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Total Synthesis of Hapalosin and Two Ring Expanded Analogs

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Dedicated to Professor Dr Richard R. Schmidt on the occasion of his 65th birthday

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Abstract—The macrocyclic depsipeptide hapalosin was assembled from three subunits. Beginning with the condensation of a protected β-hydroxy acid **13** with the α-hydroxy ester **14**, the hydroxy diester **16** was produced. This compound, in turn, was condensed with the γ-amino-β-hydroxy acid **17**. Macrocyclization was performed on the fully deprotected amino acid **20**. In a similar manner, a cyclization substrate **28** was prepared that contains valine instead of the α-hydroxy acid. In this case, however, the cyclization with the Shioiri reagent induced a Curtius rearrangement prior to the cyclization reaction. As a result the two ring expanded hapalosin analogs **29** and **30** were formed. The conformations of the three macrocycles were studied by 2D NMR spectroscopy and molecular dynamics simulation. It was found that in DMSO-d_6 all of them prefer the *s-trans*-amide rotamer around the tertiary amide.

Introduction

For the chemotherapy of cancer a large number of cytotoxic compounds that attack cells at various locations are in use. However, chemotherapy still is associated with a lot of problems due to toxic side effects and the phenomenon of resistance. In many cases resistance is caused by over-expression of the MDR 1 gene that encodes for a 170 kDa *p*-glycoprotein.[1] This membrane protein functions as a drug efflux pump thereby making drugs essentially ineffective. In order to make resistant cells susceptible for cytotoxic drugs, inhibitors of this *p*-glycoprotein are necessary. In fact, several natural and synthetic compounds are known to antagonize MDR caused by the *p*-glycoprotein.[2,3] Among these compounds, the natural product hapalosin (**1**) has aroused a great deal of interest (Fig. 1). Structurally, hapalosin is a depsipeptide consisting of three subunits, a β-hydroxy acid **A**, a γ-amino-β-hydroxy acid **B** and an α-hydroxy acid **C**.

Due to its biological activity and structure hapalosin has triggered a lot of synthetic activity. For example, since the disclosure of the hapalosin structure,[4] several syntheses of the natural product have been published.[5–14] Moreover, with a view to establish a structure–activity correlation and to improve upon the activity of hapalosin, some hapalosin analogs were prepared (Fig. 2). These include non-*N*-methyl-hapalosin **2**,[6] 8-deoxy-hapalosin **3**,[13] and the triamide analog **4**.[6]

While hapalosin and verapamil (as a control) have similar activity in reversing MDR, the triamide **4** is less active. The 8-deoxy-hapalosin is devoid of any activity. Also the non-Me-analog **2** was found to be substantially weaker. This was attributed to a change of the major conformation from the *s-cis*- to the *s-trans* amide rotamer. In order to restrain the conformation around the secondary amide, the group of Armstrong designed four proline analogs of hapalosin.[11] Among them, compounds **5** and **6** turned out to surpass hapalosin in the biological activity. The most recent paper concerning the synthesis of hapalosin analogs was published by Schwartz et al. as illustrated with compounds **7**–**9**.[14]

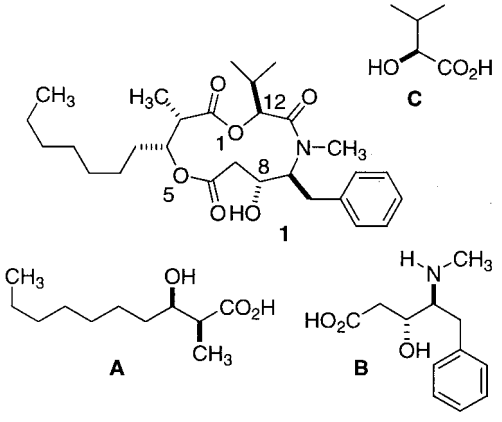

Figure 1. Structure and building blocks for hapalosin (**1**).

Keywords: conformation; depsipeptides; macrocycles; NMR; peptide analogs; rearrangements.

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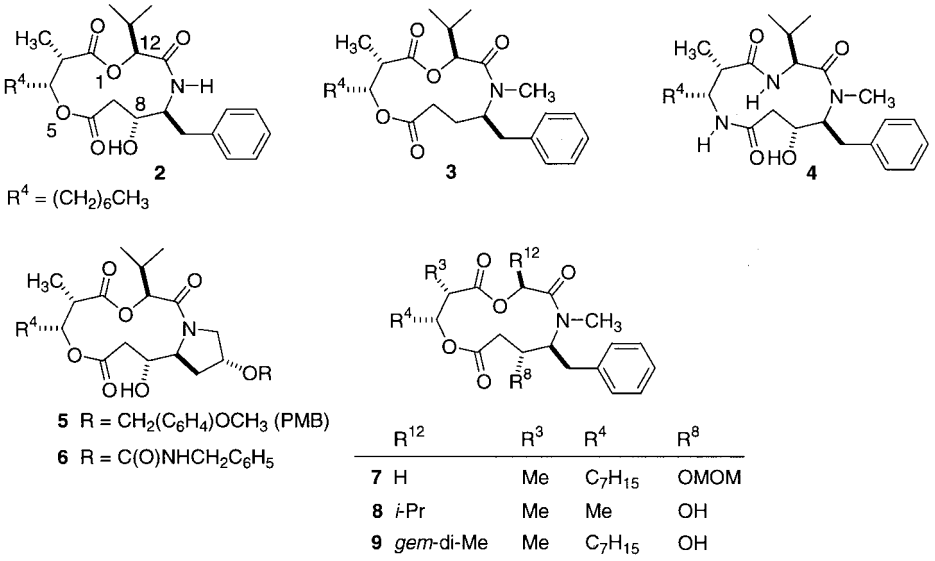


Figure 2. Structure of some hapalosin analogs from the literature.

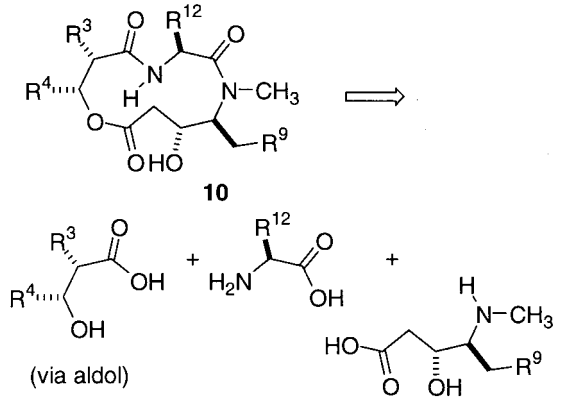


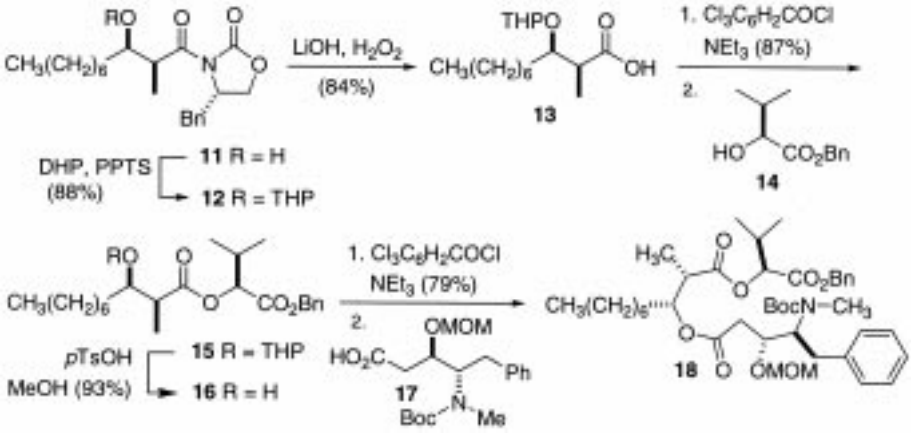
Figure 3. Design of hapalosin analogs suitable for parallel synthesis. The α-hydroxy acid is replaced by an α-amino acid.

These authors reported on variations at positions 12, 3, 4 and 8 (hapalosin numbering). Some substituent modifications resulted in lower cytotoxicities, but most structural changes were either detrimental or did not alter the MDR-reversing activity. As illustrated above hapalosin can be modified by rational design but with its modular structure it is particularly suited for variations in a more random, respectively combinatorial manner.[15,16] This way it might even be possible to generate other kinds of biological activity. Our plan for a combinatorial variation is illustrated in Fig. 3.

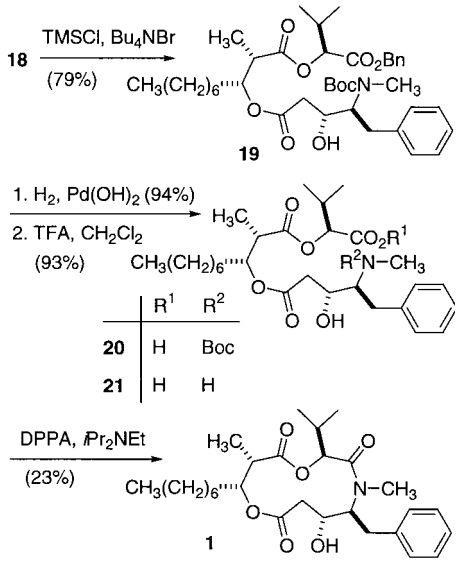
Thus, a number of β-hydroxy acids **A** could easily be prepared by an Evans aldol reaction.[17,18] In order to install different side-chains in the unusual amino acid **B**, we developed two flexible syntheses that allow for the replacement of the phenyl group. Finally, we planned to replace the α-hydroxy acid **C** with a range of α-amino acids. In this paper we report the synthesis of hapalosin (**1**) and an interesting observation during the attempted synthesis of a molecule of type **10**.

Synthesis of Hapalosin

A crucial step in the synthesis of hapalosin is obviously the macrocyclization reaction. Most of the known syntheses



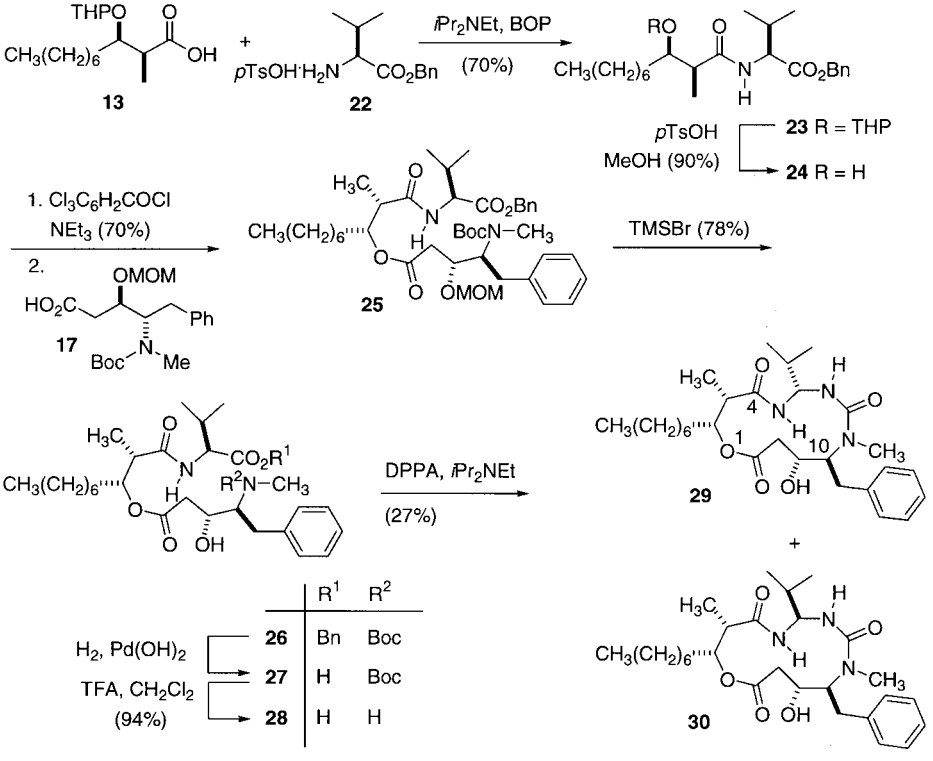
Scheme 1. Assembly of the protected acyclic precursor **18** by condensation reactions.



Scheme 2. Deprotection of **18** and macrocyclization of **21** to give hapalosin (**1**).

rely on the formation of the amide bond from a suitable precursor. These reactions are difficult because a 12-membered ring has to be formed and the amide is a tertiary one. This way moderate yields for **1** can be realized. As it turned out, however, formation of the ester bond between O5 and C6 is even less efficient.[6] The major difference between the various total syntheses are related to the choice of protecting groups. Our synthesis is patterned along similar lines. We began the synthesis of hapalosin (**1**) with the β-hydroxy acid derivative **11** which was prepared by an Evans aldol reaction (Scheme 1).[13] After protection of the hydroxyl group as its tetrahydropyranyl ether **12**, the chiral auxiliary was removed under basic conditions to provide the known acid **13**.[8] Subsequently, the acid **13** was condensed with the α-hydroxy benzyl ester[6] **14** using the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) as an activating agent. Following removal of the THP-protecting group, the alcohol **16** was acylated with the amino acid **17**. Again, the use of the Yamaguchi reagent secured a high yield in the coupling step. The synthesis of the O- and N-protected γ-amino-β-hydroxy acid **17** has been described elsewhere.[19,20] One of our routes is based on an Aldol/Curtius combination whereas the other route features an asymmetric dihydroxylation, an epoxide opening and a Mitsunobu reaction as key steps.

The next steps which are basically protecting group manipulations required some careful optimizations (Scheme 2). After some trials, the methoxymethyl group could be selectively removed with the combination of trimethylsilyl chloride and tetrabutylammonium bromide giving rise to the triester **19**. Subsequent reductive removal of the benzyl group gave the carboxylic acid **20**. This was followed by acid-induced cleavage of the *N*-boc protecting group providing the cyclization substrate **21**. The subsequent cyclization proved to be quite difficult. Using well-established reaction conditions, that is, the use of diphenylphosphoryl azide,[21,22] diisopropylethylamine in DMF under high dilution conditions, a yield of 23% for **1** could be realized. This way, sufficient material for spectroscopic studies could be secured. The structure was determined by mass spectrometry and NMR spectroscopy.



Scheme 3. Assembly of the analog precursor **28** and its cyclization to the ring expanded analogs **29** and **30**.

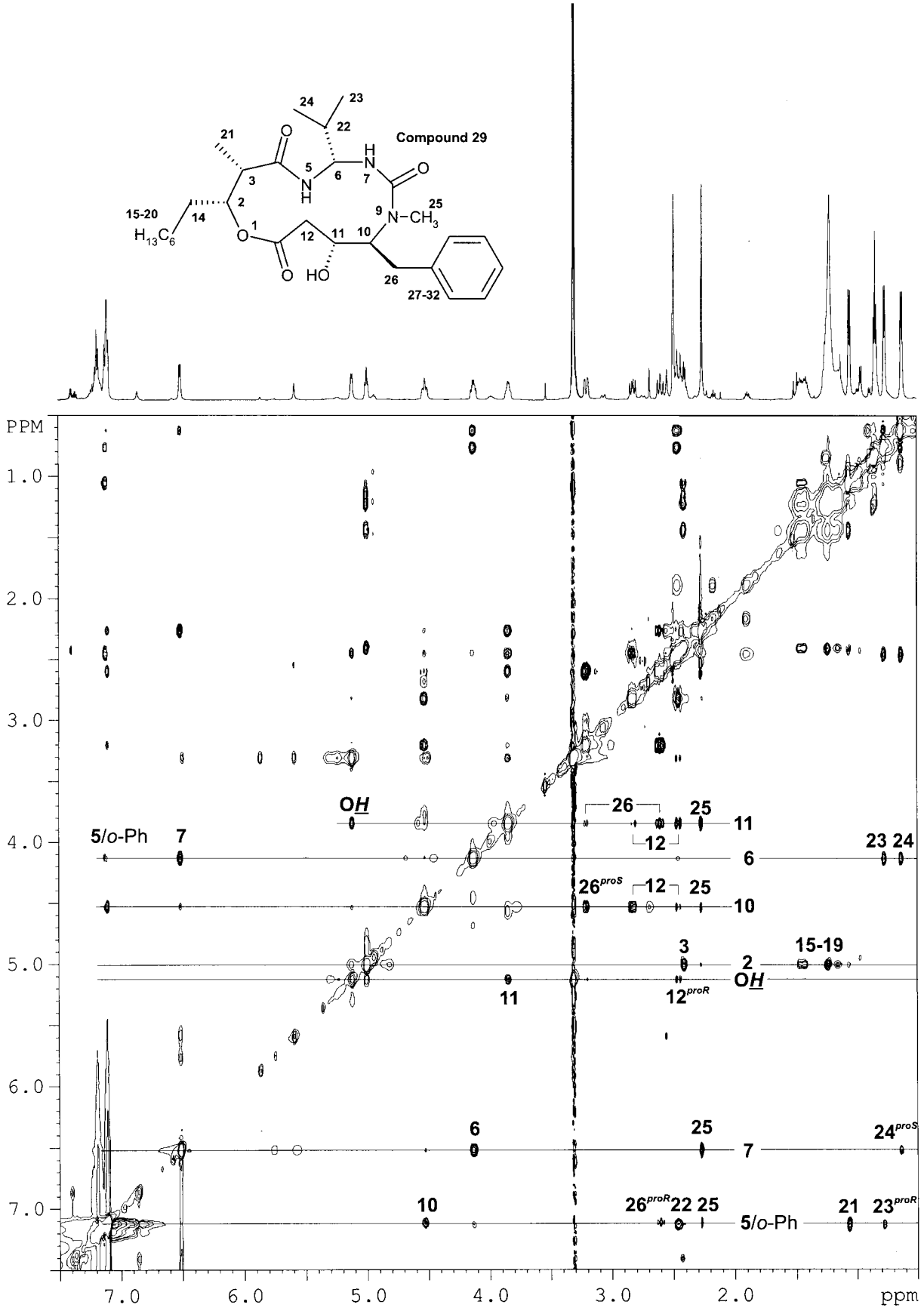


Figure 4. ROESY spectrum of the macrocycle **29** (600 MHz, 300 K). Average distances (pm) were calculated from the cross peak intensities by the two-spin approximation.

Synthesis of the Ring Expanded Analogs

Replacing the α-hydroxy acid with an α-amino acid should allow for the easy variation at that position. According to the order of events which we had established for hapalosin, the synthesis of the analog **10** was approached (Scheme 3). Thus, the *para*-toluenesulfonic acid salt of the valine benzyl ester **22** was condensed with the carboxylic acid **13** in the presence of benzotriazol-1-yloxy-tris(dimethylamino)-phosphoniumhexafluorophosphate (BOP) to provide the amide **23**. After liberation of the hydroxyl group using *p*-TsOH in MeOH, esterification of the resulting **24** with the amino acid **17** delivered compound **25**. As for the synthesis of hapalosin, all protecting groups were removed prior to the macrocyclization reaction. First, trimethylsilyl bromide caused cleavage of the MOM-protecting group providing the alcohol **26**. Subsequent hydrogenolytic removal of the benzyl group led to the amino acid **27**. This was followed by the hydrolysis of the *boc*-protecting group to yield the cyclization substrate **28**. The crucial macrocyclization of **28** was attempted under similar conditions as for the production of hapalosin **1**. Running the cyclization reaction for 3 days at room temperature produced two new products that showed the expected polarity on TLC. Compared to the ^{1}H NMR spectrum of hapalosin, the two spectra showed same characteristic differences. First, each of them was devoid of rotamers. In addition, the signal that corresponds to H-9 of hapalosin was shifted downfield from δ=3.73 to around δ=4.55 in **29** and 4.52 in **30**. A significant shift, although less pronounced was seen for H-12 (CH*i*Pr), which appears at δ=4.30 in **1**, at 4.46 in **29** and 4.12 in **30**. Particularly revealing were the mass spectra for the two macrocycles **29** and **30**. They showed masses which are by 14 amu higher than expected. Based on this and additional NMR data the structures of these macrocycles could be assigned to the cyclic diacylamines **29** and **30**. Their molecular formula were supported by high resolution mass spectra using a FT-ICR-mass spectrometer.

Conformational Studies

To further elucidate the molecular structure and conformation, compounds **1**, **29** and **30** were studied by homo- and heteronuclear NMR methods. ^{1}H and ^{13}C resonance signal assignments of **1**, **29**, and **30** were performed in DMSO-d_6 where hapalosin shows a doubled signal set due to isomerism about the tertiary amide bond. The two isomers of **1** were distinguished by the strong NOE between H-6 and H-10 which can be observed only for the *cis*-isomer. The *trans*-isomer is the dominating isomer in DMSO-d_6 (75%) while it is the less populated isomer in $CDCl_3$. The solution structure of the *trans*-isomer of Hapalosin was not solved before.[6] Since it closely resembles the two ring-expanded analogs **29** and **30**, we include the structural analysis of *trans*-**1** here. A structure of the *s-trans* rotamer of hapalosin obtained by MM2* force field calculations differs from our one in the area C2–O1–C12.[13] The gradient-selected HMBC spectrum of the ring-expanded analog **29** proved the Curtius rearrangement and the ring closure by the heteronuclear scalar couplings between C-8 (δ 157.3) and H-7 ($^2J_{C,H}$), H-6 ($^3J_{C,H}$), and H_3-25 ($^3J_{C,H}$). The resonance signal assignments were performed from DQF-COSY, TOCSY and HMQC spectra. Compensated ROESY[23–25] spectra (O1=2.1 ppm, 4 kHz pulsed spin lock, 200 ms mixing time) were acquired, an expansion is shown in Fig. 4. Spin diffusion is neglectable under these experimental conditions and the volume integral of each cross-peak correlates with a single interproton distance (two-spin approximation).[26] The macrocyclic rings effectively constrain the solution conformations of **29** and **30** to a single minimum which are characterized by well-separated NOE intensities.

The prochiral assignments of the diastereotopic methylene groups CH_2-12 and CH_2-17 are based on the combined data of the NOE intensities and the $^3J_{H,H}$ coupling constants. Even the configurational assignment of C-6 was possible by NMR spectroscopy. In isomer **29**, an intense NOE correlation was observed between H-7 and H-6 (Fig. 4) and an antiperiplanar orientation of H-5 and H-6 ($^3J_{H5,H6}$=11 Hz). **30** Exhibits an intense correlation between H-7 and H-22 and an antiperiplanar orientation of H-6 and H-7 ($^3J_{H5,H6}$=10 Hz). The cross signal intensities in the ROESY spectra of **1**, **29** and **30** were integrated and offset-corrected. The proton–proton distances of **29** listed in Table 1 were calculated according to the r^{-6}-dependence

Table 1. Interproton distances (Å) obtained from a compensated ROESY spectrum served as weak distance restraints for a 100 ms molecular dynamics simulation of **29**; averaging of ten snapshots was followed by energy minimization without distance restraints; interproton distances of this average conformation are listed in the column MD distance; deviations between experimental and calculated average distances are below 10% for short distances (<2.5 Å), and below 20% for distances above 2.5 Å; deviations above 10% are indicated

H–H	Experimental	MD distance	H–H	Experimental	MD distance
2–3	2.3	2.5	11–12^{proS}	3.2	3.1
5–6	3.05	2.95	11–26^{proR}	2.5	2.65
5–21	2.5	2.55	11–26^{proS}	3	3.3
5–22	2.4	2.5	11-O*H*	2.55	2.25 (11%)
5–24	3.0	3.15	12^{proR}-O*H*	2.8	2.35 (18%)
6–7	2.2	2.25			
6–22	3.0	3.05	H–CH_3		
7–10	3.15	4.35 (28%)	6–23^{proR}	2.7	2.7
7–22	3.2	3.70 (15%)	6–24^{proS}	2.7	2.8
10-O*H*	3.35	3.55	7–24^{proS}	3.1	3.35
10–12^{proR}	2.95	3.6	7–25	2.4	2.55
10–12^{proS}	2.3	2.4	10–25	3.2	3.45
10–26^{proS}	2.45	2.4	11–25	2.5	2.95 (15%)
11–12^{proR}	2.5	2.65	26^{proR}–25	2.7	2.9

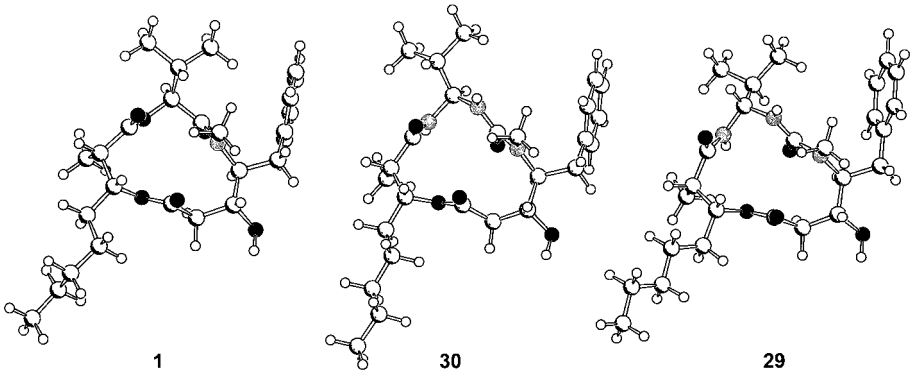


Figure 5. Energy-minimized average conformations of **1** (*trans*-conformer), **30**, and **29**. To simplify the calculation, the side-chains were shortened by two atoms.

(r=interproton distance) of the NOE.[27] The average distances served as restraints in a molecular dynamics simulation. An additional weak torsional restraint was included for the dominating -*gauche* rotamer around the benzylic side chain. The interproton distances taken from an averaged and energy-minimized computer model of **29** are also listed in Table 1. A single conformational minimum of **29** fulfills the network of 26 NOEs. The conformational homogeneity being a requirement for the direct quantification of NOEs.[28] The structures of **30** and *trans*-**1** were determined the same way, they are also shown in Fig. 5.

The solution conformation of the ring-expanded hapalosin-analog **30** closely resembles the *trans*-isomer of **1**. Both have a very similar arrangement of peptidic side-chains with the structural differences restricted to the macrolide backbone.

It is interesting to note that the presence of the amide bond in compound **28** seemingly favors the Curtius rearrangement of the intermediate acyl azide.[29–37] The Curtius rearrangement of acyl azides followed by trapping of the intermediate isocyanates with nucleophiles has been occasionally described in the context of the synthesis of peptide mimetics. Alternatively, *gem*-diamino derivatives can be accessed via this route. The current strategy might be very useful for the synthesis of other cyclic urea derivatives.

Experimental

General

^{1}H and ^{13}C NMR: Bruker AC 250, Bruker AMX 400, Bruker DRX 600; all spectra were recorded in $CDCl_3$ unless noted otherwise; chemical shifts are calibrated to residual proton resonances in $CDCl_3$ (7.24 ppm) and DMSO-d_6 (2.49 ppm), respectively. Optical rotations: JASCO P-1020 polarimeter. IR: Jasco FT/IR-430 spectrometer. EI-MS: AMD Intectra GmbH AMD 402. ES-FT-ICR-MS: Bruker Daltonic APEX II. HPLC: Hewlett–Packard HP 1100. Flash chromatography: J. T. Baker silica gel 30–60 μm. Thin-layer chromatography: Merck Si 60 F_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 35–65°C was used. The following compounds were prepared according to literature procedures: (4*S*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one,[38] (*S*)-(+)-2-hydroxy-3-methylbutyric acid benzyl ester **14**,[6] the amino acid **17**,[20] L-valine benzyl ester toluene-4-sulfonate **22**.[39–41]

Hapalosin (1). To a solution of amino acid **21** (0.065 g, 0.128 mmol) in DMF (128 ml) were added diphenylphosphoryl azide DPPA (0.083 ml, 0.385 mmol) and *i*Pr_2NEt (0.130 ml, 0.765 mmol) at 0°C. The mixture was stirred at this temperature for 3 h, then at room temperature for 4 days. The resulting mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 6:4) gave 14 mg of hapalosin (**1**). $[\alpha]_D^{25}=-41.7$ (c 0.078, CH_2Cl_2); TLC (ethyl acetate/petroleum ether, 4:6): R_f=0.43; IR (neat): 3420, 1733, 1635, 1489, 1456, 1187 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer)=0.21 (d, J=6.6 Hz, 3H, CH_3(*i*Pr)), 0.54 (d, J=7.8 Hz, 3H, CH_3(*i*Pr)), 0.85–0.89 (m, 3H, CH_3), 1.16 (d, J=7.1 Hz, 3H, Me), 1.23–1.38 (m, 10H, $(CH_2)_5$), 1.62–1.93 (m, 2H, CH_2),1.95–2.04 (m, 1H, CH(*i*Pr)), 2.56–2.68 (m, 2H, $CH_2C(O)$, CH_2Ph), 2.83 (s, 3H, NCH_3), 2.91 (dd, J=17.7, 4.9 Hz, 1H, $CH_2C(O)$), 3.21 (t, J=6.6 Hz, 1H, CH_2Ph), 3.39 (dd, J=13.7, 2.2 Hz, 1H, CH_2Ph), 3.66–3.72 (m, 1H, CHN), 3.78–3.85 (m, 1H, CHOH), 4.30 (d, J=8.4 Hz, 1H, CH*i*Pr), 5.06–5.14 (m, 1H, CHOC(O)), 7.16–7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=12.1, 14.1, 17.6, 18.3, 22.6, 26.1, 28.1, 28.8, 29.0, 29.1, 29.2, 29.3, 31.7, 36.5, 37.1, 40.7, 61.5, 70.2, 73.9, 76.4, 127.1, 128.4, 128.9, 129.7, 137.4, 168.5, 168.7, 172.7; HRMS (ESI): calcd for 490.31632, found 490.31649.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methyldecanoyl]-1,3-oxazolidin-2-one (11).[13] To a solution of (4*S*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one (3.11 g, 13.3 mmol) and triethylamine (2.34 ml, 16.8 mmol) in CH_2Cl_2 (70 ml) was added n-Bu_2BOTf (1 M in CH_2Cl_2, 15.4 ml, 15.4 mmol) in a dropwise fashion at 0°C. The mixture was stirred at the same temperature for 30 min, and then cooled to −78°C before octanal (2.3 ml, 14.7 mmol) was added dropwise at −78°C. The solution was stirred at −78°C for 1 h and at room temperature for 2 h. After quenching of the reaction with phosphate buffer (pH 7.0, 70 ml), the mixture was extracted with CH_2Cl_2 (3×70 ml). The organic extracts

were combined, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in MeOH (70 ml), and 30% aqueous H_2O_2 (42 ml) was added at 0°C. After being stirred at 0°C for 1 h, the reaction was quenched by the addition of 10% aqueous $NaHSO_4$. The mixture was extracted with ethyl acetate (3×70 ml), and the organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc in petroleum ether as eluent) to yield 4.35 g (90%) of **11** as colorless oil. $[\alpha]_D^{21}=+42.6$ (*c* 1.4, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 3:1): $R_f=0.43$; IR (neat): 3854 (s), 3087 (w), 2927 (s), 1779 (s), 1698 (s), 1386 (s), 1209 (s), 971 (s), 702 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=0.86$ (t, $J=6.5$ Hz, 3H, CH_3), 1.21–1.27 (m, 13H, $(CH_2)_5$, Me), 1.33–1.58 (m, 2H, CH_2), 2.77 (dd, $J=13.4$, 9.5 Hz, 1H, CH_2Ph), 3.23 (dd, $J=13.4$, 3.3 Hz, 1H, CH_2Ph), 3.75 (qd, $J=4.6$, 2.5 Hz, 1H, CHMe), 3.90–3.96 (m, 1H, CHOH), 4.16–4.25 (m, 2H, CH_2O), 4.66–4.73 (m, 1H, CHN), 7.17–7.21 (m, 2H), 7.23–7.36 (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta=10.4$, 14.1, 22.7, 26.1, 29.3, 29.6, 31.9, 33.9, 37.8, 42.1, 55.2, 66.2, 71.6, 127.5, 129.0, 129.5, 135.1, 153.1, 177.6; MS (EI): *m/z* (%)=361 (4) [M^+], 343 (5), 233 (8), 178 (9), 134 (11), 86 (100); HRMS (EI): calcd for 361.22529, found 361.22922.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)decanoyl]-1,3-oxazolidin-2-one (12). A solution of **11** (2.80 g, 7.76 mmol) and dihydropyran (1.30 g, 15.5 mmol) in dry dichloromethane (20 ml) containing pyridinium-*p*-toluene sulfonate (PPTS) (0.097 g, 0.388 mmol) was stirred overnight at room temperature. Then the solution was diluted with dichloromethane and washed once with half-saturated brine to remove the acid catalyst. Drying of the combined organic layers (Na_2SO_4), filtration and evaporation of the solvent provided the crude product which was purified by flash chromatography (10% EtOAc in petroleum ether) to yield 3.04 g (88%) of **12** as a colorless oil. TLC (petroleum ether/ethyl acetate, 9:1): $R_f=0.46$; IR (neat): 3063 (m), 3028 (m), 2928 (s), 2855 (s), 1782 (s), 1699 (s), 1209 (s), 702 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=0.80$ (dd, $J=0.9$, 5.5 Hz, 3H), 1.13–1.35 (m, 13H, $(CH_2)_5$, Me), 1.40–1.97 (m, 8H, CH_2, 3×CH_2(THP)), 2.70 (dd, $J=3.4$, 9.9 Hz, 1H, CH_2Ph), 3.20–3.43 (m, 2H, CH_2Ph, CHOTHP), 3.68–4.02 (m, 3H, CHMe, CH_2O(THP)), 4.06–4.11 (m, 2H, CH_2O), 4.42–4.59 (m, 2H, CHN, CH(THP)), 7.29–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=10.7$, 12.1, 14.1, 19.9, 20.4, 22.7, 25.5, 25.9, 29.3, 29.7, 29.8, 30.8, 31.2, 31.85, 31.9, 32.5, 33.4, 37.8, 37.9, 41.1, 42.1, 55.97, 56.3, 62.96, 63.6, 66.1, 66.2, 77.6, 78.4, 98.8, 98.9, 127.3, 127.4, 128.9, 129.5, 135.4, 135.8, 153.2, 153.5, 174.9, 175.6; MS (EI): *m/z* (%)=446 (14) [M^++1], 344 (7), 233 (41.3), 178 (14), 85 (100); HRMS (EI): calcd for 445.28280, found 445.28537.

(2*S*,3*R*)-2-Methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)decanoic acid (13).[8] To a solution of oxazolidinone **13** (1.50 g, 3.37 mmol) in tetrahydrofuran-distilled water (3:1 v/v, 67 ml) was added H_2O_2 (30% aqueous solution, 2.3 ml, 16.85 mmol) at 0°C via syringe over a 5-min period. This was followed by the addition of LiOH (0.283 g, 6.74 mmol), dissolved in water (6.7 ml). Some gas evolved from the clear solution. After stirring for 1 h at 0°C and for 2.5 h at room temperature, the excess H_2O_2 was quenched by the addition of sodium sulfite (2.12 g, 16.8 mmol) in distilled water (10 ml). The bulk of the tetrahydrofuran was removed by rotary evaporation at a bath temperature of 25–30°C, and the remainder was extracted with dichloromethane (3×20 ml) to remove the oxazolidinone auxiliary. The aqueous layer was cooled in an ice bath, acidified to pH 2 with aqueous 1N hydrochloric acid, and the resulting cloudy solution was then extracted with diethyl ether (5×20 ml). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give 0.81 g (84%) of **13** as a colorless oil. $[\alpha]_D^{23}=+44.7$ (*c* 1.2, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 7:3): $R_f=0.63$; IR (neat): 3500–2500 (br), 1708 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=0.81$ (t, $J=7.0$ Hz, 3H, CH_3), 1.10 (dd, $J=1.5$, 7.0 Hz, 3H, Me), 1.14–1.35 (m, 10H, $(CH_2)_5$), 1.36–1.72 (m, 8H, CH_2, 3×CH_2(THP)), 2.57–2.75 (m, 1H, CHMe), 3.39–3.45 (m, 1H, CHOTHP), 3.79–3.92 (m, 2H, CH_2O), 4.57–4.65 (m, 1H, CH(THP)), 10.87 (s, br., 1H); ^{13}C NMR: $\delta=10.9$, 11.7, 14.1, 19.8, 20.1, 22.7, 25.2, 25.4, 25.6, 25.7, 29.2, 29.6, 30.9, 31.1, 31.3, 31.8, 32.7, 42.3, 43.6, 62.8, 63.3, 78.6, 79.0, 99.1, 99.3, 179.3, 180.6; MS (EI): *m/z* (%)=287 (16) [M^++1], 203 (30), 185 (46), 101 (77), 85 (100).

(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl (2*S*,3*R*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)decanoate (15).[8] To a solution of the carboxylic acid **13** (100 mg, 0.349 mmol) and triethylamine (58 μl, 0.419 mmol) in THF (1 ml) was added the Yamaguchi reagent (568 μl, 0.349 mmol) followed by stirring of the reaction mixture at room temperature for 30 min. The amine hydrochloride salt was filtered off under argon and the filtrate concentrated under reduced pressure. The residue was redissolved in benzene (1 ml), the hydroxy compound **14** in benzene (1 ml) was added dropwise to the mixed anhydride solution, and finally dimethylaminopyridine (DMAP) (85 mg, 0.699 mmol) was added. The solution turns cloudy. After stirring the reaction mixture at room temperature for 90 min it was diluted with diethyl ether, washed successively with 3% HCl, water, saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to provide 0.140 g (87%) of **15** as a colorless oil. $[\alpha]_D^{23}=-9.2$ (*c* 1.0, $CHCl_3$); TLC: $R_f=0.44$ (petroleum ether/ethyl acetate, 9:1); IR (neat): 1742 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=0.80$ (t, $J=6.9$ Hz, 3H, CH_3), 0.84–0.95 (m, 6H, 2×CH_3(*i*Pr)), 1.12 (dd, $J=7.2$, 1.4 Hz, 3H, Me), 1.16–1.33 (m, 10H, $(CH_2)_5$), 1.38–1.75 (m, 8H, CH_2, 3×CH_2(THP)), 2.16–2.21 (m, 1H, CH(*i*Pr)), 2.63–2.68 (m, 1H, CHMe), 3.31–3.45 (m, 1H, CHOTHP), 3.79–3.91 (m, 2H, CH_2O), 4.55, 4.61 (2×m, 1H, CH(THP)), 4.78 (dd, $J=2.8$, 1.8 Hz, 1H, CH*i*Pr), 5.15 (d, $J=1.5$ Hz, 2H, CH_2(Bn)), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=11.2$, 12.9, 14.1, 17.3, 18.8, 19.9, 20.1, 22.7, 24.99, 25.5, 29.3, 29.7, 30.2, 31.0, 31.7, 31.9, 33.3, 42.8, 44.1, 62.7, 62.98, 66.7, 66.95, 76.3, 76.7, 79.0, 97.8, 99.9, 128.3, 128.5, 128.6, 135.8, 169.5, 174.6; MS (EI): *m/z* (%)=477 (10.4) [M^++1], 393 (100), 375 (19), 239 (6), 85 (27).

(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl (2*S*,3*R*)-3-hydroxy-2-methyldecanoate (16). A solution of the diester

15 (0.20 g, 0.42 mmol) and a small amount of *p*-TsOH (8 mg, 0.042 mmol) in MeOH (6 ml) was stirred at room temperature for 1 h and then quenched by the addition of aqueous 2N $NaHCO_3$ solution (5 ml). Most of the MeOH was removed under reduced pressure and the resulting slurry extracted with diethyl ether (3×20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (petroleum/ethyl acetate, 8:2) to yield 0.153 g (93%) of **16** as a colorless oil (petroleum ether/ethyl acetate, 8:2). TLC (petroleum ether/ethyl acetate, 7:3): R_f=0.62; $[\alpha]_D^{21}$=−12.2 (*c* 1.76, $CHCl_3$); IR (neat): 3544 (s), 1743 (s), 1464 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.80 (t, *J*=6.9 Hz, 3H, CH_3), 0.85, 0.94 (2 d, *J*=6.8 Hz, 6H, 2×CH_3(*i*Pr)), 1.10 (d, *J*=7.0 Hz, 3H, Me), 1.18–1.29 (m, 10H, $(CH_2)_5$), 1.30–1.42 (m, 2H, CH_2), 2.14–2.29 (m, 1H, CH(*i*Pr)), 2.62–2.75 (m, 1H, CHMe), 2.83 (dd, *J*=6.1, 5.2 Hz, 1H, OH), 3.95–4.08 (m, 1H, CHOH), 4.87–4.93 (m, 1H, CH*i*Pr), 5.11 (dd, *J*=13.7, 12.3 Hz, 2H, CH_2(Bn)), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): δ=9.6, 14.1, 17.0, 18.7, 22.7, 26.3, 29.3, 29.6, 30.0, 31.9, 33.5, 44.5, 67.3, 72.0, 76.4, 128.5, 128.6, 128.7, 135.1, 170.3, 175.2.

(1*R*)-1-[(1*S*)-2-({(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl}oxy)-1-methyl-2-oxoethyl]octyl 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2,4,5-trideoxy-3-*O*-(methoxymethyl)-5-phenyl-L-*erythro*-pentonate (18). To a solution of the amino acid **17** (0.140 g, 0.383 mmol) in THF (2 ml) and triethylamine (0.064 ml, 0.459 mmol) was added the Yamaguchi reagent in a dropwise fashion at room temperature (0.063 ml, 0.383 mmol). The resulting mixture was stirred at room temperature for 1 h. The amine hydrochloride salt was filtered off under argon and the filtrate concentrated under argon. To the residue, dissolved in dry benzene (2 ml) was added a solution of the alcohol **16** (0.180 g, 0.459 mmol) in benzene (2 ml) dropwise. Finally DMAP (0.094 g, 0.753 mmol) was added and the reaction mixture stirred at room temperature for 2 h. Afterwards, the reaction mixture was diluted with diethyl ether, washed successively with 2N HCl, water, saturated aqueous $NaHCO_3$, water, and finally with brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 85:15) to yield 0.224 g (79%) of **18** as a colorless oil. $[\alpha]_D^{21}$=−28.6 (*c* 1.0, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 85:15): R_f=0.32; IR (neat): 1742 (s), 1694 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): (both rotamers) δ=0.87 (t, *J*=7.1 Hz, 3H, CH_3), 0.92 (d, *J*=6.7 Hz, 3H, CH_3(*i*Pr)), 0.96 (d, *J*=7.1 Hz, 3H, CH_3(*i*Pr)), 1.19 (d, *J*=7.3 Hz, 3H, Me), 1.25–1.29 (m, 19H, 3×CH_3(Boc), $(CH_2)_5$), 1.60 (s, br., 2H, CH_2), 2.17–2.28 (m, 1H, CH(*i*Pr)), 2.42–2.81 (m, 7H, NCH_3, $CH_2C(O)$, CH_2Ph, CHMe), 3.17–3.22 (m, 1H, CH_2Ph), 3.39 (minor, s, 3H, CH_3(MOM)), 3.40 (major, s, 3H, CH_3(MOM)), 4.1–4.3 (m, 2H, CHN, CHOMOM), 4.68–4.81 (m, 2H, CH_2(MOM)), 4.85 (d, *J*=4.3 Hz, 1H, CH*i*Pr), 5.14–5.21 (m, 3H, CH_2(Bn), CHOC(O)), 7.13–7.23 (m, 5H), 7.33–7.34 (m, 5H); ^{13}C HMR ($CDCl_3$): (both rotamers) δ=12.5, 12.8, 14.1, 15.3, 17.2, 18.6, 18.8, 21.0, 22.6, 25.4, 28.2, 28.3, 29.2, 29.4, 30.1, 31.8, 31.95, 34.5, 37.9, 42.9, 43.2, 56.1, 56.3, 65.8, 66.8, 66.96, 74.4, 74.5, 76.6, 76.7, 97.3, 97.5, 126.1, 126.2, 128.3, 128.4, 128.6, 129.1, 135.4, 139.0, 155.5, 155.8, 169.1, 171.0, 173.3; MS (EI): *m/z* (%)=650 (9) [M^+−$PhCH_2$]; HRMS (EI): calcd for $C_{35}H_{56}NO_{10}$ [M^+−$PhCH_2$] 650.390423, found 650.38698.

(1*R*)-1-[(1*S*)-2-({(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl}oxy)-1-methyl-2-oxoethyl]octyl 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2,4,5-trideoxy-5-phenyl-L-*erythro*-pentonate (19). A mixture of the MOM ether **18** (200 mg, 0.27 mmol) and tetrabutylammonium bromide (435 mg, 1.35 mmol) in dichloromethane (10 ml) was treated with trimethylsilyl chloride (171 μl, 1.35 mmol) at 0°C. Stirring was continued for 36 h at room temperature. Thereafter, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ at 0°C. The mixture was extracted with diethyl ether (3×15 ml) and the organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 85:15) to give 0.15 g (79%) of **19** as a colorless oil. TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.39; IR (neat): 3501 (m), 1741 (s), 1694 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): (both rotamers) δ=0.81 (t, *J*=5.8 Hz, 3H, CH_3), 0.88 (d, *J*=6.8 Hz, 3H, CH_3(*i*Pr)), 0.91 (d, *J*=6.8 Hz, 3H, CH_3(*i*Pr)), 1.14–1.66 (m, 24H, Me, 3×CH_3(Boc), $(CH_2)_6$), 2.10–2.83 (m, 8H, CH(*i*Pr), NCH_3, $CH_2C(O)$, CH_2Ph, CHMe), 3.08–3.24 (m, 1H, CH_2Ph), 3.80–4.20 (m, 3H, CHN, CHOH), 4.79 (d, *J*=4.3 Hz, 1H, CH*i*Pr), 5.08–5.12 (m, 2H, CH_2(Bn)), 5.13–5.22 (m, 1H, CHOC(O)), 7.07–7.29 (m, 10H); ^{13}C HMR ($CDCl_3$): (both rotamers) δ=11.6, 11.9, 14.1, 17.2, 18.8, 22.7, 25.7, 28.2, 28.3, 29.2, 29.3, 30.1, 31.2, 31.5, 31.8, 33.3, 34.9, 39.5, 42.3, 42.6, 67.0, 67.1, 70.1, 74.4, 77.01, 79.6, 126.1, 126.2, 128.4, 128.5, 128.6, 129.1, 135.3, 139.0, 156.2, 169.3, 169.6, 171.9, 173.7; HRMS (ESI): calcd for 698.42626 (MH^+), found 698.4228.

(1*R*)-1-((1*S*)-2-{[(1*S*)-1-Carboxy-2-methylpropyl]oxy}-1-methyl-2-oxoethyl)octyl 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2,4,5-trideoxy-5-phenyl-L-*erythro*-pentonate (20). The hydroxy ester **19** (0.11 g, 0.157 mmol), dissolved in MeOH (7 ml) was hydrogenated over $Pd(OH)_2$ (0.150 g) at 5 bar pressure in an autoclave (Parr apparatus) at room temperature for 24 h. The mixture was passed through a Celite pad, washed thoroughly with MeOH, the filtrate was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography ($CHCl_3$/MeOH, 10:1) to provide **20** as a colorless oil (90 mg, 94%). $[\alpha]_D^{24}$=−25.5 (*c* 1.3, $CHCl_3$); TLC ($CHCl_3$/MeOH, 10:1): R_f=0.71; IR (neat): 3479 (br), 1739 (s), 1699 (s), 1652 (s), 1634 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): (both rotamers) δ=0.80 (t, *J*=6.8 Hz, 3H, CH_3), 0.83–0.88 (m, 6H, 2×CH_3(*i*Pr)), 1.09 (d, *J*=6.4 Hz, 3H, Me), 1.17–1.62 (m, 21H, 3×CH_3(Boc), $(CH_2)_6$), 2.35–2.65 (m, 8H, CH(*i*Pr), NCH_3, $CH_2C(O)$, CHMe, CH_2Ph), 3.13–3.22 (m, 1H, CH_2Ph), 3.38 (s, br., 1H), 4.01–4.22 (m, 2H, CHN, CHOH), 4.64 (d, *J*=3.6 Hz, 1H, CH*i*Pr), 5.31 (s, br., 1H, CHOC(O)), 7.05–7.18 (m, 5H); ^{13}C NMR ($CDCl_3$): (both rotamers) δ=10.3, 14.1, 17.3, 19.4, 22.6, 25.7, 28.3, 29.2, 29.3, 29.5, 29.8, 31.8, 32.1, 33.8, 39.5, 42.2, 50.5, 53.9, 69.8, 74.5, 79.6, 126.1, 128.2, 128.3, 129.05, 129.1, 138.9, 156.1, 172.97, 174.6, 176.6; HRMS (ESI): calcd for 608.3793 (MH^+), found 608.3785.

(1*R*)-1-((1*S*)-2-{[(1*S*)-1-Carboxy-2-methylpropyl]oxy}-1-methyl-2-oxoethyl)octyl 2,4,5-trideoxy-4-(methylamino)-

5-phenyl-L-*erythro*-pentonate (21). A mixture of the carboxylic acid **20** (90 mg, 0.148 mmol) and trifluoroacetic acid (0.609 ml) in dichloromethane (3 ml) was stirred at room temperature for 2 h. After removal of the volatile materials, the residue was purified by flash chromatography ($CHCl_3$/MeOH, 10:1) to give **21** as a colorless oil (71 mg, 93%). $[\alpha]_D^{25}=-2.3$ (*c* 1.0, $CHCl_3$); TLC ($CHCl_3$/MeOH, 10:1): $R_f=0.21$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.81$ (t, $J=6.4$ Hz, 3H, CH_3), 0.90 (d, $J=6.8$ Hz, 3H, CH_3(*i*Pr)), 0.93 (d, $J=6.7$ Hz, 3H, CH_3(*i*Pr)), 1.09 (d, $J=7.0$ Hz, 3H, Me), 1.16–1.21 (m, 10H, $(CH_2)_5$), 1.31–1.55, 1.56–1.81 (2×m, 2H, CH_2), 2.14–2.21 (m, 1H, CH(*i*Pr)), 2.36–2.42 (m, 2H, $CH_2C(O)$), 2.56 (s, 3H, NCH_3), 2.67–2.74 (m, 1H, CHMe), 2.92–3.04 (m, 2H, CH_2Ph), 3.4–3.5 (m, 1H, CHN), 4.38–4.42 (m, 1H, CHOH), 4.69 (d, $J=4.3$ Hz, 1H, CH*i*Pr), 5.21–5.25 (m, 1H, CHOC(O)), 7.18–7.29 (m, 5H), 8.44 (s, br., 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=9.4$, 14.1, 17.1, 18.8, 22.6, 25.6, 29.1, 29.3, 29.7, 30.9, 31.8, 32.1, 32.3, 38.9, 41.0, 64.7, 66.4, 75.1, 77.1, 127.5, 129.2, 135.7, 170.2, 172.4, 173.9; MS (FAB): *m/z* (%)=508 (56%) [M^++1], 408 (4), 224 (100), 206 (30).

Benzyl (2*S*)-3-methyl-2-{[(2*S*,3*R*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)decanoyl]amino}butanoate (23). Diisopropylethylamine (0.84 ml, 4.97 mmol) was added dropwise to a stirred mixture of the *p*-TSA salt of the valine benzyl ester **22** (0.957 g, 2.48 mmol), the carboxylic acid **13** (0.71 g, 2.48 mmol) and BOP (1.09 g, 2.48 mmol) in anhydrous acetonitrile (8 ml) at room temperature under argon. After 2 h, the reaction mixture was diluted with brine and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed sequentially with 10% citric acid and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 85:15) to provide 0.68 g (70%) of **23** as a colorless oil. $[\alpha]_D^{25}=+28.3$ (*c* 0.5, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 8:2): $R_f=0.43$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.78$–0.88 (m, 9H, 2×CH_3(*i*Pr), CH_3), 1.03 (dd, $J=3.0$, 4.3 Hz, 3H, Me), 1.10–1.28 (m, 10H, $(CH_2)_5$), 1.30–1.80 (m, 8H, CH_2, 3×CH_2(THP)), 2.07–2.19 (m, 1H, CH(*i*Pr)), 2.56–2.61, 2.82–2.86 (2m, 1H, CHMe), 3.40–3.50 (m, 1H, CHOTHP), 3.52–3.72 (m, 1H, CH_2O), 3.82–3.89 (m, 1H, CHOTHP), 4.45–4.58 (m, >1H, CH*i*Pr, CH(THP)), 4.68–4.71 (m, <1H, CH(THP)), 5.09 (dd, $J=1.2$, 0.9 Hz, 2H, CH_2(Bn)), 6.84 (d, $J=8.2$ Hz, 1H, NH), 7.23–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=12.7$, 12.9, 17.7, 18.9, 19.0, 19.5, 21.0, 22.6, 25.2, 25.3, 26.2, 26.3, 29.1, 29.4, 29.7, 30.6, 30.9, 31.1, 31.2, 31.8, 42.2, 43.6, 56.9, 57.2, 62.7, 64.5, 66.4, 66.7, 76.6, 76.9, 77.1, 77.3, 79.3, 81.3, 97.3, 101.2, 128.1, 128.2, 128.4, 128.5, 135.5, 171.7, 173.9; MS (EI): *m/z* (%)=476 (6) [M^++1], 392 (100); HRMS (EI): calcd for $C_{28}H_{45}NO_5$ 475.329747, found 475.322658.

Benzyl (2*S*)-2-{[(2*S*,3*R*)-3-hydroxy-2-methyldecanoyl]-amino}-3-methylbutanoate (24). A solution of the protected amide **23** (0.50 g, 1.05 mmol) and a small amount of *p*-TsOH (20 mg, 0.1 mmol) in MeOH (10 ml) was stirred at room temperature for 2 h and then quenched by the addition of aqueous 2N $KHCO_3$ solution. Most of the MeOH was removed under reduced pressure and the resulting slurry extracted with diethyl ether (3×20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave 0.37 g (90%) of **24** as colorless crystals, mp 80.8–81.8°C. $[\alpha]_D^{28}=+10.2$ (*c* 0.4, $CHCl_3$); IR (neat): 3293 (s), 1735 (s), 1642 (s), 1539 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.79$ (d, $J=7.1$ Hz, 6H, CH_3(*i*Pr), CH_3), 0.86 (d, $J=6.7$ Hz, 3H, CH_3(*i*Pr)), 1.11 (d, $J=7.0$ Hz, 3H, Me), 1.19–1.36 (m, 12H, $(CH_2)_6$), 2.07–2.19 (m, 1H, CH(*i*Pr)), 2.30–2.39 (m, 1H, CHMe), 3.72–3.77 (m, 1H, CHOH), 4.54 (dd, $J=4.6$, 4.3 Hz, 1H, CH*i*Pr), 5.08 (dd, $J=9.4$, 12.2 Hz, 2H, CH_2(Bn)), 6.29 (d, $J=8.6$ Hz, 1H, NH), 7.25–7.37 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=11.4$, 14.1, 17.6, 19.1, 22.7, 26.1, 29.3, 29.6, 31.1, 31.8, 33.3, 44.9, 56.8, 67.2, 72.3, 128.4, 128.5, 128.7, 135.3, 172.1, 176.3; MS (EI): *m/z*=392 (6) [M^++1]; HRMS (EI): calcd for $C_{23}H_{37}NO_4$ 391.27225, found 391.27108.

(1*R*)-1-[(1*S*)-2-({(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl}amino)-1-methyl-2-oxoethyl]octyl 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2,4,5-trideoxy-3-*O*-(methoxymethyl)-5-phenyl-L-*erythro*-pentonate (25). To a solution of the amino acid[20] **17** (0.34 g, 0.93 mmol) in THF (4 ml) and triethylamine (0.156 ml, 1.12 mmol) was added the Yamaguchi reagent (0.156 g, 0.93 mmol) in a dropwise fashion at room temperature. The resulting mixture was stirred at room temperature for 1 h. The amine hydrochloride salt was filtered off under argon and the filtrate concentrated under argon. To the residue, dissolved in dry benzene (4 ml) was added a solution of the alcohol **24** (0.439 g, 1.12 mmol) in benzene (4 ml) dropwise. Finally DMAP (0.227 g, 1.86 mmol) was added and the reaction mixture stirred at room temperature for 2 h. Afterwards, the reaction mixture was diluted with diethyl ether, washed successively with 2N HCl, water, saturated aqueous $NaHCO_3$, water, and finally with brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to yield 0.48 g (70%) of **25** as a colorless oil. $[\alpha]_D^{25}=+8.6$ (*c* 0.5, $CHCl_3$); IR (neat): 3333 (m), 1735 (s), 1696 (s), 1675 (s), 1667 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): (both rotamers) $\delta=0.72$–0.89 (m, 9H, 2×CH_3(*i*Pr), CH_3), 1.11 (dd, $J=4.2$, 2.8 Hz, 3H, Me), 1.17–1.29 (m, 19H, 3×CH_3(Boc), $(CH_2)_5$), 1.40–1.69 (m, 2H, CH_2), 2.03–2.16 (m, 1H, CH(*i*Pr)), 2.33–2.90 (m, 7H, $CH_2C(O)$, NCH_3, CHMe, CH_2Ph), 3.04–3.16 (m, 1H, CH_2Ph), 3.34 (s, 3H, minor, OCH_3), 3.36 (s, 3H, major, OCH_3), 4.24–4.33 (m, 2H, CHN, CHOMOM), 4.56–4.66 (m, 2H, CH*i*Pr, CH_2(MOM)), 4.79–4.91 (m, 2H, CHOC(O), CH_2(MOM)), 5.06 (dd, $J=9.2$, 3.1 Hz, 2H, minor, CH_2(Bn)), 5.13 (dd, $J=12.2$, 10.1 Hz, 2H, major, CH_2(Bn)), 6.56 (d, $J=8.2$ Hz, 1H, major, NH), 6.63 (s, br., 1H, minor, NH), 7.07–7.30 (m, 10H); ^{13}C NMR (both rotamers, $CDCl_3$): $\delta=14.1$, 14.3, 14.5, 17.6, 19.0, 22.7, 26.1, 28.1, 28.3, 29.2, 29.3, 30.4, 31.4, 31.8, 34.4, 38.2, 44.4, 44.6, 56.3, 56.5, 56.7, 56.8, 66.9, 76.1, 76.6, 76.8, 77.3, 79.4, 79.8, 97.1, 97.4, 126.3, 128.15, 128.2, 128.4, 128.6, 129.1, 135.4, 138.9, 155.6, 171.3, 172.3, 172.9, 173.1; MS (EI): *m/z* (%)=649 (yy) [M^+-PhCH_2]; HRMS (EI): calcd for $C_{35}H_{57}N_2O_9$ [M^+-PhCH_2] 649.40640, found 649.40033.

(1*R*)-1-[(1*S*)-2-({(1*S*)-1-[(Benzyloxy)carbonyl]-2-methylpropyl}amino)-1-methyl-2-oxoethyl]octyl 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2,4,5-trideoxy-5-phenyl-L-

***erythro*-pentonate (26).** A solution of MOM ether **25** (0.47 g, 0.63 mmol) in CH_2Cl_2 (5 ml) was treated with trimethylsilyl bromide (0.39 g, 2.5 mmol) at −30°C. After being stirred for 1 h at −30°C, the mixture was allowed to warm up to 0°C and stirred at this temperature for 3 h. After quenching with a saturated aqueous $NaHCO_3$ solution (6 ml) the layers were separated and the water layer extracted with CH_2Cl_2 (2×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in petroleum ether) to yield 0.34 g (78%) of **26** as a colorless oil. $[\alpha]_D^{26}=-5.7$ (*c* 0.46, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.38; IR (neat): 3330 (s), 1741 (s), 1695 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): (both rotamers) δ=0.82–0.89 (m, 9H, 2×CH_3(*i*Pr), CH_3), 1.15–1.32 (m, 22H, Me, 3×CH_3(Boc), $(CH_2)_5$), 1.50–1.72 (m, 2H, CH_2), 2.07–2.23 (m, 1H, CH(*i*Pr)), 2.30–2.78 (m, 7H, $CH_2C(O)$, NCH_3, CHMe, CH_2Ph), 2.85–3.33 (m, 1H, CH_2Ph), 3.84–3.98, 4.05–4.28, 4.31–4.43 (3m, 2H, CHN, CHOH), 4.50–4.58 (m, 1H, CH*i*Pr), 4.97–5.23 (m, 3H, CHOC(O), CH_2(Bn)), 6.30 (d, *J*=8.5 Hz, 1H, major, NH), 6.43 (d, *J*=9.4 Hz, 1H, minor, NH), 7.08–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$): (both rotamers) δ=12.4, 12.9, 14.1, 17.8, 17.9, 18.9, 22.6, 25.9, 28.3, 29.2, 29.3, 30.6, 30.9, 31.3, 31.4, 31.8, 33.4, 40.1, 40.4, 43.9, 44.2, 44.9, 57.1, 67.1, 67.3, 70.1, 74.8, 75.4, 79.6, 126.2, 128.4, 128.5, 128.6, 129.1, 129.5, 135.2, 135.3, 139.0, 156.3, 171.4, 171.5, 172.3, 173.4, 173.7.

(1*R*)-1-((1*S*)-2-{[(1*S*)-1-Carboxy-2-methylpropyl]amino}-1-methyl-2-oxoethyl)octyl 4-[(*tert*-butoxycarbonyl)(methyl)-amino]-2,4,5-trideoxy-5-phenyl-L-*erythro*-pentonate (27). A solution of the benzyl ester **26** (70 mg, 100 μmol) in MeOH (5 ml) was stirred in the presence of $Pd(OH)_2$ (70 mg) at room temperature overnight under a hydrogen balloon. The reaction mixture was filtered through a Celite pad and the filtrate evaporated to give the carboxylic acid which was used as such for the next step.

(1*R*)-1-((1*S*)-2-{[(1*S*)-1-Carboxy-2-methylpropyl]amino}-1-methyl-2-oxoethyl)octyl 2,4,5-trideoxy-4-(methylamino)-5-phenyl-L-*erythro*-pentonate (28). A mixture of the carboxylic acid **27** and TFA (0.36 ml) in dichloromethane (3 ml) was stirred at room temperature for 2 h. After removal of volatile materials, the residue was purified by flash chromatography ($CHCl_3$/MeOH, 10:1) to provide 47 mg (94%) of **28** as a colorless oil. TLC ($CHCl_3$/MeOH, 10:1): R_f=0.17; ^1H NMR (250 MHz, $CDCl_3$): δ=0.77–0.87 (m, 9H, 2×CH_3(*i*Pr), CH_3), 1.01 (d, *J*=6.9 Hz, 3H, Me), 1.14–1.28 (m, 10H, $(CH_2)_5$), 1.38–1.65 (m, 2H, CH_2), 1.97–2.13 (m, 1H, CH(*i*Pr)), 2.40–2.46 (m, 2H, $CH_2C(O)$), 2.50–2.65 (m, 4H, NCH_3, CHMe), 3.0 (d, *J*=6.8 Hz, 2H, CH_2Ph), 3.43 (s, br., 1H, CHN), 4.20–4.30 (m, 1H, CH*i*Pr), 4.40–4.45 (m, 1H, CHOH), 5.0–5.08 (m, 1H, CHOC(O)), 6.8 (d, *J*=7.9 Hz, 1H, NH), 7.0 (s, br., 1H), 7.19–7.27 (m, 5H), 8.83 (s, br., 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=11.3, 14.1, 18.1, 19.1, 22.6, 25.8, 29.1, 29.4, 30.5, 30.7, 31.8, 32.3, 32.7, 38.3, 43.2, 53.4, 58.2, 65.0, 66.5, 75.7, 127.6, 129.0, 129.3, 135.7, 170.7, 174.4, 175.1.

(2*S*,3*R*,6*S*,10*R*,11*R*)-10-Benzyl-2-heptyl-11-hydroxy-6-isopropyl-3,9-dimethyl-1-oxa-5,7,9-triazacyclotridecane-4,8,13-trione (29) and (2*S*,3*R*,6*R*,10*R*,11*R*)-10-benzyl-2-heptyl-11-hydroxy-6-isopropyl-3,9-dimethyl-1-oxa-5,7,9-triazacyclotridecane-4,8,13-trione (30). To a solution of amino acid **28** (90 mg, 0.178 mmol) in dry DMF (180 ml) were added diphenylphosphoryl azide (DPPA, 100 mg, 0.36 mmol) and diisopropylethylamine (DIEA, 137 mg, 1.06 mmol) at 0°C. The solution was stirred at this temperature for 3 h, then at room temperature for 4 days. The reaction solution was partitioned between ethyl acetate (250 ml) and water (200 ml). After extracting of the water-DMF layer with ethyl acetate (2×80 ml), the combined ethyl acetate layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (50% ethyl acetate in petroleum ether) to give the cyclic products **29** and **30** (24 mg, 0.048 mmol, 27%) in a ratio of 1:1.

*Data for **29**:* $[\alpha]_D^{25}=+62.5$ (*c* 0.079, $CHCl_3$); TLC (ethyl acetate/petroleum ether, 1:1): R_f=0.24; ^1H NMR (400 MHz, DMSO-d_6): δ=0.72–0.78 (m, 6H, 2×CH_3(*i*Pr)), 0.84 (t, *J*=6.8 Hz, 3H, CH_3), 0.97 (d, *J*=7.0 Hz, 3H, Me), 1.10–1.26 (m, 10H, $(CH_2)_5$), 1.28–1.36, 1.38–1.52 (2m, 2H, CH_2), 2.05–2.16 (m, 1H, CH(*i*Pr)), 2.32–2.40 (m, 5H, CHMe, NCH_3, $CH_2C(O)$), 2.61–2.75 (m, 2H, $CH_2C(O)$, CH_2Ph), 3.18 (dd, *J*=12, 2.7 Hz, 1H, CH_2Ph), 3.85–3.91 (m, 1H, CHOH), 4.42–4.50 (m, 1H, CH*i*Pr), 4.51–4.59 (m, 1H, CHN), 5.18 (d, *J*=6.1 Hz, 2H, CHOC(O), OH), 5.84 (d, *J*=10 Hz, 1H, NH), 7.10–7.28 (m, 5H), 7.91 (d, *J*=6.1 Hz, 1H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ=8.5, 19.4, 19.9, 22.0, 24.9, 28.5, 28.8, 30.0, 30.8, 31.1, 34.2, 40.7, 42.4, 58.6, 66.2, 67.9, 74.3, 125.7, 128.0, 128.4, 129.6, 139.3, 158.3, 169.5, 172.5; HRMS (ESI): calcd for $C_{28}H_{46}N_3O_5$ 504.34191, found 504.34320.

*Data for **30**:* $[\alpha]_D^{25}=+66.4$ (*c* 0.136, $CHCl_3$); TLC (ethyl acetate/petroleum ether, 1:1): R_f=0.37; ^1H NMR (600 MHz, DMSO-d_6): δ=0.63, 0.77 (2d, *J*=6.5 Hz, 6H, 2×CH_3(*i*Pr)), 0.85 (t, *J*=6.8 Hz, 3H, CH_3), 1.06 (d, *J*=7.1 Hz, 3H, Me), 1.13–1.26 (m, 10H, $(CH_2)_5$), 1.39–1.51 (m, 2H, CH_2), 2.26 (s, 3H, NCH_3), 2.38–2.47 (m, 3H, CHMe, CH(*i*Pr), $CH_2C(O)$), 2.60 (t(dd), *J*=12.8 Hz, 1H, CH_2Ph), 2.82 (dd, *J*=16.9, 10.4 Hz, 1H, $CH_2C(O)$), 3.20 (dd, *J*=12.5, 6.0 Hz, 1H, CH_2Ph), 3.83–3.86 (m, 1H, CHOH), 4.10–4.14 (m, 1H, CH*i*Pr), 4.50–4.54 (m, 1H, CHN), 4.98–5.00 (m, 1H, CHOC(O)), 5.11 (d, *J*=5.9 Hz, 1H, OH), 6.50 (d, *J*=5.9 Hz, 1H, NH), 7.08–7.24 (m, 6H, Ph, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ=13.9, 19.2, 20.0, 22.0, 25.1, 28.4, 28.6, 28.8, 30.1, 31.1, 31.9, 33.9, 41.9, 44.1, 57.7, 64.5, 67.1, 73.6, 125.6, 127.8, 127.9, 128.2, 128.7, 139.2, 157.3, 169.3, 173.6; HRMS (ESI): calcd for $C_{28}H_{46}N_3O_5$ 504.34191, found 504.34320.

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References

1. Lehnert, M. *Eur. J. Cancer* **1996**, *32A*, 912–920.
2. Gottesman, M. M.; Pastan, I.; Ambudkar, S. V. *Curr. Opin. Genet. Dev.* **1996**, *6*, 610–617.
3. Atadja, P.; Watanabe, T.; Xu, H.; Cohen, D. *Cancer Metastasis Rev.* **1998**, *17*, 163–168.
4. Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Org. Chem.* **1994**, *59*, 7219–7226.
5. Dinh, T. Q.; Armstrong, R. W. *J. Org. Chem.* **1995**, *60*, 8118–8119.
6. Dinh, T. Q.; Du, X.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606–6616.
7. Ohmori, K.; Okuno, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 3467–3470.
8. Ghosh, A. K.; Liu, W.; Xu, Y.; Chen, Z. *Angew. Chem.* **1996**, *108*, 73–75; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 74–76.
9. Okuno, T.; Ohmori, K.; Nishiyama, S.; Yamamura, S.; Nakamura, K.; Houk, K. N.; Okamoto, K. *Tetrahedron* **1996**, *52*, 14723–14734.
10. Wagner, B.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1996**, *37*, 6557–6560.
11. Dinh, T. Q.; Du, X.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 6773–6783.
12. Haddad, M.; Botuha, C.; Larchevêque, M. *Synlett* **1999**, 1118–1120.
13. Wagner, B.; Gonzalez, G. I.; Dau, M. E. T. H.; Zhu, J. *Bioorg. Med. Chem.* **1999**, *7*, 737–747.
14. O'Connell, C.; Salvato, K. A.; Meng, Z.; Littlefield, B. A.; Schwartz, C. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1541–1546.
15. Balkenhohl, F.; von dem Busche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288–2337.
16. Watson, C. *Angew. Chem.* **1999**, *111*, 2025–2031; *Angew. Chem., Int. Ed.* **1999**, *38*, 1903–1908.
17. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83–91.
18. Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947.
19. Pais, G. C. G.; Maier, M. E. *J. Org. Chem.* **1999**, *64*, 4551–4554.
20. Maier, M. E.; Hermann, C. *Tetrahedron* **2000**, *56*, 557–561.
21. Shioiri, T.; Yamada, S.-i. *Chem. Pharm. Bull.* **1974**, *22*, 859–863.
22. Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5155–5158.
23. Bothner-By, A. A.; Stephensen, R. L.; Lee, J.-m.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811–813.
24. Bax, A.; Davies, D. G. *J. Magn. Reson.* **1985**, *63*, 207–213.
25. Griesinger, C.; Ernst, R. R. *J. Magn. Reson.* **1987**, *75*, 261–271.
26. Kessler, H.; Bats, J. W.; Griesinger, C.; Koll, S.; Will, M.; Wagner, K. *J. Am. Chem. Soc.* **1988**, *110*, 1033–1049.
27. Kumar, A.; Wagner, G.; Ernst, R. R.; Wüthrich, K. *J. Am. Chem. Soc.* **1981**, *103*, 3654–3658.
28. Mierke, D. F.; Kurz, M.; Kessler, H. *J. Am. Chem. Soc.* **1994**, *116*, 1042–1049.
29. Riniker, B.; Schwyzer, R. *Helv. Chim. Acta* **1964**, *47*, 2375–2384.
30. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
31. Inouye, K.; Watanabe, K.; Shin, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1905–1911.
32. Rocchiccioli, F.; Jarreau, F.-X.; Païs, M. *Tetrahedron* **1978**, *34*, 2917–2926.
33. Chorev, M.; MacDonald, S. A.; Goodman, M. *J. Org. Chem.* **1984**, *49*, 821–827.
34. Rodriguez, M.; Dubreuil, P.; Bali, J.-P.; Martinez, J. *J. Med. Chem.* **1987**, *30*, 758–763.
35. Kawasaki, K.; Maeda, M.; Watanabe, J.; Kaneto, H. *Chem. Pharm. Bull.* **1988**, *36*, 1766–1771.
36. Cushman, M.; Jurayj, J.; Moyer, J. D. *J. Org. Chem.* **1990**, *55*, 3186–3194.
37. Carter, D. S.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 8537–8545.
38. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–82.
39. Gibian, H.; Schroeder, E. *Liebigs Ann. Chem.* **1961**, *642*, 145–162.
40. Shields, J. E.; Campbell, C. S.; Doyle, K. S.; Miller, R. D.; Neuss, N. *Helv. Chim. Acta* **1981**, *64*, 2587–2591.
41. O'Donnell, M. J.; Cook, G. K.; Rusterholz, D. *Synthesis* **1991**, 989–993.