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Tetrahydrofuran as a Scaffold for Peptidomimetics. Application to the Design and Synthesis of Conformationally Constrained Metalloproteinase Inhibitors

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Abstract—Enantiopure functionalized tetrahydrofurans were synthesized as prototypical conformationally constrained analogs of acyclic succinic acid-based inhibitors of metalloproteinases. While preliminary docking study showed good congruence with a potent inhibitor, the biological results were disappointing. Molecular dynamics simulation revealed the weakness of the H-bond interactions.

Introduction

Matrix metalloproteinases (MMPs), such as collagenases, stromelysins and gelatinases, represent a family of zinc-dependent proteinases that are key enzymes implicated in matrix degradation and reconstruction.[1] While the formation of MMPs in tissues is naturally regulated, certain pathological conditions can lead to their overproduction which results in a number of debilitating physiological effects such as tumor progression,[2] arthritis[3] and sclerosis.[4] Consequently, the exploration and development of inhibitors of MMPs have become important areas of research during the past decade, and several inhibitors have been reported with promising clinical profiles.[5] Initially, inhibitors consisted mainly of succinic acid derivatives such as **1** (Batimastat, British Biotech.),[6] **2** (Marimastat, British Biotech.),[7] **3** (Ro32-3555, Roche),[8] **4** (Dupont-Merck),[9] or **5** (D-2163, Chiroscience)[10] (Fig. 1).

A number of sulfonamides or sulfones were also reported with great potential, such as **6** (CGS 27023A, Novartis),[11] **7** (AG3340, Agouron)[12] and **8** (RS 130830, Roche Bioscience).[13] Our own work[14] in this area led to a novel series of sulfonamides **9** and **10** which exhibited low nanomolar inhibitory activity against a number of MMPs (Fig. 2).

The X-ray crystal structures of stromelysin-1 (MMP-3) complexed with a number of natural or synthetic inhibitors[6c,9,15] at resolutions ranging from 1.7 to 2.5 Å, have revealed unique modes of binding. NMR studies of

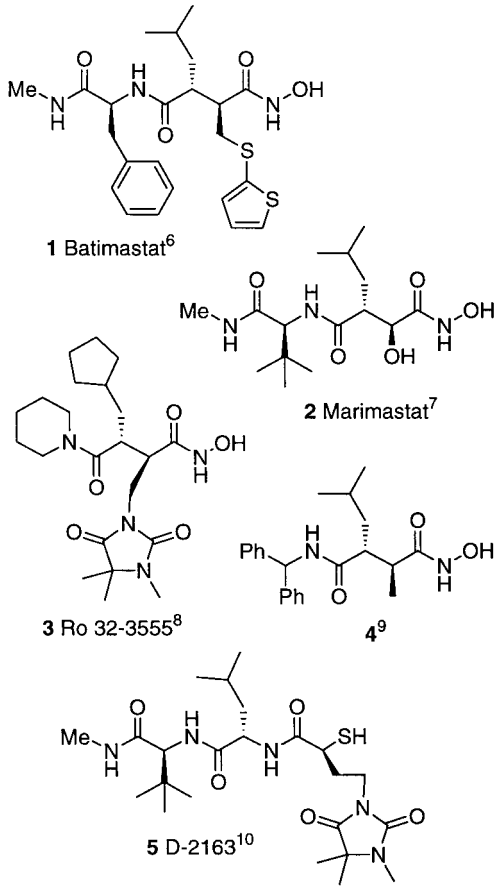

Figure 1. Selected structures of succinic-type MMP inhibitors.

Keywords: peptide mimetics; enzyme inhibitors; molecular modeling; stereocontrol.

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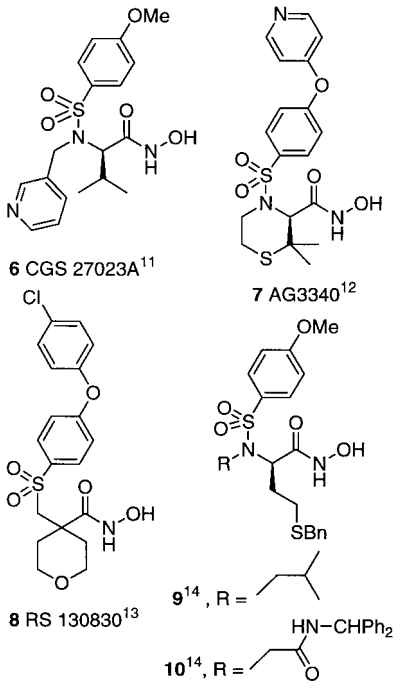


Figure 2. Selected arylsulfone or arylsulfonamide containing MMP inhibitors.

enzyme-inhibitor complexes have also been instrumental in the design of new inhibitors.[16] The three-dimensional view of the active site of MMP-3 and complexes with inhibitors has opened opportunities in the design and synthesis of molecules capable of adopting conformations that are conducive to optimal binding. In principle, this should be a relatively easy task, in view of the obviously accessible regions, and predictably advantageous interactions. For example, the active site of MMP-3 offers a zinc binding site as an anchoring point for an inhibitor harboring appropriately deployed functional groups such as P_1', P_2' and P_1 that can interact with the long narrow S_1' pocket, a shallow hydrophobic S_2' pocket and an exposed promiscious S_1 pocket, respectively (Fig. 3).

Restricting a molecule in its bioactive conformation by imposing rigidity can dramatically enhance its activity.[17] Numerous examples have been reported in which acyclic peptide-like inhibitors of enzymes were modified to non-peptidic counterparts by utilizing heterocyclic scaffolds such as lactams,[18] some of which include an *N*-sulfonyl moiety.[15f,19] In contrast, the synthesis of conformationally constrained succinic-like inhibitors of MMPs have been limited, probably due to the greater stereochemical challenge of assembling cyclic scaffolds with vicinal appendages having specific orientations. Cyclopropane[20a,b] and cyclohexene[20a] derivatives have been disclosed with little or no activity, suggesting that the enzyme has strict

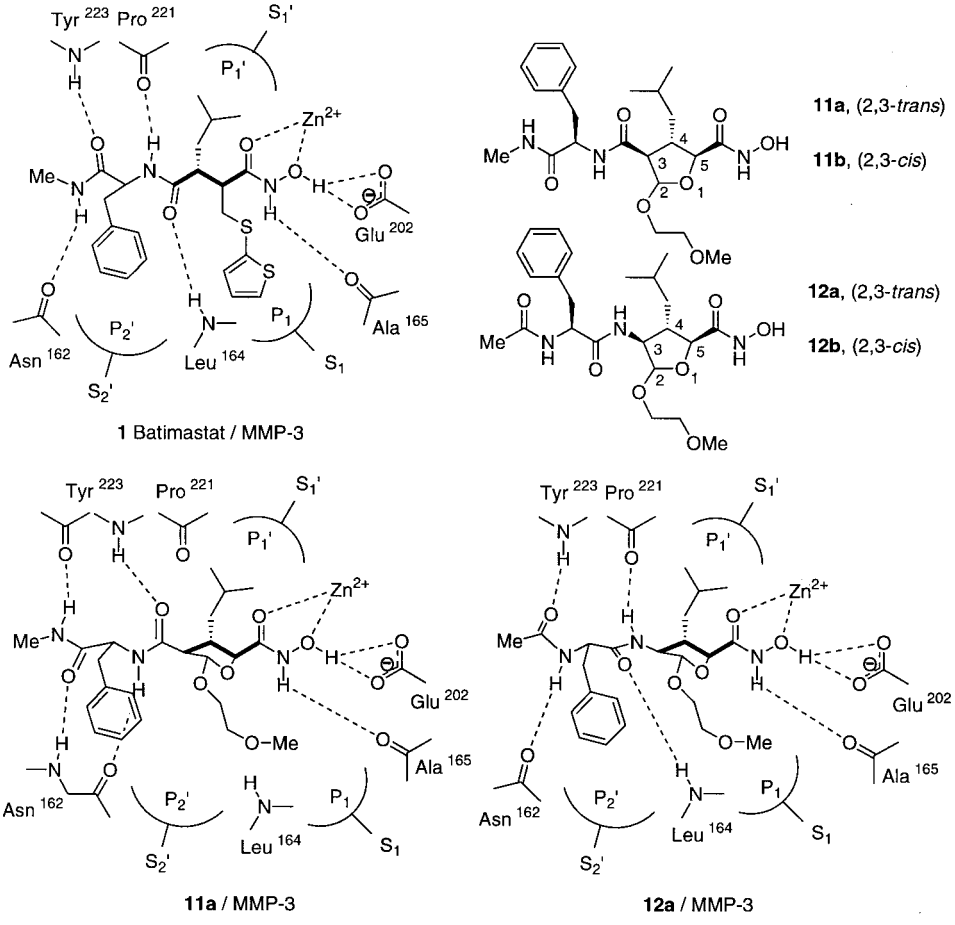


Figure 3. Bioactive conformation of Batimastat 1/MMP-3 complex, and structures of proposed constrained inhibitors **11a**,**b** and **12a**,**b** showing simulated interactions with pertinent sites.

conformational requirements. In contrast, macrocyclic analogs have been reported with excellent inhibitory properties towards several MMPs.[21]

We report herein, our studies on the computer-aided design and synthesis of enantiopure substituted tetrahydrofuran motifs as representative prototypical inhibitors of stromelysin-1 and related MMPs.

Results and Discussion

Molecular modeling and design of a constrained analog

Modeling of Batimastat **1** within the active site of stromelysin-1 was based on the previously reported crystal structure of the catalytic domain of this enzyme bound to the inhibitor L-764,004.[15c] Batimastat was manually docked by analogy to its binding mode in MMP-8.[6c] In order to explore the free energy surface and qualitatively evaluate the stability of the complex, a 100 ps molecular dynamics (MD) trajectory at 300 K was performed in aqueous medium. This resulted in a stable structure along the trajectory.

The results indicated that Batimastat, as with other inhibitors,[9,15] was bound to the catalytic domain with a strong chelation of the zinc atom by the hydroxamic acid moiety and with an hydrogen bond network between the linear main chain of the inhibitor and the surrounding backbone of the enzyme. Furthermore, the two aromatic moieties of the inhibitor acted as a wall, thus excluding water and stabilizing the complex. Indeed, the phenyl ring wedged in between the two lipophilic Val[163] and Leu[222] side-chains could be involved in strong hydrophobic interactions.

With this model in hand, we turned our attention to the design of two constrained analogs built around a tetrasubstituted tetrahydrofuran with a substitution pattern that maximizes interactions with the enzyme (Fig. 3).

We considered the 'normal' amide analog **11a**, the so-called 'reverse' amide analog **12a** and their anomeric variants. In the former case, we opted for a D-Phe rather than an L-Phe moiety (as found in Batimastat) with an amide orientation that could interact favorably to form two hydrogen bonds with Tyr[223] (Fig. 3). The 'reverse' amide analog **12a** incorporated the L-Phe moiety for better H-bond alignment. Thus, the D- and L-Phe and isobutyl moieties in **11a** and **12a** were chosen to represent the P_2' and P_1' sites, and we opted for an appendage containing heteroatoms, such as the methoxyethoxy group to simulate interaction at the P_1 site which is in part solvent exposed.[15]

Analogs **11** and **12** were prepared as individual 2,3-*cis* and 2,3-*trans* anomers (tetrahydrofuran numbering), in order to probe the effect of spatial disposition at the P_1 site. The results of a preliminary docking study of **11** and **12** in the active site of stromelysin were promising. Having reached this conclusion, we undertook the synthesis of **11a** and **12a** (and their respective anomers) in order to validate these predictions for potential activity. During the course of our studies, an excellent study based on molecular modeling of the S_1' subsite of MMP-3 was reported.[22]

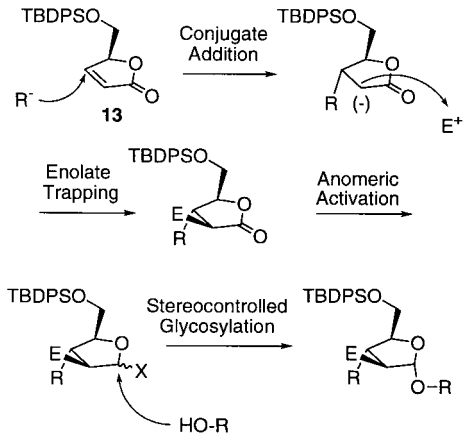
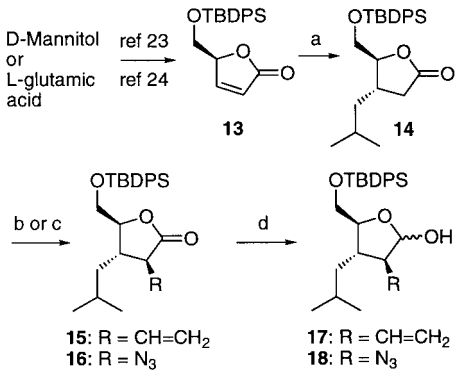


Figure 4. Stereoselective construction of tetrahydrofuran glyconsides.

Synthesis

The synthesis is based on the stereocontrolled functionalization of a suitable chiron **13** readily prepared from D-mannitol[23] or L-glutamic acid[24] (Fig. 4). The use of a bulky protecting group would allow the stereoselective functionalization of the positions 2 and 3 in a stepwise fashion to afford the all *trans* isomer as exemplified in Fig. 4.

Conjugate addition of isobutyl magnesium bromide in the presence of cuprous iodide to **13** furnished **14** as a single isomer following well documented precedents.[24] The stereocontrolled introduction of a vinyl group as a carboxyl precursor took advantage of the steric bias presented by the isobutyl group. Thus, the lithium enolate prepared from **14** was alkylated with 2-phenylselenoacetaldehyde, using Kowalski's method.[25] The resulting aldol product was mesylated, and subjected to elimination to give the all-*trans* isomer **15**, in good overall yield (d.r. 2.5:1). The minor 3-*epi*-isomer was separated by chromatography. Subjecting the enolate of **14** to trisyl azide[26] led to the expected 3-azido lactone **16** accompanied by its 3-*epi*-isomer as a minor product (d.r. 2.7:1). Stereochemical assignments for **15** and **16** were ascertained by detailed NOESY and COSY experiments. A variety of other electrophiles, that could lead to suitable precursors of **11** and **12**, were also investigated. Indeed, $CNCO_2Me$ (d.r. 8:1, 67%), benzyloxymethyl chloride (d.r 4:1, 50%), methoxymethyl iodide (d.r. 5.6:1, 84%) and allyl iodide (d.r. 4:1, 96%) afforded the expected *trans* isomers as major products, following the anticipated mode of attack. Although these ratios constituted an improvement compared to that found for **15**, conversion to the corresponding acids or alcohols was problematic or low yielding. Similarly, the electrophilic amination of the enolate derived from **14** employing di-*tert*-butylazodicarboxylate (DBAD) proceeded uneventfully (d.r. 3.6:1, 89%), but the subsequent cleavage of the intermediate hydrazine derivative met with failure. Reduction of the lactones **15** and **16** with Dibal-H under controlled conditions afforded the corresponding lactols **17** and **18** for



Scheme 1. (a) *i*-BuMgBr, CuI, DMS, THF, −78 to −40°C, then **13**, −78 to 0°C, 98%, d.r.>50:1. (b) i: LiHMDS, $PhSeCH_2CHO$, THF, −78°C, ii: MsCl, Et_3N, CH_2Cl_2, 67% (2 steps), d.r.: 2.5:1. (c) i: LiHMDS, trisyl azide, THF, −78°C, ii: AcOH, 30°C, 95% (2 steps), d.r.: 2.7:1. (d) Dibal-H, CH_2Cl_2, −60°C, 92% (for **17**); 73% (for **18**, along with 20% of recovered s.m.).

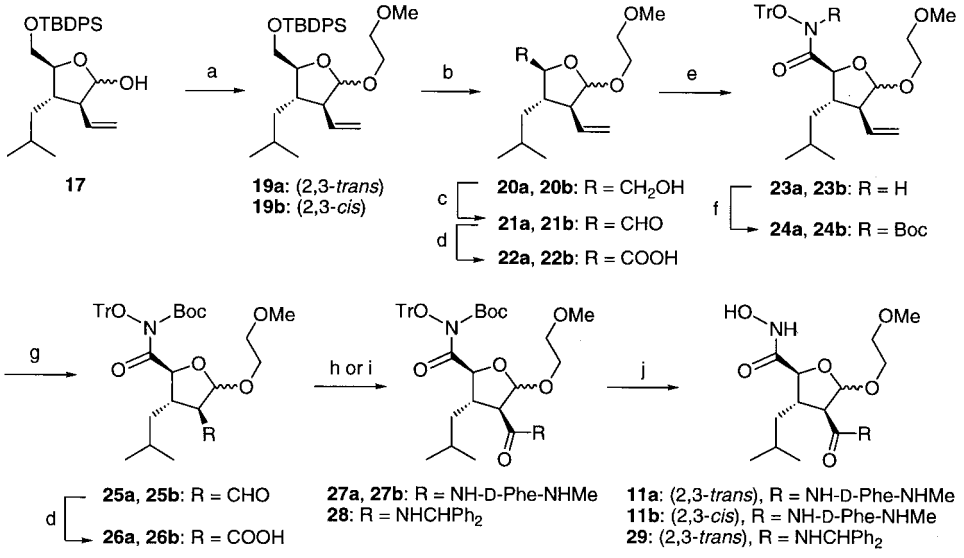
further elaboration into the intended targets **11** and **12** (Scheme 1).

The introduction of the methoxyethoxy appendage was accomplished by conversion of the lactol **17** into the corresponding 2-thiopyridylcarbonate ester followed by addition of 2-methoxyethanol, according to the protocol previously reported from this laboratory.[27] A direct Fischer[28] glycosylation was low yielding, while application of Schmidt's[29] trichloroacetimidate method led to a mixture of products, possibly due to the greater reactivity of the furanosyl donor.

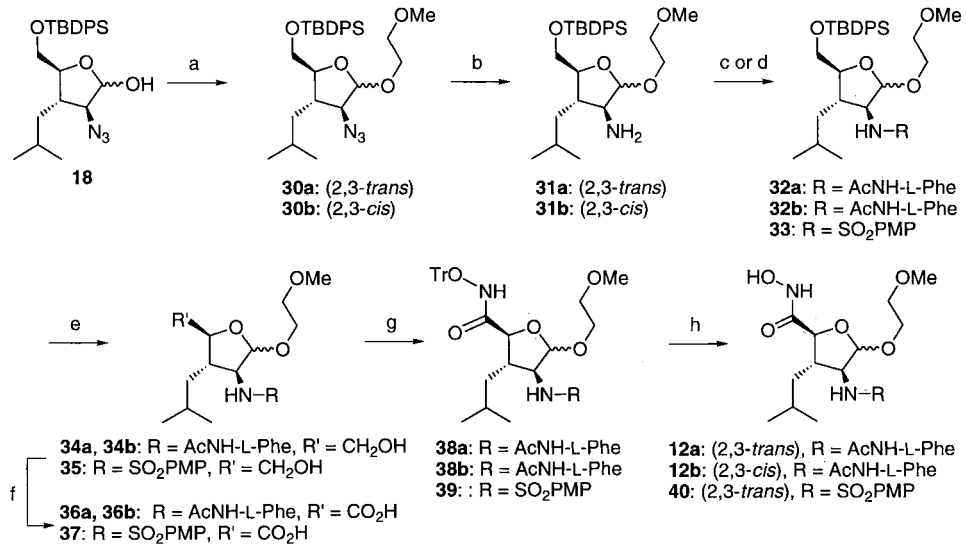
There remained to introduce the peptidic side chain and the hydroxamic acid unit at C-3 and C-5 respectively. In view of the tendency for intramolecular cyclizations resulting from the attack of the hydroxamate unit onto the appendage at C-3, particularly as the aldehyde or ester group, we opted to proceed with the *N*-Boc-*O*-trityl hydroxamate derivative. The inseparable anomeric mixture of products **19** (2,3-*trans*/2,3-*cis*, 1.8:1), was subjected to desilylation to afford the separable alcohols **20a** and **20b** which were oxidized first with tetrapropylammonium perruthenate[30] to the aldehydes **21a** and **21b**, and finally to the acids **22a** and **22b** using the Pinnick protocol.[31] Conversion of each acid to the *O*-trityl hydroxamate[32] afforded **23a** and **23b** which were protected as the *N*-Boc derivatives **24a** and **24b** respectively. Oxidative cleavage of the vinyl group led to the aldehydes **25a** and **25b** then to the acids **26a** and **26b**. Condensation with D-phenylalanine *N*-methyl amide in the presence of EDC, HOBT and *N*-methyl morpholine led to the expected amides **27a** and **27b**. The corresponding *N*-diphenylmethyl amide **28** was similarly prepared from the 2,3-*trans*-isomer **26a**. Finally, treatment with TFA in dichloromethane gave the intended prototypes **11a** and **11b** and the analog **29** from their immediate precursors (Scheme 2).[33]

Scheme 3 shows the conversion of the lactol **18** into the 'reverse' amide analogs **12a** and **12b**, essentially according to the protocol used for **11a** and **11b**. The anomeric 2-methoxyethoxy glycosides **30a** and **30b** (2.1:1 ratio) were separated by column chromatography and their stereochemical assignments were ascertained by detailed NOESY experiments.

To avoid lactam formation between the free amine on C-3 and the hydroxamic acid at position C-5, we introduced the peptidic unit first. Each anomer was then individually reduced to the corresponding amines **31a** and **31b** and acetylated with *N*-acetyl-D-phenylalanine using EDC and HOBT to afford **32a** and **32b** respectively. The *N*-*p*-methoxyphenylsulfonyl derivative **33** was prepared from the 2,3-*trans* glycoside **31a** in the usual manner. Subsequent transformations followed the protocol used for the synthesis of **11a** and **11b**. Thus, after TBAF mediated deprotection, compounds **34a**, **34b** and **35** were converted to the carboxylic acids **36a**, **36b** and **37** respectively via the corresponding aldehydes. Introduction of the *O*-trityl



Scheme 2. (a) i: Di-(*S*-2-pyridyl) thiocarbonate, Et_3N, 4 Å MS, CH_2Cl_2, ii: $MeOCH_2CH_2OH$, AgOTf, 4 Å MS, 0°C, 81%, d.r. (*trans*/*cis*): 1.8:1. (b) TBAF, AcOH, THF, 96%. (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 61–72%. (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 86–98% (for **22a/b**), 94–94% (for **26a/b**). (e) $TrONH_2$, EDC, HOBT, NMM, THF, 70–66%. (f) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 82–98%. (g) O_3, CH_2Cl_2, −78°C then DMS, 68–70%. (h) NH_2-D-NHMe, EDC, HOBT, NMM, THF, 68–93%. (i) Ph_2CHNH_2, EDC, HOBT, NMM, THF, 78%. (j) TFA, CH_2Cl_2, 83–57–83%.



Scheme 3. (a) i: Di-(S-2-pyridyl) thiocarbonate, Et_3N, 4 Å MS, CH_2Cl_2, ii: $MeOCH_2CH_2OH$, AgOTf, 4 Å MS, 0°C, 78%, d.r.(*trans*/*cis*): 2.1:1. (b) H_2, Pd/C, EtOH, 96–82%. (c) AcNH-L-Phe-OH, EDC, HOBT, NMM, THF, 66–70%. (d) *p*-methoxyphenyl sulfonyl chloride ($PMPSO_2Cl$), Et_3N, CH_2Cl_2, 88%. (e) TBAF, AcOH, THF, 87–81–91%. (f) i: TPAP, NMO, 4 Å MS, CH_2Cl_2, ii: $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 56–69–74% (2 steps). (g) $TrONH_2$, EDC, HOBT, NMM, THF, 47–57–54%. (h) TFA, CH_2Cl_2, 78–90–90%.

hydroxamate moiety afforded the reverse amide analogs **38a** and **38b** as well as the sulfonamide **39** from the 2,3-*trans* isomer **37**. Detritylation then led to the desired final products **12a**, **12b** and **40**.

Biological evaluation and modeling

Compounds **11a**, **11b**, **29**, **12a**, **12b** and **40** were tested as inhibitors of MMP-2, MMP-3 and MMP-9 but were found to be inactive (IC_{50} >100 μM).[34] In spite of our optimistic outlook based on the preliminary docking experiments discussed above, it was clear that one or more critical parameters were not satisfied. We then performed in depth molecular modeling studies with **11a** and **12a** in the binding site of MMP-3 which led to two possible conformations of each compound, differing in the orientation of the phenyl ring in relation to the peptidic chain (Fig. 5).

The results from the molecular dynamics study in aqueous medium of the 'reverse' amide analog **12a** clearly showed that conformation 1 (Fig. 5) was not stable in presence of water. On the other hand, although exclusion of water and the attainment of a stable docked inhibitor/enzyme complex was indicated in the case of conformation 2, the H-bond network was weakened all along the dynamics simulation. Fig. 6 shows the proposed structures of the Batimastat/MMP-3 and **12a** (conformation 2) modeled in the active

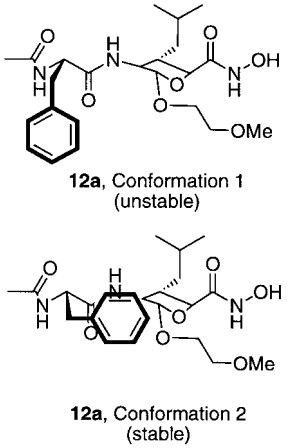


Figure 5. Refined conformations in vacuo of the analog **12a** in the catalytic site of MMP-3.

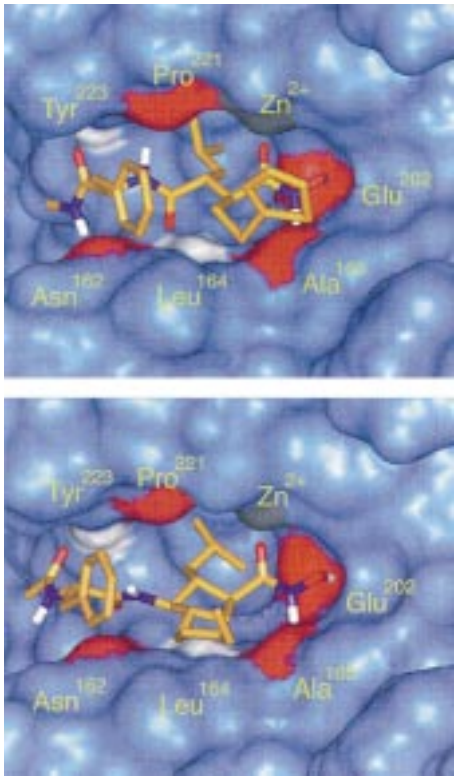


Figure 6. Connolly map surface of: (Top) bioactive conformation of Batimastat in MMP-3; (Bottom) modeled conformation of **12a** in MMP-3. Color code for enzyme: red (carbonyl); white (amide NH); grey (Zn^{2+}).

site of MMP-3. Although the interactions at the hydrophobic P_1' and P_2' sites appear to be favorable, there was considerable deviation of the amide backbone.

In the case of the normal amide analog **11a**, both conformers were unstable as the enzyme complex since water was only partly excluded from the complex.

The preliminary docking study performed at the outset of this project did not take into account the dynamic behavior of the inhibitor/enzyme complexes. On the other hand the molecular dynamics simulation was more rigorous, and revealed the weak H-bonded interactions of **12a**.

Conclusion

The synthesis of tetrahydrofuran derivatives as peptidomimetics was achieved using the stereocontrolled functionalization of a suitable chiron. Their elaboration into constrained hydroxamic acid derivatives as MMP inhibitors led to inactive compounds. Excluding undesired steric factors, it is clear that constraining part of the backbone of **1** into a tetrahydrofuran scaffold as in **11** and **12** perturbs the requisite alignment of crucial H-bonds as well as the hydrophobic interactions in the respective P and S subsites of **1** and MMP-3. Other studies have shown that minor deviations from the ideal bioactive conformation adopted by succinate-based inhibitors can result in substantial loss of activity.[35] Further studies are in progress to better understand the intricacies of scaffold design in our quest for effective metalloproteinase inhibitors.

Experimental

Molecular modeling

General. The molecular modeling was performed on Silicon Graphics Indigo2 workstation running IRIX (version 5.4) using AMBER[36] force field implemented in InsightII® version 95.0 program and Discover® package.[37] The force field was parameterized according to Guida[38] and Merz.[39] The atomic partial charges of the inhibitors were calculated using the semiempirical MNDO method implemented in the MOPAC program. The atomic partial charges of the enzyme and water molecules were calculated using the AMBER force field. A cutoff of 10 Å for the non-bonded interactions was used.

Complex building and refinement. The X-ray structure of L-764,004/stromelysin-1 complex was retrieved from the Brookhaven Protein Data Bank and used as a starting point[15c] (code 1HFS). The hydrogens were added, visually inspected, then the model was refined by a relaxation process. Two water solvent layers of 8 and 15 Å around the inhibitor, and 12 Å around the enzyme were added and the system was allowed to relax following the procedure described below. The protein and the crystallographic water oxygen atoms were held fixed, the solvent water molecules being free to move. A preliminary minimization was performed to remove close atom contacts, then the system was more completely relaxed by 2000 cycles of minimization using steepest descent followed by 5000 cycles using conjugate gradients. 6000 Steps of 1 fs of dynamics at 300 K were performed to allow the solvent molecules to orient themselves. At this point, the main chain of the protein, the heavy atoms of the inhibitor and crystallographic water oxygen atoms were tethered by a force constant. The relaxation started with a strong force constant to relax the side chains (1000 kcal/Å^2) by 1000 cycles of minimization using steepest descent followed by 5000 cycles using conjugate gradients. The last 5000 steps were reiterated with the template force stepwise decreased (100, 50, 15 and finally 0 kcal/Å^2). The inhibitor was removed and the solvated structure of the enzyme used in the following studies.

The X-ray structure of Batimastat co-crystallized in MMP-8[6c] (code 1MMB from the Protein Data Bank) was used for modeling the Batimastat/MMP-3 complex. Batimastat was manually docked in the binding site of MMP-3 according to its conformation in MMP-8. The water was temporarily removed and the molecule was positioned inside the binding site by 300 steps of minimization using steepest descent followed by 3000 cycles using conjugate gradients while keeping the enzyme fixed. Water molecules were added and the system relaxed as described above. 100 000 Steps of 1 fs of MD simulation were performed (0.1 ns). For that purpose, a core of residues was defined (10 Å from any atoms of the inhibitor) and a shell (a layer of 5 Å) on which the calculations were performed. All the atoms within the core were unconstrained while the atoms within the shell and the second layer water molecule oxygens were restrained by an energy penalty of 50 kcal/Å^2. The rest of the enzyme and the water molecules around the enzyme were frozen and a structure was archived every 100 steps. The final structure was refined by energy minimization with the same constraints by 2000 cycles of minimization using steepest descent followed by 5000 cycles using conjugate gradients and finally unconstrained by 5000 cycles using conjugate gradients.

Inhibitors 11a and 12a/MMP-3 complexes: building and refinement. The starting structure of the inhibitors/MMP-3 complexes were manually built and refined by energy minimization then using a cooling procedure. To explore the conformational space, 5000 steps of MD at 900 K were performed followed by 5000 steps at 300 K and finally 200 cycles of minimization using steepest descent followed by 1000 cycles using conjugate gradients. For these calculations, the enzyme was held fixed and a distance-dependent dielectric constant (4 r) was used. The resulting model was saved and used as a starting point for the next loop. Fifty structures were obtained and compared. For the two modeled complexes, two main structures were extracted and studied. Water molecules were added and the system studied using a similar procedure as for the Batimastat/MMP-3 complex.

Chemistry

General procedures. Solvents were distilled under positive pressure of dry nitrogen before use and dried by standard methods; THF and ether, from K/benzophenone; and CH_2Cl_2 and toluene, from $CaCl_2$. All commercially

available reagents were used without further purification. 4 Å molecular sieves were dried at 140°C prior to use. All reactions were performed under nitrogen atmosphere. NMR (^{1}H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers in $CDCl_3$ or CD_3OD with tetramethylsilane as the internal standard. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902 or Kratos MS-50 spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by UV or by development using $KMnO_4$ or $FeCl_3$ solutions. Flash column chromatography were performed using (40–60 μm) silica gel at increased pressure. Melting points recorded were uncorrected.

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5*H*-furan-2-one (13). This compound was prepared according to the reported procedure.[23,24]

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-dihydro-furan-2-one (14). Magnesium turnings (5.0 g, 206 mmol) were placed in an N_2-filled flask and covered with dry THF (10 mL). 1,2-Dibromoethane (0.15 mL) in dry THF (5 mL) was added dropwise until a vigourous reaction started and the solvent refluxed. *iso*-Butylbromide (10.6 mL, 100 mmol) in THF (100 mL) was added with a dropping funnel as to maintain a gentle reflux. The solution was stirred at 80°C for 2 h, cooled to room temperature, and immediately canulated in a N_2-filled bottle in which the solution started to crystallize (101 mL, titrated:[40] 0.74 M, 74%). To this solution (21.8 mL, 16.2 mmol) in dry THF (20 mL) was added a suspension of cuprous iodide (1.54 g, 8.09 mmol) in THF (20 mL) at −78°C. After stirring for 10 min, (0.3 mL) dimethylsulfide was added, and the greyish solution was stirred for 2 h, then allowed to warm to −40°C. After being re-cooled to −78°C, lactone **13** (949 mg, 2.70 mmol) was added in THF (20 mL), and the green solution was stirred at 0°C until it turned to a dark purple color. After stirring for a further 15 min, the mixture was quenched with saturated NH_4Cl, extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was triturated with CH_2Cl_2 and the insoluble salts were filtered off. The filtrate was dried over $MgSO_4$ and concentrated and the residue was chromatographed (hexanes/EtOAc, 9:1) to provide **14** (1.08 g, 2.63 mmol, 98%, d.r.>50:1) as a pale yellow oil; R_f=0.42 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+21.7 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 1782.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.50–7.37 (m, 6H), 4.17 (m, 1H), 3.87 (dd, 1H, *J*=3.2, 11.5 Hz), 3.69 (dd, 1H, *J*=3.6, 11.5 Hz), 2.79 (dd, 1H, *J*=8.9, 17.4 Hz), 2.58 (m, 1H), 2.20 (dd, 1H, *J*=6.8, 17.4 Hz), 1.56 (m, 1H), 1.40–1.26 (m, 2H), 1.06 (s, 9H), 0.91 (d, 3H, *J*=5.8 Hz), 0.90 (d, 3H, *J*=5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 135.6, 135.5, 132.8, 132.5, 129.8, 127.7, 85.6, 64.3, 43.0, 35.3, 34.4, 26.7, 26.0, 22.9, 21.9, 19.1; LRMS: (FAB, NBA, *m/z*, %): 433 (1.5) ($M+Na^+$), 411 (1.6) ($M+H^+$), 409 (1.1), 353 (40), 333 (43), 199 (50), 135 (95); HRMS calcd for $C_{25}H_{34}O_3SiNa$ ($M+Na^+$) 433.21750, found 433.21840.

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-3(*S*)-vinyl-dihydro-furan-2-one (15). To a stirred solution of lactone **14** (2.00 g, 4.9 mmol) in dry THF (50 mL) was added at −78°C a solution of LiHMDS (5.84 mL, 5.84 mmol, 1 M solution in THF). After stirring for 1 h at −78°C, 2-phenylselenoacetaldehyde[41] (1.26 g, 6.34 mmol) was added. After 30 min, saturated NH_4Cl was added and the mixture was extracted with ether, the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2, triethylamine (3.4 mL, 23.8 mmol) was added at 0°C followed by mesyl chloride (1.5 mL, 19.5 mmol). After 30 min, cold water was added to the cloudy mixture which was diluted with CH_2Cl_2, washed with brine and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 5:1) afforded the product **15** (1.03 g, 2.36 mmol, 48%) as a pale yellow oil, and the *cis*-epimer (0.41 g, 0.94 mmol, 19%) as pale yellow oil. The relative configuration of **15** was ascertained by a NOESY experiment; R_f=0.67 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+10.3 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 1774.2, 1654.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.65 (m, 4H), 7.49–7.36 (m, 6H), 5.80 (ddd, 1H, *J*=7.8, 9.7, 17.7 Hz), 5.33 (m, 1H), 5.29 (m, 1H), 4.09 (m, 1H), 3.92 (dd, 1H, *J*=2.7, 11.8 Hz), 3.71 (dd, 1H, *J*=3.7, 11.8 Hz), 2.96 (dd, 1H, *J*=8.0, 9.0 Hz), 2.59 (m, 1H), 1.57 (m, 1H), 1.48–1.29 (m, 2H), 1.06 (s, 9H), 0.89 (2d, 6H, *J*=5.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.1, 135.6, 135.4, 133.2, 132.9, 132.5, 129.8, 129.2, 127.7, 119.6, 84.5, 63.4, 52.1, 42.6, 39.1, 26.6, 25.3, 22.6, 22.4, 19.1; LRMS: (FAB, NBA, *m/z*, %): 873 (9) ($2\times M+H^+$), 803 (75), 745 (85), 675 (9), 437 (12) ($M+H^+$), 359 (22), 241 (26), 199 (60), 197 (68), 135 (100), 75 (41), 55 (25); HRMS calcd for $C_{27}H_{35}O_3Si$ ($M-H^+$) 435.23553, found 435.23690.

3(*S*)-Azido-5(*S*)-(*tert*-butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-dihydro-furan-2-one (16). To a solution of LiHMDS (2.66 mL, 2.66 mmol, 1 M solution in THF) cooled to −78°C and diluted with dry THF (20 mL) was added dropwise the lactone **14** (840 mg, 2.05 mmol) in dry THF (30 mL). After stirring for 1 h, a solution of triisopropyl benzenesulfonyl azide (900 mg, 3.07 mmol) in dry THF (10 mL) was added at −78°C. The resulting mixture was stirred for a further 30 min. The solution was quenched with AcOH (0.47 mL, 8.19 mmol), warmed to 30°C and stirred for 30 min. The solution was diluted with ether and the organic phase was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was flash chromatographed (hexanes/EtOAc, 9:1) to provide the expected 3(*S*)-*trans* isomer **16** (635 mg, 1.41 mmol, 69%, yellowish oil) and the corresponding 3(*R*)-*cis* isomer (240 mg, 0.53 mmol, 26%, yellowish oil); for **16**: R_f=0.52 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−44.2 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 2109.2, 1784.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.50–7.38 (m, 6H), 4.08 (ddd, 1H, *J*=2.7, 3.5, 8.8 Hz), 3.94 (d, 1H, *J*=10.1 Hz), 3.92 (dd, 1H, *J*=2.7, 11.9 Hz), 3.71 (dd, 1H, *J*=3.5, 11.9 Hz), 2.62 (m, 1H), 1.72 (m, 1H), 1.46 (ddd, 1H, *J*=5.6, 8.8, 14.5 Hz), 1.33 (ddd, 1H, *J*=6.5, 8.8, 14.5 Hz), 1.07 (s, 9H), 0.95 (2d, 6H, *J*=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 135.6, 135.5, 132.7, 132.4, 129.9, 127.8, 83.2, 63.8, 62.5, 41.0, 39.4, 26.6, 25.8, 23.2, 21.9, 19.2; LRMS: (FAB, NBA, *m/z*, %): 426 (23), 333 (8), 221 (27), 199 (47), 197 (40), 135 (100); HRMS

calcd for $C_{25}H_{33}O_3SiN_3K$ ($M+K^+$) 490.19284, found 490.19420.

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-3(*S*)-vinyl-tetrahydro-furan-2-ol (17). To a solution of lactone **15** (1.69 g, 3.88 mmol) in dry THF (40 mL) was added dropwise a solution of Dibal-H (4.65 mL, 4.65 mmol, 1 M solution in toluene) at −78°C. After stirring for 11 h at −60°C, the solution was quenched by adding EtOAc (5 mL) and allowing to warm to room temperature. A solution of $NaHCO_3$ was added and the resulting biphasic solution stirred for 1 h. The organic layer was then separated, extracted with ether, washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (hexanes/EtOAc, 9:1) to provide the lactol **17** (1.57 g, 3.58 mmol, 92%, colorless oil); R_f=0.46–0.67 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 3417.7, 1640.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.51–7.37 (m, 6H), 5.97–5.71 (m, 1H), 5.27 (d, 0.3H, J=3.5 Hz), 5.22–5.18 (m, 2.4H), 5.07 (ddd, 0.3H, J=0.7, 1.9, 10.1 Hz), 3.96 (ddd, 0.3H, J=0.1, 3.1, 4.5 Hz), 3.90–3.84 (m, 1.7H), 3.81 (dd, 0.3H, J=3.0, 11.0 Hz), 3.68 (dd, 0.3H, J=4.5, 11.0 Hz), 3.62 (d, 0.7H, J=8.1 Hz), 3.50 (dd, 0.7H, J=3.4, 11.8 Hz), 2.40 (m, 1.7H), 2.22 (m, 0.3H), 1.60–1.17 (m, 3H), 1.12 (s, 6.3H), 1.08 (s, 2.7H), 0.84 (d, 3H, J=6.2 Hz), 0.78 (d, 3H, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 136.1, 135.79, 135.66, 135.60, 132.39, 132.35, 129.98, 129.85, 129.59, 127.80, 127.77, 127.61, 117.4 (0.7C), 116.1 (0.3C), 102.8 (0.3C), 99.7 (0.7C), 86.6 (0.7C), 84.8 (0.3C), 65.6 (0.7C), 65.1 (0.3C), 58.5 (0.3C), 58.0 (0.7C), 42.74 (0.3C), 42.64 (0.7C), 42.57 (0.3C), 37.7 (0.7C), 26.84 (2.1C), 25.84 (0.9C), 25.73 (0.7C), 23.3 (0.7C), 22.9 (0.3C), 22.5 (0.3C), 22.0 (0.7C), 19.2 (0.3C), 19.1 (0.7C); LRMS: (FAB, NBA, *m*/*z*, %): 421 (38) ($M-OH^+$), 351 (17), 199 (84), 197 (75), 135 (100); HRMS calcd for $C_{27}H_{37}O_2Si$ ($M-OH^+$) 421.25629, found 421.25770.

3(*S*)-Azido-5(*S*)-(*tert*-butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-tetrahydro-furan-2-ol (18). Following the same procedure as for **17**, lactone **16** (748 mg, 1.66 mmol) in dry THF (20 mL), Dibal-H (6.63 mL, 6.63 mmol, 1 M solution in toluene) afforded after flash chromatography (hexanes/EtOAc, 9:1) the lactol **18** (551 mg, 1.22 mmol, 73%) as a colorless oil together with unreacted starting material (149 mg, 0.27 mmol, 20%); R_f=0.50 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 3411.3, 2104.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.68 (m, 4H), 7.50–7.46 (m, 6H), 5.43 (d, 0.4H, J=1.8 Hz), 5.28 (m, 0.6H), 3.98 (ddd, 0.6H, J=2.7, 3.5, 8.8 Hz), 3.9 (m, 0.4H), 3.75–3.90 (m, 2H), 3.60 (dd, 0.4H, J=1.9, 4.8 Hz), 3.49 (dd, 0.6H, J=2.5, 11.0 Hz), 3.29 (dd, 0.6H, J=3.9, 10.2 Hz), 2.60 (m, 0.6H), 2.23 (m, 0.4H), 1.72 (m, 1H), 1.50 (m, 1H), 1.33 (m, 1H), 1.11 (s, 5.4H), 1.08 (s, 3.6H), 0.98–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.6, 135.5, 133.1, 133.0, 132.1, 130.0, 129.9, 129.7, 127.8, 127.6, 101.6 (0.4C), 97.1 (0.6C), 84.7 (0.6C), 84.5 (0.4C), 72.2 (0.4C), 68.2 (0.6C), 65.0 (0.6C), 64.8 (0.4C), 43.3 (0.4C), 42.2 (0.6C), 41.7 (0.4C), 36.0 (0.6C), 26.74 (1.8C), 26.69 (1.2C), 26.2 (0.4C), 26.0 (0.6C), 23.0 (0.4C), 22.8 (0.6C), 22.6 (0.6C), 22.1 (0.4C), 19.1 (0.4C), 19.0 (0.6C); LRMS: (FAB, NBA, *m*/*z*, %): 408 (2), 223 (6), 199 (67), 135 (100), 91 (30); HRMS calcd for $C_{27}H_{35}O_3SiN_3K$ ($M+K^+$) 492.20847, found 492.21090.

***tert*-Butyl-[3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-ylmethoxy]-diphenyl-silane (19a) and *tert*-butyl-[3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-ylmethoxy]-diphenyl-silane (19b).** To a mixture of lactol **17**, (1.54 g, 3.51 mmol), were added di(S-2-pyridyl) thiocarbonate (3.9 g, 17.9 mmol) and 4 Å molecular sieves (200 mg) in CH_2Cl_2 (60 mL) followed by triethylamine (2.8 mL, 20.4 mmol). The resulting solution was stirred for 36 h at room temperature. The mixture of isomers obtained was quickly purified on silica gel and the crude was immediatly dissolved in CH_2Cl_2 (150 mL) in presence of powdered 4 Å molecular sieves. Methoxyethanol (0.80 mL, 10.5 mmol) was added and the mixture stirred 5 h at room temperature then cooled to 0°C. Freshly dried silver triflate (2.6 g, 10.5 mmol) was added and the stirring continued for 1 h at 0°C then 1 h at room temperature. The suspension was filtered, extracted with CH_2Cl_2 and the organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 19:1) gave **19a** and **19b** as a colorless oil (1.41 g, 2.84 mmol, 81%, 1.8:1 ratio): R_f=0.62 (hexanes/EtOAc, 9:1); IR (neat/NaCl) 1638.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78–7.70 (m, 4H), 7.49–7.35 (m, 6H), 5.83 (ddd, 0.35H, J=9.0, 10.1, 19.5 Hz), 5.78 (ddd, 0.65H, J=9.1, 10.3, 19.5 Hz), 5.11 (ddd, 0.65H, J=0.9, 1.7, 19.5 Hz), 5.08 (ddd, 0.35H, J=0.8, 2.0, 19.5 Hz), 5.07 (d, 0.35H, J=10.5 Hz), 5.04 (ddd, 0.65H, J=0.7, 2.0, 10.5 Hz), 4.92 (d, 1H, J=4.8 Hz), 4.90 (d, 1H, J=2.5 Hz), 3.90–3.70 (m, 4H), 3.66–3.50 (m, 2H), 3.48 (m, 1H), 3.40 (s, 1.95H), 3.32 (s, 1.05H), 2.56 (ddd, 0.65H, J=2.3, 6.0, 8.7 Hz), 2.37 (ddd, 0.35H, J=4.5, 9.2, 10.7 Hz), 2.08–1.93 (m, 1H), 1.62–1.32 (m, 2H), 1.31–1.18 (m, 1H), 1.10 (s, 3.15H), 1.09 (s, 5.85H), 0.85 (d, 3.9H, J=5.8 Hz), 0.83 (d, 3.9H, J=5.8 Hz), 0.81 (d, 2.1H, J=6.5 Hz), 0.72 (d, 2.1H, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9 (0.65C), 136.1 (0.35C), 135.68, 135.62, 133.6 (0.35C), 133.5 (0.65C), 129.6, 127.6, 117.0 (0.35C), 115.5 (0.65C), 108.6 (0.65C), 105.5 (0.35C), 87.2 (0.35C), 84.7 (0.65C), 71.9 (0.65C), 71.7 (0.35C), 68.3 (0.35C), 66.7 (0.65C), 66.4 (0.35C), 65.1 (0.65C), 59.0 (0.65C), 58.9 (0.35C), 57.0 (0.65C), 56.9 (0.35C), 43.1 (0.65C), 42.7 (0.35C), 42.4 (0.65C), 41.1 (0.35C), 26.81 (3.15C), 26.77 (5.85C), 25.9 (0.65C), 25.6 (0.35C), 23.2 (0.35C), 23.1 (0.65C), 22.3 (0.65C), 19.26 (0.35C); LRMS: (FAB, NBA, *m*/*z*, %): 495 (10), 421 (32) ($M-OCH_2CH_2OMe^+$), 351 (20), 257 (49), 199 (59), 197 (60), 135 (88), 59 (100); HRMS calcd for $C_{30}H_{44}O_4SiNa$ ($M+Na^+$) 519.29065, found 519.29190.

[3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-yl]-methanol (20a) and [3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-yl]-methanol (20b). To the mixture of anomers **19a** and **19b** (1.41 g, 2.84 mmol) in THF (100 mL) and AcOH (1 mL) was added portionwise TBAF (1.85 g, 7.11 mmol) at 0°C. The resulting mixture was stirred overnight, diluted with ether, and the organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1 to 4:1) to afford **20a** ((*S*): 451 mg, 1.75 mmol,

62%, colorless oil), and **20b** ((*R*): 251 mg, 0.97 mmol, 34%, colorless oil). The relative configuration of both **20a** and **20b** was determined by NOE spectroscopy; for **20a**: R_f=0.54 (hexanes/EtOAc, 1:1); $[\alpha]_D$=+76.0 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3467.8, 1641.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, 1H, *J*=9.1, 10.1, 17.1 Hz), 5.09 (ddd, 1H, *J*=1.0, 1.7, 17.1 Hz), 5.02 (ddd, 1H, *J*=0.9, 1.7, 10.1 Hz), 4.85 (d, 1H, *J*=2.6 Hz), 3.85–3.73 (m, 3H), 3.60–3.51 (m, 4H), 3.36 (s, 3H), 2.83 (m, 1H), 1.88 (ddd, 1H, *J*=6.3, 8.0, 16.2 Hz), 1.61 (m, 1H), 1.40 (ddd, 1H, *J*=6.4, 8.0, 14.5 Hz), 1.24 (ddd, 1H, *J*=6.3, 7.8, 14.1 Hz), 0.85 (d, 3H, *J*=5.9 Hz), 0.82 (d, 3H, *J*=5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 115.7, 108.4, 84.5, 71.7, 66.7, 63.1, 58.8, 57.2, 42.5, 41.9, 25.8, 22.8, 22.3; LRMS: (FAB, NBA, *m/z*, %): 259 (7) ($M+H^+$), 257 (7), 227 (7), 183 (100); HRMS calcd for $C_{14}H_{25}O_4$ [$M-H^+$] 257.17529, found 257.17490; for **20b**: R_f=0.57 (hexanes/EtOAc, 1:1); $[\alpha]_D$=−97.0 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3465.8, 1638.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, 1H, *J*=9.1, 9.1, 18.5 Hz), 5.12 (m, 1H), 5.08 (m, 1H), 4.83 (d, 1H, *J*=4.4 Hz), 3.88–3.78 (m, 3H), 3.65 (ddd, 1H, *J*=3.4, 4.7, 11.3 Hz), 3.58–3.53 (m, 2H), 3.48 (ddd, 1H, *J*=0.5, 3.4, 13.0 Hz), 3.39 (s, 3H), 3.15 (m, 1H), 2.54–2.33 (m, 2H), 1.62 (m, 1H), 1.32 (ddd, 1H, *J*=4.2, 9.5, 13.5 Hz), 1.19 (ddd, 1H, *J*=5.6, 8.8, 13.5 Hz), 0.88 (d, 3H, *J*=6.4 Hz), 0.86 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 117.2, 104.9, 87.4, 71.6, 67.1, 63.7, 58.6, 57.1, 42.1, 37.3, 25.9, 23.5, 21.7; LRMS: (FAB, NBA, *m/z*, %): 289 (6) ($M+Na^+$), 257 (20), 227 (6), 183 (100); HRMS calcd for $C_{14}H_{25}O_4$ ($M-H^+$) 257.17529, found 257.17460.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carbaldehyde (21a). To a solution of **20a** (414 mg, 1.60 mmol) in dry CH_2Cl_2 (50 mL) were added *N*-methyl morpholine (553 mg, 4.81 mmol) and 4 Å molecular sieves (300 mg). The suspension was stirred for 20 min. Then a catalytic amount of tetrapropylammonium perruthenate was added. The resulting mixture was stirred at room temperature for 90 min then filtered on a pad of silica gel. The residue was purified by flash chromatography (hexanes/EtOAc, 1:1 to 2:3) to provide **21a** (251 mg, 0.98 mmol, 61%, brownish oil); R_f=0.45–0.85 (hexanes/EtOAc, 2:3); $[\alpha]_D$=+24.7 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 1735.9, 1642.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, 1H, *J*=2.6 Hz), 5.71 (ddd, 1H, *J*=8.9, 10.2, 17.1 Hz), 5.13 (ddd, 1H, *J*=1.0, 1.7, 17.1 Hz), 5.08 (ddd, 1H, *J*=0.9, 1.8, 10.1 Hz), 5.02 (d, 1H, *J*=2.5 Hz), 4.08 (dd, 1H, *J*=2.5, 8.2 Hz), 3.84 (m, 1H), 3.65–3.51 (m, 3H), 3.37 (s, 3H), 2.63 (ddd, 1H, *J*=2.1, 6.0, 8.4 Hz), 2.07 (m, 1H), 1.64 (m, 1H), 1.48 (m, 2H), 0.85 (d, 3H, *J*=6.5 Hz), 0.84 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 137.0, 116.6, 109.3, 87.1, 71.6, 67.1, 58.9, 56.1, 44.5, 41.9, 25.7, 22.5, 22.3; LRMS: (FAB, NBA, *m/z*, %): 257 (12) ($M+H^+$), 227 (100), 197 (39), 181 (75); HRMS calcd for $C_{14}H_{25}O_4$ ($M+H^+$) 257.17529, found 257.17630.

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carbaldehyde (21b). Using the same procedure as for **21a**, compound **20b** (247 mg, 0.96 mmol) in dry CH_2Cl_2 (50 mL), NMO (330 mg 2.87 mmol), 4 Å molecular sieves (300 mg) and a catalytic amount of TPAP, led after flash chromatography (hexanes/EtOAc, 1:1 to 2:3) to **21b** (177 mg, 0.69 mmol, 72%, yellowish oil); R_f=0.24 (hexanes/EtOAc, 9:1); $[\alpha]_D$=−141.6 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 1733.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, 1H, *J*=3.0 Hz), 5.80 (ddd, 1H, *J*=8.5, 9.1, 18.0 Hz), 5.16 (m, 1H), 5.12 (m, 1H), 5.05 (d, 1H, *J*=4.0 Hz), 4.01–3.89 (m, 2H), 3.67–3.52 (m, 3H), 3.37 (s, 3H), 2.45–2.28 (m, 2H), 1.68 (m, 1H), 1.43–1.27 (m, 2H), 0.89 (d, 3H, *J*=6.5 Hz), 0.82 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.3, 134.5, 118.2, 106.3, 88.7, 71.6, 67.1, 59.0, 56.3, 42.5, 41.0, 25.7, 23.5, 21.7; LRMS: (FAB, NBA, *m/z*, %): 257 (16) ($M+H^+$), 227 (23), 197 (11), 181 (19), 151 (23), 59 (100); HRMS calcd for $C_{14}H_{25}O_4$ ($M+H^+$) 257.17529, found 257.17460.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid (22a). To **21a** (201 mg, 0.78 mmol) in *t*-BuOH (5 mL) were successively added a solution of NaH_2PO_4 (184 mg, 1.18 mmol) in water (1 mL), 2-methyl-2-butene (0.4 mL) and sodium chlorite (213 mg, 2.36 mmol). The mixture was stirred for 3 h and the solvents were removed. The residue was taken up in CH_2Cl_2/CH_3OH and the salts were filtered off. The residue was purified by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 19:1) to provide the acid **22a** (183 mg, 0.67 mmol, 86%, colorless oil); R_f=0.50 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=+74.0 (*c* 0.9, CH_3OH); IR (neat/NaCl) 3462.5, 3192.7, 1732.2, 1643.7 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 5.79 (ddd, 1H, *J*=8.9, 10.2, 17.2 Hz), 5.13 (ddd, 1H, *J*=1.0, 1.7, 17.2 Hz), 5.08 (ddd, 1H, *J*=0.9, 1.7, 10.2 Hz), 4.98 (d, 1H, *J*=2.7 Hz), 4.91 (m, 1H), 4.16 (d, 1H, *J*=7.9 Hz), 3.79 (m, 1H), 3.62–3.53 (m, 3H), 3.35 (s, 3H), 2.51 (ddd, 1H, *J*=2.8, 6.0, 8.1 Hz), 2.13 (ddd, 1H, *J*=6.1, 8.0, 14.1 Hz), 1.73 (m, 1H), 1.70 (m, 1H), 0.85 (d, 3H, *J*=6.5 Hz), 0.84 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4, 139.1, 116.9, 110.6, 82.6, 72.8, 68.2, 59.1, 58.0, 43.9, 26.9, 23.3, 22.7; LRMS: (FAB, NBA, *m/z*, %): 317 (8) ($M-H+2Na^+$), 295 (40) ($M+Na^+$), 273 (12) ($M+H^+$), 227 (7), 197 (48), 183 (17), 151 (61), 59 (100); HRMS calcd for $C_{14}H_{25}O_5$ ($M+H^+$) 273.17020, found 273.17110.

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid (22b). To a solution of **21b** (171 mg, 0.67 mmol) in *t*-BuOH (5 mL), were added NaH_2PO_4 (156 mg, 1.00 mmol) in water (0.9 mL), 2-methyl-2-butene (0.35 mL) and sodium chlorite (181 mg, 2.00 mmol). Purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 19:1) afforded **22b** (178 mg, 0.67 mmol, 98%, colorless oil); R_f=0.61 (EtOAc); $[\alpha]_D$=−121.1 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3166.8, 1754.3, 1642.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.1–8.5 (m, 1H), 5.73 (ddd, 1H, *J*=8.9, 9.9, 17.5 Hz), 5.15 (m, 1H), 5.10 (m, 1H), 4.98 (d, 1H, *J*=4.2 Hz), 4.14 (d, 1H, *J*=8.8 Hz), 3.88 (ddd, 1H, *J*=3.0, 5.8, 12.0 Hz), 3.75 (ddd, 1H, *J*=3.0, 6.4, 12.0 Hz), 3.62–3.50 (m, 2H), 3.38 (s, 3H), 2.48–2.31 (m, 2H), 1.88 (m, 1H), 1.47 (ddd, *J*=6.6, 6.6, 13.6 Hz), 1.36 (ddd, 1H, *J*=5.8, 8.0, 13.6 Hz), 0.89 (d, 3H, *J*=6.7 Hz), 0.82 (d, 3H, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 134.3, 118.4, 107.2, 83.4, 71.1, 68.7, 60.2, 58.5, 56.2, 43.42, 42.3, 25.0, 22.7, 22.3; LRMS: (FAB, NBA, *m/z*, %): 295 (6) ($M+Na^+$), 273 (20) ($M+H^+$), 227 (13), 197 (54), 151 (65), 137 (28), 59 (100); HRMS calcd for $C_{14}H_{25}O_5$ ($M+H^+$) 273.17020, found 273.17000.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid trityloxy-amide (23a). To **22a** (172 mg, 0.63 mmol) in THF (3 mL) were successively added EDC (186 mg, 0.95 mmol), HOBT (128 mg, 0.95 mmol) and *N*-methyl morpholine (104 μL, 0.95 mmol). After stirring for 20 min, *O*-tritylhydroxylamine (260 mg, 0.95 mmol) was added, the resulting mixture was stirred overnight then diluted with ether, washed with 0.1N HCl, water, 0.5N $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 4:1) provided the title compound **23a** (235 mg, 0.44 mmol, 70%, colorless oil); R_f=0.26 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+34.0 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3368.0, 1710.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.51–7.47 (m, 6H), 7.38–7.30 (m, 9H), 5.46 (ddd, 1H, *J*=8.9, 10.4, 17.0 Hz), 4.98 (d, 1H, *J*=17.0 Hz), 4.93 (d, 1H, *J*=7.2 Hz), 4.70 (d, 1H, *J*=2.2 Hz), 3.97 (d, 1H, *J*=7.8 Hz), 3.63 (m, 1H), 3.50–3.42 (m, 3H), 3.35 (s, 3H), 2.46 (ddd, 1H, *J*=2.3, 5.6, 8.3 Hz), 1.85 (m, 1H), 1.65 (m, 1H), 1.51 (ddd, 1H, *J*=6.1, 8.4, 13.5 Hz), 1.37 (ddd, 1H, *J*=5.8, 8.6, 13.5 Hz), 0.82 (d, 3H, *J*=6.5 Hz), 0.78 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 141.5, 137.4, 129.0, 128.8, 127.8, 127.7, 116.1, 108.8, 92.1, 82.2, 71.5, 66.9, 58.9, 55.6, 46.6, 43.2, 25.5, 23.0, 21.9; LRMS: (FAB, NBA, *m/z*, %): 528 (10), 484 (10), 454 (22), 437 (40), 243 (100); HRMS calcd for $C_{33}H_{39}O_5NNa$ ($M+Na^+$) 552.27258, found 552.27500.

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid trityloxy-amide (23b). This compound was prepared following the same procedure as for **23a**. From **22b** (172 mg, 0.63 mmol) in THF (5 mL), EDC (136 mg, 0.70 mmol), HOBt (94 mg, 0.70 mmol) *N*-methyl morpholine (76 μL, 0.70 mmol) and *O*-tritylhydroxylamine (191 mg, 0.70 mmol), was obtained after flash chromatography (hexanes/EtOAc, 4:1), **23b** (221 mg, 0.42 mmol, 66%, colorless oil); R_f=0.36 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−36.4 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3384.2, 3275.5, 1708.7, 1643.9, 1596.2 cm^{-1}; ^1H NMR (75 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.52–7.48 (m, 6H), 7.35–7.25 (m, 9H), 5.72 (ddd, 1H, *J*=9.1, 11.1, 15.5 Hz), 5.11 (m, 1H), 5.07 (m, 1H), 4.84 (d, 1H, *J*=4.8 Hz), 3.92 (d, 1H, *J*=8.8 Hz), 3.27 (s, 3H), 3.25 (m, 1H), 3.18 (m, 2H), 3.03 (ddd, 1H, *J*=3.0, 4.9, 10.8 Hz), 2.29 (m, 1H), 2.16 (m, 1H), 1.81 (m, 1H), 1.39 (ddd, *J*=6.8, 6.8, 13.5 Hz), 1.24 (ddd, 1H, *J*=6.4, 8.0, 13.5 Hz), 0.78 (d, 3H, *J*=6.5 Hz), 0.69 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.9, 141.7, 134.8, 129.1, 127.8, 127.6, 117.9, 106.7, 92.8, 84.4, 71.5, 67.6, 58.9, 56.3, 43.3, 42.9, 25.0, 22.8, 22.7; LRMS: (FAB, NBA, *m/z*, %): 552 (11) ($M+Na^+$), 528 (11), 484 (8), 454 (9), 401 (10), 345 (18), 289 (14), 259 (76), 243 (100); HRMS calcd for $C_{33}H_{39}O_5NNa$ ($M+Na^+$) 552.27258, found 552.27020.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid, *tert*-butoxycarbonyl-trityloxy-amide (24a). To **23a** (228 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) were added Boc_2O (187 μL, 0.86 mmol), triethylamine (60 μL, 0.43 mmol) and DMAP (53 mg, 0.43 mmol) at 0°C. After stirring for 16 h at room temperature, the solution was diluted with CH_2Cl_2, washed with 0.1N HCl, water, 0.5N $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to provide **24a** (221 mg, 0.35 mmol, 82%, colorless oil); R_f=0.28 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−5.9 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 1773.1, 1644.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (2 rotamers 4:1) δ 7.41–7.36 (m, 6H), 7.32–7.27 (m, 9H), 5.76 (ddd, 0.2H, *J*=8.8, 10.0, 19.1 Hz), 5.72 (ddd, 0.8H, *J*=9.1, 10.1, 19.1 Hz), 5.26 (d, 0.2H, *J*=8.0 Hz), 5.13 (d, 0.2H, *J*=17.0 Hz), 5.17–5.00 (m, 2H), 4.95 (d, 0.2H, *J*=3.1 Hz), 4.88 (d, 0.8H, *J*=3.0 Hz), 4.22 (d, 0.8H, *J*=8.3 Hz), 3.90–3.75 (m, 1H), 3.63–3.48 (m, 3H), 3.79 (s, 0.6H), 3.36 (s, 2.4H), 2.61 (ddd, 0.2H, *J*=3.0, 6.6, 9.3 Hz), 2.48 (ddd, 0.8H, *J*=3.1, 6.6, 9.4 Hz), 2.21 (ddd, 0.2H, *J*=7.5, 7.5, 7.5 Hz), 2.15 (ddd, 0.8H, *J*=7.5, 7.5, 7.5 Hz), 1.53 (s, 7.2H), 1.47 (s, 1.8H), 1.50–1.32 (m, 1H), 1.30–1.11 (m, 2H), 0.82 (d, 3H, *J*=6.5 Hz), 0.69 (d, 0.6H, *J*=6.5 Hz), 0.68 (2d, 4.8H, *J*=6.5 Hz), 0.64 (d, 0.6H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1 (0.2C), 149.3 (0.2C), 147.9 (0.8C), 146.9 (0.8C), 143.65 (0.8C), 143.56 (0.2C), 137.7 (0.8C), 137.4 (0.2C), 129.1 (1.2C), 129.0 (4.8C), 127.5 (4.8C), 127.4 (1.2C), 127.2 (0.6C), 127.1 (2.4C), 116.6 (0.2C), 116.1 (0.8C), 109.5 (0.2C), 108.9 (0.8C), 92.3 (0.2C), 91.8 (0.8C), 84.1 (0.8C), 83.8 (0.2C), 80.9 (1C), 71.7 (1C), 67.4 (0.2C), 67.2 (0.8C), 58.91 (0.2C), 58.87 (0.8C), 56.5 (0.8C), 56.4 (0.2C), 46.1 (0.2C), 44.0 (0.8C), 41.9 (0.2C), 41.8 (0.8C), 27.44 (2.4C), 27.36 (0.6C), 25.5 (0.2C), 25.3 (0.8C), 22.8 (0.2C), 22.6 (0.8C), 22.3 (0.8C), 21.9 (0.2C); LRMS: (FAB, NBA, *m/z*, %): 532 (4), 307 (11), 289 (10), 259 (23), 243 (100), 165 (42).

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-4(*S*)-vinyl-tetrahydro-furan-2(*S*)-carboxylic acid, *tert*-butoxycarbonyl-trityloxy-amide (24b). This compound was prepared following the same procedure as for **24a**. From **23b** (211 mg, 0.40 mmol) in CH_2Cl_2 (10 mL), Boc_2O (184 μL, 0.80 mmol), triethylamine (55 μL, 0.40 mmol), DMAP (49 mg, 0.40 mmol), was obtained, after flash chromatography (hexanes/EtOAc, 19:1), **24b** (247 mg, 0.39 mmol, 98%, colorless oil); R_f=0.52 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−75.2 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 1770.7, 1641.8, 1600.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.32 (m, 6H), 7.31–7.27 (m, 9H), 5.72 (ddd, 1H, *J*=9.2, 11.2, 16.8 Hz), 5.10 (m, 1H,), 5.05 (dd, 1H, *J*=2.0, 8.0 Hz), 4.92 (d, 1H, *J*=4.5 Hz), 3.92 (d, 1H, *J*=9.2 Hz), 3.80 (m, 1H), 3.56–3.48 (m, 3H), 3.37 (s, 3H), 2.49 (m, 1H), 2.30 (m, 1H), 1.52 (s, 9H), 1.31 (m, 1H), 1.14 (ddd, *J*=5.0, 7.9, 13.7 Hz) 1.00 (ddd, 1H, *J*=6.0, 8.0, 13.7 Hz), 0.63 (d, 3H, *J*=6.3 Hz), 0.57 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 147.8, 143.7, 135.0, 129.2, 129.1, 127.4, 127.1, 117.8, 105.1, 91.8, 84.0, 82.8, 71.5, 66.5, 59.0, 56.4, 41.1, 40.6, 27.5, 24.8, 23.3, 22.0; LRMS: (FAB, NBA, *m/z*, %): 652 (1) ($M+Na^+$), 243 (100).

4(*R*)-Formyl-3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid, *tert*-butoxycarbonyl-trityloxy-amide (25a). O_3 was bubbled through a vigorously stirred solution of **24a** (217 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) at −78°C for 50 min. An excess of dimethylsulfide (0.4 mL) was added, the solution allowed to warm up to 0°C then stirred for a further 15 min. The solution was concentrated in vacuo, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to

give **25a** (148 mg, 0.23 mmol, 68%, colorless oil); R_f=0.29–0.39 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−9.0 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 1770.8, 1729.1, 1651.5, 1596.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (2 rotamers 4:1) δ 9.63 (d, 0.2H, *J*=1.7 Hz), 9.58 (d, 0.8H, *J*=1.7 Hz) 7.39–7.32 (m, 6H), 7.32–7.24 (m, 9H), 5.47 (d, 0.2H, *J*=1.8 Hz), 5.38 (d, 0.8H, *J*=1.8 Hz), 5.28 (d, 0.2H, *J*=7.0 Hz), 4.29 (d, 0.8H, *J*=7.6 Hz), 3.91–3.78 (m, 1H), 3.70–3.50 (m, 3H), 3.38 (s, 0.6H), 3.35 (s, 2.4H), 2.87 (m, 0.2H), 2.77 (m, 0.8H), 2.67–2.58 (m, 1H), 1.72–1.55 (m, 1H), 1.52 (s, 7.2H), 1.43 (s, 1.8H), 1.38–1.22 (m, 2H), 0.75 (d, 0.6H, *J*=6.2 Hz), 0.73 (d, 2.4H, *J*=6.5 Hz), 0.71 (2d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3 (1C), 155.1 (0.2C), 149.3 (0.2C), 147.7 (0.8C), 146.05 (0.8C), 143.4 (2.4C), 143.3 (0.6C), 129.0 (1.2C), 128.9 (4.8C), 127.4 (4.8C), 127.3 (1.2C), 127.2 (0.6C), 127.1 (2.4C), 104.3 (0.2C), 103.7 (0.8C), 92.5 (0.2C), 92.0 (0.8C), 84.3 (0.8C), 84.0 (0.2C), 80.8 (0.8C), 76.7 (0.2C), 71.4 (1C), 67.0 (0.2C), 66.9 (0.8C), 64.3 (0.8C), 63.8 (0.2C), 58.78 (0.8C), 58.73 (0.2C), 42.3 (0.2C), 41.8 (0.8C), 41.4 (0.2C), 39.2 (0.8C), 27.3 (2.4C), 27.2 (0.6C), 26.1 (0.2C), 25.9 (0.8C), 22.9 (0.2C), 22.6 (0.8C), 21.8 (0.8C), 21.2 (0.2C); LRMS: (FAB, NBA, *m/z*, %): 648 (2) ($M+OH^+$), 307 (14), 289 (13), 259 (28), 243 (100), 165 (40).

4(*R*)-Formyl-3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2-carboxylic acid, *tert*-butoxycarbonyl-trityloxy-amide (25b). This compound was prepared by the same procedure as described above. From **24b** (239 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) was obtained **25b** (167 mg, 0.26 mmol, 70%, colorless oil) isolated by flash chromatography (hexanes/EtOAc, 9:1 then 4:1); R_f=0.75 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−70.9 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 1770.3, 1724.7, 1646.0, 1598.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (d, 1H, *J*=3.6 Hz), 7.40–7.32 (m, 6H), 7.31–7.22 (m, 9H), 5.29 (d, 1H, *J*=5.0 Hz), 4.25 (d, 1H, *J*=8.4 Hz), 3.78 (ddd, 1H, *J*=8.0, 8.0, 11.0 Hz), 3.54 (ddd, 1H, *J*=4.9, 6.2, 11.0 Hz), 3.47–3.43 (m, 2H), 3.32 (s, 3H), 3.08 (m, 1H), 2.58 (ddd, 1H, *J*=3.8, 5.1, 10.6 Hz), 1.53 (s, 9H), 1.23 (m, 1H), 1.18–1.05 (m, 2H), 0.68 (d, 3H, *J*=6.3 Hz), 0.66 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 148.1, 147.0, 143.6, 129.1, 129.0, 127.4, 127.2, 127.2, 104.2, 92.0, 84.3, 83.0, 71.4, 66.8, 62.4, 58.9, 41.7, 37.8, 27.5, 25.5, 22.4; LRMS: (FAB, NBA, *m/z*, %): 654 (1) ($M+Na^+$), 632 (1) ($M+H^+$), 243 (100).

5(*S*)-(*tert*-Butoxycarbonyl-trityloxy-carbamoyl)-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-carboxylic acid (26a). This compound was prepared following the same procedure as for **22a**. From **25a** (141 mg, 0.22 mmol) in *t*-BuOH (5 mL), NaH_2PO_4 (52 mg, 0.33 mmol) in water (1 mL), 2-methyl-2-butene (0.4 mL) and sodium chlorite (61 mg, 0.67 mmol) was obtained after purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 9:1), **26a** (136 mg, 0.21 mmol, 94%, white crystals); R_f=0.45 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=−9.8 (*c* 0.7, CH_3OH); IR (neat/NaCl) 3443.8, 1770.3, 1738.0, 1713.2, 1651.4 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) (2 rotamers 4:1) δ 7.35–7.23 (m, 15H), 5.36 (d, 0.2H, *J*=2.8 Hz), 5.27 (d, 0.8H, *J*=3.0 Hz), 5.25 (d, 0.2H, *J*=8.7 Hz), 4.11 (d, 0.8H, *J*=9.0 Hz), 3.85–3.70 (m, 1H), 3.64–3.46 (m, 3H), 3.31 (s, 0.6H), 3.28 (s, 2.4H), 2.80–2.61 (m, 1.2H), 1.51 (s, 7.2H), 1.43 (s, 1.8H), 1.58–1.38 (m, 1H), 1.33–1.12 (m, 2H), 0.75 (d, 3H, *J*=6.2 Hz), 0.70 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6 (1C), 157.0 (0.2C), 151.0 (0.2C), 149.5 (0.8C), 148.0 (0.8C), 145.0 (2.4C), 144.9 (0.6C), 130.3 (1.2C), 130.2 (4.8C), 128.63 (1.2C), 128.56 (4.8C), 128.4 (3C), 108.5 (0.2C), 108.1 (0.8C), 93.8 (0.2C), 93.3 (0.8C), 85.5 (0.8C), 85.3 (0.2C), 82.4 (0.8C), 77.7 (0.2C), 72.7 (1C), 68.3 (0.2C), 68.1 (0.8C), 59.1 (0.2C), 59.0 (0.8C), 45.0 (0.2C), 43.5 (1C), 42.8 (0.8C), 27.9 (2.4C), 27.7 (0.6C), 27.1 (0.2C), 26.9 (0.8C), 23.4 (1C), 22.7 (0.8C), 22.4 (0.2C). LRMS: (FAB, NBA, *m/z*, %): 670 (1) ($M+Na^+$), 648 (1) ($M+H^+$), 548 (71), 243 (100); HRMS calcd for $C_{37}H_{46}O_9N$ ($M+H^+$) 648.31726, found 648.31850.

5(*S*)-(*tert*-Butoxycarbonyl-trityloxy-carbamoyl)-4(*S*)-isobutyl-2(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-carboxylic acid (26b). From **25b** (79 mg, 0.12 mmol) in *t*-BuOH (2.5 mL), NaH_2PO_4 (29 mg, 0.19 mmol) in water (0.5 mL), 2-methyl-2-butene (0.2 mL) and sodium chlorite (34 mg, 0.37 mmol) was obtained after purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 9:1) **26b** (76 mg, 0.21 mmol, 94%, white foam); R_f=0.48 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=−79.3 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3412.0, 1769.8, 1723.3, 1642.0, 1596.2 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.35–7.29 (m, 6H), 7.29–7.21 (m, 9H), 5.20 (d, 1H, *J*=5.0 Hz), 4.12 (d, 1H, *J*=9.1 Hz), 3.63 (ddd, 1H, *J*=3.6, 6.0, 10.0 Hz), 3.58–3.45 (m, 3H), 3.30 (s, 3H), 2.97 (m, 1H), 2.75 (dd, 1H, *J*=5.0, 11.1 Hz), 1.50 (s, 9H), 1.32–1.22 (m, 2H), 1.10 (m, 1H), 0.68 (d, 3H, *J*=5.9 Hz), 0.65 (d, 3H, *J*=5.9 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 172.7, 149.6, 149.2, 145.0, 130.3, 128.5, 128.4, 104.6, 93.2, 85.5, 84.2, 72.5, 68.0, 59.3, 57.8, 43.3, 39.1, 28.0, 26.5, 24.2, 22.3; LRMS: (FAB, NBA, *m/z*, %): 670 (3) ($M+Na^+$), 570 (1), 243 (100); HRMS calcd for $C_{37}H_{45}O_9NNa$ ($M+Na^+$) 670.29919, found 670.30100.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 2-(*tert*-butoxycarbonyl-trityl-oxy-amide) 4-[(1-methylcarbamoyl-2(*R*)-phenyl-ethyl)-amide] (27a). To a solution of **26a** (64 mg, 0.099 mmol) in THF (2 mL) were added EDC (25 mg, 0.128 mmol), HOBT (17 mg, 0.128 mmol), *N*-methyl morpholine (31 μL, 0.277 mmol) and *N*-methyl-D-phenylalanine trifluoroacetate salt (46 mg, 0.148 mmol). After stirring for 15 h, the solution was diluted with CH_2Cl_2, washed with 0.1N HCl, water, 0.5N $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc, 1:1 to 1:4) to provide **27a** (54 mg, 0.067 mmol, 68%, colorless oil); R_f=0.53 (hexanes/EtOAc, 2:3); $[\alpha]_D$=−5.7 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 3315.8, 1775.1, 1674.7, 1629.4 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) (2 rotamers 4:1) δ 7.31–7.15 (m, 20H), 5.23 (d, 0.2H, *J*=9.0 Hz), 4.80 (d, 0.2H, *J*=3.8 Hz), 4.72 (d, 0.8H, *J*=3.5 Hz), 4.61 (2dd, 1H, *J*=6.5, 9.0 Hz), 4.08 (d, 0.8H, *J*=9.6 Hz), 3.73–3.60 (m, 1H), 3.52–3.35 (m, 3H), 3.32 (s, 0.6H), 3.30 (s, 2.4H), 3.06 (dd, 1H, *J*=6.5, 13.5 Hz), 2.86 (dd, 0.2H, *J*=8.9, 13.5 Hz), 2.85 (dd, 0.8H, *J*=9.0, 13.5 Hz), 2.70–2.54 (m, 2H), 2.65 (s, 3H), 1.48 (s, 7.2H), 1.42 (s, 1.8H), 1.40–1.27 (m, 1H), 1.10 (ddd, 1H, *J*=5.5, 8.5, 13.5 Hz), 1.00 (ddd, 1H, *J*=5.1, 9.5, 13.5 Hz), 0.70 (d, 2.4H, *J*=6.5 Hz), 0.68 (d,

0.6H, *J*=6.0 Hz), 0.60 (d, 2.4H, *J*=6.5 Hz), 0.58 (d, 0.6H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.5 (0.8C), 172.9 (1C), 172.5 (0.2C), 156.6 (0.2C), 151.0 (0.2C), 149.4 (0.8C), 147.8 (0.8C), 145.0 (2.4C), 144.9 (0.6C), 138.4 (1C), 130.6, 130.5, 130.3, 130.2, 129.92, 129.88, 129.77, 129.65, 129.4, 129.2, 129.0, 128.8, 128.6, 128.4, 127.8, 127.7, 109.0 (0.2C), 108.6 (0.8C), 93.7 (0.2C), 93.3 (0.8C), 85.6 (0.8C), 85.3 (0.2C), 82.3 (0.8C), 77.2 (0.2C), 72.7 (1C), 68.3 (0.2C), 68.1 (0.8C), 59.1 (0.2C), 59.0 (0.8C), 45.0 (0.2C), 43.5 (1C), 42.8 (0.8C), 27.9 (2.4C), 27.7 (0.6C), 27.1 (0.2C), 26.9 (0.8C), 23.4 (1C), 22.7 (0.8C), 22.4 (0.2C); LRMS: (FAB, NBA, *m/z*, %): 809 (1) ($M+H^+$), 243 (100); HRMS calcd for $C_{47}H_{59}O_9N_3$ ($M+H^+$) 809.42511, found 809.42820.

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 2-(*tert*-butoxycarbonyl trityl-oxy-amide) 4-[(1-methylcarbamoyl-2(*R*)-phenyl-ethyl)-amide] (27b). Following the procedure above, **26b** (75 mg, 0.116 mmol) in THF (3 mL), EDC (29 mg, 0.151 mmol), HOBT (20 mg, 0.151 mmol), *N*-methyl morpholine (36 μL, 0.32 mmol) and *N*-methyl-D-phenyl-alanine trifluoroacetate salt (54 mg, 0.174 mmol) afforded, after flash chromatography (hexanes/EtOAc, 1:1 to 1:4), **27b** (87 mg, 0.108 mmol, 93%, colorless oil); R_f=0.29 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−36.8 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3295.6, 3061.6, 1771.6, 1648.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.17 (m, 20H), 6.26 (d, 1H, *J*=4.6 Hz), 5.13 (d, 1H, *J*=3.6 Hz), 4.60 (ddd, 1H, *J*=6.1, 7.8, 13.5 Hz), 4.13 (d, 1H, *J*=8.8 Hz), 3.80 (ddd, 1H, *J*=3.6, 3.6, 11.0 Hz), 3.60 (ddd, 1H, *J*=4.0, 7.1, 11.0 Hz), 3.48–3.40 (m, 2H), 3.29 (s, 3H), 3.12 (dd, 1H, *J*=6.1, 13.5 Hz), 3.03 (dd, 1H, *J*=7.8, 13.5 Hz), 2.72 (d, 3H, *J*=4.5 Hz), 2.58–2.52 (m, 2H), 1.54 (s, 9H), 1.27–1.05 (m, 3H), 0.54 (d, 3H, *J*=5.9 Hz), 0.48 (d, 3H, *J*=5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 168.9, 148.1, 146.8, 143.5, 137.0, 129.2, 129.0, 128.6, 127.5, 127.2, 126.8, 101.9, 92.2, 84.4, 82.1, 70.9, 66.4, 58.6, 57.3, 54.7, 41.2, 40.7, 37.5, 27.6, 26.2, 24.9, 23.2, 21.8; LRMS: (FAB, NBA, *m/z*, %): 830 (1) ($M+Na^+$), 808 (2) ($M+H^+$), 243 (100); HRMS calcd for $C_{47}H_{57}O_9N_3$ ($M+H^+$) 808.41730, found 808.41490.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 4-benzhydryl-amide 2-(*tert*-butoxycarbonyl-trityloxy-amide) (28). To a solution of **26a** (72 mg, 0.111 mmol) in THF (2 mL) were added EDC (28 mg, 0.144 mmol), HOBT (19 mg, 0.144 mmol), *N*-methyl morpholine (16 μL, 0.144 mmol) and diphenyl-methylamine (29 μL, 0.167 mmol). The resulting solution was stirred for 14 h then diluted with CH_2Cl_2 washed with 0.1N HCl, water, 0.5N $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc, 1:1 to 1:4) to provide **28** (70 mg, 0.086 mmol, 78%, colorless oil); R_f=0.47 (hexanes/EtOAc, 3:2); $[\alpha]_D$=+3.7 (*c* 1.1, CH_3OH); IR (neat/NaCl) 3318.9, 1770.5, 1686.0 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) (2 rotamers 8:1, major rotamer described) δ 7.38–7.17 (m, 25H), 6.57 (d, 1H, *J*=8.2 Hz), 6.26 (d, 1H, *J*=8.2 Hz), 5.14 (d, 1H, *J*=5.0 Hz), 4.22 (d, 1H, *J*=9.5 Hz), 3.84 (ddd, 1H, *J*=3.1, 4.9, 11.0 Hz), 3.58 (ddd, 1H, *J*=3.6, 6.1, 11.0 Hz), 3.53–3.44 (m, 2H), 3.22 (s, 3H), 2.83 (m, 1H), 2.58 (dd, 1H, *J*=4.9, 9.5 Hz), 1.49 (s, 9H), 1.30–1.20 (m, 1H), 1.15 (ddd, 1H, *J*=5.7, 7.4, 13.3 Hz), 1.08 (ddd, 1H, *J*=6.0, 8.1, 13.3 Hz), 0.69 (d, 3H, *J*=6.1 Hz), 0.63 (d, 3H, *J*=6.1 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 72.4, 149.5, 147.8, 145.0, 142.8, 142.6, 130.3, 130.2, 129.5, 128.9, 128.6, 128.4, 128.3, 109.0, 93.3, 85.5, 82.5, 72.7, 68.8, 60.1, 59.1, 58.1, 44.2, 41.0, 27.9, 27.0, 23.9, 22.0; LRMS: (FAB, NBA, *m/z*, %): 813 (1) ($M+H^+$), 307 (28), 289 (20), 243 (100), 167 (35); HRMS calcd for $C_{50}H_{60}O_8N_3$ ($M+NH_4^+$) 830.43805, found 830.43760.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 2-hydroxyamide 4-[(1-methylcarbamoyl-2(*R*)-phenyl-ethyl)-amide] (11a). To a solution of **27a** (50 mg, 0.062 mmol) in CH_2Cl_2 (2 mL) was added a solution of 10% TFA in CH_2Cl_2 (1 mL) as to maintain a deep yellow color. The solution was stirred for 1 h then diluted by CH_2Cl_2 washed with 0.5 N $NaHCO_3$, then brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 9:1) afforded **11a** (24 mg, 0.052 mmol, 83%, colorless oil); R_f=0.19 (EtOAc); $[\alpha]_D$=+32.2 (*c* 0.8, CH_3OH); IR (neat/NaCl) 3290.1, 1652.2, 1644.2 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.30–7.15 (m, 5H), 4.80 (d, 1H, *J*=2.9 Hz), 4.61 (dd, 1H, *J*=6.1, 9.1 Hz), 4.02 (d, 1H, *J*=8.7 Hz), 3.70 (m, 1H), 3.52–3.42 (m, 3H), 3.36 (s, 3H), 3.09 (dd, 1H, *J*=6.1, 13.5 Hz), 2.87 (dd, 1H, *J*=9.1, 13.5 Hz), 2.69 (dd, 1H, *J*=2.6, 7.0 Hz), 2.67 (s, 3H), 1.62–1.35 (m, 3H), 0.86 (d, 3H, *J*=6.2 Hz), 0.76 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.6, 173.5, 169.9, 138.5, 130.3, 129.4, 127.7, 108.7, 83.2, 72.7, 68.2, 60.0, 59.2, 56.0, 46.5, 43.2, 39.1, 30.7, 27.3, 26.3, 23.8, 22.2; LRMS: (FAB, NBA, *m/z*, %): 488 (20) ($M+Na^+$), 466 (85) ($M+H^+$), 307 (66), 289 (41), 205 (52), 107 (67); HRMS calcd for $C_{23}H_{36}O_7N_3$ ($M+H^+$) 466.25534, found 466.25400.

3(*S*)-Isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 2-hydroxyamide 4-[(1-methyl-carbamoyl-2(*R*)-phenyl-ethyl)-amide] (11b). Following the same procedure as described above, **27b** (85 mg, 0.105 mmol) provided **11b** (28 mg, 0.060 mmol, 57%, colorless oil); R_f=0.21 (EtOAc); $[\alpha]_D$=−56.7 (*c* 0.8, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.30–7.15 (m, 5H), 5.09 (d, 1H, *J*=5.1 Hz), 4.53 (dd, 1H, *J*=5.9, 9.2 Hz), 4.02 (d, 1H, *J*=8.1 Hz), 3.60–3.37 (m, 4H), 3.37 (s, 3H), 3.08 (dd, 1H, *J*=5.9, 13.6 Hz), 2.92–2.81 (m, 2H), 2.74 (dd, 1H, *J*=5.2, 11.0 Hz), 2.68 (s, 3H), 1.62 (m,1H), 1.45 (ddd, 1H, *J*=6.8, 6.8, 6.8 Hz), 1.31 (ddd, 1H, *J*=6.8, 6.8, 6.8 Hz), 0.82 (d, 6H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 174.0, 171.7, 170.0, 138.6, 132.4, 130.2, 129.9, 129.5, 127.8, 105.8, 85.1, 72.2, 69.6, 59.1, 58.1, 56.3, 45.0, 43.0, 39.0, 27.0, 26.3, 23.3; LRMS: (FAB, NBA, *m/z*, %): 488 (7) ($M+Na^+$), 466 (21) ($M+H^+$), 419 (35), 390 (15), 132 (100); HRMS calcd for $C_{23}H_{36}O_7N_3$ ($M+H^+$) 466.25534, found 466.25790.

3(*S*)-Isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*),4(*S*)-dicarboxylic acid 4-benzhydryl-amide 2-hydroxy-amide (29). Compound **28** (67 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) and 10% TFA in CH_2Cl_2 (1 mL) afforded, after purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 19:1), **29** (32 mg, 0.068 mmol, 83%, colorless oil); R_f=0.58 (EtOAc); $[\alpha]_D$=+32.6 (*c* 0.9, CH_3OH); IR (neat/NaCl) 3289.8, 3063.2, 1644.9, 1538.5 cm^{-1}; ^{1}H NMR

(300 MHz, CD_3OD) δ 7.38–7.20 (m, 10H), 6.21 (s, 1H), 5.27 (d, 1H, J=2.5 Hz), 4.13 (d, 1H, J=7.9 Hz), 3.83 (ddd, 1H, J=3.0, 3.3, 8.1 Hz), 3.65 (ddd, 1H, J=3.8, 4.1, 8.5 Hz), 3.56 (m, 2H), 3.35 (s, 3H), 2.88 (dd, 1H, J=2.5, 6.0 Hz), 2.65 (m, 1H), 1.56 (m, 2H), 1.45 (m, 1H), 0.81 (d, 3H, J=6.2 Hz), 0.71 (d, 3H, J=6.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.0, 170.1, 142.8, 142.7, 129.5, 128.8, 128.5, 128.3, 128.0, 109.0, 83.3, 72.8, 68.5, 60.4, 59.1, 58.3, 47.2, 43.0, 27.3, 23.9, 22.0; LRMS: (FAB, NBA, *m/z*, %): 493 (9) ($M+Na^+$), 471 (88) ($M+H^+$), 307 (58), 289 (35), 182 (35), 167 (100); HRMS calcd for $C_{26}H_{35}O_6N_2$ ($M+H^+$) 471.25220, found 471.25040.

[4(*S*)-Azido-3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-ylmethoxy]-*tert*-butyl-diphenyl-silane (30a) and [4(*S*)-azido-3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-ylmethoxy]-*tert*-butyl-diphenyl-silane (30b). To a solution of **18** (1.05 g, 2.32 mmol) were added di(S-2-pyridyl) thiocarbonate (3.03 g, 13.9 mmol), 4 Å molecular sieves in CH_2Cl_2 (60 mL) followed by triethylamine (1.9 mL, 13.9 mmol). After stirring for 36 h, the mixture was quickly purified on silica gel and the filtrate processed as usual. Treatment of the residue with methoxyethanol (0.55 mL, 6.9 mmol) and dried silver triflate (1.79 g, 6.9 mmol) following the same procedure as for **19a** and **19b** gave the desired products. Purification by flash chromatography (hexanes/EtOAc, 50:1) gave **30a** (624 mg, 1.22 mmol, 53%, colorless oil) and **30b** (296 mg, 0.58 mmol, 25%, colorless oil) separated from the unreacted starting material (97 mg, 0.21 mmol, 9%). The relative configuration of both anomers was determined by NOE spectroscopy; for **30a** (*S*): R_f=0.64 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+52.1 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2098.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.68 (m, 4H), 7.48–7.38 (m, 6H), 5.06 (s, 1H), 3.86–3.75 (m, 4H), 3.68–3.54 (m, 4H), 3.40 (s, 3H), 2.20 (m, 1H), 1.60 (m, 1H), 1.42 (m, 1H), 1.27 (m, 1H), 1.09 (s, 9H), 0.92 (d, 3H, J=5.8 Hz), 0.89 (d, 3H, J=5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.6, 133.3, 129.7, 127.6, 106.9, 84.4, 71.7, 71.5, 66.5, 64.8, 59.0, 43.7, 41.4, 26.8, 26.4, 23.1, 22.1, 19.2; LRMS: (FAB, NBA, *m/z*, %): 408 (5), 257 (38), 213 (10), 199 (49), 197 (48), 135 (90). For **30b** (*R*): R_f=0.53 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−44.7 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2107.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.68 (m, 4H), 7.48–7.35 (m, 6H), 5.04 (d, 1H, J=4.6 Hz), 3.86–3.73 (m, 4H), 3.60 (ddd, 1H, J=4.6, 6.0, 10.8 Hz), 3.48 (m, 2H), 3.32 (s, 3H), 3.12 (dd, 1H, J=4.6, 10.8 Hz), 2.35 (m, 1H), 1.68 (m, 1H), 1.40 (m, 2H), 1.08 (s, 9H), 0.92 (d, 3H, J=5.8 Hz), 0.85 (d, 3H, J=5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 133.9, 130.2, 128.1, 103.4, 85.4, 72.2, 67.6, 67.3, 59.4, 43.0, 39.8, 27.3, 26.5, 23.7, 23.1, 19.7; LRMS: (FAB, NBA, *m/z*, %): 512 (19) ($M+H^+$), 510 (18), 408 (49), 378 (20), 351 (40), 322 (38), 257 (100), 135 (92).

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-ylamine (31a). A solution of **30a** (220 mg, 0.43 mmol) in absolute ethanol (20 mL) was stirred for 20 h in presence of 10% palladium-on-charcoal (150 mg) under hydrogen atmosphere. The suspension was then filtered on a celite pad and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:19) afforded **31a** (189 mg, 0.39 mmol, 96%, pale yellow oil); R_f=0.36 (EtOAc); $[\alpha]_D$=+41.9 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3375.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4H), 7.45–7.35 (m, 6H), 4.84 (s, 1H), 3.87–3.77 (m, 3H), 3.68 (dd, 1H, J=3.5, 10.4 Hz), 3.64–3.53 (m, 3H), 3.40 (s, 3H), 3.10 (m, 1H), 1.93 (m, 1H), 1.70 (m, 2H), 1.55 (m, 1H), 1.46 (m, 1H), 1.30 (m, 1H), 1.09 (s, 9H), 0.89 (d, 3H, J=6.1 Hz), 0.87 (d, 3H, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.65, 135.60, 133.3, 129.65, 129.61, 127.63, 127.60, 110.6, 84.8, 71.8, 66.1, 65.2, 63.5, 58.9, 45.8, 42.4, 26.8, 26.2, 22.8, 22.6, 19.2; HRMS calcd for $C_{28}H_{44}O_4NSi$ ($M+H^+$) 486.30396, found 486.30280.

5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-2(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-ylamine (31b). From **30b** (429 mg, 0.84 mmol) in absolute ethanol (20 mL) and 10% palladium-on-charcoal (150 mg) was obtained, after purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:19), **31b** (329 mg, 0.68 mmol, 82%, colorless oil); R_f=0.21 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=−35.5 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3389.0 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.72–7.67 (m, 4H), 7.48–7.36 (m, 6H), 4.80 (d, 1H, J=4.5 Hz), 3.81 (ddd, 1H, J=3.5, 5.8, 11.0 Hz), 3.78–3.67 (m, 3H), 3.56–3.44 (m, 3H), 3.28 (s, 3H), 2.83 (dd, 1H, J=4.5, 10.0 Hz), 3.10 (m, 1H), 1.75–1.63 (m, 1H), 1.49–1.33 (m, 2H), 1.25–1.17 (m, 1H), 1.05 (s, 9H), 0.83 (d, 3H, J=6.2 Hz), 0.73 (d, 3H, J=6.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 136.8, 130.9, 128.83, 128.81, 104.3, 87.4, 72.9, 69.5, 67.4, 62.4, 59.1, 44.3, 43.3, 27.5, 27.1, 24.3, 22.3, 20.1; LRMS: (FAB, NBA, *m/z*, %): 486 (24) ($M+H^+$), 428 (10), 410 (18), 241 (13), 199 (37), 197 (41), 154 (66), 135 (100); HRMS calcd for $C_{28}H_{44}O_4NSi$ ($M+H^+$) 486.30396, found 486.30190.

2(*S*)-Acetylamino-*N*-[5(*S*)-(*tert*-butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-3-phenyl-propionamide (32a). To a solution of *N*-acetyl-L-phenylalanine (164 mg, 0.79 mmol) in THF (5 mL) were successively added EDC (139 mg, 0.72 mmol), HOBT (98 mg, 0.72 mmol) and *N*-methyl morpholine (79 μL, 0.72 mmol). After stirring for 30 min, **31a** (319 mg, 0.66 mmol) in THF (1 mL) was added dropwise. The resulting mixture processed as described for **27a** to provide **32a** (291 mg, 0.43 mmol, 66%, colorless oil); R_f=0.56 (hexanes/EtOAc, 1:4); $[\alpha]_D$=+20.3 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3285.5, 1633.8 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70–7.65 (m, 4H), 7.48–7.37 (m, 6H), 7.28–7.15 (m, 5H), 4.49 (t, 1H, J=7.8 Hz), 4.43 (d, 1H, J=1.3 Hz), 3.97 (dd, 1H, J=1.3, 5.0 Hz), 3.77–3.65 (m, 4H), 3.55–3.45 (m, 3H), 3.36 (s, 3H), 2.96 (dd, 1H, J=7.8, 13.2 Hz), 2.87 (dd, 1H, J=7.8, 13.2 Hz), 1.89 (s, 3H), 1.84 (m, 1H), 1.50 (m, 1H), 1.37 (ddd, 1H, J=6.0, 9.1, 14.0 Hz), 1.21 (ddd, 1H, J=5.9, 8.0, 14.0 Hz), 1.03 (s, 9H), 0.80 (d, 3H, J=6.5 Hz), 0.78 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 172.8, 172.6, 138.2, 136.7, 134.9, 134.7, 130.9, 130.4, 129.4, 128.8, 127.8, 109.0, 85.6, 72.8, 67.3, 66.9, 62.6, 59.1, 56.0, 46.0, 42.9, 39.2, 27.4, 27.2, 23.5, 22.8, 22.4, 20.0; LRMS: (FAB, NBA, *m/z*, %): 697 (10) ($M+Na^+$), 675 (15) ($M+H^+$), 617 (21), 599 (100), 154 (84), 135 (57), 120 (94); HRMS calcd for $C_{39}H_{55}O_6N_2Si$ ($M+H^+$) 675.38293, found 675.38020.

2(*S*)-Acetylamino-*N*-[5(*S*)-(*tert*-butyl-diphenyl-silanyloxy-methyl)-4(*S*)-isobutyl-2(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-3-phenyl-propionamide (32b). From **31b** (321 mg, 0.662 mmol), *N*-acetyl-L-phenylalanine (206 mg, 0.99 mmol) in THF (5 mL), EDC (165 mg, 0.86 mmol), HOBt (116 mg, 0.86 mmol) and *N*-methyl morpholine (95 μL, 0.86 mmol) was obtained after flash chromatography (hexanes/EtOAc, 2:3 then 1:4), **32b** (315 mg, 0.47 mmol, 70%, colorless oil); R_f=0.64 (hexanes/EtOAc, 1:4); $[\alpha]_D$=−13.9 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3445.2, 3310.4, 1634.0 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.70–7.63 (m, 4H), 7.48–7.35 (m, 6H), 7.29–7.15 (m, 5H), 4.65 (d, 1H, *J*=4.4 Hz), 4.63 (dd, 1H, *J*=6.4, 8.4 Hz), 4.06 (dd, 1H, *J*=4.3, 10.4 Hz), 3.80–3.70 (m, 1H), 3.70–3.63 (m, 3H), 3.38–3.31 (m, 3H), 3.22 (s, 3H), 3.05 (dd, 1H, *J*=6.3, 13.5 Hz), 2.83 (dd, 1H, *J*=8.5, 13.5 Hz), 2.05 (m, 1H), 1.89 (s, 3H), 1.42 (m, 1H), 1.37–1.23 (m, 2H), 1.04 (s, 9H), 0.82 (d, 3H, *J*=6.3 Hz), 0.75 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.3, 172.8, 138.4, 136.7, 134.5, 134.4, 130.9, 130.3, 129.4, 128.8, 127.7, 102.2, 86.4, 72.7, 68.8, 66.9, 59.1, 59.0, 56.0, 43.2, 41.8, 39.1, 27.4, 26.7, 23.4, 23.2, 22.4, 20.0; LRMS: (FAB, NBA, *m/z*, %): 697 (10) ($M+Na^+$), 675 (72) ($M+H^+$), 617 (21), 599 (95), 307 (9), 241 (10), 199 (25), 197 (26), 154 (100), 135 (64), 120 (99); HRMS calcd for $C_{39}H_{55}O_6N_2Si$ ($M+H^+$) 675.38293, found 675.38090.

***N*-[5(*S*)-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-4-methoxy-benzenesulfonamide (33).** To *p*-methoxy-benzenesulfonyl chloride (117 mg, 0.57 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (78 μL, 0.57 mmol) at 0°C. After stirring for 30 min, **31a** (183 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at 0°C for 1 h then at room temperature for 15 h. The solution was diluted with CH_2Cl_2, washed with diluted HCl, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1 then 4:1) to provide **33** (218 mg, 0.33 mmol, 88%, colorless oil); R_f=0.75 (hexanes/EtOAc, 3:2); $[\alpha]_D$=+23.5 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3273.1, 3072.0, 3049.1, 1597.4, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J*=8.9 Hz), 7.72–7.63 (m, 4H), 7.47–7.34 (m, 6H), 6.95 (d, 2H, *J*=8.9 Hz), 4.97 (d, 1H, *J*=10 Hz), 4.80 (s, 1H), 3.88 (s, 3H), 3.82 (dd, 1H, *J*=2.5, 11.2 Hz), 3.72 (m, 1H), 3.68–3.42 (m, 6H), 3.36 (s, 3H), 1.98 (m, 1H), 1.55 (m, 1H), 1.43–1.25 (m, 3H), 1.11 (s, 9H), 0.75 (d, 3H, *J*=6.0 Hz), 0.72 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 135.6, 135.5, 132.9, 132.7, 132.6, 129.84, 129.81, 129.2, 127.80, 127.78, 114.2, 107.2, 84.1, 71.5, 65.8, 64.6, 63.7, 58.9, 55.6, 44.3, 42.4, 27.0, 25.9, 22.5, 22.3, 19.2; LRMS: (FAB, NBA, *m/z*, %): 678 (24) ($M+Na^+$), 654 (21), 486 (74), 324 (46), 135 (88), 59 (100).

2(*S*)-Acetylamino-*N*-[5(*S*)-hydroxymethyl-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-3-phenyl-propionamide (34a). The deprotection was performed following the same procedure as for **19a** and 19b. From **32a** (241 mg, 0.36 mmol) in THF (5 mL), AcOH (61 μL, 1.07 mmol) and a solution of TBAF (1.07 mL, 1.07 mmol, 1 M solution in THF) was obtained, after flash chromatography (CH_2Cl_2/CH_3OH, 97:3), **34a** (135 mg, 0.31 mmol, 87%, colorless oil); R_f=0.40 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=+19.4 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3417.6, 3300.0, 1654.8 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.30–7.17 (m, 5H), 4.49 (dd, 1H, *J*=7.0, 8.1 Hz), 4.48 (s, 1H), 4.02 (dd, 1H, *J*=0.8, 3.7 Hz), 3.78 (ddd, 1H, *J*=2.5, 4.3, 7.0 Hz), 3.57–3.42 (m, 2H), 3.56–3.44 (m, 4H), 3.36 (s, 3H), 3.05 (dd, 1H, *J*=7.0, 13.5 Hz), 2.87 (dd, 1H, *J*=8.1, 13.5 Hz), 1.92 (m, 1H), 1.90 (s, 3H), 1.62 (m, 1H), 1.49 (ddd, 1H, *J*=6.0, 8.8, 13.5 Hz), 1.32 (ddd, 1H, *J*=6.3, 8.0, 13.5 Hz), 0.88 (d, 3H, *J*=6.5 Hz), 0.86 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 172.9, 172.4, 138.3, 130.3, 129.4, 127.7, 109.1, 86.0, 72.8, 67.1, 63.6, 62.0, 59.1, 56.2, 44.8, 43.2, 39.0, 27.3, 23.4, 22.8, 22.4; LRMS: (FAB, NBA, *m/z*, %): 437 (10) ($M+H^+$), 361 (100), 242 (35), 154 (45), 136 (33), 120 (61); HRMS calcd for $C_{23}H_{37}O_6N_2$ ($M+H^+$) 437.26517, found 437.26630.

2(*S*)-Acetylamino-*N*-[5(*S*)-hydroxymethyl-4(*S*)-isobutyl-2(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-3-phenyl-propionamide (34b). The deprotection was performed following the same procedure as for **19a** and **19b**. From **32b** (305 mg, 0.45 mmol), in THF (5 mL), AcOH (75 μL, 1.31 mmol), solution of TBAF (1.36 mL, 1.36 mmol, 1 M solution in THF) was obtained **34b** (160 mg, 0.37 mmol, white crystals, 81%); R_f=0.40 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=−54.0 (*c* 0.7, $CHCl_3$); mp 134°C; IR (neat/NaCl) 3422.6, 3305.9, 1644.4 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.30–7.15 (m, 5H), 4.65 (d, 1H, *J*=4.5 Hz), 4.63 (dd, 1H, *J*=6.4, 8.4 Hz), 4.08 (dd, 1H, *J*=4.5, 10.4 Hz), 3.80–3.72 (m, 2H), 3.63 (dd, 1H, *J*=2.9, 11.7 Hz), 3.57–3.40 (m, 4H), 3.33 (s, 3H), 3.08 (dd, 1H, *J*=6.4, 13.5 Hz), 2.85 (dd, 1H, *J*=8.4, 13.5 Hz), 2.12 (m, 1H), 1.90 (s, 3H), 1.60 (m, 1H), 1.47–1.25 (m, 2H), 0.89 (d, 3H, *J*=6.5 Hz), 0.85 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.5, 172.9, 138.4, 130.3, 129.4, 127.7, 102.1, 86.8, 72. 8, 67.4, 66.2, 59.3, 58.9, 56.1, 43.0, 40.5, 39.0, 27.0, 23.6, 22.8, 22.4; LRMS: (FAB, NBA, *m/z*, %): 437 (21) ($M+H^+$), 361 (100), 307 (11), 242 (76), 154 (56), 136 (40), 120 (57); HRMS calcd for $C_{23}H_{36}O_6N_2Na$ ($M+Na^+$) 459.24710, found 459.24903.

***N*-[5(*S*)-Hydroxymethyl-4(*S*)-isobutyl-2(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-3(*S*)-yl]-4-methoxy-benzenesulfonamide (35).** The deprotection was performed following the same procedure as described above. From **33** (212 mg, 0.32 mmol), in THF (5 mL), AcOH (80 μL, 1.40 mmol) and TBAF (254 mg, 0.98 mmol) was obtained, after flash chromatography (hexanes/EtOAc, 1:1 then 2:3), **35** (123 mg, 0.29 mmol, colorless oil, 91%); R_f=0.64 (EtOAc); $[\alpha]_D$=+23.2 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 3483.8, 3272.0, 1597.1, 1579.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 2H, *J*=9.0 Hz), 6.98 (d, 2H, *J*=9.0 Hz), 5.70 (m, 1H), 4.88 (s, 1H), 3.86 (s, 3H), 3.85 (dd, 1H, *J*=2.1, 11.9 Hz), 3.79 (ddd, 1H, *J*=2.2, 2.2, 5.2 Hz), 3.66 (m, 1H), 3.50–3.42 (m, 5H), 3.35 (s, 3H), 2.47 (m, 1H), 1.85 (m, 1H), 1.37–1.22 (m, 3H), 0.72 (d, 3H, *J*=6.1 Hz), 0.88 (d, 3H, *J*=6.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.8, 132.1, 129.2, 114.2, 107.7, 84.1, 71.5, 65.8, 63.8, 62.5, 58.8, 55.5, 43.8, 42.3, 25.8, 22.5, 22.1; LRMS: (FAB, NBA, *m/z*, %): 440 (80) ($M+Na^+$), 342 (100), 171 (42); HRMS calcd for $C_{19}H_{31}O_7NSNa$ ($M+Na^+$) 440.17191, found 440.17070.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid (36a). Oxidation of **34a** (155 mg, 0.36 mmol) in dry CH_2Cl_2 (5 mL), with *N*-methyl morpholine *N*-oxide (61 mg, 0.53 mmol), 4 Å molecular sieves and a catalytic amount of tetrapropylammonium perruthenate gave the corresponding aldehyde. This was dissolved in *t*-BuOH (5 mL) and water (1 mL) containing NaH_2PO_4 (83 mg, 0.53 mmol) then 2-methyl-2-butene (0.4 mL) and sodium chlorite (96 mg, 1.07 mmol) were added. After stirring for 3 h, the residue was purified by flash chromatography (CH_2Cl_2/CH_3OH, 19:1 to 9:1) to provide **36a** (90 mg, 0.13 mmol, 56%, colorless oil); R_f=0.20 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=+42.3 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 3290.8, massif over 1700 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.30–7.14 (m, 5H), 4.71 (s, 1H), 4.52 (dd, 1H, *J*=6.3, 9.0 Hz), 4.11 (m, 2H), 3.71 (m, 1H), 3.55–3.49 (m, 3H), 3.35 (s, 3H), 3.06 (dd, 1H, *J*=6.3, 13.5 Hz), 2.86 (dd, 1H, *J*=9.0, 13.5 Hz), 2.15 (m, 1H), 1.90 (s, 3H), 1.74 (m, 1H), 1.60–1.53 (m, 2H), 0.89 (d, 3H, *J*=6.5 Hz), 0.85 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.2, 173.2, 172.9, 138.6, 130.3, 129.5, 127.8, 109.6, 83.8, 72.8, 67.5, 62.0, 59.1, 56.7, 43.4, 39.0, 27.1, 23.7, 22.5, 22.4; LRMS: (FAB, NBA, *m/z*, %): 473 (38) ($M+Na^+$), 451 (7) ($M+H^+$), 176 (32), 154 (100), 137 (65), 136 (66), 120 (26); HRMS calcd for $C_{23}H_{34}O_7N_2Na$ ($M+H^+$) 473.22638, found 473.22504.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid (36b). Compound **34b** was oxidized following the same procedure as described above. From **34b** (155 mg, 0.36 mmol) in dry CH_2Cl_2 (5 mL), *N*-methyl morpholine *N*-oxide (122 mg, 1.06 mmol), 4 Å molecular sieves, catalytic amount of tetrapropylammonium perruthenate then *t*BuOH (5 mL), NaH_2PO_4 (83 mg, 0.53 mmol) in water (1 mL), 2-methyl-2-butene (0.4 mL) and sodium chlorite (96 mg, 1.07 mmol) was obtained **36b** (112 mg, 0.24 mmol, 69%, colorless oil); R_f=0.27 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=−30.4 (*c* 0.6, $CHCl_3$); IR (neat/NaCl) 3302.0, 1731.2, 1653.3 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.30–7.15 (m, 5H), 4.73 (d, 1H, *J*=4.5 Hz), 4.64 (dd, 1H, *J*=6.4, 8.6 Hz), 4.12 (d, 1H, *J*=7.9 Hz), 4.09 (m, 1H), 3.82 (m, 1H), 3.59–3.42 (m, 3H), 3.33 (s, 3H), 3.07 (dd, 1H, *J*=6.4, 13.5 Hz), 2.85 (dd, 1H, *J*=8.6, 13.5 Hz), 2.51 (m, 1H), 1.90 (s, 3H), 1.70 (m, 1H), 1.50 (m, 2H), 0.89 (d, 3H, *J*=6.5 Hz), 0.87 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4, 173.6, 172.9, 138.4, 130.3, 129.4, 127.7, 102.6, 82.4, 72.7, 67.0, 59.0, 58.9, 56.0, 48.2, 43.9, 43.6, 39.1, 26.8, 23.2, 22.3; LRMS: (FAB, NBA, *m/z*, %): 473 (5) ($M+Na^+$), 451 (12) ($M+H^+$), 154 (100), 137 (70), 136 (69), 120 (40); HRMS calcd for $C_{23}H_{34}O_7N_2Na$ ($M+Na^+$) 473.22638, found 473.22504.

3(*S*)-Isobutyl-4(*S*)-(4-methoxy-benzenesulfonylamino)-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid (37). A solution of **35** (123 mg, 0.29 mmol) in dry CH_2Cl_2 (5 mL), *N*-methyl morpholine (102 mg, 0.88 mmol), 4 Å molecular sieves, catalytic amount of tetrapropylammonium perruthenate afforded the aldehyde as described above. Oxidation in *t*-BuOH (5 mL) containing NaH_2PO_4 (69 mg, 0.44 mmol) in water (1 mL), 2-methyl-2-butene (0.2 mL) and sodium chlorite (80 mg, 0.88 mmol), followed by flash chromatography (CH_2Cl_2/CH_3OH, 19:1 to 9:1) gave **37** (94 mg, 0.22 mmol, 74%, colorless oil); R_f=0.15 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=+30.4 (*c* 0.9, CH_3OH); IR (neat/NaCl) 3486.3, 3264.6, 1714.6, 1597.5 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.80 (d, 2H, *J*=8.9 Hz), 7.08 (d, 2H, *J*=8.9 Hz), 4.70 (s, 1H), 3.96 (d, 1H, *J*=7.5 Hz), 3.88 (s, 3H), 3.61 (m, 1H), 3.46–3.38 (m, 3H), 3.33 (s, 3H), 3.29 (m, 1H), 2.01 (m, 1H), 1.52–1.25 (m, 3H), 0.76 (d, 3H, *J*=6.0 Hz), 0.74 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 177.4, 164.5, 133.9, 130.4, 115.4, 109.2, 83.6, 72.6, 67.4, 65.9, 59.1, 56.2, 49.2, 43.5, 26.8, 23.4, 22.5; LRMS: (FAB, NBA, *m/z*, %): 454 (9%) ($M+Na^+$), 432 (8) ($M+H^+$), 154 (100), 136 (84); HRMS calcd for $C_{19}H_{29}O_8NSNa$ ($M+Na^+$) 454.15115, found 454.15260.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid trityloxy-amide (38a). The coupling was performed according to the procedure used for **23a**. Thus **36a** (61 mg, 0.135 mmol) in THF (3 mL), EDC (31 mg, 0.162 mmol), HOBT (22 mg, 0.162 mmol), *N*-methyl morpholine (18 μL, 0.162 mmol) was treated with *N*-acetyl-L-phenylalanine (42 mg, 0.20 mmol). The residue was chromatographed (CH_2Cl_2/CH_3OH, 1:0 to 19:1) to provide **38a** (45 mg, 0.063 mmol, 47%, colorless oil); R_f=0.32 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+17.3 (*c* 0.9, CH_3OH); IR (neat/NaCl) 3281.8, 1651.0 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.45–7.38 (m, 6H), 7.33–7.14 (m, 14H), 4.49 (dd, 1H, *J*=6.8, 8.2 Hz), 4.45 (s, 1H), 3.97 (dd, 1H, *J*=3.8, 9.0 Hz), 3.88 (d, 1H, *J*=6.8 Hz), 3.60 (m, 1H), 3.49–3.38 (m, 3H), 3.30 (s, 3H), 3.02 (dd, 1H, *J*=6.8, 13.5 Hz), 2.86 (dd, 1H, *J*=8.2, 13.5 Hz), 1.91 (s, 3H), 1.86 (m, 1H), 1.52 (m, 1H), 1.37 (ddd, 1H, *J*=6.0, 9.1, 13.5 Hz), 1.18 (ddd, 1H, *J*=5.5, 7.9, 13.5 Hz), 0.88 (d, 3H, *J*=6.5 Hz), 0.85 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 173.1, 172.5, 170.2, 143.3, 138.4, 130.3, 130.1, 130.0, 129.9, 129.5, 129.1, 128.9, 128.8, 128.5, 127.9, 127.8, 109.9, 94.8, 82.4, 72.7, 67.6, 61.3, 59.1, 56.4, 47.7, 42.8, 39.0, 27.2, 23.5, 22.54, 22.45; LRMS: (FAB, NBA, *m/z*, %): 730 (12) ($M+Na^+$), 708 (12) ($M+H^+$), 307 (52), 243 (100), 154 (27), 137 (19), 136 (20), 120 (12); HRMS calcd for $C_{42}H_{49}O_7N_3Na$ ($M+Na^+$) 730.34680, found 730.34820.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid trityloxy-amide (38b). The coupling was performed according to the procedure described above. From **36b** (109 mg, 0.24 mmol) in THF (4 mL), EDC (56 mg, 0.29 mmol), HOBT (39 mg, 0.29 mmol), *N*-methyl morpholine (32 μL, 0.29 mmol) and *N*-acetyl-L-phenylalanine (75 mg, 0.36 mmol) was obtained, after flash chromatography (hexanes/EtOAc, 1:1 to 1:4), **38b** (98 mg, 0.138 mmol, 57%, colorless oil); R_f=0.23 (hexanes/EtOAc, 2:3); $[\alpha]_D$=−20.1 (*c* 1.1, CH_3OH); IR (neat/NaCl) 3401.5, 1651.7 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.45–7.38 (m, 6H), 7.35–7.13 (m, 14H), 4.65 (dd, 1H, *J*=6.7, 8.4 Hz), 4.62 (d, 1H, *J*=4.5 Hz), 4.05 (dd, 1H, *J*=4.5, 11.0 Hz), 3.87 (d, 1H, *J*=8.9 Hz), 3.27 (s, 3H), 3.17–3.10 (m, 3H), 3.07 (dd, 1H, *J*=6.7, 13.6 Hz), 2.82 (dd, 1H, *J*=8.4, 13.6 Hz), 2.14 (m, 1H), 1.90 (s, 3H), 1.60–1.48 (m, 1H), 1.34–1.28 (m, 2H), 0.75 (d, 3H, *J*=6.5 Hz), 0.70 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 173.4,

172.8, 170.5, 143.1, 138.5, 130.3, 130.0, 129.4, 129.0, 128.5, 127.7, 103.1, 94.6, 83.2, 72.5, 68.1, 59.1, 58.5, 56.0, 55.9, 43.4, 43.2, 38.8, 26.4, 23.6, 23.2, 22.4; LRMS: (FAB, NBA, *m/z*, %): 730 (12) ($M+Na^+$), 708 (8) ($M+H^+$), 307 (70), 289 (50), 259 (46), 243 (100), 154 (25), 137 (19), 136 (20), 120 (13); HRMS calcd for $C_{42}H_{49}O_7N_3Na$ ($M+Na^+$) 730.34680, found 730.34550.

3(*S*)-Isobutyl-4(*S*)-(4-methoxy-benzenesulfonylamino)-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid trityloxy-amide (39). The coupling was performed according to the procedure described above. From **37** (73 mg, 0.17 mmol) in THF (3 mL), EDC (49 mg, 0.25 mmol), HOBT (34 mg, 0.25 mmol), *N*-methyl morpholine (28 μL, 0.25 mmol) and *N*-acetyl-L-phenylalanine (207 mg, 0.25 mmol) was obtained **39** (62 mg, 0.090 mmol, 54%, colorless oil) after flash chromatography (hexanes/EtOAc, 3:2); R_f=0.53 (hexanes/EtOAc, 1:1); $[\alpha]_D$=+9.4 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3253.7, 1694.0, 1597.0, 1578.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.70 (d, 2H, *J*=8.9 Hz), 7.51 (m, 5H), 7.90–7.79 (m, 10H), 6.97 (d, 2H, *J*=8.9 Hz), 4.85 (s, 1H), 4.31 (d, 1H, *J*=7.5 Hz), 3.88 (s, 3H), 3.86 (d, 1H, *J*=6.0 Hz), 3.58 (m, 1H), 3.46–3.39 (m, 3H), 3.31 (s, 3H), 3.27 (dd, 1H, *J*=1.8, 7.5 Hz), 1.50 (m, 1H), 1.41–1.10 (m, 3H), 0.63 (d, 3H, *J*=6.3 Hz), 0.61 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 167.4, 163.0, 141.5, 131.3, 129.2, 128.8, 128.2, 128.0, 127.8, 114.2, 108.3, 93.5, 81.5, 71.3, 66.3, 62.8, 55.6, 48.5, 42.6, 25.7, 22.4, 21.9; LRMS: (FAB, NBA, *m/z*, %): 711 (20) ($M+Na^+$), 578 (29), 310 (38), 286 (21), 243 (10); HRMS calcd for $C_{38}H_{44}O_8N_2SNa$ ($M+Na^+$) 711.27161, found 711.27590.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid hydroxyamide (12a). The deprotection was performed using the procedure described for **11a**, from **38a** (39 mg, 0.055 mmol) in CH_2Cl_2 (2 mL) and 10% TFA in CH_2Cl_2 (1 mL) was obtained after purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 19:1), **12a** (20 mg, 0.042 mmol, 78%, colorless oil): R_f=0.19 (EtOAc); $[\alpha]_D$=+47.7 (*c* 0.8, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 7.31–7.17 (m, 5H), 4.60 (d, 1H, *J*=0.8 Hz), 4.51 (dd, 1H, *J*=7.1, 8.1 Hz), 4.03 (m, 1H), 4.02 (d, 1H, *J*=6.8 Hz), 3.68 (m, 1H), 3.53–3.48 (m, 3H), 3.35 (s, 3H), 3.05 (dd, 1H, *J*=7.1, 13.5 Hz), 2.90 (dd, 1H, *J*=8.1, 13.5 Hz), 2.18 (m, 1H), 1.91 (s, 3H), 1.67 (m, 1H), 1.55–1.42 (m, 2H), 0.88 (d, 3H, *J*=6.5 Hz), 0.85 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 173.2, 172.7, 170.1, 138.4, 130.3, 129.5, 127.8, 109.7, 82.6, 72.7, 67.7, 61.7, 59.1, 56.4, 48.4, 43.2, 38.9, 27.2, 23.2, 22.7, 22.3; LRMS: (FAB, NBA, *m/z*, %): 466 (13) ($M+H^+$), 390 (18), 154 (100), 137 (83), 136 (76), 120 (36); HRMS calcd for $C_{23}H_{35}O_7N_3Na$ ($M+Na^+$) 488.23727, found 488.23919.

4(*S*)-(2(*S*)-Acetylamino-3-phenyl-propionylamino)-3(*S*)-isobutyl-5(*R*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid hydroxyamide (12b). The deprotection was performed using the procedure described above. Compound **38b** (71 mg, 0.100 mmol) in CH_2Cl_2 (2 mL) was treated with 10% TFA in CH_2Cl_2 (1 mL). A purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 19:1) afforded **12b** (42 mg, 0.090 mmol, 90%, colorless oil); R_f=0.35 (EtOAc); $[\alpha]_D$=−76.9 (*c* 0.7, CH_3OH); mp 152–154°C; IR (neat/NaCl) 3282.0, 1651.0 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.30–7.15 (m, 5H), 4.76 (d, 1H, *J*=4.8 Hz), 4.63 (dd, 1H, *J*=6.8, 8.4 Hz), 4.11 (dd, 1H, *J*=4.8, 10.9 Hz), 4.07 (d, 1H, *J*=8.9 Hz), 3.1 (m, 1H), 3.63–3.45 (m, 3H), 3.39 (s, 3H), 3.07 (dd, 1H, *J*=6.8, 13.6 Hz), 2.85 (dd, 1H, *J*=8.4, 13.6 Hz), 2.41 (m, 1H), 1.90 (s, 3H), 1.73 (m, 1H), 1.55–1.38 (m, 2H), 0.87 (d, 3H, *J*=6.4 Hz), 0.84 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 173.5, 173.0, 171.3, 138.4, 130.3, 129.4, 127.8, 103.2, 83.4, 72.5, 69.1, 59.1, 58.6, 56.1, 44.1, 43.2, 39.0, 26.6, 23.3, 23.2, 22.4; LRMS: (FAB, NBA, *m/z*, %): 466 (21) ($M+H^+$), 390 (24), 154 (100), 137 (69), 136 (72), 120 (46); HRMS calcd for $C_{23}H_{35}O_7N_3Na$ ($M+Na^+$) 488.23727, found 488.23820.

3(*S*)-Isobutyl-4(*S*)-(4-methoxy-benzenesulfonylamino)-5(*S*)-(2-methoxy-ethoxy)-tetrahydro-furan-2(*S*)-carboxylic acid hydroxyamide (40). The deprotection was performed using the procedure described above. Compound **39** (89 mg, 0.129 mmol) in CH_2Cl_2 (2 mL) saturated with water was treated with 10% TFA in CH_2Cl_2 (1 mL). Purification by flash chromatography (CH_2Cl_2/CH_3OH, 1:0 to 9:1) afforded **40** (42 mg, 0.117 mmol, 90%, colorless oil): R_f=0.28 (CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D$=+40.7 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3271.7, 1668.1 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.80 (d, 2H, *J*=6.3 Hz), 7.09 (d, 2H, *J*=6.3 Hz), 4.90 (m, 3H), 4.79 (s, 1H), 3.95 (d, 1H, *J*=5.1 Hz), 3.88 (s, 3H), 3.62 (m, 1H), 3.47 (m, 2H), 3.40 (m, 1H), 3.34 (s, 3H), 3.33 (m, 1H), 2.08 (m, 1H), 1.45–1.29 (m, 3H), 0.78 (d, 3H, *J*=3.9 Hz), 0.75 (d, 3H, *J*=3.9 Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 169.8, 164.5, 133.6, 130.4, 115.4, 109.6, 82.0, 72.6, 67.6, 65.8, 59.1, 56.2, 48.7, 43.2, 26.8, 23.1, 22.7; LRMS: (FAB, NBA, *m/z*, %): 469 (9) ($M+Na^+$), 447 (15) ($M+H^+$), 371 (100), 310 (66), 171 (73), 154 (66), 136 (54), 107 (46); HRMS calcd for $C_{19}H_{30}O_8N_2SNa$ ($M+Na^+$) 469.16205, found 469.16410.

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