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Nucleophilic openings of bicyclic β-lactones via acyl C–O and alkyl C–O cleavage: catalytic, asymmetric synthesis of a versatile, carbocyclic nucleoside precursor and protected transpentacin

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Abstract—A variety of carbocycle-fused β-lactones are accessible via the intramolecular catalytic, asymmetric nucleophile catalyzed aldol-lactonization reaction recently developed in our laboratory. These bicyclic β-lactones undergo facile ring cleavage under mild conditions via both acyl C–O and alkyl C–O bond cleavage. Cleavage of the acyl C–O bond with hydroxylamine nucleophiles proceeds at ambient temperature and reductive cleavage is readily accomplished with aluminum and boron reducing agents. Alternatively, alkyl C–O cleavage with various nucleophiles leads to a variety of *trans*-β-substituted cyclopentane carboxylic acids. The utility of these transformations is demonstrated by the synthesis of protected (1*S*,2*S*)-transpentacin and a versatile diol for carbocyclic nucleoside synthesis.

1. Introduction

β-Lactones are versatile synthetic intermediates, as they undergo a variety of transformations in a stereospecific fashion.[1] The utility of β-lactones stems from their inherent reactivity due to ring strain and their masked aldol functionality. Thus, the asymmetric synthesis of these useful heterocycles has experienced a renaissance in recent years. In particular, β-lactones have emerged as targets of opportunity for development of catalytic, asymmetric methods.[2] The ability to cleave β-lactones via either acyl C–O or alkyl C–O cleavage further expands the repertoire of these small rings to access a variety of functional arrays (Fig. 1). In general, addition of soft nucleophiles leads to alkyl C–O cleavage while hard nucleophiles promote acyl C–O cleavage.[1]

We recently reported catalytic, asymmetric intramolecular nucleophile catalyzed aldol-lactonization (NCAL) reactions that allow access to a variety of carbocycle-fused β-lactones.[3] As a means to exploit the reactivity of these bicyclic β-lactones, we have studied their behavior toward various nucleophiles. In general, these novel, bicyclic systems follow similar reactivity trends to those outlined above for non-ring fused β-lactones. In this Symposia-in-Print, we describe the synthesis of protected transpentacin, (1*S*,2*S*)-2-aminocyclopentane-1-carboxylic acid and a versatile, carbocyclic nucleoside precursor. These syntheses demonstrate the utility of ring cleavage of these versatile, chiral building blocks.

2. Discussion

2.1. Acyl C–O cleavage of bicyclic β-lactones

We initially studied the acyl C–O cleavage mode of bicyclic β-lactones **4a–c**. As anticipated, ring opening of bicyclic β-lactones with hydroxylamine nucleophiles occurs under very mild conditions with exclusive cleavage of the acyl C–O bond.[4] Excess *O*-benzylhydroxylamine (15–20 equiv.) was utilized to accelerate the ring cleavage at 25°C and the resulting hydroxamic acid derivatives **5a–c** were obtained as white solids (Scheme 1).[4]

We also studied reductive opening of β-lactones **4a–b** and **6**

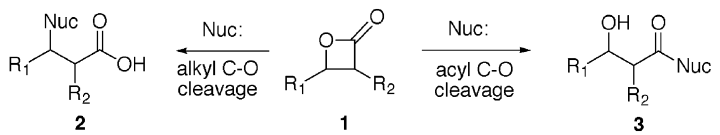

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Figure 1. Dual reactivity of β-lactones toward nucleophilic ring cleavage.

Keywords: nucleophilic ring openings; bicyclic β-lactone; nucleophile catalyzed aldol-lactonization process.

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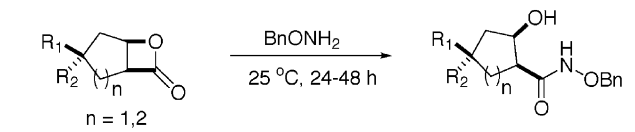
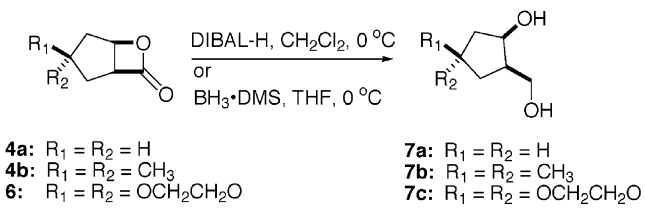


Scheme 1.



Scheme 2.

(Scheme 2). Addition of di-isobutylaluminum hydride to β-lactone **4a** resulted in smooth reduction to the corresponding diol **7a**. On the other hand, reduction of the dioxolane-containing β-lactone **6**, even at low temperature (−10°C), with various aluminum-based reductants gave small amounts of diol **7c** accompanied by compounds in which the dioxolane acetal had been cleaved competitively. However, these by-products were greatly minimized by using borane–dimethylsulfide complex as the reducing agent leading to diol **7c** in good yield. The borane reduction also cleanly delivered diol **7b** from β-lactone **4b**. In most cases, the diols obtained in this fashion did not require silica gel purification.

The utility of these bicyclic β-lactones was demonstrated by the four-step conversion of bicyclic-β-lactone **6** into the versatile carbocyclic nucleoside precursor **10** (Scheme 3). Reductive cleavage of the β-lactone **6** as described above gave the corresponding diol **7c**, which was directly subjected to aqueous acid. This resulted in hydrolysis of the dioxolane and spontaneous β-elimination to deliver α,β-unsaturated cyclopentenol **8**. Protection of the hydroxyl group as the trityl ether followed by a highly diastereoselective 1,2-reduction of enone **13** with DIBAl-H afforded the labile cyclopentenol **10**. The latter compound is the precursor to a number of antiviral carbocyclic nucleosides and serves as a key intermediate in the synthesis of (−)-aristeromycin.[5]

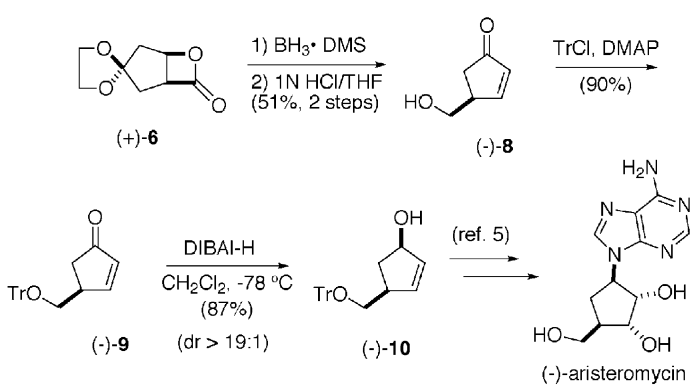
2.2. Alkyl C–O cleavage of bicyclic β-lactones

The addition of nucleophiles to bicyclic-β-lactones leading to alkyl-oxygen cleavage was also investigated. Using the bicyclic-β-lactone **6**, several nucleophiles were explored for their reactivity towards alkyl-oxygen cleavage. In most cases, nucleophilic ring opening proceeded at 50°C in DMF to deliver the *trans*-β-substituted carboxylic acids. However, the reactions were sluggish requiring >24 h to reach completion. For example, addition of thiophenol leading to the β-thiophenyl cyclopentane acid required 3 days. Use of 0.75 equiv. of Cs_2CO_3 greatly accelerated the nucleophilic addition in the case of thiophenol, hydrocinnamic acid, and *N*-Boc-cysteine ethyl ester.[6] However, only low yields were obtained in the latter case. In all cases, the nucleophilic additions proceeded with a high degree of diastereoselectivity to give the *trans* substituted cyclopentanes presumably via a S_N2 process (Table 1).

To demonstrate the utility of this mode of β-lactone ring cleavage, we targeted the synthesis of *trans*-2-amino cyclopentane carboxylic acid, transpentacin, derivative **16**. 2-Aminocyclopentanecarboxylic acids are constituents of natural products, display a range of interesting biological activities, and have recently been employed by Gellman to prepare constrained β-peptides.[7] Cispentacin, of unknown configuration, is a constituent of the antibiotic amipurimicin,[8] while (1*R*,2*S*)-cispentacin, is an antifungal antibiotic isolated from *Bacillus cereus*[9] and *Streptomyces setonii*.[10]

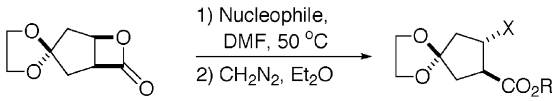
Nucleophilic ring cleavage of β-lactone **4a** with sodium azide in DMF efficiently promoted β-cleavage to give azido acid **14** (Scheme 4). Esterification followed by an azide reduction/protection sequence delivered the known *N*-Boc-protected β-amino acid ester **16**, which confirmed the stereochemistry and allowed assessment of enantiomeric purity. Spectral data for amino ester **16** matched that previously reported.[11] The optical purity of ester **16** was determined to be 89% as determined by comparative optical rotation and this correlates well with the enantiomeric excess of the starting β-lactone **4a** (92% ee).

In conclusion, we have found that bicyclic β-lactones, in a manner similar to their non-ring fused derivatives, readily

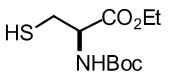
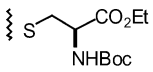
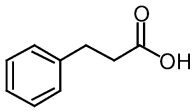
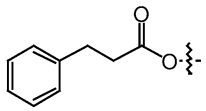


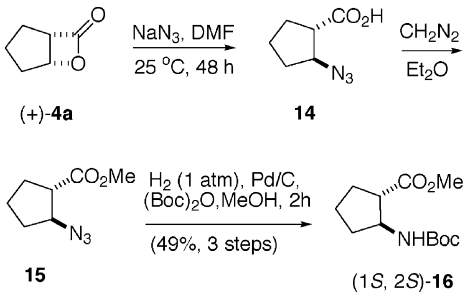
Scheme 3.

Table 1. Nucleophilic ring cleavage of β-lactone **11** with various nucleophiles and esterification



11 **12a-d**: R = H **13a-d**: R = Me

Entry	Nucleophile	Rxn conditions	Compound no.	X	% Yield
1	NaN_3	24 h	**13a**	N_3	76
2	PhSH	Cs_2CO_3, 24 h	**13b**	SPh	81
3		Cs_2CO_3, 24 h	**13c**		14
4		Cs_2CO_3, 24 h	**13d**		58



Scheme 4.

undergo both acyl C–O and alkyl C–O cleavage modes. The availability of chiral carbocycle-fused β-lactones via the NCAL process makes them versatile chiral building blocks for synthesis. The resident β-lactone enables facile functionalization, and thus these bicyclic β-lactones should prove to be useful scaffolds for displaying functionality on a carbocycle core. This concept was demonstrated by the ring opening of β-lactones with azide, thiols, and carboxylate nucleophiles. The utility of these bicyclic β-lactones was further demonstrated by the synthesis of a versatile chiral template for carbocyclic nucleoside synthesis and of a protected transpentacin.

3. Experimental

3.1. General

All reactions were carried out under N_2 in oven-dried glassware unless noted otherwise. Methylene chloride was distilled from CaH_2 immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl radical immediately prior to use. Other solvents used were also dried and distilled according to standard procedures prior to use. Flash column chromatography was done using Baxter S/P Silica Gel 60 Å (230–400 Mesh ASTM). Thin layer chromatography was done using EM silica gel 60F glass plates (0.25 mm). Mass spectra were obtained on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer at the Center for Chemical Characterization and Analysis (Texas A&M). IR spectra were recorded on a Nicolet Impact 410DSP. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA500 spectrometer or a Varian VXR300 spectrometer and chemical shifts are reported in ppm using tetramethylsilane (δ 0.0) or residual $CHCl_3$ (^1H δ 7.26, ^{13}C δ 77.0) as internal reference unless otherwise noted. β-Lactones **4a–c** by the NCAL method reported previously.[3]

3.2. General procedure for preparation of hydroxamic acid derivatives 5a–c

In a typical reaction, the β-lactone (ca. 5–10 mg, 1.0 equiv.) was treated with *O*-benzylhydroxylamine (15–20 equiv.). To aid stirring of the resulting thick mixture, anhydrous diethyl ether was added if needed. The clear solution was stirred at room temperature until complete by as monitored by TLC (24–30 h). The reaction mixture was then poured into 1N HCl, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford a white solid. Purification by flash chromatography (40% EtOAc/hexanes) delivered the hydroxamic acid derivatives as white solids (45–50% yield).

3.2.1. 2-Hydroxy-*N*-(phenylmethoxy)-cyclopentane carboxyamide (5a). 48% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 8.2–8.30 (broad s, 1H), 7.28–7.40 (m, 5H), 4.93 (broad s, 2H), 4.32–4.43 (m, 1H), 2.30–2.40 (m, 1H), 1.60–2.10 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 129.3, 128.9, 128.7, 78.3, 76.6, 74.2, 47.4, 34.4, 27.2, 21.9; FAB HRMS calcd for $C_{13}H_{17}O_3N$: 236.1287, found: 236.1277.

3.2.2. 4,4-Dimethyl-2-hydroxy-*N*-(phenylmethoxy)-cyclopentane carboxyamide (5b). 50% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (broad s, 1H), 7.30–7.40 (m, 5H), 4.93 (broad s, 2H), 4.42 (broad s, 1H), 2.00 (t, J=6.6 Hz, 1H), 1.52–1.70 (m, 4H), 1.18 (s, 3H), 0.98 (s, 3H); FAB HRMS calcd for $C_{15}H_{21}O_3N$: 264.1599, found: 264.1594.

3.2.3. 2-Hydroxy-*N*-(phenylmethoxy)-cyclohexane carboxyamide (5c). 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (broad s, 1H), 7.30–7.40 (m, 5H), 4.92 (broad s, 2H), 4.06–4.54 (m, 1H), 3.28 (broad s, 1H), 1.64–2.00 (m, 4H), 1.36–1.48 (m, 2H), 1.20–1.32 (m, 2H); FAB HRMS calcd for $C_{14}H_{20}O_3N$: 250.1443, found: 250.1454.

3.2.4. (−)-*trans*-2-Hydroxcyclopentanemethanol (7a). A solution of DIBAl-H (238 μL in 0.78 mL of CH_2Cl_2, 0.45 mmol) was added dropwise to a solution of β-lactone (+)-**4a** (53 mg, 0.47 mmol) in 5.3 mL of CH_2Cl_2 cooled to 0°C. After stirring for 5 min, the solution was warmed to 25°C and stirred for 1.0 h. The reaction mixture was then cooled to 0°C, diluted with 2.4 mL of ethyl acetate and quenched with acetone (1.5 mL) and saturated Rochelle's salt (4.0 mL). The mixture was vigorously stirred at 25°C for 10 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×4 mL). The combined organic layers were washed with brine (1×8 mL), dried over $MgSO_4$, filtered, and concentrated to give diol **7a** as a colorless oil (26.1 mg, 48% yield). Purification by flash chromatography on SiO_2 (100% EtOAc) gave an analytically pure sample: $[\alpha]_D^{25}=-33.0°$ (*c* 0.02, MeOH); lit. $[\alpha]_D^{25}=-37.7°$ (*c* 0.68, MeOH). All other spectroscopic data matched that previously reported.[12]

3.2.5. (−)-4-Hydroxy (−)-methyl-2-cyclopenten-1-one (8). A solution of (+)-β-lactone (+)-**6** (101.8 mg, 0.598 mmol) in 6.0 mL of anhydrous THF was cooled to 0°C and treated with 850 μL of neat BH_3·DMS (15 equiv., 8.97 mmol). After stirring for 18 h at 25°C, excess borane was quenched by careful addition of 5% Et_3N in anhydrous MeOH (8 mL). The solvents were removed under reduced pressure to give a residue that was dissolved in 8 mL of 5% Et_3N/MeOH. The solvent was again removed, repeating this operation a total of five times. The crude diol was dissolved in 12.0 mL of THF and treated with 2.5 mL of 1.0N aq. HCl. The yellow solution was stirred at 25°C for 20 h, at which point the reaction mixture was poured onto 10 mL of brine and 20 mL of CH_2Cl_2. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×20 mL). The organic phases were combined, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford a light yellow residue that was purified by flash chromatography on SiO_2 (EtOAc) to afford cyclopentenol **8** (34.2 mg, 51% yield for the two steps) as a colorless oil: R_f 0.45 (1:9, MeOH/EtOAc); $[\alpha]_D^{25}=15.9°$ (*c* 0.34, MeOH); IR ($CHCl_3$) ν_{max} 3435 (broad), 1703, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J*=2.4, 5.6 Hz, 1H), 6.22 (dd, *J*=2.0, 5.6 Hz, 1H), AB of ABX (δ_A=3.74, δ_B=3.69, J_{AB}=10.5 Hz, J_{AX}=6.1 Hz, J_{BX}=5.9 Hz, 2H), 3.12–3.22 (m, 1H), 2.47 (dd, *J*=6.6, 18.9 Hz, 1H), 2.16 (dd, *J*=2.1, 18.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 165.5, 135.2, 64.4, 44.1, 37.6. Satisfactory HRMS could not be obtained for this compound and may be due to the instability noted for this enone.

3.2.6. 4-Trityloxymethyl-cyclopent-2-enone (9). A solution of alcohol **8** (34.0 mg, 0.303 mmol) in 3.40 mL of anhydrous CH_2Cl_2 at ambient temperature was treated with triphenylmethyl chloride (126.0 mg, 0.453 mmol), anhydrous pyridine (60 μL, 0.727 mmol) and a catalytic amount of DMAP. After 18 h, the clear mixture was partitioned between saturated NH_4Cl (20 mL) and EtOAc (20 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford a cloudy residue that was purified by flash chromatography on SiO_2 (3:7, Et_2O/hexanes) to provide trityl ether **9** (96.6 mg, 90% yield) as a colorless residue that solidifies upon standing: R_f 0.68 (1:1, EtOAc/hexanes); $[\alpha]_D^{25}=-17°$ (*c* 0.5, MeOH); IR ($CHCl_3$) ν_{max} 1709, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J*=2.4, 5.9 Hz, 1H), 7.38–7.42 (m, 7H), 7.28–7.33 (m, 8H), 6.22 (dd, *J*=2.0, 5.4 Hz, 1H), 3.27 (dd, *J*=5.9, 8.3 Hz, 1H), 3.20 (dddd, *J*=1.9, 4.4, 8.3, 10.7 Hz, 1H), 3.12 (dd, *J*=6.3, 8.3 Hz, 1H), 2.46 (dd, *J*=6.3, 18.6 Hz, 1H), 2.10 (dd, *J*=1.9, 18.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 166.0, 143.7, 134.9, 128.6, 127.9, 127.1, 86.6, 65.2, 42.1, 38.0; FAB HRMS calcd for $C_{25}H_{24}O_2$ [M+Na] 379.1674, found 379.1670.

3.2.7. 4-Trityloxylmethyl-cyclopent-2-enol (10). Enone **9** (80.0 mg, 0.225 mmol) was dissolved in 11.5 mL of anhydrous THF, cooled to −78°C, and treated with 240 μL of DIBAl-H (1.0 M in $PhCH_3$, 0.234 mmol, 1.04 equiv.). After 30 min, an additional 0.70 equiv. of DIBAl-H was added. After 20 min, the reaction mixture was quenched by addition of 100 μL of water and 600 mg of silica gel. The resulting slurry was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The mixture was then filtered through a pad of anhydrous Na_2SO_4, washing with EtOAc. The solvent was removed under reduced pressure to give a residue (>19:1 dr, ^{1}H NMR) that was purified by flash chromatography to afford the desired *cis*-hydroxypentenol **10** (70 mg, 87% yield) as a colorless oil that solidifies upon standing: R_f 0.63 (4:1, Et_2O/hexanes); $[\alpha]_D^{25}=-66.3°$ (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D^{25}=-72.1°$ (*c* 1.2, $CHCl_3$);[5] IR ($CHCl_3$) ν_{max} 3495 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.48 (m, 6H), 7.22–7.38 (m, 9H), 5.94–6.02 (m, 2H), 4.68–4.78 (m, 1H), 3.29 (dd, *J*=4.7, 9.0 Hz, 1H), 3.07 (dd, *J*=5.0, 9.0 Hz, 1H), 2.80–2.90 (m, 1H), 2.38 (ddd, *J*=7.5, 8.6, 14.0 Hz, 1H), 2.12 (d, *J*=8.7 Hz, 1H, OH), 1.44 (dt, *J*=3.3, 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 135.7, 134.8, 128.8, 127.8, 127.0, 86.9, 76.6, 65.9, 44.8, 37.4; FAB HRMS calcd for $C_{25}H_{22}O_2$ [M+Na] 377.1517, found 377.1517.

3.3. General procedure for preparation of *trans*-β-substituted carboxylic acid esters 13a–d

In a typical reaction, β-lactone (1.0 equiv.) was dissolved in DMF (~0.13 M). To this was added the nucleophile (1.5 equiv.). In the case of hydrocinnamic acid, *N*-Boc-cysteine ethyl ester, and benzenethiol, Cs_2CO_3 (0.75 equiv. was also added), and the mixture was stirred at 50°C for 24 h. The mixture was diluted with water (100 mL/1 mmol β-lactone), carefully acidified with 1N HCl aqueous solution to pH=2. The phases were separated and the aqueous solution was extracted with ether. The combined organic layers were washed with water (50 mL), and dried over $MgSO_4$, filtered, and concentrated to afford an oil. The crude acid was dissolved in ether (~5 mL) and treated with 0.25 M diazomethane in ether (3.0 equiv.). After 15 min, excess diazomethane was quenched with glacial acetic acid

and the solvent was removed. Purification by flash chromatography gave the esters as oils.

3.3.1. 1,4-Dioxaspiro[4.4]nonane-8-azido-7-carboxylic acid, methyl ester (13a). R_f 0.59 (7:3, EtOAc/hexanes); IR ($CHCl_3$) ν_{max} 3020, 2956, 2890, 2108, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J=8.0 Hz, 1H), 3.87–3.95 (m, 4H), 3.74 (s, 3H), 2.86–2.92 (m, 1H), 2.24–2.34 (m, 2H), 2.06–2.11 (m, 1H), 1.87–1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 113.8, 64.6, 64.5, 61.3, 52.2, 48.0, 41.7, 38.6; EI HRMS calcd for $C_9H_{13}O_4N_3$ [M+Na] 250.0804, found 250.0834.

3.3.2. 1,4-Dioxaspiro[4.4]nonane-8-phenylthio-7-carboxylic acid, methyl ester (13b). R_f 0.65 (7:3, EtOAc/hexanes); IR ($CHCl_3$) ν_{max} 3005, 2979, 2880, 1732, 1439, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 77.20–7.44 (m, 5H), 3.84–3.95 (m, 5H), 3.60 (s, 3H), 2.90 (app q, J=9.0 Hz, 1H), 2.38–2.45 (m, 1H), 2.24–2.32 (m, 1H), 2.09–2.17 (m, 1H), 1.87–1.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 133.7, 132.3, 128.8, 127.2, 115.0, 64.5, 64.5, 52.0, 48.8, 46.4, 43.4, 40.2; EI HRMS calcd for $C_{15}H_{18}O_4S_4$ [M+Li] 301.1086, found 301.1058.

3.3.3. *S*-[1,4-Dioxaspiro[4.4]nonane-7-carboxylate]-*N*-[(1,1-dimethylethoxy)carbonyl]-L-cysteine dimethyl ester (13c). R_f 0.67 (7:3, EtOAc/hexanes); IR ($CHCl_3$) ν_{max} 2979, 2874, 1732, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (m, 1H), 4.51 (m, 1H), 4.21 (app q, J=7.5 Hz, 2H), 3.84–3.94 (m, 4H), 3.73 (s, 3H), 3.47 (app q, J=8.5 Hz, 1H), 2.97–3.07 (m, 2H), 2.80–2.85 (m, 1H), 2.37–2.42 (m, 1H), 2.23–2.27 (m, 1H), 2.07–2.12 (m, 1H), 1.82–1.87 (m, 1H), 1.45 (s, 9H), 1,29 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 170.6, 155.5, 114.9, 80.3, 65.8, 64.6, 64.5, 61.8, 53.2, 52.2, 49.5, 44.1, 43.9, 40.2, 34.1, 28.4, 15.4, 14.2; ESI HRMS calcd for $C_{19}H_{31}NO_8S$ [M+H] 434.1848, found 434.1861.

3.3.4. 1,4-Dioxaspiro[4.4]nonane-8-dihydrocinnamoyl-7-carboxylic acid, methyl ester (13d). IR ($CHCl_3$) ν_{max} 3026, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.30 (m, 2H), 7.18–7.22 (m, 3H), 5.35 (app dt, J=5.5, 8.0 Hz, 1H), 3.88–3.92 (m, 4H), 3.68 (s, 3H), 2.97 (ddd, J=6.4, 9.7, 18.6 Hz, 1H), 2.93 (t, J=7.8 Hz, 2H), 2.63 (app dt, J=0.7, 7.5 Hz, 2H), 2.44 (ddd, J=0.7, 8.2, 9.2 Hz, 1H), 2.22 (ddd, J=2.0, 8.8, 13.7 Hz, 1H), 2.08 (ddd, J=1.1, 9.9, 13.5 Hz, 1H), 1.85 (d, J=1.8, 5.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 172.2, 140.3, 128.4, 128.2, 126.2, 114.4, 74.3, 64.6, 64.4, 52.0, 47.9, 42.0, 38.2, 35.7, 30.8; ESI/TOF HRMS calcd for $C_{18}H_{22}O_6$ [M+Na] 357.1314, found 357.1416.

3.3.5. *N*-(*tert*-Butyloxycarbonyl)-*trans*-2-aminocyclopentanecarboxylic acid methyl ester 16. NaN_3 (0.98 g, 15.0 mmol) was added to a solution of *cis*-6-oxabicyclo-[3.2.0]heptan-7-one **4a** (150 mg, 1.50 mmol) in DMF (10 mL). The mixture was stirred at 25°C for 48 h. Water (150 mL) was added and the pH was adjusted to ~8 with saturated aq. $NaHCO_3$ solution, and then extracted with EtOAc. The aqueous solution was acidified to pH=2 with 1N HCl solution, and then extracted with Et_2O. The combined Et_2O layers were dried over $MgSO_4$, filtered, and concentrated to give azido acid **14**, which was dissolved in Et_2O (5 mL). To this was added an ~0.25 M solution of diazomethane in Et_2O (30 mL, 7.50 mmol). After 15 min, the reaction was quenched with a few drops of AcOH until the yellow color disappeared and then the solvent was removed under reduced pressure.

The crude azide **15** was dissolved in MeOH (5 mL) and then 5% Pd/C (320 mg, 0.15 mmol) and $(Boc)_2O$ (0.65 g, 3.00 mmol) were added. The reaction mixture was placed under a hydrogen atmosphere (1 atm, H_2 balloon) and stirred for 2 h. The reaction mixture was filtered through a plug of Celite, washed with MeOH and concentrated to give a white solid. The crude product was chromatographed to give transpentacin derivative **16** (0.19 g, 54%) as a white solid: R_f=0.43 (hexane/EtOAc=7:3); ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 1H), 4.08 (m, 1H), 3.67 (s, 3H), 2.56 (q, J=7.8 Hz, 1H,), 1.60–2.20 (m, 6H), 1.44 (s, 9H). The spectral data matched that previously reported in the literature.

3.3.6. *N*-(*tert*-Butyloxycarbonyl)-*trans*-(1*S*,2*S*)-2-aminocyclopentanecarboxylic acid methyl ester 16. Compound (1*S*,2*S*)-**16** (40 mg, 49%) was prepared from (1*R*,2*S*)-**4a** (35 mg, 0.36 mmol) according to the method described above for the preparation of the racemate: $[\alpha]_D^{25}$=+39.9° (*c* 1.2, $CHCl_3$); lit. $[\alpha]_D^{25}$=+44.6° (*c* 1.2, $CHCl_3$).[10]

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