A Total Synthesis of Aliskiren

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

A total synthesis of aliskiren (**20**) was accomplished. A key in our synthesis was to use the symmetric *trans-cisoid-trans*-bis-lactone **1** as a precursor. It was expediently prepared by three different routes (*Scheme 2*). Appending the end groups and functional group transformations completed the synthesis (*Scheme 3*).

Introduction. – The hydroxyethylene dipeptide isostere has been designed to mimic the transition state of the peptide bond cleavage, and has been incorporated in the structures of several drug molecules that act as protease inhibitors [1]. Among them is aliskiren, a renin inhibitor, which is unique for being the first orally active, efficient, non-peptidic drug for treatment of hypertension [2]. Aliskiren is currently marketed under the trade names *Tekturna* and *Resilez*.

The structure of aliskiren is fairly complex as drug molecules go. A key in the synthesis of aliskiren is the construction of the octanoic acid backbone, with the control of the configurations at the stereogenic centers at C(2), C(4), C(5), and C(7) (*Scheme 1*). Diverse synthetic approaches have been reported in the literature. A majority of them, including the original *Novartis* synthesis [3], utilized convergent synthetic strategies, wherein two chiral fragments had been separately prepared by the aid of various chiral auxiliary groups, and later assembled at or around the amino alcohol function [3–6][1]). *Hanessian* and co-workers reported two very distinct synthetic approaches to aliskiren [7]. In the first one, an amino acid chiral pool starting material was converted to a C_5 fragment, the isopropyl group (at C(7)) having been incorporated with a highly selective asymmetric induction. A C_3 fragment was then linked, again the required configuration having been controlled by asymmetric induction. In the second approach, a single enantiomerically pure compound, with the isopropyl group already in place with the correct (*S*)-configuration, was converted to two different fragments, which were later joined.

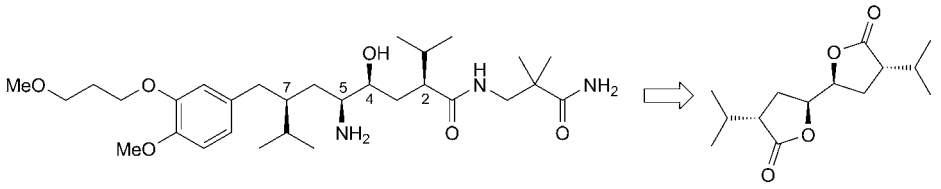
We noted a 'pseudo-symmetric' nature of the octanoic acid backbone. The two isopropyl groups are attached at the palindromic C(2) and C(7) atoms, both with (*S*)-configurations, and the two heteroatoms (amino alcohol function) are at C(5)/C(4), both with (*S*)-configurations. The use of a symmetric precursor, which would be

[1]) A nice summary of the literature synthetic strategies can be found in [6a].

expediently constructed, then later desymmetrized by sequentially introducing the end groups, would offer an efficient pathway to aliskiren.

Results and Discussion. – We envisaged the *trans-cisoid-trans*-bis-lactone **1** to be a well-suited symmetric precursor for our synthesis of aliskiren (**20**; *Scheme 1*). The two isopropyl groups are in place with the correct (*S*)-configuration, and the lactone functions are amenable for introducing the end groups. The two O-functions in the center are where the amino alcohol function is located in the target molecule **20** C(4)/C(5). Synthesis of aliskiren would require one of the two O-functions to be regioselectively transformed to an amino group with a retention of the configuration.

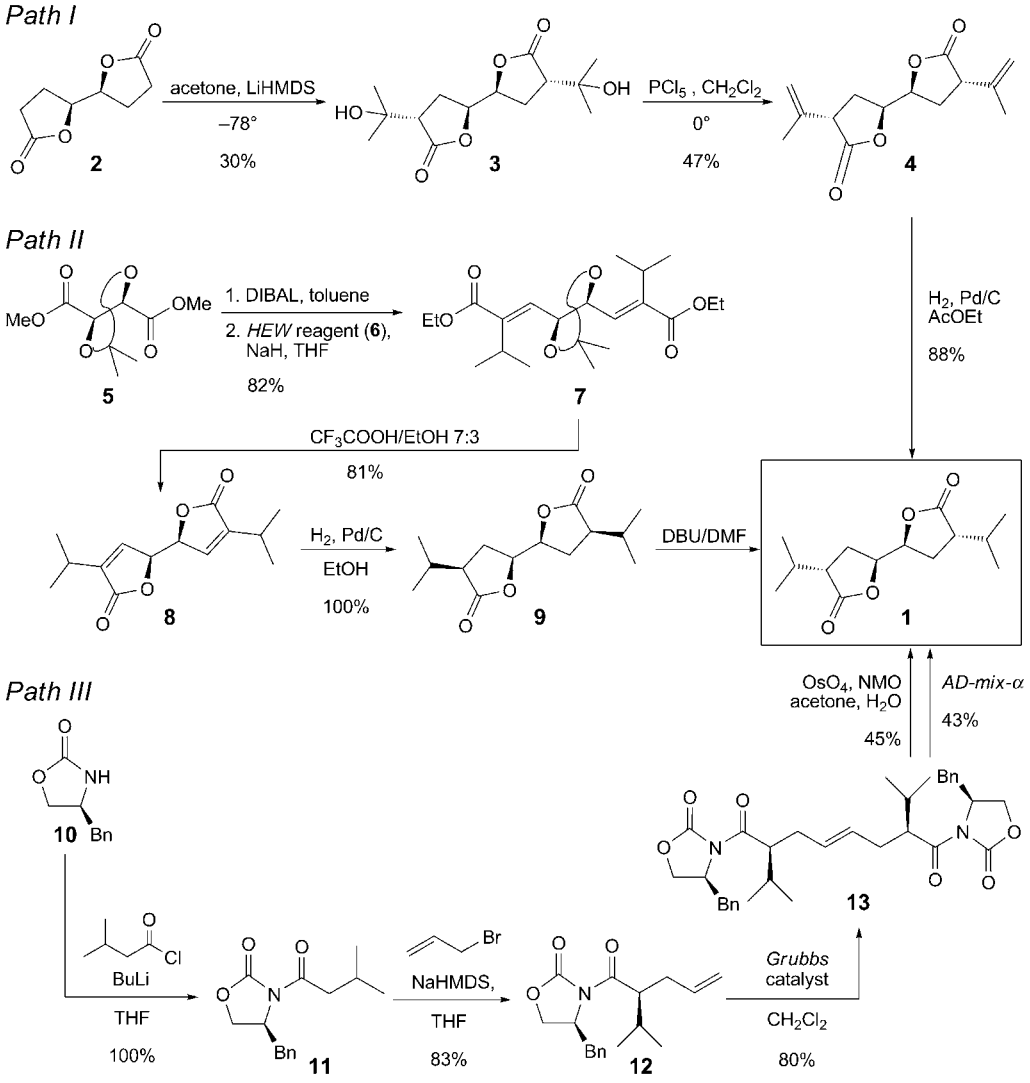
Scheme 1. *Synthetic Strategy to Aliskiren* (**20**)



Aliskiren (**20**) *trans-cisoid-trans*-Bis-lactone **1**

The *trans-cisoid-trans*-bis-lactone **1** was prepared *via* three different synthetic routes (*Scheme 2*). In *Path I*, two isopropyl groups were introduced concurrently and stereoselectively at both C(α) atoms of the known, unsubstituted bis-lactone **2** [8] in three steps: aldol addition of the bis-enolate to acetone, dehydration, and reduction. The aldol addition in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) took place stereoselectively *trans* to the existing substituent ($\rightarrow$ **3**), dehydration prompted by PCl_5 produced the diisopropenyl-substituted compound **4** [9], and catalytic hydrogenation yielded the desired *trans-cisoid-trans*-bis-lactone **1**. Direct isopropylation of the bis-enolate was not successful. In *Path II*, protected dimethyl L-tartrate **5** was the starting material. Following a reduction with diisobutylaluminium hydride (DIBAL) to the dialdehyde stage, an *in situ Horner–Emmons–Wadsworth* reaction with the isopropyl-substituted ester $(EtO)_2P(=O)–CH(CHMe_2)–COOEt$ (**6**) [10] brought us, in a single step from the commercially available starting material to the stage with the complete carbon skeleton of **1**, *i.e.*, to **7**. Product **7** was in fact a mixture of *cis*- and *trans*-isomers, in which the *cis*,*cis*-isomer was major (4 to 5:1). Upon unmasking the diol function, only the *cis*,*cis*-isomer underwent double cyclization to produce bis-lactone **8**. Reduction of **8** took place from the opposite side with respect to the existing substituent to produce the *cis-cisoid-cis*-bis-lactone **9**. Equilibration under basic conditions (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/DMF) resulted in epimerization, albeit with a disappointing selectivity (*ca.* 1:1), to produce the desired *trans-cisoid-trans*-bis-lactone **1**. When the order of the last two steps, *i.e.*, deprotection and reduction, was reversed, the bis-lactone product was obtained as a mixture of three diastereoisomers, *i.e.*, **1**, **9**, and the *trans-cisoid-cis*-isomer. Once again, epimerization

Scheme 2. *Synthetic Pathways to* trans-cisoid-trans-*Bis-lactone* **1**



shifted the distribution toward the desired *trans-cisoid-trans*-bis-lactone **1**, interestingly, however, with a selectivity worse than in the above-described case under supposedly equilibrating conditions.

In contrast to *Paths I* and *II* described above wherein the configurations of the target stereogenic centers C(4)/C(5) originated from the enantiomerically pure starting materials and those of C(2)/C(7) (isopropyl-substituted stereogenic centers) were induced relative to those at C(4)/C(5), *Path III* of the synthesis of the *trans-cisoid-trans*-bis-lactone **1** had the isopropyl-substituted target stereogenic centers C(2)/C(7)

installed first, by means of *Evans*' chiral auxiliary, *i.e.*, a substituted oxazolidinone. Thus, allylation of the enolate derived from **11** (obtained from **10**) proceeded with a high stereoselectivity (→**12**) [3a]. *Grubbs*' alkene metathesis reaction yielded then the symmetric *trans*-alkene derivative **13** as the major product [11]. The initial attempt at the *Sharpless* asymmetric dihydroxylation (AD reaction) of **13** with *AD-mix-α* was too slow to be practical under the standard conditions. With a higher catalyst loading (twice the standard protocol) at room temperature, the dihydroxylation took place, followed by *in situ* lactonization, to produce bis-lactone products. The stereoselectivity was only modest (3.3:1), however, and the desired stereoisomer **1** was isolated in 43% yield after a chromatographic purification. The low reactivity and poor stereoselectivity were probably due to the steric hindrance exerted by the isopropyl groups at the homoallylic C-atoms. When the *Evans* auxiliaries (*i.e.*, the oxazolidinone moieties) were replaced by methyl ester functions, the AD reaction was still slow, and the stereoselectivity was not much improved[2]). A practically more convenient procedure was to use OsO_4/4-methylmorpholine 4-oxide (NMO). With the achiral reagents, the bis-lactone product was formed as a 1:1 mixture of *trans-cisoid-trans* and *cis-cisoid-cis*-diastereoisomers, *i.e.*, of **1** and the enantiomer of **9**, which were separated by column chromatography (SiO_2) to yield the desired isomer **1** in 45% yield.

Having obtained the symmetric intermediate **1**, remaining tasks were appending the right- and left-end groups of **20** (*Scheme 3*), and functional-group transformations while taking into consideration the required configuration. The aryl end group was introduced by reacting bis-lactone **1** with the corresponding aryllithium (prepared from the aryl bromide). Only one of the lactone rings was opened even with a slight excess of the aryllithium, and due to the symmetric nature of bis-lactone **1**, it did not matter which one. The benzoyl group in the resulting product **14** was reduced to the benzyl group with H_2 on Pd/C (→**15**). The ring-opening **1** → **14** also released one of the OH functions, the one that needed to be converted to the amino function of aliskiren (**20**) with retention of the configuration. This meant that we needed to perform double substitution reactions for this O → N conversion. Thus, OH group of **15** was mesylated (→**16**). Subsequent S_N2 reactions first by Br^- (→**17**), then by N_3^- (→**18**) placed the N-function at the right place with the correct configuration (*S*). The remaining lactone ring was then opened with the right-end amino group, *i.e.*, with 3-amino-2,2-dimethylpropanamide, in the presence of propanoic acid [12]. Reduction of the azide group of the obtained amide **19** yielded aliskiren (**20**).

In conclusion, a total synthesis of aliskiren was accomplished. A key in our synthesis was to use the symmetric *trans-cisoid-trans*-bis-lactone **1** as a precursor. It was expediently prepared by three different routes. Appending the end groups and functional-group transformations completed the synthesis.

Experimental Part

General. Flash column ohromatography (FC): silica gel. TLC: silica gel glass-backed plates. IR Spectra: thin films on *KRS-5* plates; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 250 or 300 (^1H) and 62.5 or 75 MHz (^{13}C); δ in ppm rel. to Me_4Si as an internal standard, *J* in Hz.

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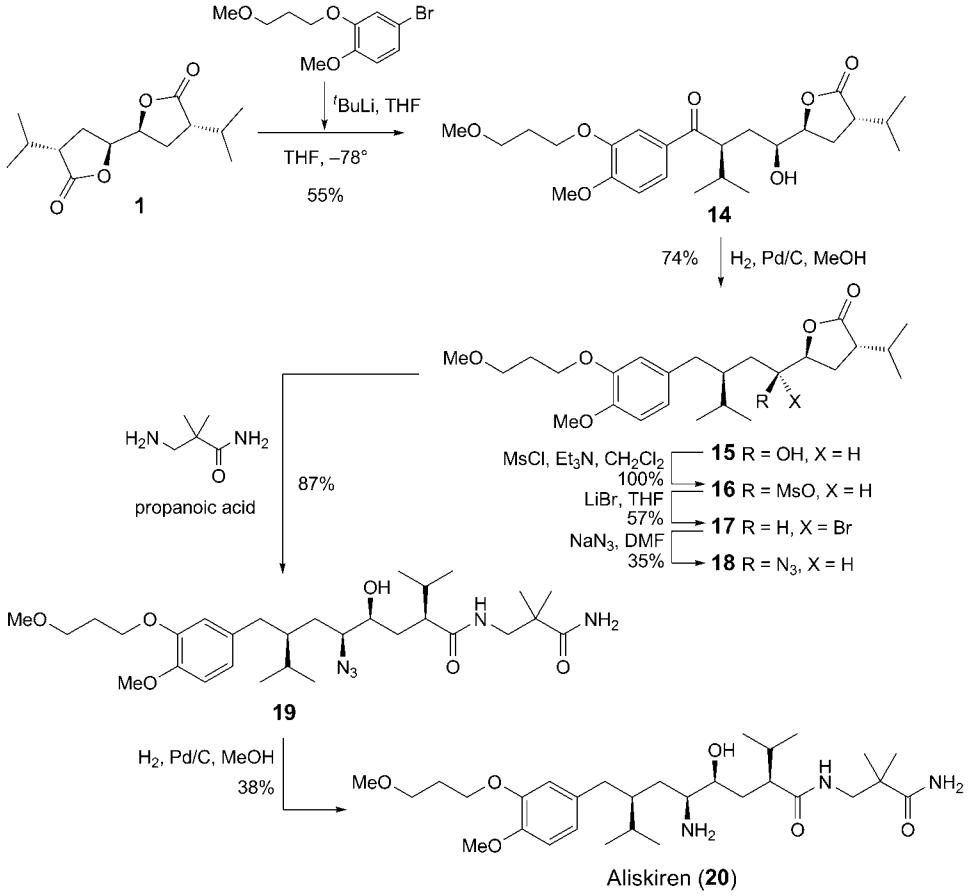
[2]) This did not seem to be a case of the mis-matched double stereoselection. The AD reactions with *AD-mix-β* were equally slow and the stereoselectivity modest (1:3).

Scheme 3. *Synthetic Pathway from Bis-lactone* **1** *to Aliskiren* (**20**)



(2S,2′S,4S,4′S)-Tetrahydro-4,4′-bis(1-hydroxy-1-methylethyl)-[2,2′-bifuran]-5,5′(2H,2′H)-dione (**3**). A soln. of bis-lactone **2** (0.190 g, 1.12 mmol) in THF (5 ml) was cooled to −78°. Then, 1M LiHMDS in THF (2.6 ml, 2.6 mmol) was added dropwise, and the mixture was stirred at −78° for 1 h. Anh. acetone (0.21 ml, 2.58 mmol) was added, and the mixture was stirred for 1 h at −78°. The reaction was quenched by adding sat. aq. NH_4Cl soln. and Et_2O. The mixture was warmed to r.t. and then extracted with $CHCl_3$. The combined org. phase was dried (Na_2SO_4) and concentrated and the residue purified by FC (AcOEt/EtOH 20:1): **3** (0.096 g, 30%). FT-IR: 3380, 3020, 1749, 1364, 1217. ^{1}H-NMR ($CDCl_3$): 4.54–4.59 (*m*, 2 H), 2.91 (*t*, *J* = 9.6, 2 H); 2.82 (*s*, 2 H); 2.28–2.47 (*m*, 4 H); 1.37 (*s*, 6 H); 1.27 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 177.3; 78.4; 71.2; 49.0; 27.7; 27.1; 26.4.

(2S,2′S,4S,4′S)-Tetrahydro-4,4-bis(1-methylethenyl)-[2,2′-bifuran]-5,5′(2H,2′H)-dione (**4**). A soln. of **3** (0.061 g, 0.214 mmol) in CH_2Cl_2 (6 ml) was cooled to 0°. PCl_5 (0.115 g, 0.515 mmol) in CH_2Cl_2 (1 ml) was added, and the mixture was stirred for 3.5 h. The reaction was quenched by adding sat. aq. $NaHCO_3$ soln. Extractive workup with CH_2Cl_2, drying (Na_2SO_4), and FC (hexane/AcOEt 2:1) yielded **4** (0.025 g, 47%). FT-IR: 3021, 2360, 1777, 1153. ^{1}H-NMR ($CDCl_3$): 5.01 (*dd*, *J* = 15.9, 2.7, 4 H); 4.56–4.62 (*m*, 2 H); 3.47–3.53 (*m*, 2 H); 2.48–2.58 (*m*, 2 H); 2.32–2.42 (*m*, 2 H); 1.82 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 175.9; 139.6; 114.9; 78.2; 46.7; 29.6; 20.3.

(2S,2′S,4S,4′S)-Tetrahydro-4,4′-bis(1-methylethyl)-[2,2′-bifuran]-5,5′(2H,2′H)-dione (**1**). To a soln. of **4** (0.022 g, 0.088 mmol) in AcOEt. Pd/C (10 mg) was added, and the mixture was stirred under H_2 (g) for 15 h at r.t. The mixture was filtered through a pad of *Celite*, which was further washed with AcOEt. The combined filtrate and washings were concentrated. FC (hexane/AcOEt 3:1) yielded **1** (0.020 g, 88%). FT-IR: 2360, 1978, 1869, 1777. ^{1}H-NMR ($CDCl_3$): 4.47–4.53 (*m*, 2 H); 2.74–2.83 (*m*, 2 H); 2.28–2.38 (*m*, 2 H); 2.14–2.24 (*m*, 4 H); 1.04 (*d*, *J* = 6.9, 6 H); 0.95 (*d*, *J* = 6.8, 6 H). ^{13}C-NMR ($CDCl_3$): 177.9; 78.5; 44.7; 28.7; 25.9; 20.3; 18.2.

(2E,2′E)-Diethyl 2,2′-{[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethylidene}bis[3-methylbutanoate] (**7**). A soln. of **5** (6.54 g, 30 mmol) in toluene (110 ml) was cooled to −78°. Then 1M DIBAL in hexane (72 ml, 72 mmol) was added slowly, and the mixture was stirred at −78° for 5 h 10 min.

In the meantime, 60% NaH in oil (4.320 g) and THF (50 ml) were cooled to 0° in a seperate flask. Ethyl 2-(diethoxyphosphinyl)-3-methylbutanoate (**6**) was added, and the mixture was stirred at 0° for 2 h 40 min. This mixture was then added slowly to the first reaction flask *via* a syringe. The mixture was stirred for 21 h 40 min, while the temp. slowly rose to r.t. The reaction was quenched by adding H_2O. Extractive workup (AcOEt, 10% citric acid), drying (Na_2SO_4), and FC (hexane/AcOEt 8:1) yielded **7** (9.465 g, 82%) *cis-cis*/*trans-cis*-product 4 to 5:1. ^{1}H-NMR ($CDCl_3$): *cis-cis*-isomer: 5.64–5.72 (*m*, 2 H); 4.74–4.82 (*m*, 2 H); 4.22 (*q*, *J* = 7.2, 4 H); 2.67–2.77 (*m*, 2 H); 1.46 (*s*, 6 H); 1.32 (*t*, *J* = 7.2, 6 H); 1.08 (*t*, *J* = 7.5, 12 H); *trans-cis*-isomer: 6.45 (*d*, *J* = 8.9, 1 H); 5.63–5.71 (*m*, 1 H); 4.74–4.86 (*m*, 1 H); 4.55 (*t*, *J* = 8.4, 1 H); 4.17–4.26 (*m*, 4 H); 2.74–2.79 (*m*, 2 H); 1.49 (*s*, 3 H); 1.47 (*s*, 3 H); 1.29–1.34 (*m*, 6 H); 1.05–1.21 (*m*, 12 H).

(2S,2′S)-4,4′-Bis(1-mehylethyl)[2,2′-bifuran]-5,5′(2H,2′H)-dione (**8**). To **7** (0.850 g, 2.22 mmol; mixture of stereoisomers) in a cooling bath maintained at −10°, CF_3COOH/EtOH 7:3 (*v*/*v*; 30 ml), which had been cooled to −10°, was added slowly. The mixture was stirred for 2 h, while the temp. was allowed to slowly rise to 0°, and after a further 1.5 h stirring, the temp. had reached r.t. Evaporation and FC (hexane/AcOEt 3:1) yielded **8** (0.614 g, 81%). ^{1}H-NMR ($CDCl_3$): 6.93 (*s*, 2 H); 5.18 (*s*, 2 H); 2.69 (*quint.*, *J* = 6.9, 2 H); 1.18 (*d*, *J* = 6.9, 12 H).

(2S,2′S,4R,4′R)-Tetrahydro-4,4′-bis(1-methylethyl)[2,2′-bifuran]-5,5′(2H,2′H)-dione (**9**). To **8** (1.150 g, 4.6 mmol) in EtOH (20 ml), Pd/C (0.46 g) was added, and the mixture was stirred under H_2 (g) for 16 h at r.t. The mixture was filtered through a pad of *Celite*, which was washed with AcOEt and EtOH. The combined filtrate and washings were concentrated. FC (hexane/AcOEt 3:2) yielded **9** (1.170 g, 100%). ^{1}H-NMR ($CDCl_3$): 4.38–4.46 (*m*, 2 H); 2.59–2.69 (*m*, 2 H); 2.18–2.31 (*m*, 4 H); 2.00–2.12 (*m*, 2 H); 1.08 (*d*, *J* = 6.6, 6 H); 0.96 (*d*, *J* = 6.9, 6 H).

*Compound **1** from **9***. To a soln. of **9** (0.136 g, 0.536 mmol) in DMF (10 ml), DBU (0.53 ml, 3.52 mmol) was added, and the mixture was heated to reflux for 12 h. After cooling to r.t., sat. aq. NH_4Cl soln. was added, and the mixture was extracted with $CHCl_3$. The combined org. phase was dried (Na_2SO_4) and concentrated and the residue subjected to FC (hexane/AcOEt 2:1): **1** (0.043 g, 31%).

(4S)-3-(3-Methyl-1-oxobutyl)-4-(phenylmethyl)oxazolidin-2-one (**11**). To (4*S*)-4-benzyloxazolidin-2-one (**10**; 7.09 g) in THF (60 ml), Ph_3CH (30 mg) was added. The soln. was cooled to −78°. 2M BuLi in hexane (20 ml, 40 mmol) was added slowly, and the mixture was stirred for 1 h. Then, 3-methylbutanoyl chloride (7.36 ml, 60 mmol) was added slowly, and the mixture was stirred at −78° for 30 min before it was warmed to r.t. where it was stirred for further 2 h. The reaction was quenched by adding 10% aq. K_2CO_3 soln. Extractive workup (AcOEt-brine), drying (Na_2SO_4), and FC (hexane/AcOEt 4:1) yielded **11** (10.41 g, 100%). FT-IR: 3544, 3381, 3028, 2960, 2873, 2360, 1962, 1782, 1699, 1454, 1389, 1211, 1096. ^{1}H-NMR ($CDCl_3$): 7.20–7.37 (*m*, 5 H); 4.64–4.71 (*m*, 1 H); 4.13–4.23 (*m*, 2 H); 3.32 (*dd*, *J* = 13.4, 3.0, 1 H); 2.71–2.94 (*m*, 3 H); 2.17–2.27 (*m*, 1 H); 0.99–1.04 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 172.7; 153.5; 135.4; 129.4; 129.0; 127.3; 66.1; 55.2; 44.0; 38.0; 25.0; 22.6; 22.5.

(4S)-3-[(2S)-2-(1-Methylethyl)-1-oxopent-4-en-1-yl]-4-(phenylmethyl)oxazolidin-2-one (**12**). To a soln. of **11** (4.31 g, 16.4 mmol) in THF (40 ml) at −78°, 1M NaHMDS in THF (24.7 ml, 24.7 mmol) was added slowly, and the mixture was stirred for 70 min. Allyl bromide (freshly distilled; 4.83 ml, 65.6 mmol) was added and the mixture was stirred for 8.5 h, during which the temp. rose from −78° to −45°. The reaction was quenched by adding sat. aq. NH_4Cl soln. Extractive workup (AcOEt, brine), drying (Na_2SO_4), and FC (hexane/AcOEt 4:1) yielded **12** (4.084 g, 83%). FT-IR: 3081, 2965, 2253, 1778, 1692, 1385. ^{1}H-NMR ($CDCl_3$): 7.24–7.35 (*m*, 5 H); 5.78–5.92 (*m*, 1 H); 5.01–5.15 (*m*, 2 H); 4.69–4.74 (*m*,

1 H); 4.14–4.17 (*m*, 2 H); 3.84–3.92 (*m*, 1 H); 3.33 (*dd*, *J* = 13.4, 3.3, 1 H); 2.66 (*dd*, *J* = 13.3, 10.1, 1 H); 2.41–2.51 (*m*, 2 H); 1.98–2.19 (*m*, 1 H); 1.00 (*d*, *J* = 6.6, 6 H). ^{13}C-NMR ($CDCl_3$): 175.8; 153.3; 135.6; 135.5; 129.5; 128.9; 127.3; 116.9; 65.8; 55.7; 48.2; 38.1; 33.7; 30.3; 20.9; 19.2.

*(2*S*,4*E*,7*S*)-2,7-Bis(1-methylethyl)-1,8-bis[(4*S*)-2-oxo-4-(phenylmethyl)oxazolidin-3-yl]oct-4-ene-1,8-dione* (**13**). To a soln. of **12** (1.528 g, 5.07 mmol) in CH_2Cl_2 (20 ml), *Grubbs* catalyst (2nd generation; 86 mg) was added, and the mixture was heated to reflux for 27 h. Solvent evaporation and FC (hexane/AcOEt 4:1) yielded **13** (1.168 g, 80%). FT-IR: 3022, 2965, 1961, 1779, 1694, 1386, 1349. ^{1}H-NMR ($CDCl_3$): 7.22–7.36 (*m*, 10 H); 5.50–5.54 (*m*, 2 H); 4.63–4.68 (*m*, 2 H); 4.08–4.16 (*m*, 4 H); 3.74–3.81 (*m*, 2 H); 3.33 (*dd*, *J* = 13.1, 3.0, 2 H), 2.68 (*dd*, *J* = 10.2, 10.1, 2 H); 2.28–2.48 (*m*, 4 H); 1.97–1.99 (*m*, 2 H); 0.93 (*t*, *J* = 6.3, 12 H). ^{13}C-NMR ($CDCl_3$): 175.7; 153.3; 135.7; 129.5; 129.4; 129.0; 127.2; 65.8; 55.6; 48.7; 37.9; 32.0; 30.1; 20.8; 19.2.

Compound **1** *from* **13**. A soln. of **13** (3.478 g, 6.05 mmol), OsO_4 (4% aq. soln.; 0.381 g, 0.060 mmol), and 4-methylmorpholine 4-oxide (1.42 g, 12.1 mmol) in acetone/H_2O 8:1 (*v*/*v*; 36 ml) was stirred at r.t. for 21 h. The reaction was quenched by adding $NaHSO_3$ soln. Extractive workup (AcOEt, brine), drying (Na_2SO_4), and FC (hexane/AcOEt 2:1) yielded **1** (0.692 g, 45%).

*(3*S*,5*S*)-Dihydro-5-{(1*S*,3*S*)-1-hydroxy-3-[4-methoxy-3-(3-methoxypropoxy)benzoyl]-4-methylpentyl}-3-(1-methylethyl)furan-2(3*H*)-one* (**14**). To a soln. of 4-bromo-1-methoxy-2-propoxybenzene (0.335 g, 1.22 mmol) in THF (7 ml) at −78°, 1.7M *t*-BuLi in pentane 1.43 ml, 2.44 mmol) was added slowly, and the mixture was stirred at −78° for 1 h 50 min. A soln. of **1** (0.238 g, 0.936 mmol) in THF (6 ml) was also cooled to −78° and added rapidly to the above soln. The entire mixture was stirred at −78° for 19 h. The reaction was quenched by adding sat. aq. NH_4Cl soln. The mixture was extracted with AcOEt. The combined org. phase was dried (Na_2SO_4) and concentrated, and the residue subjected to FC (hexane/AcOEt 2:1): **14** (0.231 g, 55%). FT-IR: 3442, 3018, 2964, 2931, 1760, 1661, 1592, 1514, 1428, 1263, 1130, 1022. ^{1}H-NMR ($CDCl_3$): 7.65 (*dd*, *J* = 8.4, 2.1, 1 H); 7.58 (*d*, *J* = 2.1, 1 H); 6.90 (*d*, *J* = 8.4, 1 H); 4.22–4.30 (*m*, 1 H); 4.19 (*t*, *J* = 6.6, 2 H); 3.94 (*s*, 3 H); 3.64–3.67 (*m*, 1 H); 3.58 (*t*, *J* = 6.0, 2 H); 3.36 (*s*, 3 H); 3.28–3.33 (*m*, 1 H); 2.53–2.59 (*m*, 1 H); 1.98–2.18 (*m*, 8 H); 1.58–1.68 (*m*, 1 H); 1.01 (*d*, *J* = 6.9, 3 H); 0.95 (*d*, *J* = 6.9, 6 H); 0.89 (*d*, *J* = 6.9, 3 H).

*(3*S*,5*S*)-Dihydro-5-{(1*S*,3*S*)-1-hydroxy-3-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-4-methylpentyl}-3-(1-methylethyl)furan-2(3*H*)-one* (**15**). To a soln. of **14** (0.846 g, 1.878 mmol) in MeOH (40 ml), Pd/C (21 mg) was added. The mixture was shaken under 57 psi of H_2 for 67 h. Then, the mixture was filtered through a pad of *Celite*, which was washed with AcOEt, then with MeOH. The combined filtrate and washings were concentrated. FC (hexane/AcOEt 2:1, then 1:1) yielded **15** (0.606 g, 74%). FT-IR: 3413, 3015, 2960, 1982, 1758, 1514, 1466, 1218. ^{1}H-NMR ($CDCl_3$): 6.68–6.79 (*m*, 3 H); 4.16–4.21 (*m*, 1 H); 4.10 (*t*, *J* = 6.6, 2 H); 3.84 (*s*, 3 H); 3.58 (*t*, *J* = 6.0, 2 H); 3.36 (*s*, 3 H); 3.35–3.36 (*m*, 1 H); 2.48–2.58 (*m*, 3 H); 1.96–2.19 (*m*, 5 H); 1.72–1.90 (*m*, 3 H); 1.50–1.60 (*m*, 1 H); 1.25–1.31 (*m*, 1 H); 1.01 (*d*, *J* = 6.9, 3 H); 0.89 (*d*, *J* = 6.9, 3 H); 0.86–0.90 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 179.0; 148.3; 147.6; 121.2; 114.2; 111.6; 82.0; 72.3; 69.4; 66.1; 58.7; 56.0; 45.6; 41.5; 37.5; 33.8; 29.5; 29.0; 26.2; 20.3; 19.9; 18.4; 17.5.

*(1*S*,3*S*)-3-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-4-methyl-1-[(2*S*,4*S*)-tetrahydro-4-isopropyl-5-oxo-furan-2-yl]pentyl Methanesulfonate* (= *(3*S*,5*S*)-Dihydro-5-{(1*S*,3*S*)-3-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-4-methyl-1-[(methylsulfonyl)oxy]pentyl}-3-(1-methylethyl)furan-2(3*H*)-one*; **16**). To a soln. of **15** (0.360 g, 0.826 mmol) in CH_2Cl_2 (15 ml) at −10°, Et_3N (0.576 ml, 4.132 mmol) was added, followed by a CH_2Cl_2 (5 ml) soln. of MsCl (0.195 ml, 2.479 mmol). The mixture was stirred at 0° for 2 h. The reaction was quenched by adding H_2O, and the mixture was extracted with AcOEt. The combined org. phase was dried (Na_2SO_4) and concentrated. FC (hexane/AcOEt 2:1) yielded **16** (0.412 g, 100%). FT-IR: 3019, 2961, 1971, 1774, 1514, 1466, 1350, 1216, 1171, 1028. ^{1}H-NMR ($CDCl_3$): 6.70–6.84 (*m*, 3 H); 4.54–4.60 (*m*, 1 H); 4.33–4.40 (*m*, 1 H); 4.12 (*t*, *J* = 6.0, 2 H); 3.84 (*s*, 3 H); 3.58 (*t*, *J* = 6.3, 2 H); 3.36 (*s*, 3 H), 3.13 (*s*, 3 H); 2.44–2.59 (*m*, 3 H); 1.90–2.16 (*m*, 5 H); 1.69–1.86 (*m*, 3 H); 1.30–1.39 (*m*, 1 H); 1.02 (*d*, *J* = 6.9, 3 H); 0.93 (*d*, *J* = 6.9, 3 H); 0.85–0.95 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 177.5; 148.4; 147.7; 132.9; 121.2; 114.2; 111.6; 82.8; 78.5; 69.4; 65.9; 58.6; 56.1; 44.8; 41.1; 39.1; 37.4; 31.3; 29.5; 28.9; 28.6; 26.4; 20.2; 20.0; 18.4; 16.9.

*(3*S*,5*S*)-5-{(1*R*,3*S*)-1-Bromo-3-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-4-methylpentyl}-dihydro-3-(1-methylethyl)furan-2(3*H*)-one* (**17**). To a soln. of **16** (0.052 g, 0.104 mmol) in THF (8 ml), LiBr (0.052 g, 0.60 mmol) was added. The mixture was heated to reflux for 23 h. The reaction was

quenched by adding H_2O, and the mixture was extracted with AcOEt. The combined org. phase was dried (Na_2SO_4) and concentrated. FC (hexane/AcOEt 2:1) yielded **17** (0.029 g, 57%). FT-IR: 2960, 1963, 1774, 1589, 1514, 1466, 1259, 1139, 1028. ^{1}H-NMR ($CDCl_3$): 6.81 (*d*, *J* = 8.1, 1 H); 6.68–6.74 (*m*, 2 H); 4.32–4.39 (*m*, 1 H), 4.13 (*t*, *J* = 7.2, 2 H); 4.00–4.01 (*m*, 1 H); 3.86 (*s*, 3 H); 3.60 (*t*, *J* = 6.0, 2 H); 3.38 (*s*, 3 H); 2.76 (*dd*, *J* = 13.8, 4.2, 1 H); 2.59–2.67 (*m*, 1 H); 2.08–2.27 (*m*, 6 H); 1.79–1.98 (*m*, 3 H); 1.57–1.66 (*m*, 1 H); 0.86–1.05 (*m*, 12 H).

*(3*S*,5*S*)-5-{(1*S*,3*S*)-1-Azido-3-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-4-methylpentyl}-dihydro-3-(1-methylethyl)furan-2(3*H*)-one* (**18**). To a soln. of **17** (0.029 g, 0.059 mmol) in DMF (5 ml), NaN_3 (0.038 g, 0.588 mmol) was added. The mixture was heated to 90° and stirred at 90° for 48 h. The mixture was concentrated. Extractive workup (AcOEt, H_2O) was followed by FC (hexane/AcOEt 2:1): **18** (0.0096 g, 35%). FT-IR: 3019, 2961, 2111, 1965, 1770, 1514, 1216, 1027. ^{1}H-NMR ($CDCl_3$): 6.70–6.83 (*m*, 3 H); 4.25–4.28 (*m*, 1 H); 4.10 (*t*, *J* = 6.3, 2 H); 3.84 (*s*, 3 H); 3.58 (*t*, *J* = 6, 2 H); 3.36 (*s*, 3 H); 2.92–2.98 (*m*, 1 H); 2.56–2.65 (*m*, 2 H); 2.43–2.51 (*m*, 1 H); 1.90–2.19 (*m*, 5 H); 1.66–1.83 (*m*, 3 H); 1.31–1.42 (*m*, 1 H); 0.90–1.04 (*m*, 12 H).

*(2*S*,4*S*,5*S*,7*S*)-*N*-(3-Amino-2,2-dimethyl-3-oxopropyl)-5-azido-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide* (*= (*αS*,*γS*,*δS*,*ζS*)-*N*-(3-Amino-2,2-dimethyl-3-oxopropyl)-δ-azido-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)benzeneoctanamide*; **19**). A mixture of **18** (0.0082 g, 0.018 mmol), 3-amino-2,2-dimethyl-propanamide (0.031 g, 0.267 mmol), and propanoic acid (4 mg, 0.053 mmol) was heated to 120° without stirring for 1.5 h. The mixture was cooled to r.t. Extractive workup (AcOEt, H_2O) was followed by FC (AcOEt/EtOH 11:1): **19** (0.0089 g, 0.015 mmol, 87%). FT-IR: 3414, 3356, 3019, 2962, 2400, 2110, 1962, 1666, 1514, 1470, 1216. ^{1}H-NMR ($CDCl_3$): 6.72–6.82 (*m*, 3 H); 6.40 (*t*, *J* = 6.3, 1 H); 6.00 (*s*, 1 H); 5.39 (*s*, 1 H); 4.13 (*t*, *J* = 6.6, 2 H); 3.86 (*s*, 3 H); 3.60 (*t*, *J* = 6.3, 2 H); 3.38 (*s*, 3 H); 3.32–3.45 (*m*, 3 H); 3.04–3.06 (*m*, 1 H); 2.88–2.92 (*m*, 1 H); 2.49–2.54 (*m*, 2 H); 2.06–2.16 (*m*, 3 H); 1.85–1.95 (*m*, 1 H); 1.54–1.79 (*m*, 5 H); 1.30–1.39 (*m*, 1 H); 1.25 (*s*, 6 H); 0.88–0.96 (*m*, 12 H).

*(2*S*,4*S*,5*S*,7*S*)-5-Amino*-*N*-*(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide* (*= Aliskiren = (*αS*,*γS*,*δS*,*ζS*)-δ-Amino*-*N*-*(3-amino-2,2-dimethyl-3-oxopropyl)-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)-benzeneoctanamide*; **20**). To **19** (20 mg, 0.034 mmol) and MeOH (2.5 ml), Pd/C (10 mg) was added, and the mixture was stirred under H_2 (g) for 3 h at r.t. Then, the mixture was filtered through a pad of *Celite*, which was washed with EtOH, then with MeOH. The combined filtrate and washings were concentrated. FC (EtOH/Et_2O 4:1) yielded **20** (0.007 g, 38%). ^{1}H-NMR (CD_3OD): 6.75–6.87 (*m*, 3 H); 4.08 (*t*, *J* = 6.3, 2 H); 3.82 (*s*, 3 H); 3.60 (*t*, *J* = 6.3, 2 H); 3.31–3.37 (*m*, 5 H); 3.10–3.15 (*m*, 1 H); 2.43–2.54 (*m*, 3 H); 2.20–2.30 (*m*, 1 H); 2.04 (*quint.*, *J* = 6.3, 2 H); 1.60–1.82 (*m*, 4 H); 1.27–1.47 (*m*, 3 H); 1.20 (*s*, 6 H); 0.90–0.98 (*m*, 12 H).

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