryl iodides **4a,b,d–h** and for subsequent decoration of the HIV-1 inhibitor *ortho*-bromo precursors **7** and **9**. Although the original ligand-free aminocarbonylative conditions developed by our laboratory for generation of secondary and tertiary benzamides from aryl iodides[8] delivered significant amounts of product, the reactions failed to reach full conversion of **4c**. It was however found that addition of phosphine ligands, especially $[(t\text{-Bu})_3PH]BF_4$ and the bidentate ligand dppf, dramatically improved both conversion and yield (Table 2).

This finding was unexpected since aryl iodides normally do not need sophisticated phosphines to undergo activation by palladium(0) catalysts. Thus, by employing lower reaction temperatures (110–130 °C) but with an otherwise identical reaction system as the corresponding aryl bromides, we could isolate the primary amide **3c** in 69–84% yield (Table 2,

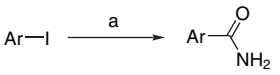
Table 1. Preparation of benzamides from aryl bromides by in situ carbonylation

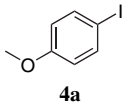
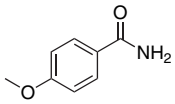
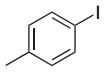
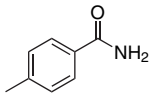
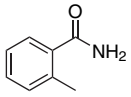
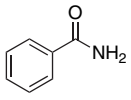
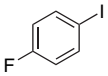
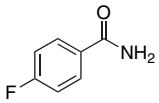
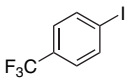
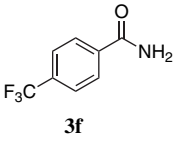
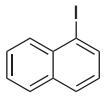
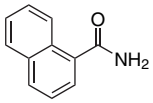
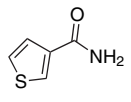


Entry	Ar-Br	Benzamide	Isolated yield (%)
1	 **2a**	 **3a**	71
2	 **2b**	 **3b**	81
3	 **2c**	 **3c**	78
4	 **2d**	 **3d**	75 69[b]
5	 **2e**	 **3e**	81
6	 **2f**	 **3f**	80
7	 **2g**	 **3g**	71 55[b]
8	 **2h**	 **3h**	70

[a] Aryl bromide (0.8 mmol), $Mo(CO)_6$ (0.4 mmol), NH_2OH HCl (1.6 mmol), Herrmann's palladacycle **5** (5 mol %), $[(t\text{-Bu})_3PH]BF_4$ (10 mol %), DBU (0.8 mmol), DIEA (1.6 mmol), dioxane (2.0 mL), microwave irradiation at 150 °C for 20 min in a sealed vial.
[b] NH_4Cl as ammonia source.

Table 2. Preparation of benzamides from aryl iodides by in situ carbonylation



Entry	Ar-I	Benzamide	Temp (°C)	Isolated yield (%)
1	 **4a**	 **3a**	130 110	67 78
2	 **4b**	 **3b**	130 110	74 80
3	 **4c**	 **3c**	130 110	69 84
4	 **4d**	 **3d**	130 110	74 77
5	 **4e**	 **3e**	110	76
6	 **4f**	 **3f**	130 110	73 76
7	 **4g**	 **3g**	110	83
8	 **4h**	 **3h**	110	80

[a] Aryl iodide (0.8 mmol), $Mo(CO)_6$ (0.4 mmol), NH_2OH HCl (1.6 mmol), Herrmann's palladacycle **5** (5 mol %), $[(t\text{-}Bu)_3PH]BF_4$ (10 mol %), DBU (0.8 mmol), DIEA (1.6 mmol), dioxane (2.0 mL), microwave irradiation for 20 min in a sealed vial.

entry 3). Furthermore, from Table 2 it is clear that this is a general microwave method that tolerates electronically diverse coupling partners **4**. This trend also held true with electron-rich thiophene **4h**. It is noteworthy that in all cases a reaction time of 20 min was sufficient for complete consumption of the aryl iodide and that an increase of the reaction temperature to 130 °C afforded reduced yields (Table 2).

2.3. Synthesis of HIV-1 protease inhibitors

The 1,2-dihydroxyethylene structure derived from L-mannitol and depicted in Figure 1 has been shown to be an effective transition-state mimic in inhibitors of aspartic proteases. By using this C_2-symmetric core scaffold, compounds inhibiting the HIV-1 protease enzyme at low nanomolar or even sub-nanomolar concentrations have been reported.[17,18]

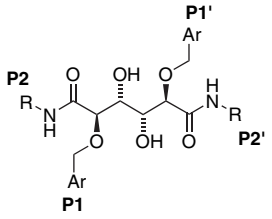


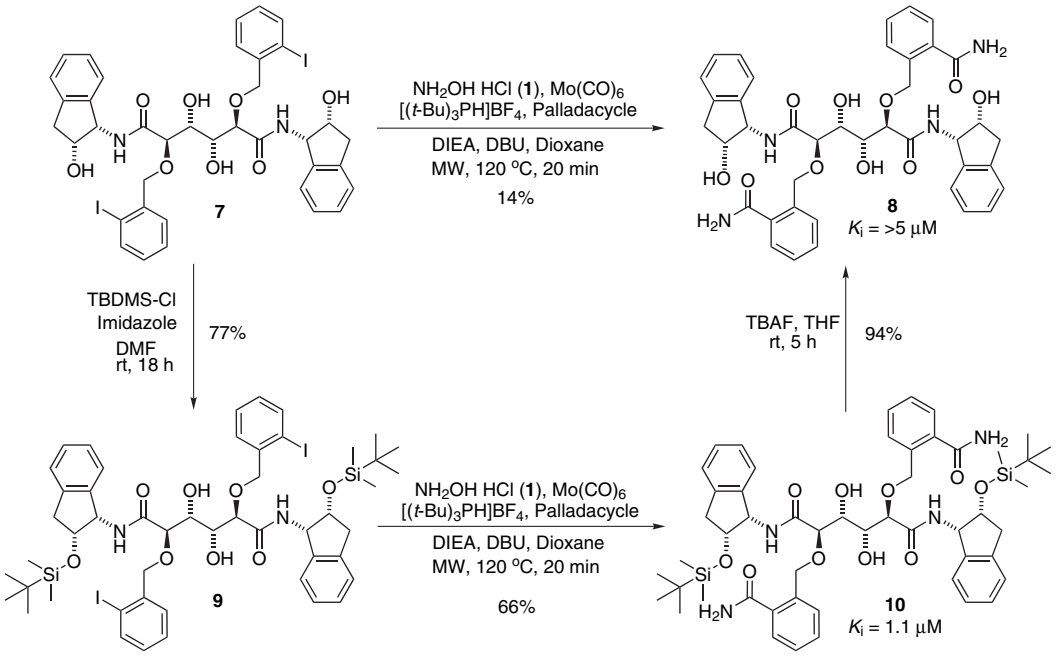
Figure 1.

The benzylic P1/P1′ side chains of these inhibitors have also been previously decorated in the 2-, 3-, and 4-positions by palladium(0)-catalyzed couplings and aminocarbonylation reactions.[17,19] Up to this point, however, synthesis of inhibitors including a primary benzamide functionality in the P1/P1′ positions has not been accomplished.

After preparing **7** according to the literature procedure,[18] we attempted the first carbonylation using **1** as the ammonia surrogate (Scheme 1). The conditions for aryl iodides identified above furnished complete conversion at 120 °C but in a complex product mixture. The purification of the product was further hampered by the poor solubility and high retention of **8** on silica. We then decided to protect the hydroxyl groups of compound **7** in an attempt to block the possibility of intramolecular alkoxycarbonylation and to improve the solubility of the product.[20] Standard conditions for TBDMS protection of alcohols produced the bis-protected compound **9** as the main product.[21] Carbonylation of **9** proceeded smoothly using slightly modified conditions and product **10** could be isolated in a satisfying 66% yield. Compound **10** was subsequently deprotected with TBAF to deliver inhibitor **8** (Scheme 1). Even though biological testing of compounds **8** and **10** showed that only **10** was a full inhibitor at 5 μM, the synthesis of **8** and **10** exemplifies the usefulness of the developed method also when dealing with more complex substrates.

2.4. Discussion

We propose that the investigated palladium(0)-catalyzed carbonylation follows the same general pathway as the analogous reaction with gaseous carbon monoxide and ammonia.[22] To examine the hypothesis that ammonia, and not hydroxylamine, acts as the principal nucleophile in the aminocarbonylation, we decided to conduct a series of control reactions. First, benzohydroxamic acid was cleanly reduced to benzamide **3d** under aryl bromide carbonylation conditions without the palladium catalyst and **1**. At room temperature, no benzamide formation was detected. These



Scheme 1.

two experiments established that hydroxylamine might operate as the nucleophile attacking the intermediate palladium acyl complex, affording **3d** after reduction at 150 °C. The next step was to study the reduction of hydroxylamine hydrochloride (**1**) to ammonia. A complete aminocarbonylation cocktail (entry 4, Table 1) was stirred for 20 min at room temperature with subsequent addition of benzoyl chloride to trap all free amines and revealed that only benzamide **3d** was formed without any trace of benzohydroxamic acid. Increase of the reaction temperature afforded an identical outcome, strongly supporting the suggestion that hydroxylamine is directly reduced to ammonia in the presence of $Mo(CO)_6$. Thus, in summary we believe benzamide products **3a**–**h** are formed as a result of a carbonylation process with free ammonia, and not hydroxylamine, as the reactive nucleophile.

3. Conclusion

A new $Mo(CO)_6$ promoted and microwave-accelerated route to primary benzamides from aryl bromides or iodides has been developed utilizing hydroxylamine hydrochloride as the solid source of ammonia. Consequently, no cumbersome handling of gases is needed following this in situ carbonylation protocol. The synthetic method is rapid, efficient, and quite practical and we envision that the procedure may find applications as a valuable amidation reaction. Employing this in situ ammoniacarbonylation approach, we successfully prepared a novel HIV-1 protease inhibitor in a straightforward manner.

4. Experimental

4.1. General

All microwave-assisted reactions were carried out using a single-mode microwave cavity (Smith Synthesizer, Biotage AB, Uppsala, Sweden) producing controlled irradiation at 2450 MHz. Reaction temperatures were determined and controlled via the built-in, on-line IR-sensor. Thin-layer chromatography was performed using aluminum or glass supported Merck Silica gel 60 F_{254} TLC plates and visualized with UV light. Flash column chromatography was performed using Merck Silica gel 60 (0.040–0.063 mm). Mass spectra (EI, 70 eV) of compounds **3a**–**h** were recorded with a mass-selective detector interfaced with a gas chromatograph equipped with a 30 m×0.25 mm CP-Sil 8 CB capillary column. RPLC–MS analysis of compounds **7**–**10** were performed using a Gilson HPLC system with a Chromolith SpeedROD RP-18e column (50×4.6 mm) and a Finnigan AQA quadropole mass spectrometer using a 4 mL/min CH_3CN/H_2O gradient (0.05% HCOOH) and detection by both UV (DAD, 190–350 nm) and MS (ESI+). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer at 400 and 100.5 MHz, respectively. Chemical shifts were referenced to internal tetramethylsilane when using $CDCl_3/CD_3OD$ mixtures and indirectly to tetramethylsilane via the residual solvent signal when using pure solvents.

All starting materials and reagents were commercially available and used as received. Herrmann's palladacycle, *trans*-di(μ-acetato)bis[*o*-tolylphosphino)benzyl]dipalladium (II) **5** was purchased from Strem. $Mo(CO)_6$ was obtained from Acros. Products **3a**,[15] **3b**,[15] **3c**,[15] **3d**,[15] **3f**,[15] **3g**,[15] **3e**,[23] and **3h**[24] are known compounds and analytical data were consistent with literature values.

4.2. General procedure for aminocarbonylation with hydroxylamine hydrochloride salt (1)

A 2–5 mL process vial was charged with **1** (112 mg, 1.60 mmol) or NH_4Cl (86 mg, 1.60 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (38 mg, 0.040 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (22 mg, 0.080 mmol), DBU (0.120 mL, 0.80 mmol), DIEA (0.277 mL, 1.6 mmol), aryl bromides **2**

(0.80 mmol) or iodides **4** (0.80 mmol), and dioxane 2.0 mL. The vessel was sealed under air and exposed to microwave heating for 20 min at 150 °C (for bromides) or 110–130 °C (for iodides). The reaction tube was thereafter cooled to room temperature and the mixture was diluted with 5.0 mL CH_2Cl_2 and purified on silica gel (30:70 to 100:0 EtOAc/hexane) to give the corresponding benzamides **3a**–**h**.

4.3. Synthesis of HIV-1 protease inhibitors

4.3.1. *N*1,*N*6-Bis[(1*S*,2*R*)-2-hydroxy-1-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-iodobenzyloxy)-3,4-dihydroxyhexane-1,6-diamide (7). Synthesized according to the procedure in Ref. 18. MS (ESI+) *m*/*z*=905.3 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, *J*=7.9, 1.2 Hz, 2H), 7.44–7.37 (m, 4H), 7.31 (ddd, *J*=7.9, 7.6, 1.2 Hz, 2H), 7.26–7.18 (m, 8H), 6.99 (ddd, *J*=7.9, 7.4, 1.7 Hz, 2H), 5.31 (dd, *J*=8.8, 5.2 Hz, 2H), 4.74 (d, *J*=11.8 Hz, 2H), 4.70 (d, *J*=11.8 Hz, 2H), 4.63 (app. dt, *J*=5.4, 2.5 Hz, 2H), 4.34 (AA′ part of AA′BB′, 2H), 4.26 (BB′ part of AA′BB′, 2H), 3.08 (dd, *J*=16.6, 5.6 Hz, 2H), 2.88 (dd, *J*=16.6, 2.5 Hz, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.4, 141.0, 139.8, 139.7, 139.2, 130.2, 128.7, 128.5, 127.2, 125.5, 124.5, 99.0, 82.3, 72.7, 71.5, 58.0, 39.4. Anal. Calcd (%) for $C_{38}H_{38}I_2N_2O_8$+H_2O: C, 49.47; H, 4.37; N, 3.04. Found: C, 49.3; H, 4.6; N, 3.1.

4.3.2. *N*1,*N*6-Bis[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyl-oxy)-indan-1-yl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-iodobenzyl-oxy)-3,4-dihydroxyhexane-1,6-diamide (9). Imidazole (272 mg, 4.00 mmol), TBDMSCl (301 mg, 2.00 mmol), and DMAP (10 mg, catalyst) were added sequentially to a solution of **7** (181 mg, 0.200 mmol) in 2 mL of DMF. After stirring at room temperature for 18 h, the reaction mixture was quenched with MeOH, diluted with ethyl acetate (40 mL), washed with water (3×30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexanes/EtOAc gradient). A side product consistent with tris-protected **7** was isolated (43.6 mg, 18%) but the main product was identified as **9** (176 mg, 77%). MS (ESI+) *m*/*z*=1133.6 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J*=7.9, 1.3 Hz, 2H), 7.65 (d, *J*=9.1 Hz, 2H), 7.39 (dd, *J*=7.6, 1.8 Hz, 2H), 7.28–7.12 (m, 10H), 6.97 (dt, *J*=7.6, 1.8 Hz, 2H), 5.44 (dd, *J*=9.1, 5.4 Hz, 2H), 4.82 (d, *J*=11.7 Hz, 2H), 4.76 (d, *J*=11.7 Hz, 2H), 4.68–4.66 (m, 2H), 4.63 (app. dt, *J*=5.3, 2.4 Hz, 2H), 4.29 (d, *J*=7.9 Hz, 2H), 4.16–4.09 (m, 2H), 3.11 (dd, *J*=16.2, 5.3 Hz, 2H), 2.91 (dd, *J*=16.2, 2.5 Hz, 2H), 0.76 (s, 18H), 0.04 (s, 6H), 0.01 (s, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.0, 140.9, 140.1, 139.6, 139.4, 130.5, 130.0, 128.5, 128.1, 127.0, 125.04, 124.99, 99.4, 77.92, 77.87, 74.1, 71.3, 56.4, 40.8, 26.0, 18.2, −4.6. Anal. Calcd (%) for $C_{50}H_{66}I_2N_2O_8Si_2$: C, 53.00; H, 5.87; N, 2.47. Found: C, 53.29; H, 6.04; N, 2.33.

4.3.3. *N*1,*N*6-Bis[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyl-oxy)-indan-1-yl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-carbamoyl-benzyloxy)-3,4-dihydroxyhexane-1,6-diamide (10). A 0.5–2 mL microwave vial was charged with **9** (170 mg, 0.150 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (19 mg, 0.020 mmol), [(*t*-Bu)$_3$PH]BF_4 (11 mg, 0.040 mmol), hydroxylamine hydrochloride (112 mg, 1.60 mmol), dioxane (2 mL), and DIEA (0.247 mL, 1.40 mmol). Finally DBU (0.120 mL, 0.80 mmol) was added and the vial was capped with a Teflon septum and irradiated with microwaves to 120 °C for 20 min. After cooling to room temperature the reaction mixture was filtered through a short Celite pad and the solvent was evaporated. The residue was purified by silica column flash chromatography (EtOAc/MeOH gradient) to give **10** (98.6 mg, 66%) as a light yellow solid. MS (ESI+) *m*/*z*=967.7 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J*=5.6, 3.4 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 2H), 7.38–7.19 (m, 14H), 6.65 (s, 2H), 6.52 (s, 2H), 5.42 (dd, *J*=8.6, 5.3 Hz, 2H), 5.00–4.73 (m, 2H), 4.68 (d, *J*=10.2 Hz, 2H), 4.60 (app. dt, *J*=5.2, 2.2 Hz, 2H), 4.16 (app. s, 4H), 3.10 (dd, *J*=16.2, 5.2 Hz, 2H), 2.90 (dd, *J*=16.2, 2.3 Hz, 2H), 0.76 (s, 18H), 0.05 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 172.04, 172.02, 141.3, 140.0, 135.7, 134.6, 131.3, 130.8, 128.9, 128.4, 128.1, 127.2, 125.0, 124.9, 80.6, 74.2, 71.9, 70.9, 56.8, 40.7, 25.8, 18.2, −4.7. Anal. Calcd (%) for $C_{52}H_{70}N_4O_{10}Si_2$: C, 64.57; H, 7.29; N, 5.79. Found: C, 64.30; H, 7.39; N, 5.65.

4.3.4. *N*1,*N*6-Bis[(1*S*,2*R*)-2-hydroxy-1-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(2-carbamoyl-benzyloxy)-3,4-dihydroxyhexane-1,6-diamide (8).

4.3.4.1. Carbonylation of 7. A 0.5–2 mL microwave vial was charged with **7** (136 mg, 0.150 mmol), $Mo(CO)_6$ (106 mg, 0.40 mmol), palladacycle **5** (19 mg, 0.020 mmol), [(*t*-Bu)$_3$PH]BF_4 (11 mg, 0.040 mmol), hydroxylamine hydrochloride (112 mg, 1.60 mmol), dioxane (2 mL), and DIEA (0.247 mL, 1.40 mmol). Finally DBU (0.120 mL, 0.80 mmol) was added and the vial was capped with a Teflon septum and irradiated with microwaves to 120 °C for 20 min. After cooling to room temperature the reaction mixture was filtered through a short Celite pad and the solvent was evaporated. The residue was purified by silica column flash chromatography (10% MeOH in $CHCl_3$) to give **8** (15.5 mg, 14%) as a white solid.

4.3.4.2. Deprotection of 10. To a solution of **10** (61.1 mg, 0.063 mmol) in THF (2 mL) was added tetrabutylammoniumfluoride (TBAF, 1 M in THF, 0.14 mL, 0.14 mmol) and the mixture was stirred at room temperature. After 5 h the solvent was evaporated and the solid residue suspended in 10 mL of water and stirred for 15 min. The water was decanted off and the water wash was repeated once. The suspension was then filtered and the solid was washed with 10 mL of ether and thereafter dried to give **8** (43.8 mg, 94%) as a white solid. MS (ESI+) *m*/*z*=739.5 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD, 1:1): δ 7.53–7.48 (m, 2H), 7.44–7.35 (m, 6H), 7.31–7.19 (m, 8H), 5.41 (d, *J*=5.3 Hz, 2H), 4.85 (d, *J*=11.1 Hz, 2H), 4.81 (d, *J*=11.1 Hz, 2H), 4.66–4.61 (m, 2H), 4.19–4.12 (m, 4H), 3.19 (dd, *J*=16.6, 5.3 Hz, 2H), 2.98 (dd, *J*=16.6, 2.3 Hz, 2H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 171.1, 170.5, 142.0, 140.6, 136.3, 135.0, 129.7, 128.1, 127.3, 127.2, 127.1, 126.3, 124.7, 124.3, 79.7, 72.3, 70.0, 69.1, 56.8, 39.9. Anal. Calcd (%) for $C_{40}H_{42}N_4O_{10}$+H_2O: C, 63.48; H, 5.86; N, 7.40. Found: C, 63.38; H, 5.94; N, 7.27.

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