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A Total Synthesis of Aliskiren Starting from D-Tartrate Diester

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A formal total synthesis of aliskiren was accomplished. A key in our synthesis was to use the symmetric *cis-cisoid-cis*-bis-lactone **3'** as a precursor, which was prepared from D-tartrate diester. Appending the end groups and functional group transformations completed the synthesis.

Key Words : Aliskiren, Total synthesis, D-tartrate diester, Symmetric precursor

Introduction

Aliskiren is the first orally active, non-peptidic renin inhibitor, effective for treatment of hypertension.[1] It is currently marketed under the trade name Tekturna and Rasilez. 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, -4, -5 and C-7. A popular approach to address these stereochemical issues is to install the stereogenic centers, one at a time, using chiral auxiliary groups.[2-5] While this is a straightforward approach as far as the stereochemical control is concerned, it is perhaps not a very economical one as multiple, independent operations are needed for the stereocontrol of the four stereogenic centers. The original Novartis synthesis, for example, employed the Evans (twice) and Schöllkopf auxiliary groups to set up three of the four stereogenic centers.[2]

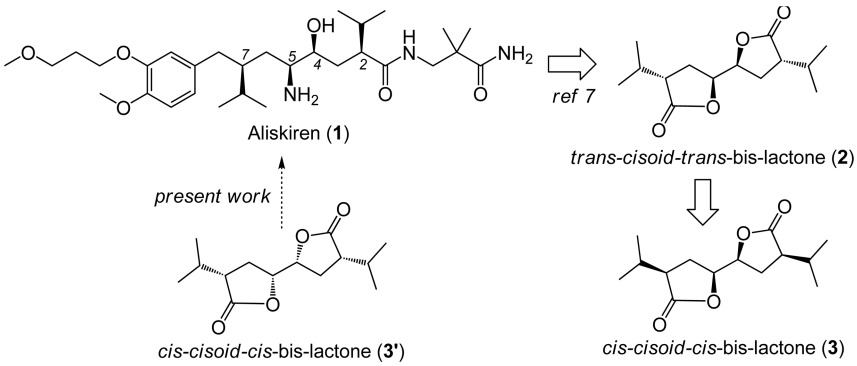
A more efficient strategy would be to recognize some sorts of connections among the four stereogenic centers so that fewer than four independent asymmetric operations would be sufficient for the full stereocontrols.

Hanessian reported two very distinct synthetic approaches to aliskiren, which serve as good examples of efficient stereocontrols.[6] In the first, an amino acid chiral pool starting material was converted to the aliskiren skeleton. In the process, the N-functionalized stereocenter at C-5 had been given in the starting material; all the other stereocenters incorporated sequentially in highly diastereoselective asymmetric induction steps. In the second approach, a single enantiopure compound, with the isopropyl group already in place with the correct configuration (*S*), was converted to two different fragments, which were then joined. The ^{i}Pr-substituted stereogenic centers at C-2 and C-7 were thus set up from a single source. The remaining stereogenic centers were subsequently installed in highly stereoselective transformations to yield the target alsikiren.

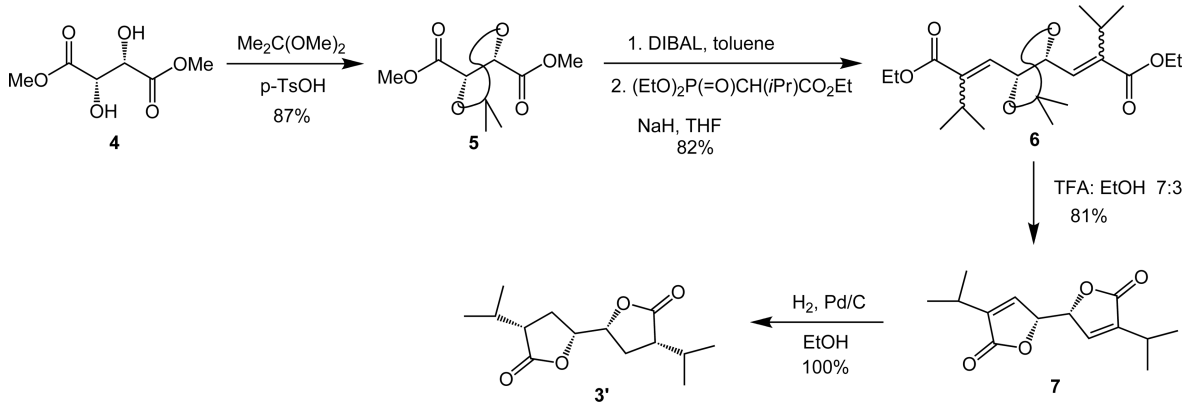
Our efforts in the field of aliskiren synthesis resulted in a synthetic approach in which we noted a "pseudo-symmetric" nature of the octanoic acid backbone and employed a symmetric intermediate, which was later desymmetrized by sequentially introducing the end groups to yield aliskiren (Scheme 1).[7] Stemming from this work, another synthetic pathway has emerged, which is in some aspects parallel with the first route, but distinct in its stereochemical considerations, and in our opinion is more efficient than the first route. Disclosed herein is our second synthetic route to alsikiren.

Results and Discussions

The intermediate that we employed in our first synthesis was *trans-cisoid-trans*-bis-lactone **2**, the symmetric nature of which allowed us to install the stereogenic centers in very economical ways. The (*S*)-configurations at the ^{i}Pr-substituted stereogenic centers in **2** were the correct ones to be found at the C-2 and C-7 of the central octanoic acid portion of aliskiren, while the (*S*)-configurations at the two O-substituted



Scheme 1. Synthetic Strategies for Aliskiren from the symmetric precursors **2** and **3'**.



Scheme 2. Synthesis of the symmetric cis-cisoid-cis-bis-lactone precursor **3'**.

stereogenic centers in **2** meant that one of the oxygen functions needed to be converted to an amino group *via* double inversion to form the 4*S*,5*S*-hydroxyamino portion of aliskiren.

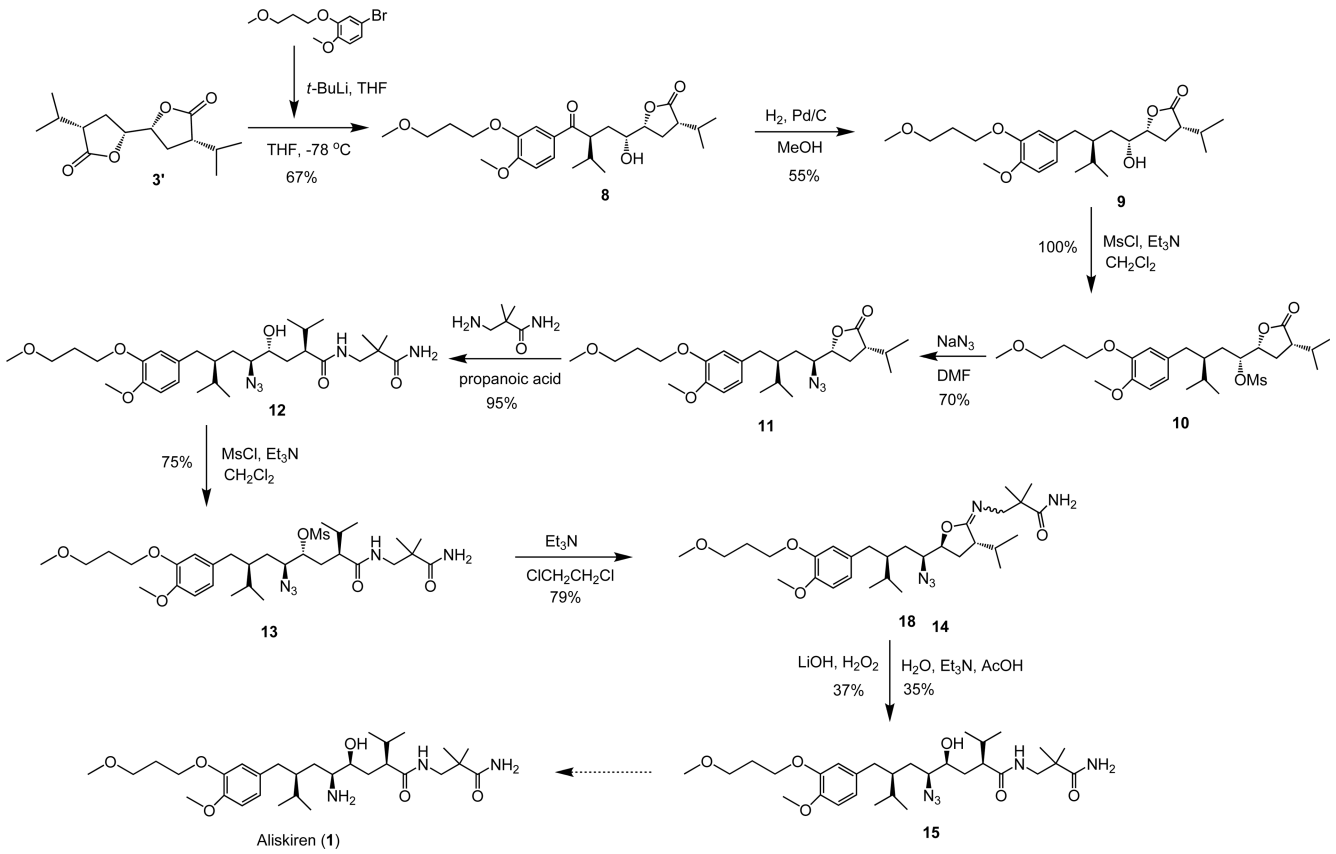
We worked out several synthetic pathways for the symmetric intermediate **2**, some of which involved *cis-cisoid-cis*-bis-lactone diastereomer **3**, either as a precursor to **2** or as a by-product in the production of **2**. Clearly, the *cis-cisoid-cis* diastereomer **3** was synthetically more easily accessible than the *trans-cisoid-trans* counterpart **2**, and seemed to be a more attractive intermediate for aliskiren. The (*S*)-configurations at the two ^{i}Pr-substituted stereogenic centers in aliskiren meant that (2*R*,2'*R*,4*S*,4'*S*)-tetrahydro-4,4'-bisisopropyl-2,2'-bifuran-5,5'(2*H*,2'*H*)-dione (**3'**, the antipodal enantiomer of **3**) was the one we required for aliskiren synthesis (Scheme 1). The 4*S*,5*S*-hydroxyamino portion of aliskiren would then require the two O-substituted stereogenic centers [(*R*) in **3'**] to be inverted at *both* carbons in the process of diol to hydroxylamine transformation – in principle, same number of steps as in our earlier synthesis of aliskiren *via* the *trans-cisoid-trans*-bis-lactone intermediate **2**.[8]

A very efficient synthetic pathway for the *cis-cisoid-cis*-bis-lactone intermediate was to start from tartrate diester. The (2*R*,2'*R*,4*S*,4'*S*)-stereoisomer **3'** that we required in the present synthesis was prepared from dimethyl (D)-tartrate diester starting material (Scheme 2). The diol function was protected as acetonide (dimethoxypropane, p-TsOH, 87%). Reduction (DIBAL) followed by the Horner-Emmons-Wadsworth reaction [$(EtO)_2P(=O)$-CH($CHMe_2$)-COOEt], without isolating the dialdehyde intermediate, gave the C-8 skeleton as the mixture of *cis/trans* isomers (**6**, 82% overall), in which the *cis,cis*-isomer was the major (4 to 5:1).[9] Upon deprotection of the diol function (TFA/EtOH), only the *cis,cis*-isomer underwent double cyclization to produce bis-lactone **7** (81%). Reduction (H_2, Pd/C) took place *anti* to the existing substituent to produce the *cis-cisoid-cis*-bis-lactone **3'** (100%). When the hydrogenation was performed *before* the diol deprotection, the bis-lactone compound was obtained as a mixture of diastereomers. Attempts were made to siphon these diastereomeric mixture into the desired *cis-cisoid-cis*-bis-lactone by enolate formation/kinetic protonation sequence, but the overall results were not as satisfactory as the one obtained *via* diastereoselective hydrogenation procedure.

The key intermediate **3'** was now in hand, and the end groups would need to be appended, which was accomplished by generally following the sequence of reactions established in our previous synthesis of aliskiren (Scheme 3).[7] Thus, the right-hand side aryl group was introduced *via* ring-opening of the one of the bis-lactone rings by ArLi (**8**, 67%). Deoxygenation from benzoyl to benzyl then followed (H_2, Pd/C, **9**, 55%). The OH function, which had been released during the lactone opening reaction, needed to be converted to the amino function of aliskiren with the (*S*)-configuration at C-5, *i.e.*, with an inversion of configuration. The hydroxyl group was therefore activated (MsCl, Et_3N, **10**, 100%), then replaced by azide (NaN_3, **11**, 70%). The remaining lactone ring was then opened by the right-hand side amino group (3-amino-2,2-dimethylpropanamide, propanoic acid, **12**, 95%).[10] The intermediate **12** now had all the appearances of aliskiren except for two aspects: the configuration of the OH-bonded C-4 needed to be inverted; and of course the reduction of the C-5 N_3 group.

In order to invert the configuration at C-4, the hydroxyl group was activated (MsCl, Et_3N, **13**, 75%). The reaction needed to be carefully monitored to ensure the maximum yield of the mesylate; longer reaction time resulted in a side reaction (conversion of the terminal amide function to nitrile, which could be hydrolyzed back to the amide group later, if necessary). The C-4 center having been activated, we could have used any external oxygen nucleophile to install the O-function with the required (*S*)-configuration. Instead, we enlisted the neighboring amide function as a source of the O-nucleophile in an atom-economic intramolecular nucleophilic substitution reaction. Thus, the mesylate **13** was treated with Et_3N to yield the iminolactone (**14**, a mixture of *cis/trans* isomers, 79%), in which the configuration at C-4 had been inverted to (S).[11] Hydrolysis (either by LiOH, H_2O_2, 37%; or by H_2O, AcOH, Et_3N, 35%) opened the iminolactone ring to yield the hydroxyazide compound **15**, which was identical in every aspect to the one reported earlier by our laboratories,[7] and just one step (reduction) away from aliskiren.

Thus, we completed a formal synthesis of aliskiren, start-



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

ing from D-tartrate diester and employing symmetric *cis-cisoid-cis*-bis-lactone intermediate. The *cis-cisoid-cis*-isomer (**3'**) is synthetically more easily accessible than the *trans-cisoid-trans*-diastereomer (**2**) that we employed in our earlier aliskiren synthesis. The two pathways then proceed in parallel, and following stereochemical adjustments, to produce aliskiren.

Experimental Part

General Information. Reactions were monitored by TLC on silica gel glass-backed plates. Proton (250 or 300 MHz) and ^{13}C NMR (62.5 or 75 MHz) spectra were recorded in ppm relative to TMS as an internal standard. The following abbreviations designate splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublet), m (multiplet), br (broad). IR spectra were recorded as thin films on KRS-5 plates.

(2*R*,2'*R*,4*R*,4'*R*)-4,4'-Diisopropyl-tetrahydro-2,2'-bifuran-5,5'(2*H*,2'*H*)-dione (Compound 3'). This compound was prepared following the same sequence as reported earlier for the (2*S*,2'*S*,4*S*,4'*S*)-isomer **3**.[7]

FT-IR: 3597, 3021, 2963, 2876, 2461, 2413, 2340, 1780, 1468, 1372, 1338, 1297, 1158, 1044, 1015, 974, 934, 750, 710, 667, 564, 491. ^{1}H NMR ($CDCl_3$) δ 4.37-4.44 (m, 2H), 2.60-2.69 (m, 2H), 2.23-2.28 (m, 4H), 2.00-2.16 (m, 2H), 1.08 (d, 6H, J = 6.6 Hz), 0.96 (d, 6H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 176.8, 77.0, 46.4, 27.7, 25.8, 20.6, 18.3.

(3*S*,5*R*)-5-((1*R*,3*S*)-1-Hydroxy-3-(4-methoxy-3-(methoxymethoxy)benzoyl)-4-methylpentyl)-3-isopropyl-dihydrofuran-2(3*H*)-one (8). 4-Bromo-1-methoxy-2-propoxybenzene (0.609 g, 2.37mmol) was dissolved in THF (3 mL) and the solution was cooled to −78 °C. *t*-BuLi (1.7 M in pentane, 2.76 mL, 4.7 mmol) was added slowly and the mixture was stirred at −78 °C for 2 h. It was added slowly to a solution of compound **3'** (0.427 g, 1.68 mmol) in THF (6 mL), which had also been cooled to −78 °C. The entire mixture was stirred at −78 °C for 4 h. The reaction was quenched by adding sat'd aq. NH_4Cl solution. The mixture was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated. Flash silica column chromatographic purification (Hexane-EtOAc 1:1) yielded compound **8** (0.506 g, 1.12 mmol, 67%), together with the recovered starting material **3'** (0.076 g, 0.3 mmol, 18%).

^{1}H NMR ($CDCl_3$) δ 7.62-7.59 (1H, d, 1H, d), 6.91-6.88 (1H, d, J = 8.7 Hz), 4.21-4.09 (2H, t, 1H, m), 3.95 (3H, s), 3.93-3.53 (2H, t), 3.52-3.48 (1H, m), 2.65-2.54 (1H, m), 2.26-1.99 (7H, m), 1.93-1.72 (2H, m), 1.04-1.97 (6H, m), 0.92-0.88 (6H, m).

(3*S*,5*R*)-5-((1*R*,3*S*)-1-Hydroxy-3-(4-methoxy-3-(methoxymethoxy)benzyl)-4-methylpentyl)-3-isopropyl-dihydrofuran-2(3*H*)-one (9). Compound **8** (0.170 g, 0.38 mmol) was dissolved in MeOH (13 mL). Pd/C (86 mg) was added. The mixture was shaken under 55psi of H_2 for 60 h. It was filtered through a pad of Celite, which was then washed with EtOAc, then with MeOH. The combined filtrate and wash-

ings were concentrated. Flash silica column chromatographic purification (Hexane-EtOAc 3:2) yielded compound **9** (0.091 g, 0.21 mmol, 55%).

FT-IR: 3440, 2959, 2931, 2874, 1963, 1765, 1514, 1466, 1260, 1024, 753. ^{1}H NMR ($CDCl_3$) δ 6.79-6.67 (3H, m), 4.17-4.09 (1H, 2H, m, t), 3.84 (3H, s), 3.61-3.49 (2H, 1H, t, m), 3.36 (3H, s), 2.71 (1H, dd, J_1 = 13.8, J_2 = 5.1), 2.61-2.53 (1H, m), 2.30-1.98 (5H, m), 1.93-1.78 (3H, m), 1.42-1.40 (2H, t, J = 7.2), 1.01-0.98 (6H, m), 0.91-0.87 (6H, m). ^{13}C NMR ($CDCl_3$) δ 177.7, 148.2, 147.6, 133.9, 121.2, 114.2, 111.8, 81.0, 77.4, 76.7, 71.4, 69.3, 66.0, 58.6, 56.0, 46.7, 41.5, 36.2, 33.6, 31.6, 29.5, 28.5, 27.5, 25.9, 20.5, 19.6, 18.1, 17.7, 14.1.

(1*R*,3*S*)-1-((2*R*,4*S*)-4-Isopropyl-5-oxo-tetrahydrofuran-2-yl)-3-(4-methoxy-3-(methoxymethoxy)benzyl)-4-methylpentyl methanesulfonate (10). Compound **9** (0.348 g, 0.80 mmol) was dissolved in CH_2Cl_2 (8 mL). Et_3N (0.39 mL, 2.24 mmol) was added, followed by MsCl (0.21 mL, 2.24 mmol). The mixture was stirred at room temperature for 70 min. The reaction was quenched by adding H_2O. It was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. Flash silica column chromatographic purification (Hexane-EtOAc 3:2) yielded compound **10** (0.411 g, 0.80 mmol, 100%).

FT-IR: 3597, 2959, 2928, 2342, 2014, 1980, 1778, 1514, 1465, 1369, 1258, 1159, 1080, 1027. ^{1}H NMR ($CDCl_3$) δ 6.78-6.69 (3H, m), 4.70-4.63 (1H, m), 4.30-4.27 (1H, m) 4.13-4.10 (2H, m), 3.85 (3H, s), 3.58 (2H, t, J = 6.3), 3.36 (3H, s), 3.06 (3H, s), 2.75 (1H, dd, J_1 = 13.2, J_2 = 3.9), 2.59-2.51 (1H, m), 2.15-2.08 (3H, m), 2.21-1.87 (3H, m), 1.68-1.53 (2H, sm), 1.30-1.20 (2H, m), 1.04-1.02 (6H, m), 0.92-0.88 (6H, m). ^{13}C NMR ($CDCl_3$) δ 176.4, 148.4, 147.6, 133.3, 122.0 121.2, 114.1, 111.7, 81.7, 77.3, 69.4, 66.0, 58.9, 58.7, 56.0, 46.3, 40.8, 39.0, 35.7, 29.6, 28.7, 27.5, 26.6, 20.5, 19.7, 18.1, 17.3.

(3*S*,5*R*)-5-((1*S*,3*S*)-1-Azido-3-(4-methoxy-3-(methoxymethoxy)benzyl)-4-methylpentyl)-3-isopropyl-dihydrofuran-2(3*H*)-one (11). Compound **10** (0.128 g, 0.24 mmol) was dissolved in DMF (10 mL). NaN_3 (0.650 g, 2.4 mmol) was added. The mixture was heated to 80 °C and stirred at that temperature for 25 h. The mixture was concentrated. Extractive work-up (EtOAc-H_2O) was followed by flash silica column chromatographic purification (Hexane-EtOAc 3:2) to yield compound **11** (0.078 g, 0.17 mmol, 70%).

FT-IR: 3521, 3052, 2959, 2356, 2110, 1967, 1776, 1515, 1261, 1237, 1020. ^{1}H NMR ($CDCl_3$) δ 6.79 (1H, d, J = 7.8 Hz), 6.72-6.69 (2H, m), 4.16-4.08 (1H, m, 2H, t), 3.83 (3H, s), 3.58 (2H, t, J = 6.3 Hz), 3.36 (3H, s), 2.65-2.60 (1H, m), 2.58-2.49 (1H, m), 2.48-2.37 (1H, m), 2.12-2.05 (3H, m), 1.99-1.87 (1H, m) 1.78-1.70 (3H, m), 1.42-1.38 (2H, m), 1.02 (3H, d, J = 6.9), 0.92-0.90 (9H, m). ^{13}C NMR ($CDCl_3$) δ 177.0, 148.6, 147.9, 133.4, 121.2, 114.0, 111.8, 79.2, 69.3, 66.1, 62.9, 58.7, 56.0, 46.3, 42.3, 37.4, 31.7, 30.3, 29.6, 27.6, 25.0, 20.5, 19.5, 18.0, 18.0.

(2*S*,4*R*,5*S*,7*S*)-*N*-(3-Amino-2,2-dimethyl-3-oxopropyl)-5-azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(methoxymethoxy)benzyl)-8-methylnonanamide (12). A mixture of compound **11** (0.079 g, 0.17 mmol), 3-amino-2,2-dimethylpropionamide (0.28 g, 2.4 mmol), and propanoic acid (0.035 mL, 0.48 mmol) was heated to 110 °C without stirring for 2 h. It was cooled to rt. Extractive work-up (EtOAc-H_2O) was followed by flash silica column chromatographic purification (EtOAc-EtOH 20:1) to yield compound **12** (0.094 g, 0.16 mmol, 95%).

FT-IR: 3477, 3265, 2962, 2356, 2323, 2105, 1941, 1668, 1516, 1372, 1234. ^{1}H NMR ($CDCl_3$) δ 6.83-6.70 (3H, m), 6.48 (1H, s), 6.01 (1H, s), 5.49 (1H, s), 4.12 (2H, t, J = 6.6 Hz), 3.85 (3H, s), 3.59 (2H, t, J = 6.6 Hz), 3.38 (1H, m), 3.41-3.39 (2H, d, J = 6.3 Hz), 3.37 (3H, s), 3.19 (1H, d, J = 5.1 Hz), 3.12-3.08 (1H, m), 2.59-2.42 (2H, m), 2.12-2.06 (2H, m), 1.90-1.74 (5H, m), 1.55-1.50 (2H, m), 1.42-1.31 (2H, m), 1.26 (12H, m). ^{13}C NMR ($CDCl_3$) δ 180.1, 176.4, 148.3, 147.7, 133.9, 121.3, 114.3, 111.8, 69.4, 66.1, 65.6, 58.6, 56.1, 47.3, 43.0, 42.6, 31.3, 29.6, 24.3, 20.5, 20.4, 19.7, 19.7, 19.6, 17.8, 17.7.

(3*S*,5*R*,6*S*,8*S*)-3-(3-Amino-2,2-dimethyl-3-oxopropylcarbamoyl)-6-azido-8-(4-methoxy-3-(methoxymethoxy)benzyl)-2,9-dimethyldecan-5-yl methanesulfonate (13). Compound **12** (0.116 g, 0.20 mmol) was dissolved in CH_2Cl_2 (15 mL). Et_3N (0.307 mL, 2 mmol) and MsCl (0.127 mL, 1.5 mmol) were added and the mixture was stirred at rt for 20 min. The reaction was quenched by adding H_2O. It was extracted with $CHCl_3$ (four times), then with EtOAc (three times). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash silica column chromatographic purification (EtOAc:EtOH = 20:1) yielded compound **13** (0.099 g, 0.15 mmol, 75%). ^{1}H NMR ($CDCl_3$) δ 6.85-6.71 (3H, m), 6.31-6.26 (2H, m), 5.40 (1H, s), 4.59-4.10 (1H, m), 4.08 (2H, t, J = 6.6), 3.81 (3H, s), 3.55 (2H, t, J = 6.6), 3.41-3.39 (1H, m), 3.37-3.28 (3H, s, 1H, m) 3.05 (3H, s), 2.64-2.57 (1H, m), 2.40-2.30 (1H, m), 2.15-2.05 (3H, m) 1.78-1.72 (4H, m), 1.64-1.62 (1H, m), 1.51-1.50 (1H, m), 1.40-1.22 (2H, m), 1.20 (6H, s), 0.88-0.85 (12H, m). ^{13}C NMR ($CDCl_3$) δ 179.7, 174.5, 148.5, 147.8, 133.5, 121.1, 114.0, 112.0, 83.5, 69.3, 66.0, 58.6, 56.0, 45.2, 42.9, 38.8, 30.8, 29.5, 24.2, 20.2, 19.9, 19.3, 18.2, 9.3, 8.6.

3-((3*S*,5*S*)-5-((1*S*,3*S*)-1-Azido-3-(4-methoxy-3-(methoxymethoxy)benzyl)-4-methylpentyl)-3-isopropyl-dihydrofuran-2(3*H*)-ylidene)amino)-2,2-dimethylpropanamide (14). Compound **13** (0.099 g, 0.15 mmol) was dissolved in 1,2-dichloroethane (3 mL) and Et_3N (1 mL) was added. The mixture was heated to 80 °C for 21 h. The reaction was quenched by adding H_2O. It was extracted with $CHCl_3$ (four times), then with EtOAc (three times). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash silica column chromatographic purification (EtOAc:EtOH = 16:1) yielded compound **14** as a mixture of isomers (0.066 g, 0.117 mmol, 79%).

FT-IR: 3739, 3684, 3546, 3465, 3367, 3960, 2932, 2874, 2370, 2109, 1710, 1665, 1591, 1514, 1466, 1390, 1369, 1260, 1184, 1138, 1027. ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, s), 6.97-6.68 (3H, m), 5.28 (1H, s), 4.30-4.20 (1H, m), 4.10 (2H, t, J = 6.5), 3.83 (3H, s), 3.58 (2H, t, J = 6.3), 3.36 (3H, s), 3.30-2.80 (2H, d, J = 7.8 Hz), 3.11-2.8 (1H, m), 2.70-2.53

(1H, m, 1H, m), 2.50-2.40 (1H, m), 2.15-1.85 (4H, m), 1.85-1.78 (3H, m), 1.60-1.50 (1H, m), 1.28 (2H, s), 1.16 (6H, s), 1.12-0.99 (3H, m), 0.94-0.91 (9H, m). ^{13}C NMR ($CDCl_3$) δ 181.2, 164.1, 148.5, 147.9, 133.5, 121.1, 114.1, 111.8, 83.3, 77.1, 69.6, 66.1, 64.5, 58.6, 56.1, 55.2, 46.0, 42.1, 41.9, 37.5, 31.5, 29.6, 28.0, 24.5, 24.3, 20.5, 19.6, 18.0, 17.8.

(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-(methoxymethoxy)benzyl)-8-methylnonanamide (15). Compound **14** (0.061 g, 0.11 mmol) was dissolved in THF (18 mL). H_2O (11.5 mL), H_2O_2 (15 mL) were added followed by LiOH (0.178 g, 7.45 mmol). The mixture was heated to 55 °C for 6 days. The reaction was quenched by adding $NaHSO_3$. The mixture was extracted with EtOAc. Flash silica column chromatography (EtOAc:EtOH = 25:1) yielded compound **15** (0.023 g, 0.040 mmol, 37%).

Alternatively, compound **14** (0.036 g, 0.064 mmol) was dissolved in THF (3 mL). Water (2 mL), Et_3N (0.0358 mL, 0.257 mmol) and AcOH (0.0088 mL, 0.154 mmol) were added. The mixture was stirred at rt for 18 h. The reaction was quenched by adding water. The mixture was extracted with EtOAc. Flash silica column chromatography (EtOAc: EtOH = 25:1) yielded compound **15** (0.011 g, 0.023 mmol, 35%).

FT-IR: 3414, 3356, 3019, 2962, 2400, 2110, 1962, 1666, 1514, 1470, 1216. ^{1}H NMR ($CDCl_3$) δ 6.81 (1H, d, J = 6.3), 6.76-6.74 (1H, m), 6.71 (1H, s), 6.02 (1H, s), 5.42 (1H, s), 4.12 (2H, t, J = 6.3), 3.85 (3H, s), 3.59 (2H, t, J = 6.3), 3.42-3.39 (2H, m), 3.37 (3H, s), 2.93-2.91 (1H, m), 2.89-2.81 (1H, m), 2.52 (2H, t, J = 7.5), 2.15-2.00 (3H, m), 1.96-1.84 (3H, m), 1.77-1.54 (5H, m), 1.41-1.27 (1H, m), 1.25 (6H, d, J = 4.8), 0.95-0.89 (12H, m).

References and Notes

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