DOI: 10.1002/chem.200500515

Regioselective Conversion of the Secondary Hydroxyl Groups of D-Glucuronic Acid without the Requirement of *O*-Protecting Groups

Károly Ágoston[a] and Armin Geyer*[b]

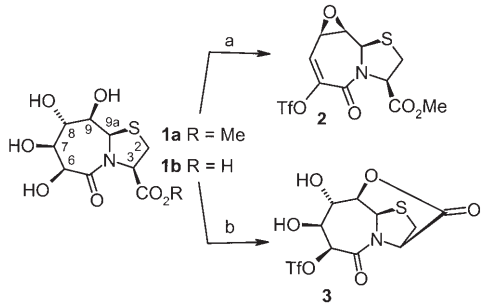
Abstract: Trifluoromethanesulfonic acid anhydride (triflic acid anhydride) transforms the bicyclic thiazolidinlactam **1a** into the crystalline elimination product **2**, in which all four secondary hydroxyl groups of **1a** are differently functionalized. Compound **2** can then add nucleophiles with high chemo- and stereoselectivity. Altogether, the four secondary hydroxyl groups of D-glucuronic acid are selectively transformed without the need for any *O*-protecting groups. Minimizing the number of *O*-protecting groups is a prerequisite for the use of sugar scaffolds in molecular libraries. The hapalosin analogues **15**, **16**, **19**, and **22** outline the strategy towards *O*-diversified glucose derivatives.

Keywords: carbohydrates · glucose · hapalosin · synthetic methods · thiazolidinlactams

Introduction

The combination of protection and activation in a single functional group, which can be an epoxide or an active ester, allows the straightforward modification of sugar secondary hydroxyl groups. For example, the Cerny epoxide is an activated D-glucose derivative that adds nucleophiles selectively without the need for *O*-protecting groups.[1] The regioselective functionalization of equally reactive secondary hydroxyl groups in as few as possible synthetic steps is a prerequisite for the synthesis of sugar-based[2] or other small-molecule libraries.[3] Carbohydrate scaffolds that bear a different activating group on every carbon atom offer interesting options for molecular diversity-based synthetic strategies. Carbohydrate-based chiral-pool strategies are well established in organic chemistry, but only a few synthetic approaches do not require the tedious shuffling of protecting groups. Here, we describe the transformation of the chiral-pool bulk material D-glucuronic acid into selectively *O*-diversified products, by the generation of orthogonal reactive sites at the positions of the secondary hydroxyl groups, followed by the addition of nucleophiles with high regio- and stereoselectivity to the sterically and functionally overcrowded synthesis intermediates.

The elimination cascade that converts polyol **1a** into elimination product **2** was observed in an effort to regioselectively functionalize all four hydroxy groups of **1a** (Scheme 1), to obtain bicyclic dipeptides[4] with diversified



Scheme 1. Reaction conditions: a) 5 equiv Tf_2O, DMAP (cat.), pyridine/DCM, 0 °C→RT, 12 h, 80 %; b) 2.5 equiv Tf_2O, pyridine/DCM, 0 °C→RT, 1 h, 37 %.

side-chains. The transformation of **2** into hapalosin[5] analogues is shown here as a possible application of the azepane scaffold. Hydroxyazepanes[6] and other perfunctionalized medium-sized rings[7] are recurring scaffolds in medicinal chemistry, and derivatives of **2** have additional functions. Peptidomimetics that are based on bicyclic medium-sized thiazolidinlactam rings have applications ranging from model peptides[8] to drugs.[9]

[a] Dr. K. Ágoston
Fakultät für Chemie und Pharmazie
Universität Regensburg, 93040 Regensburg (Germany)
[b] Prof. Dr. A. Geyer
Fachbereich Chemie der Philipps-Universität Marburg
35032 Marburg (Germany)
Fax: (+49) 6421-282-2021
E-mail: geyer@staff.uni-marburg.de

Results and Discussion

Although the simultaneous activation of several sugar hydroxyl groups as sulfonate esters has been investigated, the study of possible applications of sugar polysulfonates has remained limited.[10] The treatment of bicyclic thiazolidinlactam **1a** (Scheme 1) with excess triflic acid anhydride does not result in a polysulfonate, but rather a stable, crystalline elimination product **2** (Figure 1) in a yield of 80%.[11] The

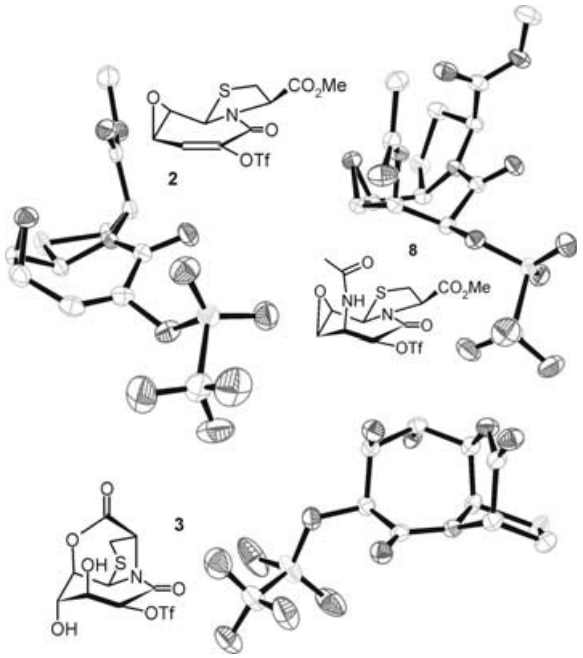
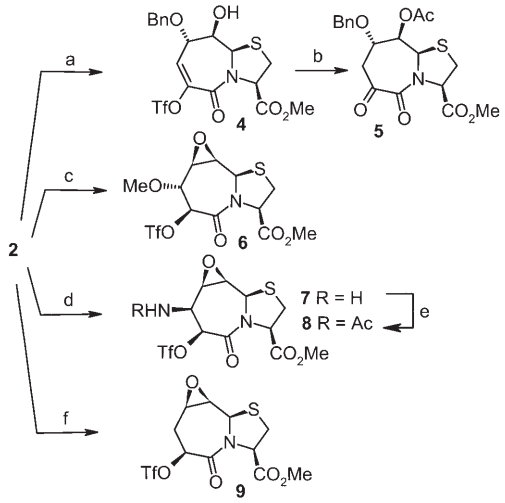


Figure 1. Crystal structures of elimination product **2**, lactone **3**, and Michael adduct **8**.

four secondary hydroxyl groups of **1a** (D-*gluco*-configuration) are transformed into complementary reactive sites in **2** via sulfonate ester intermediates in a single synthetic step. No comparable activation/elimination sequences are known for *gluco*-pyranoses that bear their hydroxyl groups in equatorial positions. The axial orientation of the three hydroxyl groups 7-O, 8-O, and 9-O in **1a** is a key requirement for the observed formation of the oxirane ring and the enol ether. The sequence of events, however, remains unclear, because no intermediates are observed during the conversion of **1a** into **2**. The first triflation probably occurs in the α position to the amide carbonyl group; the only equatorial hydroxyl group is located at this position.[4,8] Subsequent triflation of O-7 triggers the elimination reaction to form the vinyltriflate, and the triflation of O-8 induces the oxirane ring formation by nucleophilic attack of O-9. Other 7,5-membered thiazolidinlactams, of which only the acid **1b** is shown, yield partially sulfonated reaction products with triflic anhydride in lower yields. Crystalline lactone **3** (Scheme 1) is shown as an example in Figure 1.

Different nucleophiles add selectively to one of the four electrophilic sites of **2**, thus permitting the stepwise modification of all four stereocenters, as shown in Scheme 2. The selectivity of the first addition is the most critical step, because in principle, each of the nucleophiles can add to alternative ring positions of **2**, leading to complex reaction mix-



Scheme 2. Reaction conditions: a) BnOH, $CHCl_3$, BF_3/Et_2O, 50 °C, 20 h, 75%; b) Ac_2O, pyridine, RT, 8 h, quant, then H_2O/MeOH, K_2CO_3, $CHCl_3$, RT, 1 h, quant; c) MeOH, K_2CO_3, DCM, RT, 5 d, 78%; d) NH_4HCOO, MeOH, DCM, 50 °C, 3 d, 82%; e) Ac_2O, pyridine, RT, 8 h, 95%; f) $NaBH_4$, MeOH, DCM, RT, 10 min, 90%.

tures. Conjugate addition to C-7 renders the O-6-triflate susceptible to nucleophilic exchange. However, no over-reactions from the several-fold addition of the same nucleophile are observed under the conditions used here.

Benzyl alcohol opens the oxirane ring of **2** under Lewis acid assistance (**4**, Scheme 2). Other alcohols show the same regioselectivity and the enol triflate remains intact under the reaction conditions. A selective hydrolysis of the acetylated enol-triflate **4** generates the α-ketoamide **5**. In the presence of potassium carbonate, an oxa-Michael reaction is observed for methanol, which attacks C-7. As expected, methanol adds to the less-hindered side of the double bond in **2**, affording **6**. Compound **2** decomposes in the presence of alkyl amines, but ammonium formate adds as an N-nucleophile cleanly to C-7, thus transforming **2** into **7** in 82% yield. Surprisingly, this attack proceeds from the more-hindered side of **2**, resulting in the opposite stereochemistry of C-7. Acylation of **7** yields the crystalline product **8** (Figure 1).[11] In spite of kinetic studies, the reason for these opposite selectivities could not be clarified. The amide proton and the ester carbonyl group form a hydrogen bond in the crystal structure of **8**, suggesting that this carbonyl group assists the nucleophilic attack of NH_3 to C-7 of **2**. The alternative stereochemistries of compounds **6** and **8** at C-7 were confirmed by the results of NMR spectroscopy (see Table 1). The chemical shifts and the coupling constants $^3J_{9H,9aH}$ and $^3J_{8H,9H}$ indicate that the epoxide remains intact. Differences in $J_{7,8}$ and $J_{6,7}$ between both compounds prove the inverted stereochemistry at C-7. The *anti* orientation of

Table 1. ^{1}H NMR chemical shifts (600 MHz, [D$_6$]DMSO) and ^3J-couplings of **6** and **8**.

	6		**8**	
δ [ppm]	$J_{H,H}$ [Hz]	δ [ppm]	$J_{H,H}$[Hz]	
6	5.20	$J_{6,7}=9.9$	6.18	$J_{6,7}=2.6$
7	3.85	$J_{7,8}<1$	5.07	$J_{7,8}=7.6$
8	3.35	$J_{8,9}=3.8$	3.60	$J_{8,9}=4.3$
9	3.29	$J_{9,9a}<1$	3.42	$J_{9,9a}<1$
9a	5.48		5.98	

the two groups in compound **6** explains the high value of $^3J_{6H,7H}$. Strong NOEs between the 9a-H and 6-H in compounds **6** and **8** determine the equatorial orientation of the *O*-triflate groups. Sodium borohydride cleanly adds hydride equivalents from the less-hindered side of the double bond in **2**, leading to the deoxyhexuronic derivative **9**[11] shown in Scheme 2 and Figure 2.

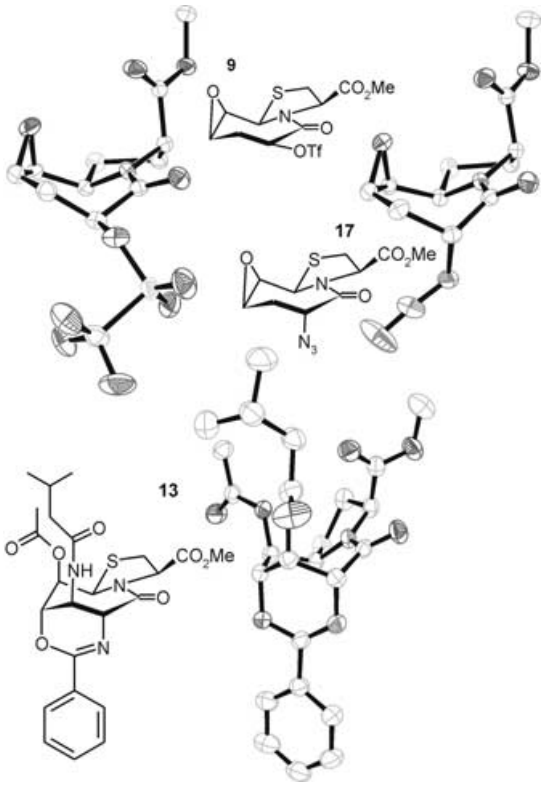
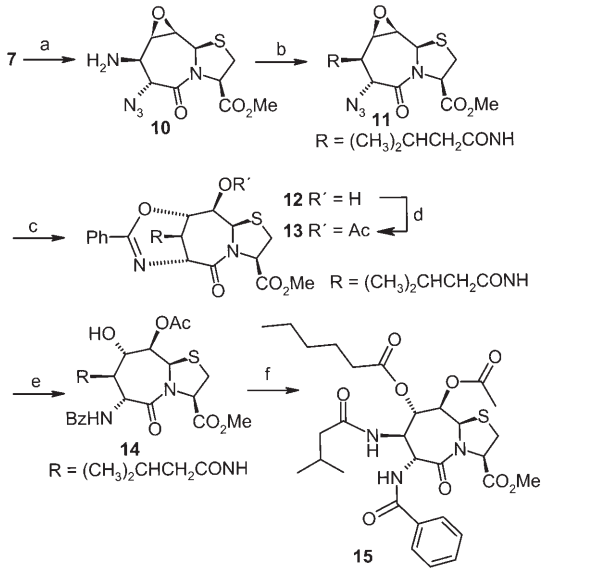


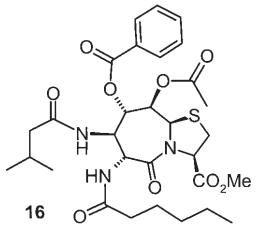
Figure 2. Crystal structures of triflate **9**, oxazine **13**, and azide **17**.

In principle, each of the monoadducts **4**, **6**, **8**, and **9** can add a second and even a third nucleophile. Only a few of the many possible combinations have been studied to date, and only *O*- and *N*-nucleophiles are described in this manuscript. The reaction sequence in Scheme 3 shows that all of the reactive sites of **2** remain accessible to nucleophiles, in spite of the increasing steric bulk visible in the crystal structures of Figure 1. The triflate group of **7** was exchanged against azide to form compound **10** (Scheme 3). An S_N2-type reaction is expected, although the stereochemistry at



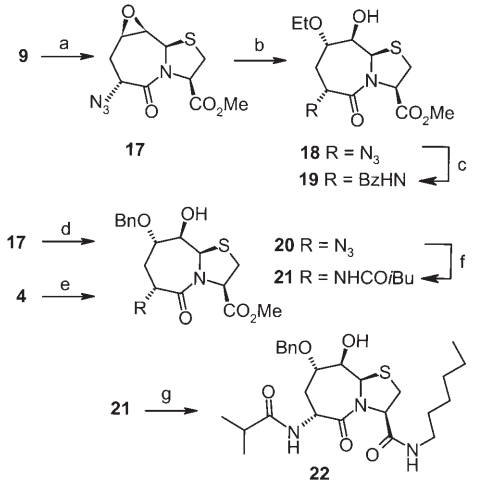
Scheme 3. Reaction conditions: a) NaN_3, $CHCl_3$, DMF, 8 h, 78%; b) isovaleryl chloride, DMF, pyridine, 20 min, 87%; c) Pd/C, H_2, MeOH, 3 h, then benzoyl chloride, pyridine, 30 min, 80%; d) Ac_2O, pyridine, 40 °C, 48 h, quant; e) AcOH, MeOH, H_2O, 24 h, 77%; f) caproyl chloride, pyridine, 8 h, 85%.

C-6 opposes the one observed in the reaction of azide with the 6-O-triflate of the parent compound **1a**, as described in the literature [8]. Acylation of **10** with isovaleryl chloride afforded **11**. Subsequently, the azide was reduced and the resulting amine was acylated with benzoyl chloride. Unexpectedly, in a one-pot reaction, the benzoyl carbonyl oxygen attacked the epoxide regioselectively, thus forming the oxazine **12** and rendering O-9 accessible for further transformations. Crystalline **13**[11] (Figure 2) was obtained after acylation of O-9 with Ac_2O. The six-membered oxazine ring was opened under mild acidic conditions (**13**→**14**) and the resulting derivative was acylated with caproyl chloride, yielding **15**. The thiazolidine ring remains intact under the transformations studied so far. Compound **15** can be obtained from the commercial sugar precursor D-glucorono-1,3-lactone in only nine steps, and contains all of the pharmacophoric groups that were identified for the macrolide hapalosin in sugar molecular libraries: methyl, branched alkyl, long-chain alkyl, and aromatic side-chains.[12] The seven-membered ring populates a twist-boat conformation because it cannot bear four axial groups, and the substituents in ring positions 6 and 7 assume pseudoequatorial orientations. As a consequence, large ^3J coupling constants are measured for $^3J_{6H,7H}$ (10.1 Hz) and $^3J_{7H,8H}$ (9.1 Hz), whereas $^3J_{8H,9H}$ (2.5 Hz) and $^3J_{9H,9aH}$ (<2 Hz) remain small. The unexpectedly stable oxazine derivative is not only formed with benzoyl chloride: acylation of **11** with caproyl chloride (Scheme 3 step c) followed by benzoyl chloride (step f) leads to **16**, in which the side chains in ring



positions 6 and 8 are swapped relative to the situation in compound **15**.

The C-7 defunctionalized thiazolidinlactam **9** can also be converted into bicyclic peptidomimetics, as shown in Scheme 4. Clean inversion of the configuration at C-6 is ob-



Scheme 4. Reaction conditions: a) NaN_3, $CHCl_3$, DMF, 0.5 h, 80%; b) EtOH, $CHCl_3$, BF_3/Et_2O, 7 d, 85%; c) HS-$(CH_2)_3$-SH, MeOH, 5 h, then benzoyl chloride, pyridine, 2 h, 60%; d) BnOH, $CHCl_3$, BF_3/Et_2O, 7 d, 85%; e) $NaBH_4$, MeOH, DCM, RT, 30 min, then NaN_3, DMF, 2 h, 75%; f) Pd/C, H_2, MeOH, 1 h, then isobutyryl chloride, pyridine, 30 min, 68%; g) 1 N LiOH, MeOH, then neutralization with HCl and hexylamine, pyBOP, DMF, 2 h, 60%.

served with the azide nucleophile, leading to **17**. The S_N2-type reaction is proven by the crystal structures of **9** and **17** shown in Figure 2. Reduction of the azide and subsequent acylation yielded the benzamide **19**. The azide **20** was obtained by two routes: Firstly, by the BF_3/Et_2O-catalyzed nucleophilic opening of the oxirane **17**. Secondly, along an exchanged order of Lewis acid-catalyzed oxirane opening (**2**→**4**), double-bond reduction with $NaBH_4$, and triflate-to-azide exchange, yielding **20**. A branched alkyl chain was introduced by reduction and amide bond formation with isobutyryl chloride, yielding **21**. The linear alkyl chain was introduced by ester saponification and coupling to hexylamine with benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate pyBOP (**22**).

Conclusion

The axial hydroxyl groups of **1** react in elimination reactions and can be refunctionalized subsequently by the addition of nucleophiles. The 7,5-bicyclic thiazolidinlactam scaffold can lock substituents in preferred conformations more efficiently than is possible with a monocyclic pyranose ring. Thus, some reaction channels are opened and others are closed, with the effect that Michael addition, epoxide opening, and triflate exchange have different susceptibilities towards nucleophilic attack. Compound **2** can be obtained from the cheap starting materials D-glucuronic acid and L-cysteine methyl ester in only two synthetic steps, and has as many orthogonal reaction centers as other molecular library templates.[3a] Compound **2** offers alternative reaction scenarios, such as the one exemplified in Scheme 3, and the methyl ester function of compound **1** remains intact in all transformations. This allows the syntheses shown here to be transferred to a solid support to diversify the key intermediate **2** into a four-point molecular library.

Experimental Section

General remarks: Solvents were purified according to standard procedures. Flash chromatography was performed by using J. T. Baker silica gel 60 (0.040–0.063 mm) at a pressure of 0.4 bar. Thin layer chromatography was performed by using Merck silica gel plastic plates, $60F_{254}$; compounds were visualized by treatment with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL) and heating at 150 °C. All compounds had a white to yellowish color, unless otherwise indicated. NMR spectra were recorded by using Bruker Avance 400 or 600 spectrometers. TMS, or the resonance of the residual solvent ([D_6]DMSO: $\delta = 2.49$ ppm), was used as internal standard. All ^{13}C assignments are based on inverse CH correlations (HMQC and HMBC). ROESY spectra were aquired for most of the compounds, to confirm relative stereochemistries.

Compound 2: Tf_2O (81.9 mmol, 13.8 mL) was added dropwise to a solution of alcohol **1a** (4 g, 13.6 mmol) and 4-dimethylaminopyridine (DMAP) (200 mg) in pyridine (30 mL) and dry DCM (200 mL) at 0 °C. The mixture was stirred for 12 h at RT, then diluted with toluene (500 mL) and washed with water (2×100 mL). The organic phase was dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded crystalline elimination product **2** (4.2 g, 80%). $[\alpha]_D^{20} = -207.8$ ($c = 1$, $CHCl_3$); ^1H NMR (600 MHz, [D_6]DMSO): $\delta = 7.03$ (d, $^3J_{7,8} = 5.71$ Hz, 1H; H-7), 5.35 (s, 1H; H-9a), 5.01 (dd, $^3J_{3,2} = 6.78$, 4.94 Hz, 1H; H-3), 3.88 (d, $^3J_{8,9} = 4.06$ Hz, 1H; H-9), 3.66 (s, 3H; OMe), 3.62 (dd, 1H; H-8), 3.42, 3.26 ppm (each dd, $J_{gem} = 11.89$ Hz, 2H; H-2, 2a); ^{13}C NMR: $\delta = 168.29$, 158.08 (C=O), 140.29 (C-6), 128.16 (C-7), 67.73 (C-9), 63.81 (C-3), 58.46 (C-9a), 52.26 (OMe), 46.90 (C-8), 31.35 ppm (C-2); ESI-MS: m/z: 407.0 [$M^+ + NH_4$], 796.1 [$2M^+ + NH_4$]; HRMS: m/z: calcd for $C_{11}H_{11}F_3NO_7S_2$: 389.9924; found: 389.9923 [M^+].

Compound 3: Tf_2O (3 mL) was added dropwise to a solution of acid **1b** (1.5 g 5.37 mmol) in pyridine (50 mL) and dry DCM (25 mL) at 0 °C. The mixture was stirred for 1 h at RT, then diluted with toluene (500 mL) and washed with water (2×100 mL). The organic phase was dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 2:3) afforded lactone **3** (790 mg, 37%). ^1H NMR (600 MHz, [D_6]DMSO): $\delta = 6.29$ (s, 1H; H-6), 6.28 (d, $J_{7,OH} = 4.80$ Hz, 1H; 7-OH), 6.25 (d, $J_{8,OH} = 4.30$ Hz, 1H; 8-OH), 6.23 (s, 1H; H-9a), 5.31 (d, $J_{2,3} = 5.29$ Hz, 1H; H-3), 4.36 (d, $J_{8,9} = 3.71$ Hz, 1H; H-9), 4.07 (m, 1H; H-8), 4.05 (m, 1H; H-7), 3.33 ppm (m, 2H; H-2); ^{13}C NMR: $\delta = 165.52$ (CO_2), 164.02 (C-5), 84.42 (C-6), 83.95 (C-9), 72.85 (C-7), 69.10 (C-8), 61.15 (C-3), 52.67 (C-9a), 33.53 ppm (C-2); HMBC: $J_{H9,COO}$.

Compound 4: BF_3/EtO_2 (100 μL) was added to a solution of epoxide **2** (1 g, 2.57 mmol) and benzyl alcohol (12.8 mmol, 1.32 mL) in dry $CHCl_3$ (50 mL). The mixture was stirred for 20 h at 50 °C, then diluted with DCM (200 mL), washed with saturated $NaHCO_3$ (2×50 mL) and water (2×50 mL), dried ($NaSO_4$), filtered, and concentrated. Column chromatography (dichloromethane/ethyl acetate 97:3) of the residue afforded benzyl ether **4** (960 mg, 75%) as a syrup. ^1H NMR (600 MHz, [D_6]DMSO): $\delta = 7.38$ (m, 5H; Ph), 6.97 (d, $^3J_{7,8} = 4.04$ Hz, 1H; H-7), 6.09 (d, $^3J_{OH,9} = 4.64$ Hz, 1H; OH), 5.26 (d, $^3J_{9,9a} = 3.03$ Hz, 1H; H-9a), 4.89 (dd, $^3J_{3,2} = 6.86$, 9.08 Hz, 1H; H-3), 4.66 (ABq, 2H; CH_2Ph), 4.34 (dd, $^3J_{8,9} = 7.06$ Hz, 1H; H-8), 4.11 (ddd, 1H; H-9), 3.63 (s, 3H; OMe), 3.41, 3.34 ppm (each dd, $J_{gem} = 11.10$ Hz, 2H; H-2, 2a); ^{13}C NMR: $\delta = 168.81$,

159.63 (C=O), 138.35, 137.62 (C-6, aromatic quat), 133.78 (C-7), 128.80, 128.50 (Ph), 79.74 (C-9), 79.50 (C-8), 72.19 (CH_2Ph), 66.37 (C-9a), 62.68 (C-3), 52.42 (OMe), 32.61 ppm (C-2); ESI-MS: m/z: 498.0 [M^++H], 515.0 [M^++NH_4], 536.0 [M^++K].

Compound 5: Ac_2O (1 mL) was added to a solution of alcohol **4** (100 mg, 200 μmol) in pyridine (2 mL). The mixture was maintained for 8 h at RT, then concentrated. K_2CO_3 (200 mg) was added to a solution of the crude intermediate in $CHCl_3$ (10 mL), MeOH (10 mL), and water (0.5 mL). The mixture was stirred for 1 h, then diluted with ethyl acetate (50 mL) and washed with water (2×10 mL). The organic phase was dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded ketoamide **5** (80 mg quant). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=7.40–7.25 (m, 5H; aromatic), 5.61 (d, $J_{9,9a}$=2.22 Hz, 1H; H-9a), 5.32 (dd, $J_{8,9}$=6.86 Hz, 1H; H-9), 4.97 (pt, $J_{2,3}$=6.46 Hz, 1H; H-3), 4.58 (ABq, 2H; -CH_2Ph), 4.10 (ddd, $J_{7,8}$=3.03, 10.70 Hz, 1H; H-8), 3.61 (s, 3H; OMe), 3.35, 3.24 (each dd, J_{gem}=11.30 Hz, 2H; H-2), 3.13, 2.96 (each dd, J_{gem}=14.56 Hz, H-7), 2.03 ppm (s, 3H; OAc); ^{13}C NMR: δ=196.48 (C-6), 169.36, 168.68, 161.78 (C=O), 137.96, 128.21, 127.65, 127.56 (aromatic), 74.67 (C-9), 74.42 (C-8), 70.49 (-CH_2Ph), 61.98 (C-3), 61.26 (C-9a), 52.29 (OMe), 41.17 (C-7), 31.57 (C-2), 20.54 ppm (Ac); ESI-MS: m/z: 407.2 [M^+]; elemental analysis calcd (%) for $C_{19}H_{21}NO_7S$ (407.44): C 56.01, H 5.20, N 3.44; found: C 56.21, H 5.20, N 3.41.

Compound 6: K_2CO_3 (100 mg) was added to a solution of enol-triflate **2** (100 mg, 0.26 mmol) in MeOH (1 mL) and DCM (5 mL). The mixture was stirred for 5 d, then diluted with DCM (50 mL), and washed with water (3×20 mL). The organic phase was dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 6:4) of the residue afforded methyl ether **6** (82 mg, 78%) as a syrup. ^{1}H NMR (600 MHz, $CDCl_3$): δ=5.48 (s, 1H; H-9a), 5.20 (d, $^3J_{6,7}$=9.87 Hz, 1H; H-6), 5.08 (dd, $^3J_{3,2}$=5.43, 5.46 Hz, 1H; H-3), 3.85 (d, 1H; H-7), 3.78 (s, 3H; OMe), 3.63 (s, 3H; OMe), 3.43, 3.25 (each dd, J_{gem}=11.85 Hz, 2H; H-2, 2a), 3.35 (d, $^3J_{8,9}$=3.75 Hz, 1H; H-8), 3.29 ppm (d, 1H; H-9); ^{13}C NMR: δ=167.95, 160.90 (C=O), 82.17 (C-6), 73.93 (C-7), 64.45 (C-3), 60.13 (OMe), 59.32 (C-9a), 55.31 (C-8), 55.16 (C-9), 52.79 (OMe), 31.23 ppm (C-2); MS (in DCM + NH_4Ac): m/z: 438.9 [M^++NH_4].

Compound 7: Ammonium formiate (1 g) was added to a solution of enol-triflate **2** (1 g, 2.57 mmol) in MeOH (20 mL) and DCM (2 mL). The mixture was kept for 3 d at 50°C, then the solvents were removed and the residue was redissolved in ethyl acetate (500 mL), then washed with water (3×100 mL). The organic phase was dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:4) of the residue afforded amine **7** (855 mg, 82%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=5.95 (d, $^3J_{6,7}$=2.75 Hz, 1H; H-6), 5.92 (s, 1H; H-9a), 4.93 (dd, $^3J_{3,2}$=6.60, 6.24 Hz, 1H; H-3), 3.68 (dd, $^3J_{7,8}$=7.16 Hz, 1H; H-7), 3.66 (s, 3H; OMe), 3.48 (dd, $^3J_{8,9}$=4.22 Hz, 1H; H-8), 3.36 (d, 1H; H-9), 3.34, 3.19 (each dd, J_{gem}=11.55 Hz, 2H; H-2, 2a), 1.75 ppm (d, 2H; NH_2); ^{13}C NMR: δ=168.49, 162.92 (C=O), 85.36 (C-6), 63.91 (C-3), 59.51 (C-9), 58.03 (C-9a), 55.01 (C-8), 52.29 (OMe), 48.94 (C-7), 30.50 ppm (C-2); ESI-MS: m/z: 406.8 [M^++H], 423.9 [M^++NH_4].

Compound 8: Ac_2O (1 mL) was added to a solution of amine **7** (100 mg, 0.24 mmol) in pyridine (2 mL) and kept for 8 h at RT, then the mixture was concentrated. Column chromatography (petroleum ether/ethyl acetate 6:4) of the residue afforded acetamide **8** (105 mg, 95%) as crystals. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=7.07 (d, $^3J_{NH,7}$=10.22 Hz, 1H; NH), 6.16 (d, $^3J_{6,7}$=2.61 Hz, 1H; H-6), 5.97 (s, 1H; H-9a), 5.06 (ddd, $^3J_{7,8}$=7.16 Hz, 1H; H-7), 4.94 (dd, $^3J_{3,2}$=6.89, 7.30 Hz, 1H; H-3), 3.76 (s, 3H; OMe), 3.60 (dd, $^3J_{8,9}$=4.28 Hz, 1H; H-8), 3.44 (d, 1H; H-9), 3.42, 3.18 (each dd, J_{gem}=11.89 Hz, 2H; H-2, 2a), 1.91 ppm (s, 3H; NHAc); ^{13}C NMR: δ=169.60, 168.66, 163.02 (C=O), 83.46 (C-6), 64.24 (C-3), 59.67 (C-9a), 57.99 (C-9), 2×52.92 (C-8, OMe), 44.92 (C-7), 30.51 (C-2), 22.59 ppm (NHAc); ESI-MS: m/z: 449.0 [M^++H], 466.0 [M^++NH_4].

Compound 9: $NaBH_4$ (1.42 mmol, 54 mg) was added to a solution of enol-triflate **2** (500 mg, 1.29 mmol) in MeOH (15 mL) and stirred for 10 min. Then the mixture was diluted with DCM (100 mL) and washed with water (2×20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded crystalline triflate **9** (450 mg, 90%). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=5.93 (dd, $^3J_{6,7}$=4.12, 12.08 Hz, 1H; H-6), 5.90 (s, 1H; H-9a), 4.98 (pt, $^3J_{3,2}$=5.76 Hz, 1H; H-3), 3.65 (s, 3H; OMe), 3.42–3.12 (m, 4H; H-8, H-9, H-2, 2a), 2.55, 2.35 (each m, 2H; H-7, 7a); ESI-MS: m/z: 409.0 [M^++NH_4], 800.0 [2M^++NH_4].

Compound 10: NaN_3 (320 mg, 4.92 mmol) was added to a solution of triflate **7** (1.00 g, 2.46 mmol) in DMF (20 mL) and DCM (5 mL), and the mixture was stirred for 8 h at RT. Then the solvents were removed and column chromatography (toluene/ethyl acetate/methanol 1:4:1) of the residue gave azide **10** (574 mg, 78%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=5.85 (s, 1H; H-9a), 4.88 (dd, $J_{2,3}$=4.42, 6.30 Hz, 1H; H-3), 4.30 (d, $J_{6,7}$=5.45 Hz, 1H; H-6), 3.63 (s, 3H; OMe), 3.48 (dd, $J_{7,8}$<2 Hz, 1H; H-7), 3.38–3.15 (m, 4H; H-8, H-9, H-2), 1.80 ppm (brs, 1H; NH_2); ^{13}C NMR: δ=168.77, 164.73 (C=O), 68.15 (C-6), 64.49 (C-3), 59.22 (C-9a), 56.98, 55.04 (C-8, C-9), 52.09 (OMe), 47.07 (C-7), 29.85 ppm (C-2); ESI-MS: m/z: 299.8 [M^++H], 599.2 [2M^++H]; elemental analysis calcd (%) for $C_{10}H_{13}N_5O_4S$ (299.31): C 40.13, H 4.38, N 23.40; found: C 39.98, H 4.34, N 23.21.

Compound 11: Isovaleryl chloride (300 μL) was added to a solution of amine **10** (500 mg, 1.67 mmol) in DMF (5 mL) and pyridine (1 mL), and the mixture was kept for 20 min at RT. Then the solvents were removed and column chromatography (petroleum ether/ethyl acetate1:2) of the residue gave amide **11** (556 mg, 87%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=7.00 (d, $J_{7,NH}$=8.68 Hz, 1H; NH), 5.89 (s, 1H; H-9a), 4.90 (dd, $J_{2,3}$=5.04, 6.46 Hz, 1H; H-3), 3.48 (ddd, $J_{6,7}$=5.86 Hz, $J_{7,8}$<2 Hz, 1H; H-7), 4.37 (d, 1H; H-6), 3.70 (s, 3H; OMe), 3.47 (m, 2H; H-8, H-9), 3.38, 3.15 (each dd, J_{gem}=11.70 Hz, 2H; H-2), 2.01 (m, 2H; $COCH_2$-), 1.95 (m, 1H; -CH(CH_3)$_2$), 0.89, 0.87 ppm (each d, 6H; -CH-(CH_3)$_2$); ^{13}C NMR: δ=171.24, 169.58, 164.34 (C=O), 64.62 (C-3), 64.04 (C-6), 59.18 (C-9a), 56.58, 52.58 (C-8, C-9), 52.46 (OMe), 44.56 (CO-CH_2-), 43.68 (C-7), 29.92 (C-2), 25.45 (CH(CH_3)$_2$), 22.28, 22.19 ppm (CH-(CH_3)$_2$); ESI-MS: m/z: 383.9 [M^++H], 405.9 [M^++Na]; elemental analysis calcd (%) for $C_{15}H_{21}N_5O_5S$ (383.42): C 46.99, H 5.52, N 18.27; found: C 46.79, H 5.50, N 18.11.

Compound 12

Procedure A: Propanedithiol (100 μL) was added to a solution of azide **11** (100 mg, 0.26 mmol) in MeOH (10 mL) and the mixture was kept for two days at RT, then benzoyl chloride (150 μL) was added at 0°C and stirred for 30 min. The solvents were removed and column chromatography (petroleum ether to petroleum ether/ethyl acetate 4:1) of the residue gave oxazine **12** (78 mg, 65%) as a syrup.

Procedure B: The mixture of Pd/C (100 mg) and azide **11** (500 mg, 1.30 mmol) in MeOH (15 mL) was stirred under H_2 for 3 h. Then the mixture was filtered through celite, washed with MeOH, and concentrated. The residue was dissolved in pyridine (5 mL), then benzoyl chloride (200 μL) was added and stirred for 30 min. Then the mixture was concentrated. Column chromatography (petroleum ether to petroleum ether/ethyl acetate 4:1) of the residue gave oxazine **12** (480 mg, 80%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=7.92–7.41 (m, 5H; aromatic), 7.52 (d, $J_{7,NH}$=9.50 Hz, 1H; NH), 6.56 (d, $J_{9,OH}$=5.23 Hz, 1H; 9-OH), 5.10 (s, 1H; H-9a), 4.67 (dd, $J_{2,3}$=9.30, 6.95 Hz, 1H; H-3), 4.65 (ddd, $J_{7,8}$=4.35 Hz, $J_{8,9}$=5.23 Hz, $^4J_{6,8}$<2 Hz, 1H; H-8), 4.62 (ddd, $J_{6,7}$=6.42 Hz, 1H; H-7), 4.31 (dd, 1H; H-6), 4.08 (dd, 1H; H-9), 3.70 (s, 3H; OMe), 3.28, 3.24 (each dd, J_{gem}=11.37 Hz, 2H; H-2), 2.10–2.00 (m, 3H; $COCH_2$-, -CH(CH_3)$_2$), 0.91, 0.88 ppm (each d, 6H; -CH(CH_3)$_2$); ^{13}C NMR: δ=171.32, 169.97, 165.87 (C=O), 155.31 (O−C=N), 131.68, 131.51, 128.24, 127.63 (aromatic), 72.79 (C-8), 72.45 (C-9), 65.63 (C-3), 61.09 (C-9a), 60.95 (C-6), 52.25 (OMe), 44.65 (COCH_2-), 41.91 (C-7), 30.68 (C-2), 25.29 (CH(CH_3)$_2$), 22.43, 22.16 ppm (CH(CH_3)$_2$); ESI-MS: m/z: 462.1 [M^++H], 479.1 [M^++NH_4], 923 [2M^++H]; elemental analysis calcd (%) for $C_{22}H_{27}N_3O_6S$ (461.53): C 57.25, H 5.90, N 9.10; found: C 57.29, H 5.88, N 9.04.

Compound 13: Ac_2O (2 mL) was added to a solution of alcohol **12** (100 mg, 0.22 mmol) in pyridine (5 mL) and the mixture was maintained at 40°C for 48 h. Then the mixture was concentrated and column chromatography (petroleum ether/ethyl acetate 3:2) of the residue gave ester **13** (102 mg, quant) crystals. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=7.85–7.38 (m, 5H; aromatic), 7.34 (d, $J_{7,NH}$=10.03 Hz, 1H; NH), 5.34 (s, 1H;

H-9a), 5.22 (dd, $J_{8,9}=4.12$ Hz, 1H; H-9), 4.92 (dd, $J_{2,3}=6.96$, 7.95 Hz, 1H; H-3), 4.82 (ddd, $J_{6,7}=6.64$ Hz, $J_{7,8}=5.22$ Hz, 1H; H-7), 4.72 (ddd, $^4J_{6,8}=1.95$ Hz, 1H; H-8), 4.38 (dd, 1H; H-6), 3.78 (s, 3H; OMe), 3.25, 3.15 (each dd, $J_{gem}=11.37$ Hz, 2H; H-2), 2.10–2.00 (m, 3H; $COCH_2$-, -CH-$(CH_3)_2$), 2.09 (s, 3H; OAc), 0.91, 0.88 ppm (each d, 6H; -CH(CH_3)$_2$); ^{13}C NMR: $\delta=171.47$, 170.91, 168.7, 165.93 (C=O), 155.35 (O−*C*=N), 131.62, 131.39, 128.18, 127.84 (aromatic), 71.64 (C-9), 69.95 (C-8), 65.27 (C-3), 60.71 (C-6), 59.75 (C-9a), 52.75 (OMe), 44.58 (CO*C*H_2-), 40.96 (C-7), 30.25 (C-2), 25.46 (*C*H(CH_3)$_2$), 22.44, 22.09 (CH(*C*H_3)$_2$), 20.43 ppm (OAc); ESI-MS: *m*/*z*: 503.2 [M^+]; elemental analysis calcd (%) for $C_{24}H_{29}N_3O_7S$ (503.57): C 57.24, H 5.80, N 8.34; found: C 57.02, H 5.76, N 8.30.

Compound 14: AcOH (300 μL) was added to a solution of oxazine **13** (100 mg, 0.20 mmol) in MeOH (2 mL) and water (5 mL), and the mixture kept at room temperature for 24 h. Then the mixture was concentrated and subjected to column chromatography (petroleum ether/ethyl acetate 1:3) to give benzamide **14** (80 mg, 77%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=8.53$, 8.03 (each brs, 2H; 2NH), 7.75–7.48 (m, 5H; aromatic), 6.28 (d, $J_{9,9a}=2.47$ Hz, 1H; H-9a), 5.43 (brs, 1H; OH), 5.00 (dd, $J_{8,9}=6.59$ Hz, 1H; H-9), 4.73 (pt, $J_{2,3}=5.53$ Hz, 1H; H-3), 4.52–4.38 (m, 2H; H-6, H-7), 3.82 (ddd, $J_{7,8}=7.55$ Hz, 1H; H-8), 3.68 (s, 3H; OMe), 3.30, 3.13 (each dd, $J_{gem}=11.25$ Hz, 2H; H-2), 2.07 (s, 3H; OAc), 2.00–1.90 (m, 3H; $COCH_2$-, -CH(CH_3)$_2$), 0.85 ppm (2×d, 6H; -CH(CH_3)$_2$); ^{13}C NMR: $\delta=171.66$, 169.32, 169.26, 167.43, 166.2 (C=O), 134.69, 130.98, 128.02, 127.20 (aromatic), 78.04 (C-9), 69.77 (C-8), 65.60 (C-3), 59.72 (C-9a), 57.53 (C-6), 52.10 (OMe), 44.20 (CO*C*H_2-), 31.19 (C-2), 25.42 (*C*H-$(CH_3)_2$), 22.16 (2CH(*C*H_3)$_2$), 20.71 ppm (OAc); ESI-MS: *m*/*z*: 522.3 [M^++H], 544.3 [M^++Na], 1043.5 [2M^++H].

Compound 15: Caproyl chloride (50 μL) was added to a solution of alcohol **14** (50 mg, 96 μmol) in pyridine (2 mL) and the mixture was stirred for 8 h. Then the mixture was diluted with ethyl acetate, washed three times with water, the organic phase was dried, filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded ester **15** (49 mg, 85%) as a syrup. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.75$–7.38 (m, 5H; aromatic), 7.07 (d, $J_{7,NH}=9.33$ Hz, 1H; 7-NH), 6.59 (d, $J_{6,NH}=4.94$ Hz, 1H; 6-NH), 5.65 (s, 1H; H-9a), 5.47 (d, $J_{8,9}=2.47$ Hz, 1H; H-9), 5.36 (dd, $J_{7,8}=9.06$ Hz, 1H; H-8), 4.99 (dd, $J_{2,3}=2.31$, 7.17 Hz, 1H; H-3), 4.94 (ddd, $J_{6,7}=10.08$ Hz, 1H; H-7), 4.86 (dd, 1H; H-6), 3.67 (s, 3H; OMe), 3.37, 3.19 (each dd, $J_{gem}=12.35$ Hz, 2H; H-2), 2.23 (s, 3H; OAc), 2.25, 2.04, 1,49, 1.2, 1.13 (each m, 11H; aliphatic), 0.80, 0.68 (each d, 6H; -CH(CH_3)$_2$), 0.72 ppm (t, 3H; -CH_2CH_3); ^{13}C NMR: $\delta=174.80$, 174.54, 169.19, 169.03, 167.25, 167.13 (C=O), 133.01, 132.01, 128.62, 127.13 (aromatic), 73.94 (C-8), 69.33 (C-9), 64.72 (C-3), 62.62 (C-9a), 53.46 (C-6), 52.71 (OMe), 50.90 (C-7), 45.43, (CO*C*H_2-), 34.06 (-CO*C*H_2CH_2-), 31.50, 29.71, 22.28 (-$COCH_2$*C*H_2CH_2*C*H_2-), 31.05 (C-2), 24.43 (-*C*H(CH_3)$_2$), 22.50, 22.14, 20.73, 13.67 ppm (4×CH_3); ESI-MS: *m*/*z*: 620.3 [M^++H], 642.3 [M^++Na]. $C_{30}H_{41}N_3O_9S$ (619.73): calcd C 58.14, H 6.67, N 6.78; found: C 58.31, H 6.64, N, 6.58.

Analytical data of compound 16: ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=8.70$ (d, $J_{6,NH}=7.23$ Hz, 1H; 6-NH), 7.75–7.40 (m, 5H; aromatic), 7.71 (brs, 1H; 7-NH), 6.37 (d, $J_{9a,9}<2$ Hz, 1H; H-9a), 5.37 (dd, $J_{8,9}=6.80$ Hz, 1H; H-9), 5.22 (dd, $J_{7,8}=10.3$ Hz, 1H; H-8), 4.73 (pt, $J_{2,3}=7.02$ Hz, 1H; H-3), 4.62 (m, 1H; H-7), 4.11 (m, 1H; H-6), 3.70 (s, 3H; OMe), 3.30, 3.11 (each dd, $J_{gem}=11.18$ Hz, 2H; H-2), 2.10–1.85 (m, 3H; $COCH_2$CH-, -CH(CH_3)$_2$), 2.05 (s, 3H; OAc), 1.45, 1.20 (each m, 6H; -$CH_2CH_2CH_2CH_3$), 0.88 ppm (m, 9H; 3×CH_3); ^{13}C NMR: $\delta=172.68$, 171.47, 169.28, 169.22, 167.06, 164.83 (C=O), 133.48, 129.20, 128.59, 128.15 (aromatic), 76.04 (C-9), 72.38 (C-8), 63.78 (C-3), 59.91 (C-9a), 57.79 (C-6), 52.25 (OMe), 44.59 (CO*C*H_2CH-), 34.67 (-CO*C*H_2CH_2-), 30.70 (C-2), 30.59 ($COCH_2$*C*H_2-), 24.52 (-*C*H(CH_3)$_2$), 25.00. 21.67 (-$COCH_2CH_2$*C*H_2*C*H_2-), 22.09, 21.82, 21.82 (CH_3), 20.41 ppm (Ac); ESI-MS: *m*/*z*: 620.3 [M^++H], 642.3 [M^++Na]; $C_{30}H_{41}N_3O_9S$ (619.73): calcd C 58.14, H 6.67, N 6.78; found: C 58.41, H 6.65, N 6.89.

Compound 17: NaN_3 (26 mg, 0.4 mmol) was added to a solution of triflate **9** (80 mg, 0.2 mmol) in DCM (5 mL) and DMF (5 mL). The mixture was stirred for 30 min, then diluted with toluene (50 mL) and washed with water (3×10 mL). The organic phase was dried, filtered, and evaporated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded crystalline azide **17** (47 mg, 80%). ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=5.82$ (s, 1H; H-9a), 4.82 (dd, $^3J_{3,2}=3.67$, 6.42 Hz, 1H; H-3), 4.40 (dd, $^3J_{6,7}=2.38$, 5.14 Hz, 1H; H-6), 3.56 (s, 3H; OMe), 3.26, 3.11 (each dd, $J_{gem}=11.73$ Hz, 2H; H-2, H-2a), 3.22–3.20 (m, 2H; H-8, H-9), 2.42, 2.18 ppm (each m, $J_{gem}=14.12$ Hz, 2H; H-7, 7a); ^{13}C NMR: $\delta=168.72$, 165.77 (C=O), 64.48 (C-3), 62.23 (C-6), 58.98 (C-9a), 54.52 (C-9), 51.96 (OMe), 51.10 (C-8), 30.07 (C-2), 26.24 ppm (C-7); ESI-MS: *m*/*z*: 285.0 [M^++H], 302.0 [M^++NH$_4$]. $C_{10}H_{12}N_4O_4S$ (284.29): calcd C 42.25, H 4.25, N 19.71; found: C 42.04, H 4.23, N 19.60.

Compound 18: BF_3/EtO_2 (50 μL) was added to a solution of azide **17** (100 mg, 0.35 mmol) and absolute EtOH (1.0 mL) in dry $CHCl_3$ (10 mL). The mixture was stirred for 1 week at RT, then diluted with DCM (200 mL), washed with saturated $NaHCO_3$ (2×50 mL) and water (2×50 mL), dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 3:2) of the residue afforded ethyl ether **18** (98 mg, 85%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=5.53$ (s, 1H; H-9a), 5.20 (d, $^3J_{9,OH}=4.52$ Hz, 1H; 9-OH), 4.75 (dd, $^3J_{3,2}=5.70$, 6.89 Hz, 1H; H-3), 4.58 (dd, $^3J_{6,7}=4.52$, 8.08 Hz, 1H; H-6), 3.56 (m, 4H; H-9, OMe), 3.58–3.45 (m, 3H; H-8, -OCH_2CH_3), 3.31, 3.23 (each dd, $J_{gem}=11.47$ Hz, 2H; H-2, H-2a), 2.11, 2.00 (each m, $J_{gem}=15.03$ Hz, 2H; H-7, 7a), 1.12 ppm (t, $^3J=6.89$ Hz, 3H; -CH_3); ^{13}C NMR: $\delta=170.4$, 166.84 (C=O), 77.91 (C-8), 73.04 (C-9), 64.53 (-O*C*H_2CH_3), 63.79 (C-3), 61.42 (C-9a), 61.27 (C-6), 52.37 (OMe), 30.97 (C-2), 28.11 (C-7), 15.25 ppm (CH_3). $C_{12}H_{18}N_4O_5S$ (330.36): calcd C 43.63, H 5.49, N 16.96; found: C 43.44, H 5.45; N 17.04.

Compound 19: Propanedithiol (10 μL) was added to a solution of azide **18** (50 mg, 0.15 mmol) in MeOH (5 mL) and the mixture was kept for 5 h at RT, then benzoyl chloride (100 μL) was added at 0°C and stirred for 2 h. The solvents were removed and column chromatography (petroleum ether/ethyl acetate 1:2) of the residue gave benzamide **19** (38 mg, 60%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=8.91$ (brs, 1H; 6-NH), 7.80, 7.55, 7.48 (each m, 5H; aromatic), 5.80 (s, 1H; H-9a), 5.28 (d, $^3J_{9,OH}=4.60$ Hz, 1H; 9-OH), 4.67 (pt, $^3J_{3,2}=6.58$ Hz, 1H; H-3), 4.52 (m, 1H; H-6), 3.72 (pt, $^3J_{8,9}=4.60$ Hz, 1H; H-9), 3.66 (s, 3H; OMe), 3.60–3.52 (m, 3H; H-8, -OCH_2CH_3), 3.33, 3.22 (each dd, $J_{gem}=11.18$ Hz, 2H; H-2, H-2a), 2.17, 2.02 (each m, $J_{gem}=14.69$ Hz, 2H; H-7, 7a), 1.12 ppm (t, $^3J=6.80$ Hz, 3H; -CH_3); ^{13}C NMR: $\delta=170.60$, 168.85, 165.57 (C=O), 133.70, 131.37, 128.36, 127.04 (aromatic), 79.21 (C-8), 73.99 (C-9), 64.54 (-OCH_2CH_3), 64.28 (C-3), 61.72 (C-9a), 52.89 (C-6), 52.24 (OMe), 30.88 (C-2), 26.43 (C-7), 15.41 ppm (-CH_3); ESI-MS: *m*/*z*: 409.0 [M^++H], 431.0 [M^++Na], 447.0 [M^++K], 839.5 [2M^++Na]. $C_{19}H_{24}N_2O_6S$ (408.47): calcd C 55.87, H 5.92, N 6.86; found: C 56.01, H 5.94, N 6.69.

Compound 20

Procedure A: BF_3/EtO_2 (50 μL) was added to a solution of epoxide **17** (100 mg, 0.35 mmol) and absolute BnOH (1.0 mL) in dry $CHCl_3$ (10 mL). The mixture was stirred for 1 week at RT, then diluted with DCM (200 mL), washed with saturated $NaHCO_3$ (2×50 mL) and water (2×50 mL), dried ($NaSO_4$), filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 3:2) of the residue afforded benzylether **20** (110 mg, 85%) as a syrup.

Procedure B: $NaBH_4$ (38 mg, 1.0 mmol) was added to a solution of enoltriflate **4** (400 mg, 0.80 mmol) in DCM (1 mL) and MeOH (10 mL), and stirred for 30 min. Then the mixture was diluted with DCM (50 mL) and washed with water (3×10 mL), dried, filtered, and concentrated. The residue was dissolved in DMF (10 mL), NaN_3 (104 mg, 1.6 mmol) was added and the mixture was stirred for 2 h, then diluted with toluene (50 mL), and washed with water (3×10 mL), dried, filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate 1:1) of the residue afforded azide **20** (235 mg, 75% over two steps) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=7.40$–7.20 (m, 5H; aromatic), 5.27 (s, 1H; H-9a), 5.27 (d, $J_{9,OH}=5.06$ Hz, 1H; OH), 4.76 (dd, $J_{2,3}=5.61$, 7.09 Hz, 1H; H-3), 4.60 (ABq, $J_{gem}=12.05$ Hz, 2H; -CH_2Ph), 4.59 (dd, $J_{6,7}=4.64$, 8.26 Hz, 1H; H-6), 3.75 (dd, $J_{8,9}=4.32$, 1H; H-9), 3.68 (s, 3H; OMe), 3.60 (ddd, $J_{7,8}=3.58$, 7.71, 1H; H-8), 3.32, 3.24 (each dd, $J_{gem}=11.56$ Hz, 2H; H-2), 2.18, 2.08 ppm (each ddd, $J_{gem}=15.11$ Hz, 2H, H-7); ^{13}C NMR: $\delta=170.45$, 166.86 (C=O), 138.37, 128.17, 127.97, 127.45, 127.45, 127.39 (aromatic), 77.73 (C-8), 72.97 (C-9), 70.73 (-CH_2Ph), 63.83 (C-3), 61.47

(C-9a), 61.29 (C-6), 52.36 (OMe), 30.97 (C-2), 28.18 ppm (C-7); ESI-MS: *m/z*: 393.0 [M^++H], 410.1 [M^++NH_4], 415.0 [M^++Na]. $C_{17}H_{20}N_4O_5S$ (392.43): calcd C 52.03, H 5.14, N 14.28; found: C 51.91, H 5.14, N 14.09.

Compound 21: The mixture of azide **20** (200 mg, 0.51 mmol) and Pd/C (50 mg) in MeOH (5 mL) was stirred under H_2 for 1 h. Then the mixture was filtered through celite and concentrated. The residue was dissolved in DMF (5 mL) and pyridine (2 mL), and isobutyryl chloride (100 μL) was added and stirred for 30 min. Then the mixture was diluted with toluene (50 mL), and washed with water (3×10 mL), dried, filtered, and concentrated. Column chromatography (petroleum ether/ethyl acetate/methanol 3:2:1) of the residue afforded amide **21** (151 mg, 68%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=8.16 (d, $J_{6,NH}$=6.14 Hz, 1H; NH), 7.40–7.20 (m, 5H; aromatic), 5.77 (s, 1H; H-9a), 5.30 (d, $J_{9,OH}$=4.86 Hz, 1H; OH), 4.68 (dd, $J_{2,3}$=6.91, 7.17 Hz, 1H; H-3), 4.58 (ABq, 2H; -C*H*$_2$Ph), 4.36 (m, 1H; H-6), 3.75 (dd, $J_{8,9}$=5.39 Hz, 1H; H-9), 3.62 (s, 3H; OMe), 3.60 (m, 1H; H-8), 3.24, 3.22 (each dd, J_{gem}=11.52 Hz, 2H; H-2), 2.29 (m, 1H; -C*H*(CH$_3$)$_2$), 2.08, 1.96 (each ddd, J_{gem}=14.59 Hz, 2H, H-7), 0.94, 0.91 ppm (each d, 6H; 2×CH$_3$); ^{13}C NMR: δ=177.76, 175.52, 170.62 (C=O), 138.43, 128.16, 128.09, 127.82, 127.58, 127.50 (aromatic), 79.04 (C-8), 70.81 (C-9), 64.17 (-*C*H$_2$Ph), 61.86 (C-3), 61.86 (C-9a), 52.23, 52.09 (C-6, OMe), 33.75 (-*C*H(CH$_3$)$_2$), 30.98 (C-2), 29.56 (C-7), 19.31, 19.17 ppm (2×CH$_3$); ESI-MS: *m/z*: 436 (in DCM + NH_4Ac), 437.1 [M^++H], 454.1 [M^++NH_4]. $C_{21}H_{28}N_2O_6S$ (436.52): calcd C 57.78, H 6.47, N 6.42; found: C 57.49, H 6.44, N 6.40.

Compound 22: 1N LiOH solution (344 μL) was added to a solution of methyl ester **21** (75 mg, 0.17 mmol) in MeOH (1 mL): when TLC showed the disappearance of the starting compound, 1N HCl (344 μL) was added to neutralize the solution, and the mixture was concentrated. The residue was dissolved in DMF (2 mL), pyBOP (88 mg, 0.17 mmol) was added, and the pH was adjusted to 7–8 by adding *N,N*-diisopropylethylamine (DIPEA). Then the solution of hexylamine (20 μL, 0.17 mmol) in DMF (200 μL) was added to the mixture and stirred for 2 h. The solvent was removed and column chromatography (dichloromethane/acetone 3:2) of the residue afforded hexylamide **22** (51 mg, 60%) as a syrup. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=8.29 (t, $J_{CH_2,NH}$=4.95 Hz, 1H; NH-hexyl), 7.92 (d, $J_{6,NH}$=6.86 Hz, 1H; 6-NH), 7.40–7.20 (m, 5H; aromatic), 6.72 (d, $J_{9,OH}$=5.49 Hz, 1H; OH), 5.72 (s, 1H; H-9a), 4.63 (dd, $J_{2,3}$=3.29, 7.41 Hz, 1H; H-3), 4.52 (ABq, 2H; -C*H*$_2$Ph), 4.42 (m, $J_{6,7}$=2.47, 7.41 Hz, 1H; H-6), 3.85 (dd, $J_{8,9}$=3.84 Hz, 1H; H-9), 3.71 (m, $J_{7,8}$=3.48, 5.00 Hz, 1H; H-8), 3.26, 3.05 (each dd, J_{gem}=11.80 Hz, 2H; H-2), 3.05 (m, 1H; -NH$_2$C*H*$_2$-), 2.28 (m, 1H; -C*H*(CH$_3$)$_2$), 2.20, 1.95 (each ddd, J_{gem}=15.13 Hz, 2H, H-7), 1.20 (m, 8H; -(C*H*$_2$)$_4$CH$_3$), 0.88 ppm (m, 9H; 3×CH$_3$); ^{13}C NMR: δ= 175.22, 170.80, 168.62 (C=O), 138.00, 128.19, 127.56, 127.48 (aromatic), 78.91 (C-8), 71.05 (C-9), 70.71 (-*C*H$_2$Ph), 65.36 (C-3), 60.38 (C-9a), 52.73 (C-6), 38.07 (-NH$_2$*C*H$_2$-), 33.89 (-*C*H(CH$_3$)$_2$), 31.89 (C-2), 29.53 (C-7), 30.84, 28.67, 25.80, 21.99 (-(*C*H$_2$)$_4$CH$_3$), 19.30, 19.10, 19.07 ppm (-CH$_3$); ESI-MS: *m/z*: 506.3 [M^++H], 523.3 [M^++NH_4], 528.3 [M^++Na], 1011.6 [2M^++H], 1033.7 [2M^++Na]. $C_{26}H_{39}N_3O_5S$ (505.67): calcd C 61.76, H 7.77, N 8.31; found: C 61.73, H 7.69, N 8.05.

Acknowledgements

The authors thank Dr. M. Zabel (Fachbereich Chemie, Universität Regensburg) for crystal structure analysis of compounds **2**, **3**, **8**, **9**, **13**, and **17**. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Innovatec program of the DAAD.

[1] J. Xue, Z. Guo, *Tetrahedron Lett.* **2001**, *42*, 6487–6489.
[2] a) R. Hirschmann, K. C. Nicolaou, S. Pietranico, E. M. Leahy, J. Salvino, B. Arison, M. A. Cichy, P. G. Spoors, W. C. Shakespeare, P. A. Sprengeler, P. Hamley, A. B. Smith III, T. Reisine, K. Raynor, L. Maechler, C. Donaldson, W. Vale, R. M. Freidinger, M. R. Cascieri, C. D. Strader, *J. Am. Chem. Soc.* **1993**, *115*, 12550–12568; b) K. C. Nicolaou, J. L. Trujillo, K. Chibale, *Tetrahedron* **1997**, *53*, 8751–8778; c) T. Wunberg, C. Kallus, T. Opatz, S. Henke, W. Schmidt, H. Kunz, *Angew. Chem.* **1998**, *110*, 2620–2622; *Angew. Chem. Int. Ed.* **1998**, *37*, 2503–2505; d) R. Hirschmann, J. Hynes M. A. Cichy-Knight, R. D. van Rijn, P. A. Sprengeler, P. G. Spoors, W. C. Shakespeare, S. Pietranico-Cole, J. Barbosa, J. Liu, W. Yao, S. Rohrer, A. B. Smith III, *J. Med. Chem.* **1998**, *41*, 1382–1391; e) J. Boer, D. Gottschling, A. Schuster, B. Holzmann, H. Kessler, *Angew. Chem.* **2001**, *113*, 3988–3991; *Angew. Chem. Int. Ed.* **2001**, *40*, 3870–3873; f) L. Abrous, J. Hynes, S. A. Friedrich, A. B. Smith III, R. Hirschmann, *Org. Lett.* **2001**, *3*, 1089–1092; g) R. Jain, M. Kamau, W. Wang, R. Ippolito, H. Wang, R. Dulina, J. Anderson, D. Gange, M. J. Sofia, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2185–2189; h) F. Schweizer, *Angew. Chem.* **2002**, *114*, 240–264; *Angew. Chem. Int. Ed.* **2002**, *41*, 230–253; i) T. Opatz, C. Kallus, T. Wunberg, W. Schmidt, S. Henke, H. Kunz, *Eur. J. Org. Chem.* **2003**, 1527–1536.
[3] a) D. S. Tan, M. A. Foley, B. R. Stockwell, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087; b) Y. Kim, M. A. Arai, T. Arai, J. O. Lamenzo, E. F. Dean, N. Patterson, P. A. Clemons, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 14740–14745.
[4] P. Tremmel, A. Geyer, *Angew. Chem.* **2004**, *116*, 5913–5915; *Angew. Chem. Int. Ed.* **2004**, *43*, 5789–5791.
[5] K. Stratmann, D. L. Burgoyne, R. E. Moore, G. M. L. Patterson, S. D. Smith, *J. Org. Chem.* **1994**, *59*, 7219–7226.
[6] a) H. Paulsen, K. Todt, *Chem. Ber.* **1967**, *100*, 512–520; b) G. F. Painter, A. Falshaw, H. Wong, *Org. Biomol. Chem.* **2004**, *2*, 1007–1012; c) A. Vasudevan, C. I. Villamil, S. W. Djuric, *Org. Lett.* **2004**, *6*, 3361–3364.
[7] a) J. Armbruster, S. Grabowski, T. Ruch, H. Prinzbach, *Angew. Chem.* **1998**, *110*, 2359–2362; *Angew. Chem. Int. Ed.* **1998**, *37*, 2242–2245; b) O. David, W. J. N. Meester, H. Bieräugel, H. E. Shoemaker, H. Hiemstra, J. H. van Maarsveen, *Angew. Chem.* **2004**, *116*, 4509–4511; *Angew. Chem. Int. Ed.* **2004**, *43*, 4373–4375.
[8] A. Geyer, F. Moser, *Eur. J. Org. Chem.* **2000**, 1113–1120; P. Tremmel, A. Geyer, *J. Am. Chem. Soc.* **2002**, *124*, 8548–8549.
[9] J. A. Robl, US Patent 5508272, **1996** (Omapatrilat).
[10] R. P. McGeary, S. R. Amini, V. W. S. Tang, I. Toth, *J. Org. Chem.* **2004**, *69*, 2727–2730.
[11] CCDC 250242 (**2**), 270029 (**3**), 250244 (**8**), 250243 (**9**), 250241 (**13**), and 270028 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[12] a) D. Q. Dinh, C. D. Smith, X. Du, R. W. Armstrong, *J. Med. Chem.* **1998**, *41*, 981–987; b) J. A. Olsen, K. J. Jensen, J. Nielsen, *J. Comb. Chem.* **2000**, *2*, 143–150; c) S. Sasmal, A. Geyer, M. E. Maier, *J. Org. Chem.* **2002**, *67*, 6260–6263; d) S. Borman, *Chem. Eng. News* **2003**, *81*, 45–56.

Received: May 9, 2005
Published online: August 11, 2005

