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Synthesis of a tetrabenzyl-substituted 10-membered cyclic diamide

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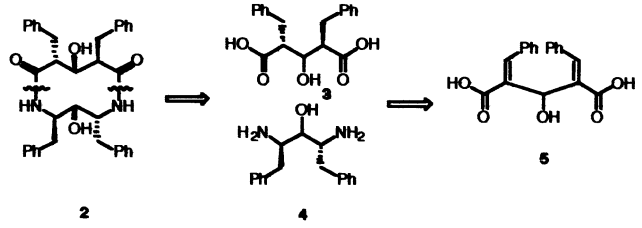
Abstract—A conformationally constrained 10-membered cyclic diamide was designed and synthesized. Conformational analysis suggested that the 9-membered ring formation was preferred to the direct formation of 10-membered ring. On the basis of the prediction, lactonization of 9-membered lactone, followed by intramolecular ester–amide transformation afforded the desired 10-membered cyclic diamide.

The cyclic urea DMP323 (**1**) has been reported as a potential inhibitor of HIV protease and many analogues have been synthesized in the process of drug discovery.[1]

Important features of this 7-membered ring skeleton, elucidated by X-ray analysis of a complex of HIV protease and XK263 that is an analogue of **1**,[1a] are as follows: (i) the 7-membered ring is conformationally constrained and the side chains on the ring can fit into pockets of the HIV protease; (ii) the two hydroxy groups are bound to aspartic acids of dimeric HIV protease; (iii) a carbonyl group of the cyclic urea can replace a water molecule in the HIV protease.

We have designed the 10-membered cyclic diamide **2** to mimic the above features (Scheme 1). In particular conformational analysis shows that for the low energy conformers the benzyl side chains are oriented in such a way as to fit inside the pockets of HIV protease (Fig. 1).

Our three synthetic strategies for the synthesis of **2** are as follows (Fig. 2): (i) one-pot diamidation of (*R*,*R*)-diacid **3** with (*R*,*R*)-diamine **4**; (ii) sequential formation of two amide bonds; (iii) ester formation, followed by transformation of ester to amide by rearrangement. The diacid (*R*,*R*)-**3** and diamine (*R*,*R*)-**4**[2,3] can be prepared from the common intermediate **5** by sequential asymmetric hydrogenation.[4]



Scheme 1.

Lithiation of vinyl bromide **6** with butyllithium, followed by addition of *N*,*N*-dimethylformamide gave aldehyde **7** in quantitative yield (Scheme 2). Coupling of the lithiated **6** with aldehyde **7** gave **8** in 85% yield. Hydrolysis of acetal **8**

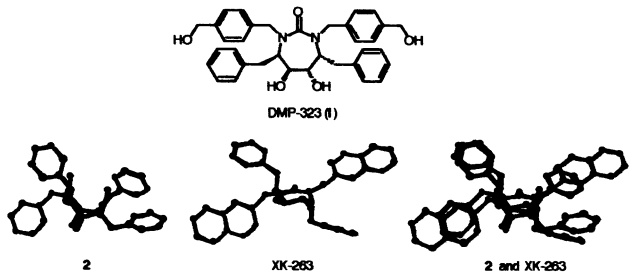


Figure 1. The optimized conformer of **2** (left), the X-ray structure of XK-263 binding to HIV protease (middle), and superimposition of **2** and XK-263 (right).

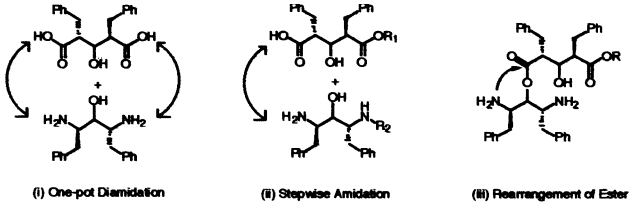


Figure 2. (i) One-pot diamidation; (ii) stepwise amidation; (iii) rearrangement of ester.

Keywords: diamide; ester–amide transformation; amidation.

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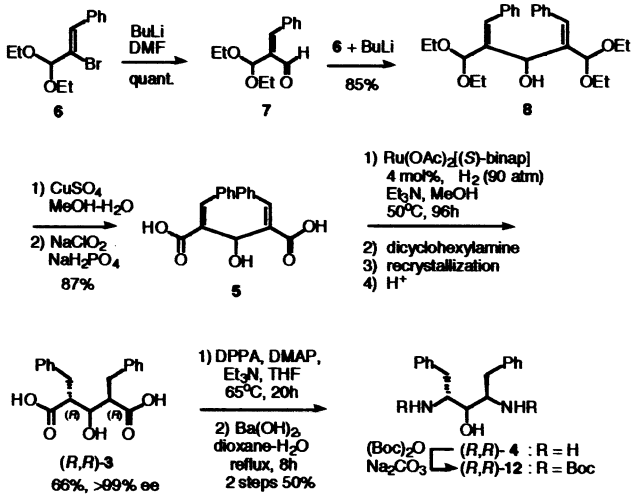
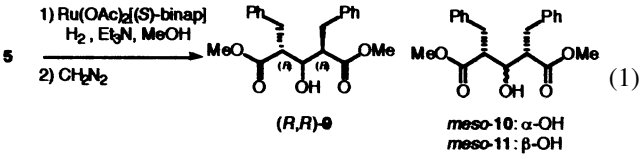


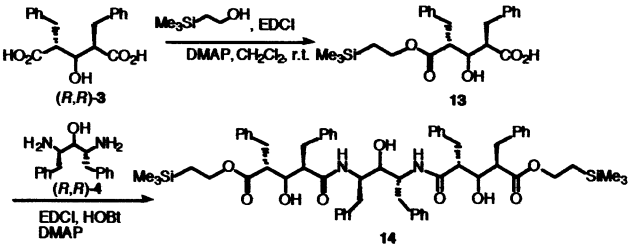
Scheme 2.

with copper sulfate in methanol–water (40%), followed by oxidation with sodium chlorite provided the diacid **5** in 87% yield. Asymmetric hydrogenation of the bis-cinnamic acid **5** was carried out in the presence of $Ru(OAc)_2$[(*S*)-binap][5] and the enantiomeric purity was analyzed after esterification with diazomethane (Eq. (1) and Table 1).[4] The reaction proceeded under 90 atm. pressure at 50 and at 30°C with high enantioselectivity (91–94% ee) while at the higher temperature higher diastereoselectivity was exhibited (80% cf 65%). Addition of 2 equiv. of triethylamine is essential for high enantioselection and at 50°C, 4 mol% of catalyst is necessary.



(1)

The best reaction conditions are recorded in entry 4 (Table 1). The crude product was treated with dicyclohexylamine to give its salt. The minor *meso*-isomers were removed by crystallization of the reaction mixture from 2-propanol. The mother liquid, after evaporation, was dissolved in toluene and recrystallization gave the (*R*,*R*)-salts, which was acidified to (*R*,*R*)-diacid **3** (66% yield, >99% ee). The modified Curtius rearrangement[6] of **3** with diphenylphosphoryl azide (DPPA), followed by hydrolysis of the isocyanate with barium hydroxide provided (*R*,*R*)-diamine **4** in 50% overall yield. Di-Boc protection of **4** afforded quantitatively a single compound **12**.



Scheme 3.

Attempts to couple diacid **3** and diamine **4** to provide the desired cyclic diamide **2** in one pot (method (i)) was not successful.[7] We therefore investigated the sequential coupling and cyclization (method (ii)). Mono-protection of diacid **3** with 1 mol equiv. of 2-trimethylsilylethanol successfully gave the half ester **13**. Attempts at mono protection of diamine **4** were however unsuccessful and the coupling reaction of diamine **4** with **13** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), and 4-dimethylaminopyridine (DMAP), gave only the unwanted bis-adduct **14** (Scheme 3).

To overcome this problem, we considered an ester–amide rearrangement to provide mono-amide as shown in Scheme 4. Treatment of diacid **3** with EDCI and allyl alcohol afforded β-lactone **15** in good yield. Esterification of di-Boc protected diamino alcohol **12** with **15** using *iso*-propylmagnesium chloride as base afforded ester **16**.[8] After deprotection of di-Boc groups of **16**, treatment with trimethylaluminum gave no reaction.[9] However, the desired ester–amide rearrangement took place by simply heating in toluene with diisopropylethylamine leading to amide **17**.[10] Deprotection of allyl ester **17** gave acid **18**[11] but we were not able to effect cyclization even when the two hydroxy groups of **18** were protected by acetates.

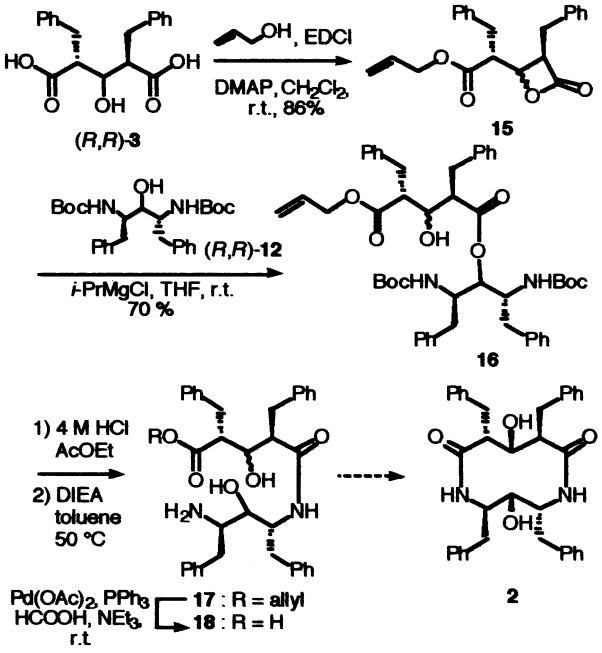
Conformational analysis of **19** in chloroform was carried out[12] by molecular mechanics calculations using a Monte Carlo method and the MMFF force field.[13] The molecule exists in an ensemble of extended conformations, i.e. **A** shown in Fig. 3, rather than as conformers that would facilitate cyclization.

To explore potential synthetic intermediates suitable for ring cyclization, conformational analysis of several possible structures was carried out. Modeling of **20** showed the molecule to dominantly exist in a conformation **B** (Fig. 3) with the carboxyl and an amino groups separated by only ca.

Table 1. Sequential asymmetric hydrogenation of **5**

Entry	Temperature (°C)	H_2 (atm.)	Time (h)	Yield (%)	(*R*,*R*)-**9** (%ee)	*meso*-**10**	*meso*-**11**
1	50	50	70	>95	62 (70)	35	3
2	50	70	70	>95	80 (88)	15	5
3	50	90	90	>95	80 (94)	19	1
4[a]	50	90	96	>95	80 (94)	19	1
5	30	55	160	>95	80 (72)	19	1
6	30	90	240	>95	65 (91)	34	1

Determined by HPLC with intensity of refractive index after esterification with diazomethane. $Ru(OAc)_2$[(*S*)-binap] (10 mol%) was used as a catalyst.
[a] 4 mol% of the catalyst was used.



Scheme 4.

3.9 Å such that 9-membered ring formation may be possible. **22** was prepared as follows (Scheme 5). Deprotection of allyl ester **16** using palladium catalyst[11] was followed by formation of the activated ester, pentafluorophenyl ester **21**. After removal of di-Boc groups by acid hydrolysis, cyclization was carried in the presence of diisopropylethylamine in dichloromethane at room temperature. The desired lactam **22** was isolated by preparative TLC. Rearrangement[10] of **22** to **2** was successfully accomplished by heating in toluene with diisopropylethylamine. The product **2** was isolated by preparative TLC in overall 36% yield.

The bioactivity of the 10-membered cyclic diamide **2** is

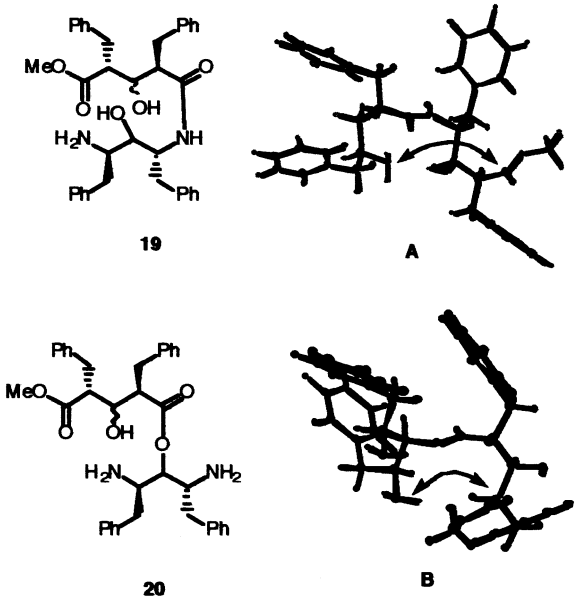
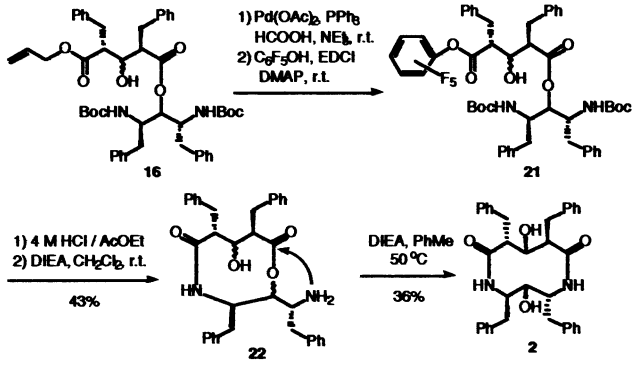


Figure 3. Energy-minimized structures (MMFF force field, in chloroform) of **19** shown in the structure **A** (extended form) and that of **20** as shown in the structure **B** (bending form).



Scheme 5.

under investigation. The cytopathic effect towards HIV-1 IIIb in MT4 cells and cytotoxicity and inhibition of HIV-1 protease were observed in levels greater than 10 μg/mL.

We have demonstrated the formation of a sterically hindered tetrabenzyl-substituted 10-membered cyclic diamide. Ring expansion from the nine-to-ten-membered ring was accomplished by rearrangement of an ester to amide. The cyclic diamide **2** is not adequately biologically active without modification. The novel method for construction of the highly strained tetrabenzyl-substituted 10-membered cyclic diamide offers considerable synthetic potential.

1. Experimental

1.1. General information

^{1}H NMR spectra were recorded on a JEOL Model EX-270 (270 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (chloroform-*d*: δ 7.26, methanol-d_4: δ 3.30). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR spectra were recorded on the JEOL Model EX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (chloroform-*d*: δ 77.1, methanol-d_4: δ 49.0). ^{31}P NMR spectra were recorded on the JEOL EX-270 (109.3 MHz) spectrometer. Chemical shifts are reported in ppm from phosphoric acid in 85% aqueous phosphoric acid as an external standard (δ 0.0). Mass spectra were obtained on an AppliedBioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometers. HRMS (ESI-TOF) were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard.

Analytical thin layer chromatography was performed on silica gel precoated aluminum TLC plates (Merck 60 F_{254}). Visualization was accomplished with UV light and anisaldehyde–H_2SO_4 ethanol solution, phosphomolybdic acid ethanol solution, or ninhydrin–H_2O 1-butanol solution followed by heating. Column chromatography was

performed on Merck silica gel 60 (0.063–0.200 mm). Preparative thin layer chromatography was performed on silica gel precoated glass TLC plate (Merck silica gel 60 F_{254}, 2 mm).

Optical rotations were measured on a Yanaco Model OR-50 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T^{\circ}C}$ (c=g/100 mL, solvent). Infrared spectra were recorded on a JASCO Model IR-700 spectrometer. Only the strongest and/or structurally important absorption are reported as the IR data given in cm^{-1}.

Solvents were distilled under an argon atmosphere as follows: dioxane, hexane, ether, and tetrahydrofuran were distilled at atmospheric pressure from sodium and catalytic amount of benzophenone. Dichloromethane was distilled at atmospheric pressure from phosphorus pentoxide. Triethylamine and pyridine were distilled at atmospheric pressure from calcium hydride. *N*,*N*-dimethylformamide was distilled under reduced pressure from calcium hydride. Methanol and ethanol were distilled from magnesium methoxide or magnesium ethoxide, respectively.

1.1.1. (*E*)-2-(Diethoxymethyl)cinnamaldehyde (7).[4] A solution of **6** (31.2 g, 109 mmol) in freshly distilled dry hexane (300 mL) was treated dropwise with butyllithium in hexanes (1.61 M, 74.8 mL, 120.5 mmol) at −78°C and stirred at the same temperature for 1 h. The solution was warmed to −50°C, stirred at −50°C for 30 min, and cooled to −78°C. To the reaction mixture was added a solution of DMF (16.3 mL, 210.4 mmol) in THF (50 mL) dropwise at −78°C. The solution was stirred at −78°C for 30 min and poured into NH_4Cl (saturated aqueous solution) and ether. The aqueous layer was separated and was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ether=15:1) to afford 25.7 g (quant.) of desired product **7** as a yellow oil. **7**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, J=6.9 Hz, 6H, CH_3–CH_2), 3.59 (q, J=6.9 Hz, 1H, CH_3–CH_2), 3.63 (q, J=6.9 Hz, 1H, CH_3–CH_2), 3.72 (q, J=6.9 Hz, 1H, CH_3–CH_2), 3.76 (q, J=6.9 Hz, 1H, CH_3–CH_2), 5.46 (s, 1H, –C*H*–$(OR)_2$), 7.35–7.43 (m, 5H), 7.96 (s, 1H, –C*H*=C), 9.91 (s, 1H, –C*H*O); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 191.5, 146.0, 137.8, 133.3, 130.1, 129.6, 128.4, 97.5, 63.0, 15.2; IR (neat) 2970, 2870, 1674, 1113, 1059, 788, 760 cm^{-1}.

1.1.2. 2,4-Di[(*E*)-benzylidene]-1,1,5,5-tetraethoxy-3-pentanol (8).[4] A solution of **6** (3.23 g, 11.3 mmol) in freshly distilled dry hexane (100 mL) was treated dropwise with butyllithium in hexanes (1.58 M, 7.86 mL, 12.4 mmol) at −78°C and stirred at the same temperature for 1 h. The solution was warmed to −50°C, stirred for 30 min, and cooled to −78°C. To the resulting mixture was added a solution of **7** (2.36 g, 10.1 mmol) in hexane dropwise at −78°C. The reaction solution was stirred at −78°C for 30 min, and poured into NH_4Cl (saturated aqueous solution) and ether. The layers were separated. The aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ether=9:1) to afford 3.79 g (85% yield) of desired product **8** as a yellow oil. **8**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (t, J=6.9 Hz, 6H, CH_3–CH_2), 1.24 (t, J=6.9 Hz, 6H, CH_3–CH_2), 3.43–3.80 (m, 8H, CH_3–CH_2), 5.26 (s, 2H, –C*H*–$(OR)_2$), 6.90 (s, 1H, –C*H*–), 6.95–7.60 (m, 12H, aromatic and alkenic); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.3, 137.0, 135.9, 130.0, 129.1, 128.9, 128.5, 128.3, 128.1, 127.9, 127.1, 101.0, 67.7, 63.9, 62.9, 61.4, 15.2, 15.1; IR (neat) 3480, 2970, 2922, 2876, 1162, 1098, 1056 cm^{-1}.

1.1.3. 2,4-Di[(*E*)-benzylidene]-3-hydroxypentanedioic acid (5).[4] To a solution of copper sulfate pentahydrate (4.90 g, 19.6 mmol) in water (60 mL) was added a solution of **8** (17.3 g, 39.2 mmol) in methanol (240 mL) at room temperature. The mixture was stirred at 40°C and filtered. The filtrate was concentrated in vacuo and diluted with ether. The aqueous phase was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by recrystallization from EtOAc to afford 4.50 g (40% yield) of 2,4-di[(*E*)-benzylidene]-3-hydroxypentanedial as a lemon yellow solid. To a solution of the dialdehyde (5.94 g, 20.3 mmol), 2-methyl-2-butene (15.6 mL, 147.2 mmol), and NaH_2PO_4 (4.88 g, 40.6 mmol) in *t*-BuOH/H_2O (210 mL/52 mL) was added $NaClO_2$ (12.9 g, 142 mmol) portionwise at 0°C. The reaction mixture was stirred at room temperature for 2.5 h and acidified with 40.6 mL of HCl (1 M aqueous solution) at 0°C. After removal of *t*-BuOH, the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by crystallization from EtOAc–hexane to afford 5.75 g (87% yield) of desired product **5** as a white solid. **5**: ^{1}H NMR (270 MHz, CD_3OD) δ 5.69 (brs, 1H, –C*H*–), 7.10–7.30 (m, 10H, aromatic), 7.84 (brs, 2H, –C*H*=C); ^{13}C NMR (67.5 MHz, CD_3OD) δ 171.5, 142.4, 135.6, 134.1, 130.3, 130.0, 129.4, 66.7; IR (KBr) 2962, 1662, 1585, 1434, 1248, 1009, 939, 917 cm^{-1}.

1.1.4. $[Ru(cod)Cl_2]_n$. To a solution of ruthenium(III) chloride trihydrate (2.18 g, 8.34 mmol) in degassed EtOH (49 mL) was added 1,5-cyclooctadiene (11.4 g, 105 mmol) at room temperature. The reaction mixture was stirred under reflux for 45 h, cooled to room temperature, and filtered. The solid was washed with degassed EtOH (2×30 mL) and dried in vacuo. A 2.36 g (quant.) of insoluble polymer was obtained.

1.1.5. $[RuCl_2[(S)\text{-binap}]]_2(NEt_3)$.[14] A suspension of $[Ru(cod)Cl_2]_n$ (500 mg, 1.78 mmol), (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (1.22 g, 1.96 mmol), and NEt_3 (2.49 mL, 1.81 g, 17.8 mmol) in degassed toluene (100 mL) was stirred under reflux for 13 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to afford crude complex. The crude solid was used for the next reaction without further purification.

1.1.6. $Ru(OAc)_2[(S)\text{-binap}]$.[5] A suspension of crude $[RuCl_2[(S)\text{-binap}]]_2(NEt_3)$, and NaOAc (2.93 g, 35.7 mmol) in degassed *t*-BuOH (75 mL) was stirred under reflux for 12 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in degassed ether (20 mL) and filtered through Celite under an argon atmosphere. The

filtrate was concentrated in vacuo, dissolved in degassed EtOH (10 mL), and filtered. The filtrate was concentrated in vacuo to afford 1.39 g (2 steps, 92% yield) of desired product $Ru(OAc)_2$[(*S*)-binap] as a pale yellow solid. ^{31}P NMR (109.3 MHz, $CDCl_3$) δ 65.1.

1.1.7. (2*R*,4*R*)-2,4-Dibenzyl-3-hydroxypentanedioic acid (3). In a 50 mL of autoclave containing glass tube was placed $Ru(OAc)_2$[(*S*)-binap] (104 mg, 0.123 mmol) as a catalyst, diene **5** (1.00 g, 3.09 mmol), dry methanol (14 mL), and dry NEt_3 (0.86 mg, 6.2 mmol). The autoclave was filled with hydrogen (90 atm.) after repeated (3 times) filling and purging of hydrogen. The reaction was carried out under an appropriate hydrogen pressure at 50°C for 96 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc, and poured into 6.2 mL of HCl (1 M aqueous solution) at 0°C. The layers were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was eluted through a short florisil plug to remove catalyst. The eluent was concentrated in vacuo to afford 1.01 g (quant.) of the saturated diacid **3**.

1.1.8. Purification of (*R*,*R*)-3. To a solution of the diacid **3** in methanol (20 mL) was added dicyclohexylamine (1.35 mL, 1.23 g, 6.79 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 1 h, and concentrated in vacuo. The residue was recrystallized from EtOAc–hexane to remove the minor diastereomers and the filtrate was replaced by a toluene solution. Recrystallization provided the (*R*,*R*)-salt (1.45 g, 2.09 mmol, 68% yield). To a suspension of the pure dicyclohexylamine salt (1.45 g, 2.09 mmol) in EtOAc (15 mL) was added a solution of HCl in EtOAc (4 M, 15 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography (SiO_2, hexanes/ethyl acetate=1:1) to afford 660 mg (97% yield) of the desired product (*R*,*R*)-**3** as a brown oil. (*R*,*R*)-**3**: ^1H NMR (270 MHz, CD_3OD) δ 2.78–3.14 (m, 7H), 7.11–7.27 (m, 10H, aromatic); $[\alpha]_D^{20}$= +27.2° (*c*=0.714, MeOH, dicyclohexylamine salt); HRMS (ESI-TOF) Calcd for $[C_{19}H_{20}O_5+Na]^+$ 351.1203, found 351.1204.

1.1.9. (2*R*,4*R*)-2,4-Diamino-1,5-diphenyl-3-hydroxypentane (4) and di-Boc protection. A solution of **3** (150 mg, 0.455 mmol), NEt_3 (0.25 mL, 1.8 mmol), catalytic amount of 4-dimethylaminopyridine (5 mg), and diphenylphosphoryl azide (0.39 mL, 1.8 mmol) in THF (10 mL) was stirred at 65°C for 20 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between water and 10% 2-propanol in $CHCl_3$. The aqueous phase was extracted with 10% 2-propanol in $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was filtered through a short pad of silica gel to afford the oxazolidinone-isocyanate, which was used for the next reaction without further purification. A solution of the crude isocyanate (80 mg, 0.25 mg) and $Ba(OH)_2{\cdot}8H_2O$ (200 mg, 0.63 mmol) in dioxane/H_2O (3.6 mL/2.4 mL) was stirred under reflux for 4 h, cooled to room temperature, and filtered through glass wool plug (elution 10% IPA–$CHCl_3$). The filtrate was concentrated in vacuo. The residue was suspended with 10% IPA–$CHCl_3$ and filtered. The filtrate was concentrated in vacuo to afford 61.5 mg (2 steps, 50% yield) of diamine (*R*,*R*)-**4**, which was used for the next reaction without further purification. To a solution of diamine (*R*,*R*)-**4** (61.5 mg, 0.228 mmol) and Na_2CO_3 (12.3 mg, 11.6 mmol) in dioxane/H_2O (0.5 mL/1 mL) was added di-*tert*-butyl dicarbonate (20 mL, 8.74 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 h, concentrated in vacuo. After dilution of the residue with EtOAc, the solution was neutralized by HCl (1 M aqueous solution) at 0°C. The layers were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=7:1) to afford 107 mg (quant.) of the desired product (*R*,*R*)-**12** as a white solid. (*R*,*R*)-**12**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (brs, 9 H, *t*-Bu), 1.41 (brs, 9H, *t*-Bu), 2.73–2.98 (m, 4 H, Ph-CH_2–), 3.57 (m, 1H, –C*H*–O–), 3.89–3.92 (m, 2H, –C*H*–NH–), 4.73 (m, 1H, –N*H*–), 5.03 (m, 1H, –N*H*–), 7.07–7.30 (m, 10H, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.9, 156.5, 138.2, 137.9, 129.5, 129.3, 129.2, 128.4×2, 126.4, 126.3, 79.8, 73.2, 55.7, 52.2, 39.0, 36.5, 28.3, 28.2; IR ($CHCl_3$) 3352, 1693, 1663, 1525, 1167, 758 cm^{-1}; HRMS (ESI-TOF) Calcd for $[C_{27}H_{38}N_2O_5+Na]^+$ 493.2673, found 493.2674.

1.1.10. Allyl ester β-lactone 15. To a solution of (*R*,*R*)-**3** (300 mg, 0.914 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (527 mg, 2.74 mmol), and a catalytic amount of 4-dimethylaminopyridine (10 mg) in CH_2Cl_2 (20 mL) was added allyl alcohol (0.094 mL, 1.37 mmol) at 0°C. The mixture was stirred at room temperature for 5 h. The reaction mixture was treated with additional allyl alcohol (0.624 mL, 9.14 mmol), stirred at room temperature for 10 h, poured into HCl (1 M aqueous solution) and $CHCl_3$ at 0°C. The layers were separated. The aqueous phase was extracted with $CHCl_3$. The combined organic layer was washed with HCl (1 M aqueous solution), washed with $NaHCO_3$ (saturated aqueous solution), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ether=4:1) to afford 277 mg (86% yield) of desired product **15** as a colorless oil. **15**: ^1H NMR (270 MHz, $CDCl_3$) δ 2.83–3.14 (m, 6H), 3.81 (dt, *J*=4.0, 6.9 Hz, 1H, –C*H*–(C=O)–O–CH–), 4.31–4.38 (m, 2H), 5.12–5.20 (m, 2H, CH_2=CH–), 5.62–5.77 (m, 1H, CH_2=C*H*–), 7.06–7.34 (m, 10H, aromatic); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.4, 169.8, 137.0, 136.5, 131.3, 129.2, 129.0, 128.9, 128.7×2, 128.5, 127.2, 127.0, 119.2, 65.8, 60.5, 56.7, 51.3, 34.7, 33.5, 14.3; IR (neat) 3358, 2964, 2868, 1807 (β-lactone), 1713 (ester), 1481, 1440, 1232, 1160, 1106 cm^{-1}; HRMS (ESI-TOF) Calcd for $[C_{22}H_{22}O_4+H]^+$ 351.1596, found 351.1595.

1.1.11. Intermolecular esterification of β-lactone 16. A solution of Boc protected diamine (*R*,*R*)-**12** (456 mg, 0.969 mmol) in THF (5 mL) was treated dropwise with a solution of *i*-PrMgCl in ether (0.75 M, 1.4 mL, 1.03 mmol) at 0°C and stirred at 0°C for 1 h. To the resulting solution was added a solution of allyl ester β-lactone **15** (250 mg, 0.712 mmol) in THF dropwise at 0°C. The reaction mixture

was stirred at room temperature for 24 h, and poured into HCl (1 M aqueous solution) and $CHCl_3$ at 0°C. The layers were separated. The aqueous phase was extracted with $CHCl_3$. The combined organic layer was washed with HCl (1 M aqueous solution), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=9:1) to afford 289 mg (50% yield) of desired product **16** as a colorless oil. **16**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (brs, 9H, *t*-Bu), 1.52 (brs, 9H, *t*-Bu), 2.72–3.19 (m, 8H, Ph-C*H*$_2$–), 3.21–3.25 (m, 1 H, –C*H*–COO-allyl), 3.75–4.00 (m, 2H, –C*H*–COO–, –C*H*–NH), 4.05–4.23 (m, 1 H, –C*H*–NH), 4.35–4.58 (m, 2 H, –C*H*$_2$–CH=CH$_2$), 4.60–4.80 (m, 1H, –C*H*–O–), 4.87–5.05 (m, 1H, –C*H*–OH), 5.10–5.25 (m, 2H, C*H*$_2$=CH–), 5.57–5.81 (m, 1H, CH$_2$=C*H*–), 7.00–7.35 (m, 20H, aromatic); IR (neat) 3422, 3010, 2972, 2924, 1700, 1496, 1365, 1247, 1215, 1163 cm^{-1}; HRMS (ESI-TOF) Calcd for $[C_{49}H_{60}N_2O_9+Na]^+$ 843.4191, found 843.4197.

1.1.12. Activated ester 21. A solution of palladium(II) acetate (7.83 mg, 0.035 mmol) and triphenylphosphine (36.9 mg, 0.141 mmol) in dry THF was stirred at room temperature for 1 h under an argon atmosphere. To the resulting solution was added a solution of allyl ester **16** (289.1 mg, 0.35 mmol) in THF at room temperature. The mixture was stirred at room temperature for 30 min. To the resulting solution was added NEt_3 (0.118 mL, 0.845 mmol) and formic acid (32.0 mL, 0.845 mmol) at 0°C. The reaction mixture was stirred at room temperature for 40 h, and concentrated in vacuo. The residue was purified by preparative glass TLC (SiO_2, chloroform/methanol=19:1) to afford 162 mg (59% yield) of acid as a yellow oil. To a solution of the acid (162 mg, 0.207 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (120 mg, 0.622 mmol), and a catalytic amount of 4-dimethylaminopyridine (10 mg) in CH_2Cl_2 (10 mL) was added pentafluorophenol (57.0 mg, 0.311 mmol) at room temperature. The mixture was stirred at room temperature for 6 h and poured into HCl (1 M aqueous solution) and $CHCl_3$ at 0°C. The layers were separated. The aqueous phase was extracted with $CHCl_3$. The combined organic layer was washed with HCl (1 M aqueous solution), washed with $NaHCO_3$ (saturated aqueous solution), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=7:1) to afford 98.4 mg (50% yield) of desired product **21** as a colorless oil. **21**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (brs, 9H, *t*-Bu), 1.36 (brs, 9H, *t*-Bu), 2.70–2.85 (m, 2 H, Ph-C*H*$_2$–), 3.02–3.25 (m, 4 H, Ph-C*H*$_2$–), 3.35–3.50 (m, 2 H, Ph-C*H*$_2$–), 3.97–4.05 (m, 1 H, –C*H*–CO$_2$–C$_6$F$_5$), 4.10–4.30 (m, 3H, –C*H*–COO–, –C*H*–NH), 4.50–4.60 (m, 1H, –C*H*–O–), 4.85–5.00 (m, 1 H, –C*H*–OH), 6.97–7.40 (m, 20H, aromatic); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.3, 170.0, 156.2, 155.9, 139.7, 138.4, 138.0, 137.8, 137.2, 137.0, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 127.3, 127.1, 126.9, 126.7, 126.5, 96.2, 80.1, 79.9, 79.8, 75.2, 72.9, 52.3, 39.8, 39.3, 36.7, 36.3, 35.5, 35.4, 28.4, 28.2; IR (neat) 3402, 3022, 2972, 2924, 1699, 1161, 1000 cm^{-1}; HRMS (ESI-TOF) Calcd for $[C_{52}H_{55}F_5N_2O_9+Na]^+$ 969.3720, found 969.3715.

1.1.13. Formation of 10-membered lactam 2. To a solution of activated ester **21** (32.8 mg, 0.035 mmol) in EtOAc (1 mL) was added a solution of HCl in EtOAc (4 M, 1 mL) at 0°C. The mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was azeotroped twice with toluene to afford crude diamine as an oil. The oil was used for the next reaction without further purification. To a solution of diisopropylethylamine (0.16 mL, 0.91 mmol) in CH_2Cl_2 (30 mL) was added a solution of the above diamino activated ester (32.8 mg, 0.0453 mmol) in CH_2Cl_2 (15 mL) dropwise over 7 h at room temperature. The mixture was stirred at room temperature for 72 h, concentrated in vacuo, and azeotroped twice with toluene. The residue was purified by preparative glass TLC (SiO_2, chloroform/methanol=19:1) to afford 8.3 mg (2 steps 43% yield) of the cyclized product **22**. The transformation of ester to amide was carried out as follows: a solution of 9-membered amide-lactone **22** (8.3 mg, 0.015 mmol) and DIEA (5.4 mL) in toluene (15 mL) was stirred at 50°C for 48 h. The reaction mixture was concentrated in vacuo and azeotroped twice with toluene. The residue was purified by preparative glass TLC (SiO_2, hexanes/ethyl acetate=1:1) to afford 3.0 mg (36% yield) of desired product **2** as an oil. **2**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.60–3.05 (m, 8 H, Ph-C*H*$_2$–), 3.40–3.90 (m, 4 H, –C*H*–C=O, –C*H*–NH–), 4.45–4.60 (m, 1H, –C*H*–OH), 4.60–4.73 (m, 1H, –C*H*–OH), 7.03–7.40 (m, 20H, aromatic); IR (neat) 3278, 3020, 2920, 2848, 1626, 1535, 1493, 1452, 1215 cm^{-1}; HRMS (ESI-TOF) Calcd for $[C_{36}H_{38}N_2O_4+Na]^+$ 585.2724, found 585.2730.

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