

# Design and Synthesis of Novel Arylketo-containing P1-P3 Linked Macrocyclic BACE-1 Inhibitors

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**Abstract:** A series of arylketo-containing P1-P3 linked macrocyclic BACE-1 inhibitors were designed, synthesized, and compared with compounds with a previously known and extensively studied corresponding P2 isophthalamide moiety with the aim to improve on permeability whilst retaining the enzyme- and cell-based activities. Several inhibitors displayed substantial increases in Caco-2 cell-based permeability compared to earlier synthesized inhibitors and notably also with retained activities, showing that this approach might yield BACE-1 inhibitors with improved properties.

**Keywords:** Alzheimer's disease, BACE-1 inhibition, cellular permeability, macrocycles, ring-closing metathesis, X-ray structure.

## INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder and the most common form of dementia among the elderly. It is believed that 24 million people worldwide suffer from the disease [1], and with an aging population the number of patients with AD is expected to rise. To develop disease-modifying drugs is therefore of paramount importance. The pathological findings associated with AD are insoluble extracellular amyloid  $\beta$ -plaques, consisting of  $A\beta$ -peptides, and intracellular neurofibrillary tangles found in the brain [2]. The human aspartic protease BACE-1 ( $\beta$ -secretase) initiates the cleavage of the amyloid precursor protein (APP) followed by  $\gamma$ -secretase which generates the  $A\beta$ -peptides, where BACE-1 catalyzes the rate-limiting step in this sequence [3]. This, together with the knowledge that BACE-1 knockout mice are viable and fertile, suggests that inhibition of BACE-1 could be a promising therapeutic target for the treatment of AD [4, 5]. However, the development of potent and selective BACE-1 inhibitors able to cross the blood-brain barrier (BBB) and avoid P-glycoprotein (P-gp) efflux shuffling has proven to be challenging [6, 7]. Notably though, in December 2013, Merck announced that they plan to initiate a new phase III study for their BACE-1 inhibitor MK-8931. Also, in September 2014 AstraZeneca and Eli Lilly & Company announced that they will develop and commercialize AZD3293. This proves that it is possible to design and synthesize potent and selective BACE-1 inhibitors [8].

Earlier studies in our laboratory [9] led to the development of a series of macrocyclic BACE-1 inhibitors, e.g. compound **1a** (Fig. 1), where both promising enzymatic and cell-based activities were observed. However, as these

inhibitors suffered from low permeability, we have in this study focused on improving the cell-based permeability by replacing the terminal amide of the P2 isophthalamide moiety with an acetophenone-type ketone group, thus rendering the molecules less peptidic (Fig. 1). Earlier studies have shown that the amide carbonyl oxygen of the P2 isophthalamide moiety forms a hydrogen bond with Thr232 in BACE-1, whilst the amide nitrogen does not make significant interactions with the enzyme [10, 11]. Moreover, it has been shown that the amide group of the P2 isophthalamide moiety can be replaced by a carbon chain, without significant loss in potency [6, 11], which renders the BACE-1 10s loop in a closed conformation with a hydrogen bond between Ser10 and Thr232, stabilizing the closed conformation. We thus hypothesized that an acetophenone-type carbonyl would provide an advantageous bioisostere to the amide group in this position, resulting in higher permeability through making less overall hydrogen bonds and provide inhibitors with retained good activity compared to their isophthalamide analogues. Also, further attempts to improve the cell-based permeability were performed by replacing the P2 sulfonamide functionality with a less polar methyl group.

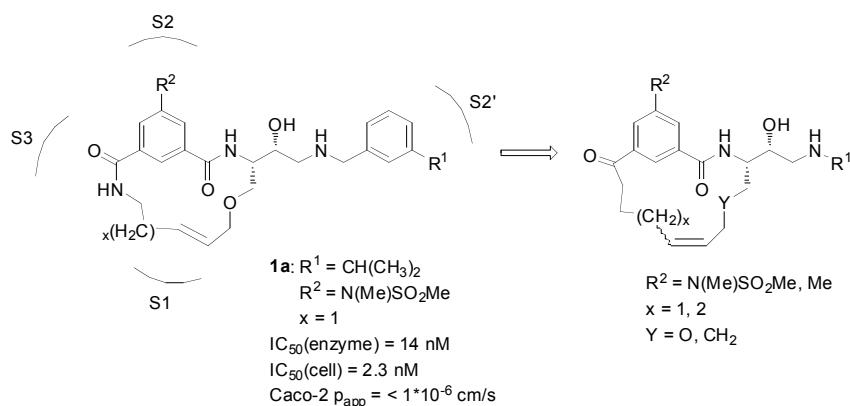
We have also investigated the effect of replacing the oxygen atom in the macrocyclic ring structure, used in some of our earlier inhibitors [9], with a carbon atom and in the P2' position replacing the 3-isopropylbenzylamine moiety with 2-(5-(*tert*-butyl)oxazol-2-yl)propan-2-amine, aiming at improving the overall pharmacokinetic properties.

## RESULTS AND DISCUSSION

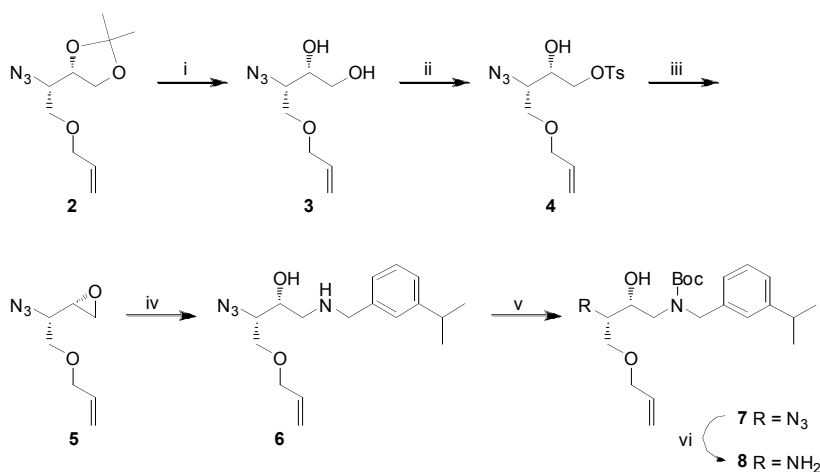
### Chemistry

The target compounds **28-36** were prepared according to Schemes **1-4** (see also Table **1**). The synthesis of compound **8** is outlined in Scheme **1**. Compound **2** was synthesized according to an already published procedure [9]. The acetal in **2** was hydrolyzed with AcOH (aq.) at 60 °C to give the

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**Fig. (1).** Lead compound **1a** together with a general structure of the target macrocycles presented in this paper.



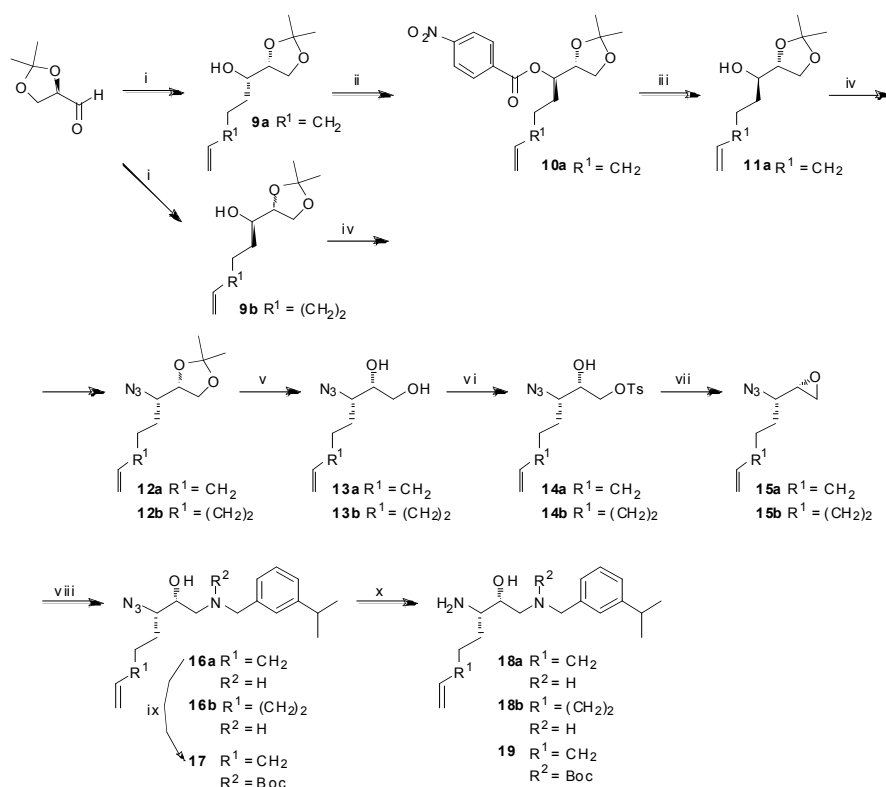
**Scheme 1.** Synthesis of building block **8**. Reagents and conditions: (i) AcOH (aq.), 60 °C, 3 h, 78%; (ii) TEA,  $\text{Bu}_2\text{SnO}$ , *p*-TsCl, dry DCM, rt, 3.5 h, 74%; (iii)  $\text{K}_2\text{CO}_3$ , MeOH, 0 °C to rt, 3 h, 84%; (iv) 3-isopropylbenzylamine, TEA, MeOH, 30 °C, 44 h, 56%; (v)  $\text{Boc}_2\text{O}$ , TEA, MeOH, rt, 1 h, 81%; (vi) 1,3-propanedithiol, TEA, Aliquat 336, MeOH, rt, 6 days, 76%.

diol **3** in 78% yield. The primary hydroxyl group in **3** was selectively tosylated using *p*-TsCl,  $\text{Bu}_2\text{SnO}$ , and TEA in dry DCM [12] to generate compound **4** (74%). The tosylated compound was then converted into the corresponding epoxide **5** in 84% yield, using  $\text{K}_2\text{CO}_3$  in MeOH. The epoxide was thereafter opened with 3-isopropylbenzylamine furnishing compound **6** in 56% yield. For purification reasons, the prepared amine was protected using  $\text{Boc}_2\text{O}$  and TEA in MeOH to give compound **7** (81%). Finally, the azide **7** was reduced using 1,3-propanedithiol, TEA, and Aliquat 336 in MeOH to afford the amine **8** in 76% yield.

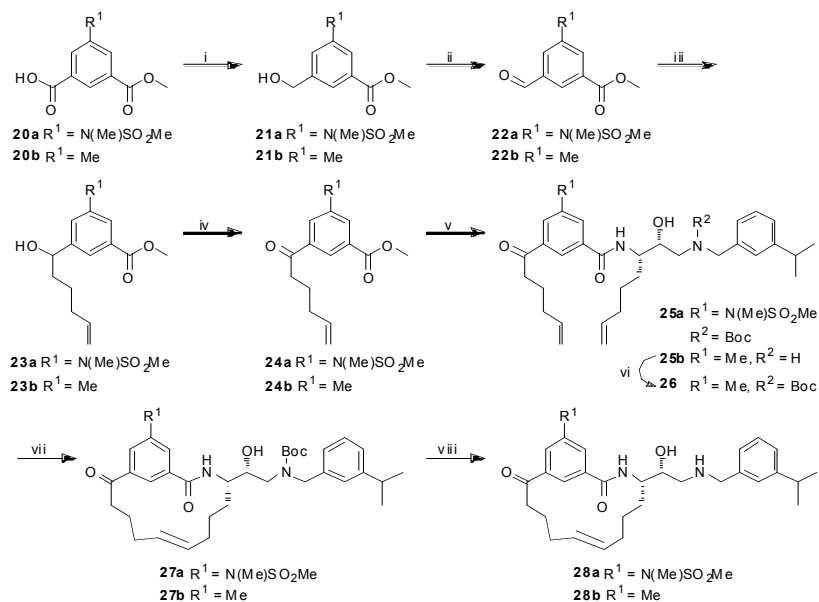
The synthesis of compounds **18a**, **18b**, and **19** is depicted in Scheme 2. 2,3-*O*-Isopropylidene-D-glyceraldehyde was synthesized according to a literature procedure [13] and the addition of a freshly prepared Grignard reagent, pent-4-enylmagnesium bromide or hex-5-enylmagnesium bromide, produced the two compounds **9a** and **9b** in diastereomeric mixtures which were subsequently separated. In the case of **9b** we had enough material of the correct diastereomer after the chromatography separation to proceed directly to **12b**. (The various stereoisomers were identified by NMR analyses). The hydroxyl group in (*S,R*)-**9a** was reacted with  $\text{PPh}_3$ , DIAD, and *p*-nitrobenzoic acid in THF, furnishing compound **10a** in 91% yield. The benzoate ester was cleaved using NaOMe in MeOH to give the inverted alcohol **11a** in

68% yield. Mitsunobu conditions, utilizing DPPA [14], generated the azide **12a** with inversion of configuration in 98% yield. The acetal in **12a** was hydrolyzed in AcOH (aq.) at 60 °C (74%) and the primary alcohol in the formed diol **13a** was selectively tosylated, using TEA,  $\text{Bu}_2\text{SnO}$ , and *p*-TsCl in DCM and DMF, to give compound **14a** in 84% yield. The epoxide **15a** was prepared in 90% yield using  $\text{Na}_2\text{CO}_3$  in MeOH, and was then opened with 3-isopropylbenzylamine and TEA in MeOH at 30 °C to give compound **16a** (61%). Compound **16b** was synthesized, with comparable yields, in the same manner from **12b**. Finally, reduction of the azide group in compounds **16a**, **16b**, and **17** was achieved using 1,3-propanedithiol, TEA, and Aliquat 336 in MeOH, providing the amines **18a** and **18b** in 83% and 81% yield, respectively. As an alternative synthetic route, for purification reasons, compound **16a** was treated with  $\text{Boc}_2\text{O}$  and TEA in MeOH to afford the Boc-protected compound **17** in 97% yield. **17** was then reduced as above, yielding **19** (88 %).

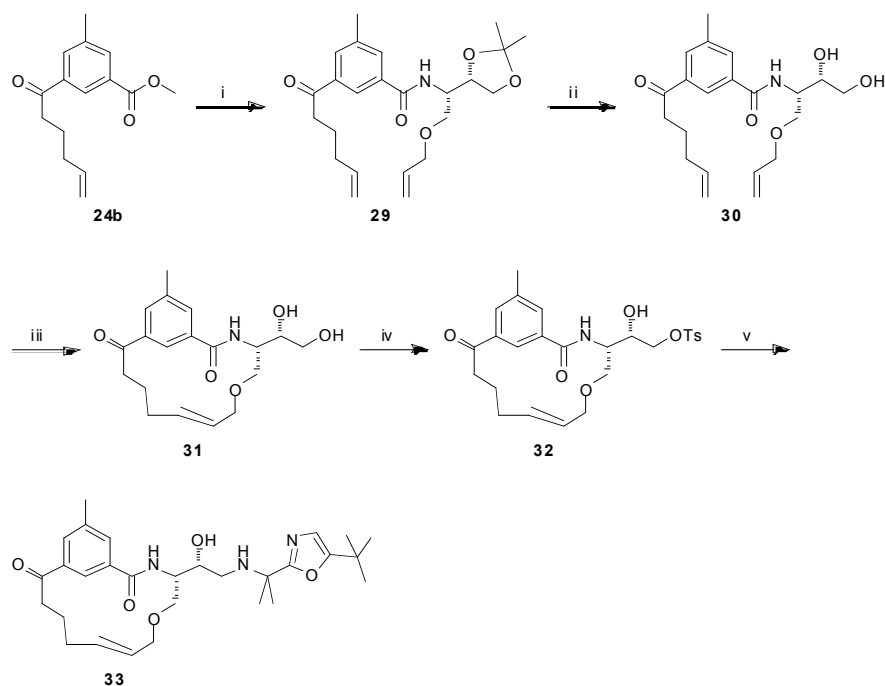
The synthesis of target compounds **28a** and **28b** is outlined in Scheme 3. The compounds were synthesized using two slightly different routes, depending on if the amine (see Scheme 2) was Boc-protected before the peptide coupling step or after. Compound **20a** was synthesized according to a reported procedure [15] and the carboxylic acid was selectively reduced with  $\text{BH}_3 \cdot \text{SMe}_2$  in dry THF to give the alcohol



**Scheme 2.** Synthesis of building blocks **18a-b** and **19**. Reagents and conditions: (i) pent-4-enylmagnesium bromide or hex-5-enylmagnesium bromide in THF, Et<sub>2</sub>O (dry), -30 °C to rt, 21 h, 80% and 87%, respectively; (ii) *p*-nitrobenzoic acid, DIAD, PPh<sub>3</sub>, THF, rt, overnight, 91%; (iii) NaOMe, MeOH, rt, 1 h 45 min, 68%; (iv) DPPA, PPh<sub>3</sub>, DIAD, THF (dry), -30 °C to rt, 24 h, 98% and 88%, respectively; (v) 70% AcOH (aq.), 60 °C, 3 h, 74% and quant., respectively; (vi) TEA, Bu<sub>2</sub>SnO, *p*-TsCl, DCM, DMF, rt, overnight, 84% and 88%, respectively; (vii) Na<sub>2</sub>CO<sub>3</sub>, MeOH, 0 °C to rt, 24 h, 100% and 97%, respectively; (viii) 3-isopropylbenzylamine, TEA, MeOH, 30 °C, 24 h, 61% and 53%, respectively; (ix) Boc<sub>2</sub>O, TEA, MeOH, rt, 1.5 h, 97%; (x) 1,3-dipropanedithiol, TEA, aliquat 336, MeOH, rt, 5 days, 83%, 81%, and 88%, respectively.



**Scheme 3.** Synthesis of target compounds **28a** and **28b**. Reagents and conditions: (i) BH<sub>3</sub>SMe<sub>2</sub>, THF (dry), Ar, 0 °C to rt, 24 h, 95% and 69%, respectively; (ii) SO<sub>3</sub>-pyridine, TEA, DMSO (dry), rt, 1.5 h, 84% and 73%, respectively; (iii) pent-4-enylmagnesium bromide in THF, Et<sub>2</sub>O (dry), 0 °C, 3 h, 65% and 79%, respectively; (iv) Dess-Martin periodinane, DCM, rt, 24 h, 76% and 89%, respectively; (v) (a) LiOH (aq.), dioxane, rt, 3 h; (b) compound **19** or **18a**, HATU, DIPEA, DMF, 0 °C to rt, 24 h, 89% and 85% over two steps, respectively; (vi) Boc<sub>2</sub>O, TEA, MeOH, rt, 3 h, 65%; (vii) Hoveyda-Grubbs 2<sup>nd</sup> generation, DCM (dry), reflux, 24 h, 21% and 47%, respectively; (viii) Et<sub>3</sub>SiH, TFA, DCM, rt, 1 h, 91% and 91%, respectively.



**Scheme 4.** Synthesis of target compound **33**. Reagents and conditions: (i) (a) LiOH (aq.), dioxane/H<sub>2</sub>O, 6 h; (b) (*S*)-2-(allyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamine, HATU, DIPEA, DMF, 4 h, 57% over two steps; (ii) 80% AcOH, 60 °C, 1 h, 95%; (iii) Hoveyda-Grubbs 2<sup>nd</sup> generation, DCM (dry), reflux, 16 h, 88%; (iv) TEA, Bu<sub>2</sub>SnO, *p*-TsCl, DCM, DMF, rt, overnight, 57%; (v) 2-(5-(*tert*-butyl)oxazol-2-yl)propan-2-amine, DIPEA, EtOH, reflux, 4 days, 5%.

**21a** in 95% yield. A Parikh-Doering oxidation [16] generated the aldehyde **22a** (95%) and the subsequent addition of the Grignard reagent pent-4-enylmagnesium bromide furnished the alcohol **23a** in 65% yield. This compound was oxidized to the corresponding ketone **24a** in 76% yield using Dess-Martin periodinane in DCM [17]. The ester functionality in **24a** was hydrolyzed using aqueous LiOH in dioxane and the resulting carboxylic acid was coupled with compound **19** using HATU and DIPEA in DMF to afford compound **25a** in 89% yield over two steps. Compound **25b** was synthesized in the same manner as **25a** using commercially available **20b** instead of **20a**, and amine **18a** instead of **19** in the coupling reaction. For purification reasons, the amino group in compound **25b** was protected using Boc<sub>2</sub>O and TEA in MeOH to give compound **26** in 69% yield. A ring-closing metathesis protocol was performed on compound **25a** and **26** using Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst in refluxing DCM to furnish the macrocyclic compounds **27a** and **27b** in 21% and 47% yield, respectively. The cyclization resulted in exclusive formation of the *trans* isomers, as confirmed by <sup>1</sup>H-NMR analyses. Finally, deprotection of the Boc group was achieved with Et<sub>3</sub>SiH and TFA in DCM to give the two target compounds **28a** and **28b** in 91% yield in both cases. Targets **34** and **35** (see Table 1) were synthesized according to the same synthetic route as **28a**, using amine **8** instead of **19** and the methyl ester **24b** instead of **24a** for compound **35**. Target **36** (see Table 1) was synthesized in the same manner as **28b** using amine **18b** instead of **18a**.

When using the route described in Scheme 3, the ring-closing metathesis step was unsuccessful when trying to synthesize target **33** (see Table 1). The reason for this is at this stage unknown. Therefore, a different synthetic route was outlined for **33**, as shown in Scheme 4. The methyl ester

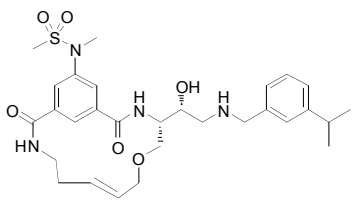
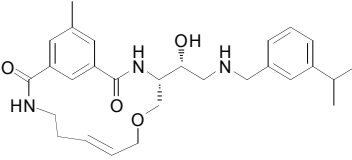
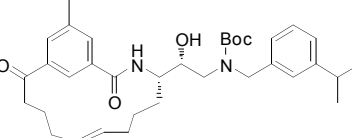
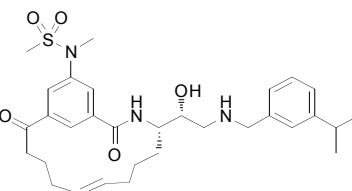
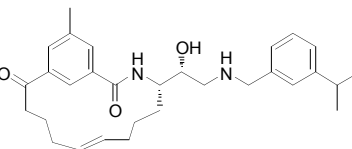
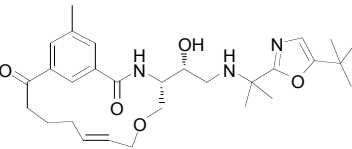
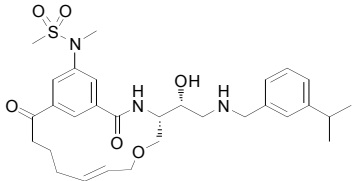
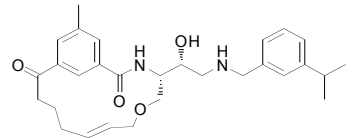
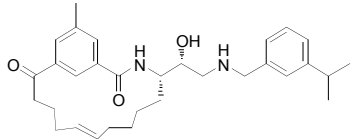
functionality in compound **24b** was hydrolyzed using LiOH (aq.) in dioxane/H<sub>2</sub>O to furnish the corresponding carboxylic acid, which was subsequently used in a peptide coupling step with the amine (*S*)-2-(allyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamine [9] using HATU and DIPEA in DMF to give compound **29** in 57% yield. The acetal was hydrolyzed with 80% AcOH to generate the diol **30** in 95% yield. The ring-closing metathesis protocol, using Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst in refluxing DCM, was now successful and rendered the macrocycle **31** in 88% yield. The primary hydroxyl group in **31** was tosylated by the use of TEA, Bu<sub>2</sub>SnO, and *p*-TsCl in DCM and DMF, which furnished compound **32** (57%). Finally, the tosylated compound was reacted with the amine 2-(5-(*tert*-butyl)oxazol-2-yl)propan-2-amine (see supp. info.) and DIPEA in refluxing EtOH to give the target compound **33** in 5% yield.

### Structure Activity Relationships

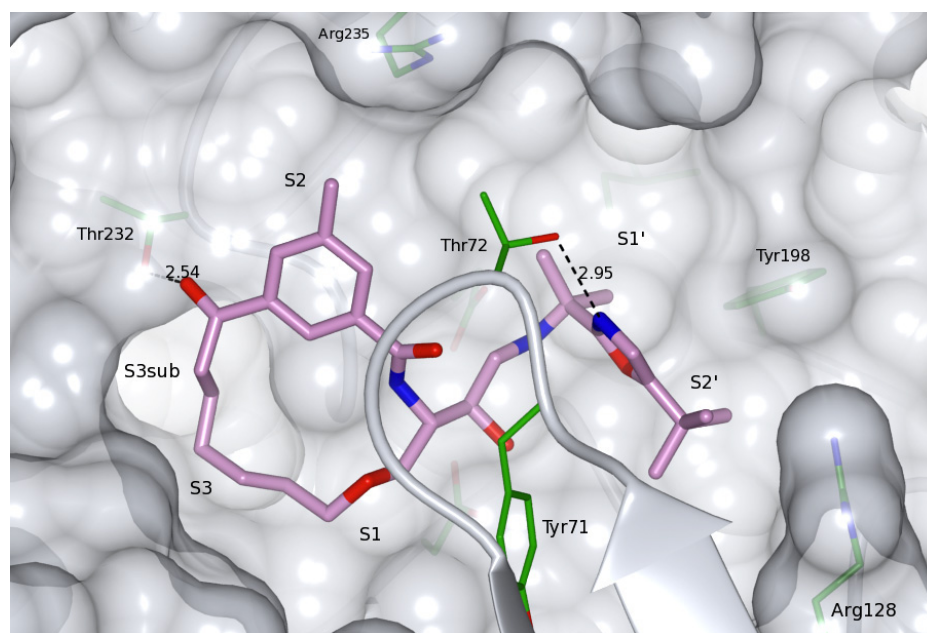
All target compounds were screened against BACE-1, both in enzyme- and cell-based assays, and the IC<sub>50</sub> values are shown in Table 1, along with Caco-2 *p*<sub>app</sub> values for selected compounds. The macrocycles were all 15-membered, except for compound **36** which was 16-membered.

Replacement of the terminal P2 amide functionality in the lead compound **1a** [9] with a keto group resulted in target product **34** which showed retained potencies against BACE-1 although without displaying improved permeability. It has earlier been found that BACE-1 inhibitors with a sulfonamide substituted isophthalamide in the P2 position are substrates for P-gp efflux [18], which could explain the low permeability of compound **34**. Replacement of the P2 sulfonamide functionality with a less polar methyl group

Table 1. BACE-1 inhibition data and cell permeability values.

Cpd.	Structure	IC <sub>50</sub> enzyme (nM)	IC <sub>50</sub> cell (nM)	Caco-2 p <sub>app</sub> (*10 <sup>-6</sup> cm/s)
1a <sup>a</sup>		14	2.3	< 1
1b <sup>a</sup>		500	220	< 1
27b		> 10000	> 10000	ND
28a		8.9	3	< 1
28b		280	970	13
33		1500	3300	32
34		12	4.6	< 1
35		1100	1400	13
36 <sup>b</sup>		260	1000	7.3

<sup>a</sup> Previously reported by our laboratory<sup>b</sup> 16-membered macrocycle



**Fig. (2).** Compound **33** bound to the active site of BACE-1 (PDB id: 4GMI).

furnished compound **35**, resulting in a significantly improved ( $p_{app} = 13 \times 10^{-6}$  cm/s) permeability. However, with the P2 sulfonamide replaced with a methyl group the BACE-1 activity was substantially reduced, but this compound exhibited comparable BACE-1 activities as the amide analogue **1b** [9] (Table 1) published earlier (a BACE-1  $IC_{50}$  value of 1100 vs. 500 nM and a cell-based  $IC_{50}$  value of 1400 vs. 220 nM, respectively), but with significantly better permeability (a Caco-2 value of  $13 \times 10^{-6}$  cm/s, as mentioned above, vs.  $< 1 \times 10^{-6}$  cm/s, respectively). In-house studies have shown that the introduction of an oxazole group (see supplementary material) in the P2' position can give rise to highly active compounds and with improved permeability. Introduction of this oxazole group provided compound **33** which exhibited additional improvement in permeability compared with inhibitor **35** whilst retaining enzyme- and cell-based activity compared with compound **35**. The X-ray structure of **33** (PDB id: 4GMI) in complex with BACE-1 shows that the gem-methyl groups shielding the secondary nitrogen atom are well accommodated for and, as such, are not exerting any steric impediment on compound binding (Fig. 2). Moreover, the P2' *tert*-butyl substituted oxazole has a good fit to the S2' subsite, including a hydrogen bond to Thr72 of the flap.

Generally, we have noted that replacing the macrocyclic ether oxygen with a carbon in these inhibitors often results in increased potency [19]. However, the carbon analogue to compound **34**, inhibitor **28a**, showed similar potent activities (a BACE-1  $IC_{50}$  value of 8.9 vs. 12 nM and a cell-based  $IC_{50}$  value of 3.0 vs. 4.6 nM, respectively). As expected, with a P2 sulfonamide moiety, compound **28a** also displayed a similar low Caco-2 permeability value ( $< 1 \times 10^{-6}$  cm/s). As foreseen, the Boc-protected compound **27b** was inactive. (It is well established that hydroxyethylamine-based BACE-1 inhibitors bind to the catalytic aspartates Asp32 and Asp228 *via* the protonated amino and hydroxy groups [9, 20, 21]). Compound **28b**, incorporating a toluene core in the P2 position, displayed an improved potency compared to its analogue **35** ( $IC_{50}$  280 vs. 1100 nM, respectively) and equal

permeability ( $p_{app} = 13 \times 10^{-6}$  cm/s). The 16-membered macrocycle **36** showed similar activity and permeability as its corresponding 15-membered macrocycle **28b**. Attempts to synthesize the corresponding 14-membered macrocycle were unsuccessful, likely due to a high ring strain of the target product.

## CONCLUSION

A novel series of macrocyclic BACE-1 inhibitors incorporating a P2/P3 keto functionality was investigated, with some inhibitors showing highly promising low nanomolar activities against the BACE-1 enzyme and in the cell-based assay. Moreover, several inhibitors exhibited improved cell-based permeability compared to inhibitors previously synthesized, but, not unexpectedly, these target compounds displayed decreased potency due to replacement of the sulfonamide functionality in the P2 position with a methyl group, where the sulfonamide moiety has been shown to be important for the activity in this type of inhibitor compounds. In summary, improved permeability could be achieved compared to earlier published inhibitors from our group whilst retaining the overall BACE-1 inhibitory activities.

Further work on this series is highly warranted exploring sulfonamide replacements in the P2-position, *e.g.* by use of small lipophilic groups and by introducing potency-enhancing lipophilic substituents protruding into the S3 sub pocket.

## EXPERIMENTAL SECTION

### General

NMR-spectra were recorded on a Varian 300 MHz instrument using  $CDCl_3$ ,  $CD_3OD$  or  $DMSO-d_6$  as solvents. Thin layer chromatography (TLC) was carried out on Merck precoated 60  $F_{254}$  plates using UV-light and charring with ethanol/sulfuric acid/*p*-anisaldehyde/acetic acid 90:3:2:1, or

a solution of 0.5% ninhydrin in ethanol, for visualization. Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm, Merck). Organic phases were dried over anhydrous magnesium sulfate. Optical rotations were measured using a Perkin-Elmer 141 polarimeter at 22 °C. Gradient LC-MS was performed on a Gilson system (column: Phenomenex C18, 100 x 21 mm, 5 µm for preparative runs and xBridge™ C18, 50 x 4.6 mm, 2.5 µm for analytical runs; pump: Gilson gradient pump 322; UV/VIS-detector: Gilson 152; MS detector: Thermo Finnigan Surveyor MSQ; Gilson Fraction Collector FC204) using acetonitrile with 0.05% formic acid and deionized water with 0.05% formic acid as mobile phases. High resolution mass spectra (HRMS) were recorded on a Waters Synapt HDMS instrument equipped with an electrospray interface.

### BACE-1 Enzyme Assay

The BACE-1 assay was performed as previously described [22].

### BACE-1 Cell Assay

The cell-based assay was performed as previously described [23].

### Caco-2 Assay

The permeability coefficients ( $P_{app}$ ) were performed as previously described [24].

### LC-MS Purity Measurements

**Chromatography system A.** Column: Phenomenex C18, 50 x 4.6 mm, 3 µm; pump: Gilson gradient pump 322; UV/VIS-detector: Gilson 152; MS detector: Thermo Finnigan Surveyor MSQ; Software: Gilson Unipoint 4.0 and Xcalibur 1.3. Mobile phase A: 10 mM NH<sub>4</sub>OAc in water; mobile phase B: 10 mM NH<sub>4</sub>OAc in 90% acetonitrile; gradient: 20-100% B over 6 min at 1 mL/min followed by 100% of B for 4 min at 1 mL/min. Peaks were detected at 254 nm.

**Chromatography system B.** Column: XBridge C8, 50 x 4.6 mm, 2.5 µm; pump: Gilson gradient pump 322; UV/VIS-detector: Gilson 152; MS detector: Thermo Finnigan Surveyor MSQ; Software: Gilson Unipoint 4.0 and Xcalibur 1.3. Mobile phase A: 10 mM NH<sub>4</sub>OAc in water; mobile phase B: 10 mM NH<sub>4</sub>OAc in 90% acetonitrile; gradient: 40-100% B over 7 min at 1 mL/min followed by 100% of B for 3 min at 1 mL/min. Peaks were detected at 254 nm.

### SYNTHETIC PROCEDURES

**(2S,3S)-4-(Allyloxy)-3-azidobutane-1,2-diol (3).** Compound **2** (1.82 g, 8.0 mmol) was dissolved in AcOH/H<sub>2</sub>O (40:15 mL) and the solution was stirred for 3 hours at 60 °C. The mixture was concentrated, co-evaporated with toluene and purified using flash column chromatography (toluene/EtOAc 1:1) to give compound **3** (1.17 g, 78%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.73 (bs, 2H), 3.58–3.66 (m, 2H), 3.67–3.77 (m, 4H), 4.03 (d, *J* = 5.7 Hz, 2H), 5.19–5.32 (m, 2H), 5.82–5.95 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 62.1, 63.6, 70.0, 71.9, 72.6, 117.9, 134.0. MS-analysis resulted in decomposition. No mass peak could be detected.

**(2S,3S)-4-(Allyloxy)-3-azido-2-hydroxybutyl 4-methyl benzenesulfonate (4).** TEA (830 µL, 6.0 mmol), Bu<sub>2</sub>SnO (124 mg, 0.5 mmol) and *p*-TsCl (1.13 g, 5.9 mmol) were added to a solution of compound **3** (930 mg, 4.9 mmol) in dry DCM (30 mL). The mixture was stirred for 3.5 hours at room temperature. The solution was thereafter diluted with DCM, washed two times with brine and the organic phase was dried, filtered and concentrated. Purification using flash column chromatography (toluene/EtOAc 19:1) gave compound **4** (1.25 g, 74%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.45 (s, 3H), 2.87 (bs, 1H), 3.55–3.61 (m, 1H), 3.66 (dd, *J* = 6.0, 10.2 Hz, 1H), 3.75 (dd, *J* = 3.6, 10.2 Hz, 1H), 3.83–3.90 (m, 1H), 4.01 (dt, *J* = 1.5, 5.7 Hz, 2H), 4.10 (dd, *J* = 5.7, 10.5 Hz, 1H), 4.20 (dd, *J* = 3.3, 10.5 Hz, 1H), 5.18–5.31 (m, 2H), 5.80–5.93 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.7, 61.4, 69.5, 69.6, 71.1, 72.5, 117.7, 128.1, 130.1, 132.5, 134.0, 145.4. MS-analysis resulted in decomposition. No mass peak could be detected.

**(S)-2-((S)-2-(Allyloxy)-1-azidoethyl)oxirane (5).** Compound **4** (1.25 g, 3.7 mmol) was dissolved in MeOH (28 mL). K<sub>2</sub>CO<sub>3</sub> (830 mg, 6.0 mmol) was added at 0 °C and the solution was left to reach room temperature and stirred for 3 hours. H<sub>2</sub>O and DCM were added and the organic phase was dried, filtered and concentrated. The crude material was purified using flash column chromatography (toluene/EtOAc 19:1) and compound **5** (521 mg, 84%) was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.75–2.77 (m, 1H), 2.79–2.83 (m, 1H), 3.06–3.10 (m, 1H), 3.46–3.51 (m, 1H), 3.58 (dd, *J* = 6.3, 9.9 Hz, 1H), 3.66 (dd, *J* = 3.9, 9.9 Hz, 1H), 4.03 (dt, *J* = 1.5, 5.7 Hz, 2H), 5.18–5.21 (m, 1H), 5.24–5.31 (m, 1H), 5.83–5.96 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 45.2, 50.8, 61.8, 70.0, 72.5, 117.6, 134.1. MS (2M+Na)<sup>+</sup> calcd: 361.2; found: 360.7.

**(2R,3S)-4-(Allyloxy)-3-azido-1-((3-isopropylbenzyl) amino)butan-2-ol (6).** Compound **5** (385 mg, 2.3 mmol) and 3-isopropylbenzylamine (510 mg, 3.4 mmol) were dissolved in MeOH (2.5 mL). TEA (640 µL, 4.6 mmol) was added and the solution was stirred for 44 hours at 30 °C. The mixture was concentrated and purified using flash column chromatography (toluene/EtOAc 3:1 + 1% TEA) to give compound **6** (405 mg, 56%) as a slightly yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.25 (d, *J* = 6.9 Hz, 6H), 2.70 (dd, *J* = 8.1, 12.3 Hz, 1H), 2.83–2.94 (m, 2H), 3.52–3.57 (m, 1H), 3.58–3.64 (m, 1H), 3.65–3.71 (m, 1H), 3.74 (dd, *J* = 3.6, 9.9 Hz, 1H), 3.77 (d, *J* = 3.6 Hz, 2H), 4.02 (dt, *J* = 1.5, 5.7 Hz, 2H), 5.17–5.32 (m, 2H), 5.83–5.96 (m, 1H), 7.09–7.18 (m, 3H), 7.22–7.28 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.0, 34.1, 50.9, 53.8, 63.9, 68.9, 70.1, 72.3, 117.3, 125.3, 125.5, 126.2, 128.5, 134.2, 139.7, 149.2. MS (M+H)<sup>+</sup> calcd: 319.2; found: 319.6.

**tert-Butyl ((2R,3S)-4-(allyloxy)-3-azido-2-hydroxybutyl) (3-isopropyl-benzyl)carbamate (7).** Compound **6** (228 mg, 0.7 mmol) was dissolved in MeOH (7 mL). TEA (200 µL, 1.4 mmol) and Boc<sub>2</sub>O (229 mg, 1.0 mmol) were added and the mixture was stirred for 1 h. The solution was concentrated and purified using flash column chromatography (toluene/EtOAc 19:1), which gave compound **7** (243 mg, 81%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.25 (d, *J* = 6.9 Hz, 6H), 1.47 (s, 9H), 2.85–2.94 (m, 1H), 3.36 (dd, *J* = 2.4, 14.7 Hz, 1H), 3.45 (td, *J* = 3.3, 7.2 Hz, 1H),

3.63 (dd,  $J = 7.2, 10.2$  Hz, 1H), 3.72 (bs, 1H), 3.79 (bs, 1H), 4.02 (dt,  $J = 1.5, 5.4$  Hz, 2H), 4.45 (bs, 2H), 4.63 (bs, 1H), 5.17-5.22 (m, 1H), 5.25-5.32 (m, 1H), 5.83-5.96 (m, 1H), 7.09 (s, 1H), 7.13-7.18 (m, 2H), 7.23-7.24 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  24.0, 28.4, 34.1, 51.1, 52.8, 63.4, 70.1, 71.6, 72.3, 79.1, 117.3, 124.9, 125.3, 126.2, 129.0, 134.3, 137.7, 149.4, 153.1. MS ( $\text{M}+\text{H}^+$ ) calcd: 419.3; found: 419.5.

**tert-Butyl ((2*R*,3*S*)-4-(allyloxy)-3-amino-2-hydroxybutyl) (3-isopropyl-benzyl)carbamate (8).** Compound **7** (114 mg, 0.3 mmol) was dissolved in MeOH (3 mL). Aliquat 336 (1 drop), TEA (190  $\mu\text{L}$ , 1.3 mmol) and 1,3-propanedithiol (135  $\mu\text{L}$ , 1.3 mmol) were added to the solution and the mixture was stirred for 6 days at room temperature. The reaction mixture was filtered, concentrated and purified using flash column chromatography (MeOH/EtOAc 1:9 + 1% TEA) to give compound **8** (82 mg, 76%) as a colorless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.24 (d,  $J = 6.9$  Hz, 6H), 1.46 (s, 9H), 2.84-2.93 (m, 3H), 2.96-3.02 (m, 1H), 3.35-3.39 (m, 1H), 3.44-3.49 (m, 2H), 3.55-3.57 (m, 1H), 3.75-3.85 (m, 1H), 3.96-3.98 (m, 2H), 4.50 (bs, 2H), 5.14-5.17 (m, 1H), 5.21-5.28 (m, 1H), 5.81-5.94 (m, 1H), 7.02-7.18 (m, 3H), 7.21-7.27 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  24.1, 28.5, 34.2, 50.4, 52.4, 53.8, 71.8, 72.3, 73.6, 80.7, 117.3, 124.9, 125.4, 128.6, 134.6, 138.2, 149.3, 153.2. MS ( $\text{M}+\text{H}^+$ ) calcd: 393.3; found: 393.6.

**(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hex-5-en-1-ol (9a).** Magnesium turnings (1.71 g, 70.3 mmol), a crystal of iodine and dry THF (30 mL) were mixed in a two-necked round-bottom flask equipped with a cooler. The mixture was heated gently and 5-bromopent-1-ene (8.3 mL, 70.2 mmol) was added slowly to maintain a steady reflux. After the addition was complete, 30 mL of dry THF was added, and the solution was refluxed for 1 h. The resulting Grignard mixture was thereafter cooled to  $-30^\circ\text{C}$  and isopropylidene-protected D-glyceraldehyde (6.03 g, 46.4 mmol) dissolved in dry THF (50 mL) was added dropwise over a period of 30 min. The resulting solution was allowed to obtain room temperature overnight, after which  $\text{Et}_2\text{O}$  and saturated  $\text{NH}_4\text{Cl}$  were added. The water phase was extracted with  $\text{Et}_2\text{O}$  twice and the combined organic phases were dried, filtered and evaporated. The crude material was purified using flash column chromatography (heptane/EtOAc 10:1) to yield **9a** (6.31 g, 68%) as a colorless oil. (*S,R*):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.31-1.38 (m, 1H), 1.36 (s, 3H), 1.39-1.54 (m, 2H), 1.42 (s, 3H), 1.57-1.68 (m, 1H), 2.04-2.13 (m, 2H), 2.15 (d,  $J = 3.5$  Hz, 1H), 3.71-3.80 (m, 1H), 3.86-4.05 (m, 3H), 4.93-5.06 (m, 2H), 5.73-5.88 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  25.1, 25.4, 26.6, 32.2, 33.7, 64.7, 70.7, 78.8, 109.0, 114.9, 138.5.

**1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hept-6-en-1-ol (9b).** Compound **9b** (9.62 g, total yield 87%, (*S*)/(*R*) 75:25) was synthesized from isopropylidene-protected D-glyceraldehyde in the same manner as **9a**. The two diastereomers were separated and collected as yellow oils. (*S,R*):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.31-1.64 (m, overlapped, 6H), 1.37 (s, overlapped, 3H), 1.43 (s, overlapped, 3H), 1.93 (d,  $J = 3.0$  Hz, 1H), 2.07 (app. q,  $J = 6.6$  Hz, 2H), 3.76-3.81 (m, 1H), 3.88-3.97 (m, 2H), 3.99-4.06 (m, 1H), 4.93-5.04 (m, 2H), 5.74-5.87 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  25.4, 25.5, 26.6, 29.0, 32.6, 33.8, 64.6, 70.8,

78.8, 109.1, 114.6, 138.9. MS ( $\text{M}+\text{H}^+$ ) calcd: 214.2; found: 213.9. (*R,R*):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.29-1.63 (m, overlapped, 6H), 1.37 (s, overlapped, 3H), 1.44 (s, overlapped, 3H), 2.04-2.10 (m, 2H), 2.12 (d,  $J = 5.1$  Hz, 1H), 3.45-3.53 (m, 1H), 3.69-3.77 (m, 1H), 3.95-4.04 (m, 2H), 4.93-5.03 (m, 2H), 5.74-5.88 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  25.2, 25.5, 26.8, 29.0, 33.7, 33.8, 66.3, 72.4, 79.3, 109.5, 114.6, 138.9. MS ( $\text{M}+\text{H}^+$ ) calcd: 214.2; found: 213.8.

**(*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hex-5-en-1-yl 4-nitrobenzoate (10a).** To a solution of **9a** (1.63 g, 8.15 mmol) in dry THF (50 mL), *p*-nitrobenzoic acid (2.23 g, 13.3 mmol) and  $\text{Ph}_3\text{P}$  (3.42 g, 13.0 mmol) were added. DIAD (2.57 mL, 13.1 mmol) was added dropwise over a period of 30 min and the resulting reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the crude remainder was purified by flash column chromatography (toluene  $\rightarrow$  toluene/EtOAc 18:1) to furnish compound **10a** (2.60 g, 91%) as a slightly yellow oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.35 (s, 3H), 1.42-1.56 (m, 2H), 1.45 (s, 3H), 1.66-1.85 (m, 2H), 2.03-2.19 (m, 2H), 3.79 (dd,  $J = 6.0, 8.6$  Hz, 1H), 4.03-4.12 (m, 1H), 4.30 (dd,  $J = 6.0, 11.9$  Hz, 1H), 4.92-5.06 (m, 2H), 5.25 (dt,  $J = 4.9, 9.9$  Hz, 1H), 5.69-5.85 (m, 1H), 8.23 (d,  $J = 9.2$  Hz, 2H), 8.29 (d,  $J = 9.2$  Hz, 2H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  24.6, 25.3, 26.4, 30.2, 33.4, 65.8, 75.3, 76.6, 109.8, 115.2, 123.6, 130.9, 135.7, 138.0, 150.7, 164.5. MS ( $\text{M}+\text{H}^+$ ) calcd: 350.2; found: 350.5.

**(*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hex-5-en-1-ol (11a).** Compound **10a** (2.55 g, 7.31 mmol) was dissolved in MeOH (40 mL) and NaOMe in MeOH (0.5 M, 15 mL, 7.5 mmol) was added dropwise during 20 min. The solution was stirred at room temperature for 1 h and 45 min, after which it was neutralized with HOAc and evaporated. DCM and saturated  $\text{NaHCO}_3$  were added and the water phase was extracted with DCM once. The organic phases were dried, filtered and evaporated and the crude material was purified using flash column chromatography (heptane/EtOAc 9:1) to yield **11a** (1.00 g, 68%) as a colorless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.32-1.56 (m, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.57-1.72 (m, 1H), 2.01-2.14 (m, 2H), 2.42 (d,  $J = 4.7$  Hz, 1H), 3.42-3.54 (m, 1H), 3.66-3.76 (m, 1H), 3.93-4.04 (m, 2H), 4.92-5.06 (m, 2H), 5.73-5.87 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  24.8, 25.4, 26.7, 33.0, 33.6, 66.2, 72.1, 79.3, 109.4, 114.8, 138.5.

**(*S*)-4-((*S*)-1-Azidohex-5-en-1-yl)-2,2-dimethyl-1,3-dioxolane (12a).** To a solution of **11a** (993 mg, 4.97 mmol) in dry THF (30 mL),  $\text{Ph}_3\text{P}$  (2.06 g, 7.85 mmol) was added and the temperature was lowered to  $-5^\circ\text{C}$ . DIAD (1.60 mL, 8.13 mmol) and DPPA (2.17 g, 7.89 mmol) were added dropwise during 20 min and 5 min, respectively, and the stirred solution was allowed to reach room temperature overnight. After evaporation of the solvent the crude mixture was purified using flash column chromatography (2.5% EtOAc in heptane) to give **12a** (1.10 g, 98%) as a slightly yellow oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.28-1.46 (m, 1H), 1.35 (s, 3H), 1.45 (s, 3H), 1.47-1.70 (m, 3H), 2.04-2.14 (m, 2H), 3.44-3.53 (m, 1H), 3.83-3.90 (m, 1H), 3.98-4.10 (m, 2H), 4.95-5.08 (m, 2H), 5.72-5.86 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  25.3, 25.5, 26.3, 30.4, 33.4, 63.7,



66.0, 78.0, 109.7, 115.2, 138.1. MS (M+H)<sup>+</sup> calcd: 226.2; found: 226.3.

**(S)-4-((S)-1-Azidohept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolane (12b).** Compound **12b** (357 mg, 88%) was synthesized from (*R,R*)-**9b** in the same manner as **12a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.34-1.47 (m, overlapped, 6H), 1.36 (s, overlapped, 3H), 1.46 (s, overlapped, 3H), 1.53-1.58 (m, 2H), 3.45-3.49 (m, 1H), 3.84-3.91 (m, 1H), 3.99-4.09 (m, 2H), 4.93-5.05 (m, 2H), 5.73-5.87 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 25.4, 25.8, 26.4, 28.7, 31.0, 33.6, 64.0, 66.1, 78.0, 109.8, 114.8, 138.6. MS (M+H)<sup>+</sup> calcd: 240.2; found: 239.9.

**(2S,3S)-3-Azidoct-7-ene-1,2-diol (13a).** Compound **12a** (1.07 g, 4.76 mmol) was dissolved in a mixture of HOAc (20 mL) and H<sub>2</sub>O (10 mL). The solution was stirred at 60 °C for 3 h after which the solvents were evaporated. The crude material was purified using flash column chromatography (toluene/EtOAc 2:1) to yield **13a** (650 mg, 74%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.40-1.72 (m, 4H), 2.02-2.18 (m, 2H), 3.36-3.46 (m, 1H), 3.57-3.75 (m, 3H), 3.85 (br s, 1H), 4.10 (br s, 1H), 4.95-5.08 (m, 2H), 5.72-5.87 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 25.5, 29.8, 33.3, 63.2, 64.4, 73.9, 115.1, 138.0. MS-analysis resulted in decomposition. No mass peak could be detected.

**(2S,3S)-3-Azidonon-8-ene-1,2-diol (13b).** Compound **13b** (290 mg, quant.) was synthesized from **12b** in the same manner as **13a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.41-1.49 (m, 2H), 1.50-1.57 (m, 2H), 1.58-1.68 (m, 2H), 2.04-2.12 (m, 2H), 3.42-3.48 (m, 1H), 3.67-3.69 (m, 1H), 3.71-3.75 (m, 2H), 4.94-5.05 (m, 2H), 5.74-5.87 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 25.8, 28.8, 30.5, 33.6, 63.3, 64.8, 73.6, 114.8, 138.6. MS-analysis resulted in decomposition. No mass peak could be detected.

**(2S,3S)-3-Azido-2-hydroxyoct-7-en-1-yl 4-methyl benzenesulfonate (14a).** To a solution of **13a** (588 mg, 3.18 mmol) in a mixture of DCM (50 mL) and DMF (10 mL), TEA (885 μL, 6.35 mmol), Bu<sub>2</sub>SnO (81 mg, 0.33 mmol) and TsCl (750 mg, 3.93 mmol) were added. The reaction mixture was stirred at room temperature overnight. DCM and brine were added, and the organic phase was dried, filtered and evaporated. Flash column chromatography (toluene/EtOAc 9:1) afforded compound **14a** (900 mg, 84%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.38-1.70 (m, 4H), 2.01-2.14 (m, 2H), 2.45 (s, 3H), 2.64 (d, *J* = 5.0 Hz, 1H), 3.35-3.46 (m, 1H), 3.75-3.85 (m, 1H), 4.07 (dd, *J* = 6.6, 10.4 Hz, 1H), 4.17 (dd, *J* = 3.1, 10.4 Hz, 1H), 4.94-5.06 (m, 2H), 5.70-5.85 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 2.83 (d, *J* = 8.2 Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.8, 25.3, 29.8, 33.4, 63.6, 71.1, 71.6, 115.3, 128.1, 130.1, 132.5, 138.0, 145.5. MS-analysis resulted in decomposition. No mass peak could be detected.

**(2S,3S)-3-Azido-2-hydroxynon-8-en-1-yl 4-methyl benzenesulfonate (14b).** Compound **14b** (395 mg, 88%) was synthesized from **13b** in the same manner as **14a** and was collected as a pale yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.36-1.46 (m, 3H), 1.49-1.57 (m, 2H), 1.60-1.68 (m, 1H), 2.03-2.10 (m, 2H), 2.36-2.38 (m, 1H), 2.46 (s, 3H), 3.38-3.44 (m, 1H), 3.76-3.84 (m, 1H), 4.08 (dd, *J* = 6.6, 10.5 Hz, 1H), 4.19 (dd, *J* = 3.0, 10.5 Hz, 1H), 4.94-5.05 (m, 2H), 5.72-5.86 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4

Hz, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.8, 25.5, 28.7, 33.6, 63.7, 71.1, 71.7, 114.9, 128.2, 130.2, 132.6, 138.5, 145.5. MS-analysis resulted in decomposition. No mass peak could be detected.

**(S)-2-((S)-1-Azidohex-5-en-1-yl)oxirane (15a).** Compound **14a** (320 mg, 0.94 mmol) was dissolved in MeOH (10 mL) and the temperature of the solution was lowered to 0 °C. Na<sub>2</sub>CO<sub>3</sub> (175 mg, 1.65 mmol) was added and the stirred mixture was allowed to obtain room temperature overnight. Saturated NH<sub>4</sub>Cl was added and the resulting mixture was extracted with DCM. The organic phase was dried, filtered and evaporated and the crude remainder was purified using flash column chromatography (toluene) to provide the somewhat volatile **15a** (157 mg, 100%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.43-1.72 (m, 4H), 2.08 (q, *J* = 6.6 Hz, 2H), 2.72-2.79 (m, 2H), 2.94-3.00 (m, 1H), 3.26-3.34 (m, 1H), 4.94-5.08 (m, 2H), 5.71-5.86 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.9, 31.3, 33.4, 44.8, 53.4, 62.5, 115.1, 138.0. MS (2M+H)<sup>+</sup> calcd: 335.2; found: 335.6.

**(S)-2-((S)-1-Azidohept-6-en-1-yl)oxirane (15b).** Compound **15b** (192 mg, 97%) was synthesized from **14b** in the same manner as **15a** and was collected as a pale yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.40-1.48 (m, 2H), 1.50-1.60 (m, 2H), 1.62-1.72 (m, 2H), 2.04-2.12 (m, 2H), 2.76-2.79 (m, 1H), 2.80-2.83 (m, 1H), 2.99-3.03 (m, 1H), 3.31 (dt, *J* = 5.1, 8.1 Hz, 1H), 4.94-5.05 (m, 2H), 5.74-5.87 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 25.3, 28.7, 31.9, 33.6, 45.0, 53.6, 62.8, 114.8, 138.6. MS (2M+H)<sup>+</sup> calcd: 363.2; found: 362.9.

**(2R,3S)-3-Azido-1-((3-isopropylbenzyl)amino)oct-7-en-2-ol (16a).** Compound **15a** (112 mg, 0.67 mmol) was dissolved in MeOH (1 mL) and 3-isopropylbenzylamine (145 mg, 0.97 mmol) and TEA (185 μL, 1.33 mmol) were added. The solution was stirred overnight at 30 °C and was then evaporated. The crude material was purified using flash column chromatography (toluene/EtOAc 3:1 → toluene/EtOAc 1:1 + 1% TEA), yielding compound **16a** (130 mg, 61%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.25 (d, *J* = 6.9 Hz, 6H), 1.34-1.80 (m, 4H), 1.98-2.14 (m, 2H), 2.68 (dd, *J* = 8.5, 12.2 Hz, 1H), 2.81 (dd, *J* = 3.6, 12.2 Hz, 1H), 2.84-2.96 (m, 2H), 3.02 (bs, 2H), 3.32-3.42 (m, 1H), 3.58-3.67 (m, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.80 (d, *J* = 13.0 Hz, 1H), 4.92-5.07 (m, 2H), 5.70-5.86 (m, 1H), 7.07-7.17 (m, 2H), 7.21-7.29 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.1, 25.7, 29.9, 33.5, 34.1, 50.3, 53.9, 65.7, 71.4, 115.1, 125.4, 125.6, 126.4, 128.6, 138.2, 139.6, 149.3. MS (M+H)<sup>+</sup> calcd: 317.2; found: 317.6.

**(2R,3S)-3-Azido-1-((3-isopropylbenzyl)amino)non-8-en-2-ol (16b).** Compound **16b** (177 mg, 53%) was synthesized from **15b** in the same manner as **16a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.26 (d, *J* = 6.9 Hz, 6H), 1.37-1.50 (m, 4H), 1.52-1.66 (m, 2H), 2.04-2.11 (m, 2H), 2.71 (dd, *J* = 8.7, 12.3 Hz, 1H), 2.85 (dd, *J* = 3.6, 12.3 Hz, 1H), 2.87-2.96 (m, 1H), 3.36-3.42 (m, 1H), 3.60-3.66 (m, 1H), 3.79 (d, *J* = 4.2 Hz, 2H), 4.94-5.05 (m, 2H), 5.74-5.88 (m, 1H), 7.11-7.16 (m, 3H), 7.25-7.30 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.1, 26.0, 28.8, 30.5, 33.7, 34.2, 50.2, 54.0, 65.8, 71.4, 114.7, 125.5, 125.6, 126.4, 128.7, 138.7, 139.8, 149.4. MS (M+H)<sup>+</sup> calcd: 331.2; found: 330.9.

**tert-Butyl ((2*R*,3*S*)-3-azido-2-hydroxyoct-7-en-1-yl)(3-isopropylbenzyl)carbamate (17).** Compound **17** (193 mg, 97%) was synthesized from **16a** according to the synthesis of compound **7** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.25 (d, *J* = 6.9 Hz, 6H), 1.49 (s, 9H), 1.53-1.63 (m, 4H), 2.05-2.10 (m, 2H), 2.85-2.94 (m, 1H), 3.19-3.25 (m, 2H), 3.50-3.60 (m, 1H), 3.65-3.75 (m, 1H), 4.45 (bs, 2H), 4.94-5.05 (m, 2H), 5.71-5.85 (m, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 7.14-7.19 (m, 1H), 7.24-7.29 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.1, 25.6, 28.5, 29.7, 33.6, 34.2, 52.9, 54.9, 65.4, 74.2, 81.4, 115.2, 125.1, 125.9, 128.8, 137.8, 138.2, 149.6, 153.3. MS (M+H)<sup>+</sup> calcd: 417.2; found: 417.0.

**(2*R*,3*S*)-3-Amino-1-((3-isopropylbenzyl)amino)oct-7-en-2-ol (18a).** To a solution of **16a** (115 mg, 0.36 mmol) in MeOH (1.5 mL), TEA (250 μL, 1.79 mmol), 1,3-propanedithiol (180 μL, 1.79 mmol) and Aliquat 336 (2 drops) were added. The solution was stirred at room temperature for 5 days, after which 1 M HCl, H<sub>2</sub>O and DCM were added. The aqueous phase was washed with DCM and was then made basic with 1 M NaOH. Subsequently, the water phase was extracted with EtOAc and the organic phase was dried, filtered and evaporated to yield **18a** (88 mg, 83%) as a colorless oil. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 1.24 (d, *J* = 6.9 Hz, 6H), 1.27-1.60 (m, 4H), 2.01-2.12 (m, 2H), 2.59-2.71 (m, 2H), 2.72-2.83 (m, 1H), 2.83-2.95 (m, 2H), 3.59-3.68 (m, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.80 (d, *J* = 13.0 Hz, 1H), 4.88-5.06 (m, 2H), 5.72-5.90 (m, 1H), 7.06-7.28 (m, 3H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 24.5, 26.6, 32.7, 34.8, 35.3, 51.3, 54.6, 56.0, 73.6, 115.2, 126.3, 127.0, 127.6, 129.5, 139.7, 140.5, 150.4. MS (M+H)<sup>+</sup> calcd: 291.2; found: 291.6.

**(2*R*,3*S*)-3-Amino-1-((3-isopropylbenzyl)amino)non-8-en-2-ol (18b).** Compound **18b** (128 mg, 81%) was synthesized in the same manner as **18a** from **16b** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.24 (d, *J* = 6.9 Hz, 6H), 1.27-1.45 (m, 6H), 2.01-2.08 (m, 2H), 2.43 (bs, 3H), 2.67 (dd, *J* = 8.7, 12.0 Hz, 1H), 2.79 (dd, *J* = 3.6, 12.0 Hz, 1H), 2.85-2.94 (m, 2H), 3.54-3.59 (m, 1H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.82 (d, *J* = 12.9 Hz, 1H), 4.91-5.02 (m, 2H), 5.72-5.85 (m, 1H), 7.11-7.16 (m, 3H), 7.22-7.27 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.1, 26.0, 29.0, 33.1, 33.7, 34.2, 50.0, 54.0, 54.5, 72.0, 114.6, 125.4, 125.7, 126.5, 128.6, 138.9, 139.7, 149.3. MS (M+H)<sup>+</sup> calcd: 305.3; found: 305.4.

**tert-Butyl ((2*R*,3*S*)-3-amino-2-hydroxyoct-7-en-1-yl)(3-isopropylbenzyl)carbamate (19).** Compound **19** (151 mg, 88%) was synthesized in the same manner as **18a** from **17** and was collected as a colorless oil. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 1.23 (d, *J* = 6.9 Hz, 6H), 1.27-1.60 (m, 13H), 2.03-2.10 (m, 2H), 2.67-2.72 (m, 1H), 2.82-2.92 (m, 1H), 3.00-3.10 (m, 1H), 3.35-3.42 (m, 1H), 3.65-3.80 (m, 1H), 4.35-4.50 (m, 1H), 4.55-4.65 (m, 1H), 4.89-5.02 (m, 2H), 5.74-5.87 (m, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.10-7.14 (m, 2H), 7.20-7.25 (m, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 24.5, 26.7, 28.8, 32.7, 34.9, 35.3, 50.0, 53.1, 55.4, 74.7, 81.3, 115.1, 125.8, 126.3, 129.5, 139.7, 150.3, 158.0. MS (M+H)<sup>+</sup> calcd: 391.3; found: 391.0.

**Methyl 3-(hydroxymethyl)-5-(*N*-methylmethylsulfonamido)benzoate (21a).** A solution of **20a** (1.65 g, 5.75

mmol) in THF (30 mL, dry) was flushed with Ar at 0°C. After 10 minutes BH<sub>3</sub>SMe<sub>2</sub> (930 μL, 9.81 mmol) was added slowly and the mixture was left to reach room temperature and was stirred under Ar for 24 hours. The mixture was quenched with MeOH, concentrated, re-dissolved in EtOAc, washed with NaHCO<sub>3</sub> (sat. aq.) and brine. The organic phase was dried, filtered and concentrated. Finally, purification using flash column chromatography (toluene/EtOAc 3:1) gave compound **21a** (1.49 g, 95%) as white crystals. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 2.90 (s, 3H), 3.33 (s, 3H), 3.90 (s, 3H), 4.66 (s, 2H), 7.33 (s, 1H), 7.65 (s, 1H), 7.94 (s, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 35.6, 38.4, 53.8, 64.1, 126.9, 127.3, 130.1, 132.5, 143.6, 145.1, 167.7.

**Methyl 3-(hydroxymethyl)-5-methylbenzoate (21b).** Compound **21b** (6.8 g, 69%) was synthesized from **20b** in the same manner as **21a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400MHz) δ 1.80 (t, *J* = 5.9 Hz, 1H), 2.41 (s, 3H), 3.91 (s, 3H), 4.70 (d, *J* = 5.9 Hz, 2H), 7.40 (s, 1H), 7.79 (s, 1H), 7.83 (s, 1H).

**Methyl 3-formyl-5-(*N*-methylmethylsulfonamido)benzoate (22a).** A mixture of SO<sub>3</sub>-pyridine complex (2.65 g, 16.6 mmol) in dry DMSO (8 mL) was added to a solution of **21a** (1.42 g, 5.20 mmol) and TEA (8.7 mL, 62.4 mmol) in DMSO (17 mL) and the mixture was stirred for 90 minutes at room temperature. Water was added and the product was extracted into EtOAc three times. The combined organic extracts were dried, filtered and concentrated. Finally, purification using flash column chromatography (toluene/EtOAc 3:1) gave compound **22a** (1.18 g, 84%) as a yellowish solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.91 (s, 3H), 3.41 (s, 3H), 3.98 (s, 3H), 8.09 (s, 1H), 8.28 (s, 1H), 8.43 (s, 1H), 10.06 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 36.0, 37.9, 52.8, 129.4, 129.8, 131.8, 132.6, 137.6, 143.0, 165.2, 190.5.

**Methyl 3-formyl-5-methylbenzoate (22b).** Compound **22b** (4.9 g, 73%) was synthesized from **21b** in the same manner as **22a** and was collected as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 2.49 (s, 3H), 4.00 (s, 3H), 7.89 (s, 1H), 8.11 (s, 1H), 8.32 (s, 1H), 10.04 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.2, 52.6, 129.0, 131.3, 133.5, 136.0, 136.8, 139.6, 163.5, 191.7.

**Methyl 3-(1-hydroxyhex-5-en-1-yl)-5-(*N*-methylmethylsulfonamido)benzoate (23a).** Freshly made pent-4-enylmagnesium bromide in THF (720 μL, 0.65 mmol, 0.9 M) was added slowly to a solution of **22a** (160 mg, 0.59 mmol) in dry Et<sub>2</sub>O (20 mL) and the mixture was stirred for 3 h at 0 °C. The reaction was quenched with NH<sub>4</sub>Cl (sat. aq.) and the product was extracted into EtOAc three times. The combined organic extracts were dried, filtered and concentrated. Finally, purification using flash column chromatography (toluene/EtOAc 3:1) gave compound **23a** (130 mg, 65%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.66-1.81 (m, 4H), 2.05-2.12 (m, 2H), 2.23 (bs, 1H), 2.85 (s, 3H), 3.35 (s, 3H), 3.93 (s, 3H), 4.75 (t, *J* = 6.4 Hz, 1H), 4.93-5.03 (m, 2H), 5.71-5.84 (m, 1H), 7.61 (s, 1H), 7.88 (s, 1H), 7.94 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 25.0, 33.5, 35.7, 38.2, 38.7, 52.5, 73.6, 115.0, 125.1, 126.0, 129.1, 131.6, 138.4, 142.0, 147.1, 166.3. MS (M+Na)<sup>+</sup> calcd: 364.1; found: 364.6.

**Methyl 3-(1-hydroxyhex-5-en-1-yl)-5-methylbenzoate (23b).** Compound **23b** (580 mg, 79%) was synthesized from

**22b** in the same manner as **23a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.34-1.59 (m, 2H), 1.67-1.80 (m, 2H), 1.83-1.84 (m, 1H), 2.04-2.12 (m, 2H), 2.04 (s, 3H), 3.91 (s, 3H), 4.68-4.73 (m, 1H), 4.92-5.03 (m, 2H), 5.71-5.85 (m, 1H), 7.37 (s, 1H), 7.77 (s, 1H), 7.80 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.4, 25.2, 33.7, 38.7, 52.2, 74.3, 114.9, 124.4, 129.5, 130.4, 131.3, 132.5, 138.6, 145.3, 164.4. MS (M+H)<sup>+</sup> calcd: 249.1; found: 249.5.

**Methyl 3-(hex-5-enoyl)-5-(N-methylmethylsulfonamido)benzoate (24a).** Dess-Martin periodinane (248 mg, 0.59 mmol) was added to a solution of **23a** (133 mg, 0.39 mmol) in DCM (3 mL) and the solution was stirred for 24 h at room temperature. The solution was diluted with Et<sub>2</sub>O and washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub> (sat.). The organic phase was dried, filtered and concentrated. Purification using flash column chromatography (toluene/EtOAc 39:1) gave **24a** (100 mg, 76%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.81-1.91 (m, 2H), 2.13-2.20 (m, 2H), 2.87 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 3.38 (s, 3H), 3.96 (s, 3H), 4.99-5.09 (m, 2H), 5.75-5.89 (m, 1H), 7.95 (s, 1H), 8.04 (s, 1H), 8.38 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.6, 23.2, 33.2, 35.9, 38.0, 52.8, 115.7, 125.4, 127.8, 128.4, 129.2, 130.8, 138.0, 142.6, 165.7, 198.6. MS (M+H)<sup>+</sup> calcd: 340.1; found: 340.6.

**Methyl 3-(hex-5-enoyl)-5-methylbenzoate (24b).** Compound **24b** (317 mg, 89%) was synthesized from **23b** in the same manner as **24a** and was collected as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.86 (quintet, *J* = 7.2 Hz, 2H), 2.13-2.20 (m, 2H), 2.46 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 4.99-5.08 (m, 2H), 5.76-5.90 (m, 1H), 7.96 (s, 1H), 8.04 (s, 1H), 8.38 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.3, 23.4, 33.2, 38.0, 52.4, 115.5, 126.7, 130.7, 132.8, 134.5, 137.5, 138.1, 139.0, 166.6, 199.7. MS (M+H)<sup>+</sup> calcd: 247.1; found: 247.5.

**tert-Butyl ((2R,3S)-3-(3-(hex-5-enoyl)-5-(N-methylmethylsulfonamido)benzamido)-2-hydroxyoct-7-en-1-yl)(3-isopropylbenzyl)carbamate (25a).** Aqueous LiOH (40 mg/mL, 324 μL, 0.54 mmol) was added to a solution of **24a** (61 mg, 0.18 mmol) in a mixture of dioxane (10 mL) and water (5 mL) and the solution was stirred at room temperature for 2 h. After neutralization with 1 M HCl, the volatiles were evaporated and the crude remainder was dissolved in DMF (10 mL). DIPEA (105 μL, 0.60 mmol) and compound **19** (46 mg, 0.12 mmol) were added and the temperature was lowered to 0 °C. HATU (59 mg, 0.16 mmol) was added and the solution was allowed to obtain room temperature overnight. The DMF was subsequently evaporated and the crude product was purified using flash column chromatography (toluene/EtOAc 3:1 → toluene/EtOAc 1:1) to give **25a** (73 mg, 89% over two steps) as a colorless glue. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.23 (d, *J* = 7.1 Hz, 6H), 1.47 (s, 9H), 1.50-1.67 (m, 4H), 1.78-1.91 (m, 2H), 2.00-2.20 (m, 5H), 2.80-2.93 (m, 1H), 2.87 (s, 3H), 3.02 (t, *J* = 7.3 Hz, 2H), 3.25-3.42 (m, 2H), 3.38 (s, 3H), 3.95 (br s, 2H), 4.23 (br s, 1H), 4.43 (br s, 2H), 4.87-5.09 (m, 4H), 5.67-5.89 (m, 2H), 6.94-7.29 (m, 3H), 7.34 (br s, 1H), 8.02-8.13 (m, 2H), 8.35 (br s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 23.2, 24.1, 25.8, 28.5, 28.6, 29.3, 33.1, 33.6, 34.1, 35.7, 38.0, 50.2, 52.2, 54.0, 73.1, 81.3, 115.1, 115.6, 125.0, 125.1, 125.4, 125.8, 128.3, 128.7, 129.1, 136.0, 137.6, 137.9, 138.3, 138.4, 142.6, 149.5, 157.5, 166.0, 198.9. MS (2M+Na)<sup>+</sup> calcd: 1417.7; found: 1417.1.

**3-(Hex-5-enoyl)-N-((2R,3S)-2-hydroxy-1-((3-isopropylbenzyl)amino)oct-7-en-3-yl)-5-methylbenzamide (25b).** Compound **25b** (117 mg, 85% over two steps) was synthesized from **24b** in the same manner as **25a** using amine **18a** instead of **19** and was collected as a white solid. [α]<sub>D</sub> +0.5 (c 0.1, MeOH). <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 1.20 (d, *J* = 6.9 Hz, 6H), 1.34-1.73 (m, 6H), 1.74-1.86 (m, 2H), 1.87-2.01 (m, 1H), 2.04-2.20 (m, 3H), 2.47 (s, 3H), 2.79-2.93 (m, 1H), 2.96-3.18 (m, 3H), 3.83-3.92 (m, 1H), 3.95-4.05 (m, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 4.21 (d, *J* = 13.2 Hz, 1H), 4.88-5.08 (m, 4H), 5.73-5.92 (m, 2H), 7.21-7.38 (m, 3H), 7.73 (s, 1H), 7.96 (s, 1H), 8.19 (s, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 21.2, 24.2, 24.4, 26.6, 30.4, 34.1, 34.3, 35.1, 38.8, 51.0, 52.5, 54.3, 70.7, 115.2, 115.6, 128.4, 128.5, 128.6, 129.1, 130.1, 132.8, 133.3, 135.5, 138.6, 139.3, 139.5, 140.5, 151.2, 170.3, 201.9. HRMS calcd (M+H)<sup>+</sup>: 505.3430; found 505.3437. LC-MS Purity System A: *t*<sub>R</sub> = 3.15 min, 100%; System B: *t*<sub>R</sub> = 1.89 min, 100%.

**tert-Butyl ((2R,3S)-3-(3-(hex-5-enoyl)-5-methylbenzamido)-2-hydroxyoct-7-en-1-yl)(3-isopropylbenzyl)carbamate (26).** To a solution of **25b** (40 mg, 0.079 mmol) in MeOH (8 mL) were added Boc<sub>2</sub>O (25 mg, 0.11 mmol) and TEA (22 μL, 0.16 mmol). The mixture was stirred at room temperature for 3 h, and the solvent was then evaporated. Flash column chromatography (toluene/EtOAc 6:1 → toluene/EtOAc 3:1) provided compound **26** (31 mg, 65%) as a colorless glue. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.22 (d, *J* = 6.9 Hz, 6H), 1.48 (s, 9H), 1.50-1.65 (m, 6H), 1.72-1.91 (m, 2H), 1.96-2.20 (m, 4H), 2.44 (s, 3H), 2.86 (septet, *J* = 6.9 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 3.29 (dd, *J* = 4.4, 14.6 Hz, 1H), 3.35-3.51 (m, 1H), 3.92 (br s, 1H), 4.03-4.27 (m, 2H), 4.33-4.56 (m, 2H), 4.87-5.09 (m, 4H), 5.67-5.90 (m, 2H), 6.92-7.28 (m, 3H), 7.78-7.90 (m, 2H), 8.18 (br s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.4, 23.4, 24.1, 25.7, 28.5, 29.1, 33.2, 33.6, 34.2, 38.0, 50.4, 52.3, 53.7, 73.6, 81.2, 115.1, 115.5, 124.1, 125.0, 125.7, 125.8, 128.7, 131.6, 132.2, 134.8, 137.5, 137.7, 138.1, 138.4, 139.1, 149.5, 158.9, 167.2, 199.9. MS (M+H)<sup>+</sup> calcd: 605.4; found: 604.9.

**{(R)-2-Hydroxy-2-[(E)-(S)-16-(methanesulfonyl-methylamino)-2,13-dioxo-3-aza-bicyclo[12.3.1]octadeca-1(17),8,14,(18),15-tetraen-4-yl]-ethyl}-(3-isopropylbenzyl)-carbamate tert-butyl ester (27a).** Compound **25a** (65 mg, 0.093 mmol) was dissolved in dry DCM (100 mL) and the solution was degassed with N<sub>2</sub>. Hoveyda-Grubbs catalyst 2<sup>nd</sup> generation (30 mg, 0.048 mmol) was added and the mixture was refluxed under N<sub>2</sub> overnight. After evaporation of the solvent, the crude material was purified by flash column chromatography (toluene/EtOAc 3:1 → toluene/EtOAc 1:1) to yield **27a** (13 mg, 21%) as a colorless glue. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.14-1.30 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.34-2.38 (m, 10H), 1.42 (s, 9H), 2.65-3.15 (m, 3H), 2.87 (s, 3H), 3.20-3.53 (m, 2H), 3.35 (s, 3H), 3.93 (br s, 2H), 4.25-4.58 (m, 3H), 5.55-5.93 (m, 2H), 6.87-7.38 (m, 3H), 7.88-8.15 (m, 3H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 24.8, 25.4, 27.3, 28.4, 29.0, 29.5, 31.2, 32.2, 36.4, 37.9, 38.3, 50.1, 52.5, 54.8, 74.1, 80.8, 124.2, 124.5, 125.1, 127.2, 128.5, 128.7, 129.9, 130.7, 133.1, 137.6, 137.5, 139.0, 143.1, 149.4, 158.0, 167.8, 199.5. MS (M+H)<sup>+</sup> calcd: 670.4; found: 670.9.

**{(R)-2-Hydroxy-2-[(E)-(S)-16-methyl-2,13-dioxo-3-aza-bicyclo[12.3.1]octadeca-1(17),8,14(18),15-tetraen-4-yl]-**

**ethyl]-3-isopropyl-benzyl)-carbamic acid tert-butyl ester (27b).** Compound **27b** (14 mg, 47%) was synthesized in the same manner as **27a** from **26** and was collected as a white powder.  $[\alpha]_D^{+16}$  (*c* 0.1, MeOH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.21 (d, *J* = 6.9 Hz, 6H), 1.40 (s, 9H), 1.42-2.30 (m, 11H), 2.44 (s, 3H), 2.65-2.78 (m, 1H), 2.81-2.96 (m, 1H), 2.97-3.12 (m, 1H), 3.31 (dd, *J* = 4.1, 14.2 Hz, 1H), 3.35-3.52 (m, 1H), 3.84-4.07 (m, 2H), 4.34-4.62 (m, 3H), 5.71 (dt, *J* = 6.3, 15.4 Hz, 1H), 5.78-5.91 (m, 1H), 6.27 (br s, 1H), 6.97-7.28 (m, 3H), 7.78 (s, 1H), 7.86-7.96 (m, 2H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  21.4, 24.2, 27.6, 27.7, 28.5, 29.8, 30.7, 30.9, 34.2, 37.7, 50.0, 52.5, 54.7, 73.9, 80.9, 125.0, 125.1, 125.6, 128.4, 128.7, 130.8, 131.5, 132.8, 133.3, 136.1, 136.3, 138.0, 140.2, 149.4, 157.9, 169.7, 200.9. HRMS calcd ( $\text{M}+\text{H}$ ) $^+$ : 577.3641; found 577.3647. LC-MS Purity System A:  $t_R$  = 3.70 min, 100%; System B:  $t_R$  = 2.06 min, 98%.

***N*-{(E)-(S)-4-[(R)-1-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-2,13-dioxo-3-aza-bicyclo[12.3.1]octadeca-1(17),8,14(18),15-tetraen-16-yl}-N-methyl-methanesulfonamide (28a).** Compound **27a** (13 mg, 0.019 mmol) was dissolved in a mixture of DCM (10 mL) and TFA (2.5 mL). Triethylsilane (TES) (10  $\mu\text{L}$ , 0.063 mmol) was added and the solution was stirred at room temperature for 1 h. The volatiles were evaporated and the remainder was dissolved in DCM and washed with 1 M NaOH. The organic phase was dried, filtered and evaporated to yield **28a** (10 mg, 91%) as a colorless glue.  $[\alpha]_D^{+7}$  (*c* 0.1, MeOH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.24 (d, *J* = 7.1 Hz, 6H), 1.43-2.11 (m, 12H), 2.12-2.27 (m, 2H), 2.70-2.80 (m, 2H), 2.82-2.93 (m, 1H), 2.88 (s, 3H), 2.95-3.12 (m, 1H), 3.35 (s, 3H), 3.64-3.72 (m, 1H), 3.79 (s, 2H), 3.87-3.98 (m, 1H), 5.73 (dt, *J* = 6.3, 15.1 Hz, 1H), 5.80-5.91 (m, 1H), 6.08 (d, *J* = 8.8 Hz, 1H), 7.09-7.19 (m, 2H), 7.21-7.29 (m, 1H), 7.95-8.02 (m, 2H), 8.04-8.10 (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  24.2, 27.4, 28.4, 28.9, 29.8, 30.8, 34.2, 36.4, 37.6, 38.0, 51.3, 53.6, 54.2, 71.8, 125.4, 125.6, 125.7, 126.4, 127.2, 128.6, 130.0, 130.7, 133.0, 137.5, 138.0, 139.9, 143.5, 149.3, 168.0, 199.5. HRMS calcd ( $\text{M}+\text{H}$ ) $^+$ : 570.3002; found 570.3011. LC-MS Purity System A:  $t_R$  = 2.46 min, 97%; System B:  $t_R$  = 1.57 min, 99%.

***(E)-(S)-4-[(R)-1-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-16-methyl-3-aza-bicyclo[12.3.1]octadeca-1(17),8,14(18),15-tetraene-2,13-dione (28b).*** Compound **28b** (10 mg, 91%) was synthesized from **27b** in the same manner as **28a** and was collected as a colorless glue.  $[\alpha]_D^{+11}$  (*c* 0.1, MeOH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.24 (d, *J* = 6.9 Hz, 6H), 1.47-1.68 (m, 2H), 1.70-2.08 (m, 8H), 2.10-2.37 (m, 2H), 2.41 (s, 3H), 2.62-2.95 (m, 5H), 2.96-3.10 (m, 1H), 3.65 (q, *J* = 5.3 Hz, 1H), 3.76 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.86-4.00 (m, 1H), 5.67-5.91 (m, 2H), 5.98 (d, *J* = 8.5 Hz, 1H), 7.08-7.26 (m, 3H), 7.76 (s, 1H), 7.84-7.96 (m, 2H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  21.4, 24.2, 27.5, 28.6, 29.3, 30.8, 30.9, 34.2, 37.8, 51.2, 53.7, 54.2, 72.2, 124.7, 125.2, 125.3, 125.7, 126.4. HRMS calcd ( $\text{M}+\text{H}$ ) $^+$ : 477.3117; found 477.3118. LC-MS Purity System A:  $t_R$  = 2.65 min, 96%; System B:  $t_R$  = 1.76 min, 97%.

***N-((S)-2-(Allyloxy)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-(hex-5-enoyl)-5-methylbenzamide (29).*** Compound **24b** (31 mg, 0.12 mmol) was dissolved in di-

oxane/ $\text{H}_2\text{O}$  (2:0.5 mL) and aqueous LiOH (40 mg/mL, 150  $\mu\text{L}$ , 0.25 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then co-evaporated with toluene. The crude material was re-dissolved in DMF (1 mL) and *(S)*-2-(allyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanamine (21 mg, 0.10 mmol), HATU (71 mg, 0.18 mmol) and DIPEA (65  $\mu\text{L}$ , 0.37 mmol) were added. The reaction mixture was stirred at room temperature for 4 h, evaporated and purified using flash column chromatography (toluene/EtOAc 3:1) to give compound **29** (25 mg, 57%) as a colorless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.50 (s, 6H), 1.61-1.67 (m, 2H), 2.14-2.18 (m, 2H), 3.04 (s, 3H), 2.57 (t, *J* = 6.3 Hz, 2H), 3.59 (dd, *J* = 6.8, 11.6 Hz, 1H), 3.77 (dd, *J* = 6.0, 9.9 Hz, 1H), 3.88-3.92 (m, 2H), 3.99 (dd, *J* = 6.0, 9.9 Hz, 1H), 4.04 (d, *J* = 5.0 Hz, 2H), 4.56 (m, 1H), 4.98-5.00 (m, 1H), 5.01-5.03 (m, 1H), 5.12 (bs, 1H), 5.13-5.15 (m, 1H), 5.67-5.75 (m, 2H), 5.79-5.87 (m, 1H), 7.93 (s, 1H), 8.02 (s, 1H), 8.36 (s, 1H). MS ( $\text{M}+\text{H}$ ) $^+$  calcd: 416.2; found: 416.2.

***N-((2S,3S)-1-(Allyloxy)-3,4-dihydroxybutan-2-yl)-3-(hex-5-enoyl)-5-methylbenzamide (30).*** Compound **30** (656 mg, 95%) was synthesized from **29** in the same manner as compound **3**.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  0.95 (s, 1H), 1.54-1.60 (m, 2H), 2.13-2.18 (m, 2H), 2.36 (s, 3H), 2.53 (s, 1H), 2.74 (t, *J* = 6.3 Hz, 2H), 3.49 (dd, *J* = 4.7, 9.6 Hz, 1H), 3.53-3.57 (m, 2H), 3.70 (dd, *J* = 4.7, 9.7 Hz, 1H), 3.78 (dd, *J* = 1.3, 9.9 Hz, 1H), 3.99 (d, *J* = 4.9 Hz, 2H), 4.10-4.12 (m, 1H), 4.73 (s, 1H), 4.98-5.01 (m, 1H), 5.02-5.05 (m, 3H), 5.64-5.72 (m, 1H), 5.75-5.83 (m, 1H), 7.92 (s, 1H), 8.00 (s, 1H), 8.32 (s, 1H). MS ( $\text{M}+\text{H}$ ) $^+$  calcd: 376.2; found: 376.1.

***(E)-(S)-4-((S)-1,2-Dihydroxy-ethyl)-16-methyl-6-oxa-3-aza bicyclo[12.3.1]octadeca-1(18),8,14,16-tetraene-2,13-dione (31).*** Compound **31** (533 mg, 88%) was synthesized from **30** in the same manner as compound **27a** and was collected as a white powder.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  0.70 (s, 1H), 1.70-1.76 (m, 3H), 1.92-1.96 (m, 2H), 2.41 (s, 3H), 2.73 (t, *J* = 5.7 Hz, 2H), 3.48 (dd, *J* = 1.6, 9.8 Hz, 1H), 3.55 (dd, *J* = 4.0, 9.9 Hz, 1H), 3.70 (m, 1H), 3.73 (dd, *J* = 1.6, 9.8 Hz, 1H), 3.87 (dd, *J* = 4.0, 9.9 Hz, 1H), 4.02-4.06 (m, 2H), 4.11-4.13 (m, 1H), 5.54-5.63 (m, 2H), 6.16 (s, 1H), 7.63 (s, 1H), 7.79 (s, 1H), 7.92 (s, 1H). MS ( $\text{M}+\text{H}$ ) $^+$  calcd: 348.2; found: 348.1.

***Toluene-4-sulfonic acid (S)-2-hydroxy-2-((E)-(S)-16-methyl-2,13-dioxo-6-oxa-3-aza-bicyclo[12.3.1]octadeca-1(18),8,14,16-tetraen-4-yl)-ethyl ester (32).*** Compound **32** (434 mg, 57%) was synthesized from **31** in the same manner as compound **4** and was collected as a white powder.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.36 (s, 1H), 1.71-1.76 (m, 2H), 1.92-1.96 (m, 2H), 2.37 (s, 3H), 2.39 (s, 3H), 2.73 (t, *J* = 5.7 Hz, 2H), 3.48 (dd, *J* = 3.1, 9.5 Hz, 1H), 3.58 (dd, *J* = 5.6, 9.9 Hz, 1H), 3.69-3.75 (m, 2H), 3.85 (dd, *J* = 5.7, 9.9 Hz, 1H), 4.00-4.07 (m, 2H), 4.26 (t, *J* = 5.6 Hz, 1H), 5.61-5.72 (m, 2H), 6.10 (s, 1H), 7.46 (d, *J* = 6.0 Hz, 2H), 7.72 (bs, 1H), 7.74 (bs, 1H), 7.89 (bs, 1H), 8.03 (d, *J* = 6.0 Hz, 2H). MS ( $\text{M}+\text{H}$ ) $^+$  calcd: 502.2; found: 502.1.

***(E)-(S)-4-((R)-2-[1-(5-tert-Butyl-oxazol-2-yl)-1-methyl-ethylamino]-1-hydroxy-ethyl)-16-methyl-6-oxa-3-aza-bicyclo[12.3.1]octadeca-1(18),8,14,16-tetraene-2,13-dione***

(33). Compound **32** (199 mg, 0.40 mmol) was dissolved in EtOH (1.5 mL). 2-(5-(*tert*-butyl)oxazol-2-yl)propan-2-amine (180 mg, 0.99 mmol) and DIEPA (1.5 mL) were added and the reaction mixture was refluxed for 4 days. The solvent was evaporated and the crude material was purified using prep. LC-MS to give compound **33** (11 mg, 5%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.40 (s, 1H), 1.45 (s, 9H), 1.62 (s, 6H), 1.72-1.76 (m, 2H), 1.92-1.96 (m, 2H), 2.45 (s, 3H), 2.62 (dd, *J* = 5.7, 9.9 Hz, 1H), 2.73 (t, *J* = 4.3 Hz, 2H), 2.87 (dd, *J* = 5.7, 9.9 Hz, 1H), 3.48 (dd, *J* = 3.4, 9.4 Hz, 1H), 3.69-3.75 (m, 2H), 4.03-4.08 (m, 3H), 4.52 (s, 1H), 5.59-5.69 (m, 2H), 6.17 (s, 1H), 6.83 (s, 1H), 7.62 (bs, 1H), 7.79 (bs, 1H), 7.98 (bs, 1H). HRMS calcd (M+H)<sup>+</sup>: 512.3119; found 512.3109.

*N*-{(*E*)-(*S*)-4-[(*R*)-1-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-2,13-dioxo-6-oxa-3-aza-bicyclo[12.3.1] octadeca-1(17),8,14(18),15-tetraen-16-yl]-*N*-methylmethanesulfonamide (**34**). Compound **34** was synthesized according to the synthetic route for **28a**, using compound **8** instead of **19**, and was collected as a white solid. [α]<sub>D</sub><sup>+41</sup> (c 0.1, MeOH). <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 1.23 (d, *J* = 6.9 Hz, 6H), 1.74-1.94 (m, 2H), 2.16-2.22 (m, 2H), 2.64-2.75 (m, 1H), 2.78-2.93 (m, 3H), 2.96 (s, 3H), 3.19-3.28 (m, 1H), 3.38 (s, 3H), 3.72 (dd, *J* = 3.9, 9.3 Hz, 1H), 3.83 (d, *J* = 6.9 Hz, 2H), 3.88-4.02 (m, 3H), 4.08-4.17 (m, 2H), 5.84 (dt, *J* = 5.1, 15.4 Hz, 1H), 5.98 (dt, *J* = 6.7, 15.4 Hz, 1H), 7.12-7.16 (m, 2H), 7.21-7.27 (m, 2H), 8.04-8.05 (m, 1H), 8.10-8.11 (m, 1H), 8.21-8.22 (m, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 22.8, 25.8, 30.0, 33.4, 34.5, 35.8, 36.6, 51.2, 52.7, 52.9, 68.3, 70.2, 124.8, 125.2, 125.9, 126.3, 126.9, 127.8, 128.3, 129.3, 131.9, 136.2, 136.4, 137.5, 142.6, 148.6, 167.2, 200.0. HRMS calcd (M+H)<sup>+</sup>: 572.2794; found 572.2797. LC-MS Purity System A: *t*<sub>R</sub> = 2.30 min, 100%; System B: *t*<sub>R</sub> = 1.69 min, 100%.

(*E*)-(*S*)-4-[(*R*)-1-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-16-methyl-6-oxa-3-aza-bicyclo[12.3.1]octadeca-1(17),8,14(18),15-tetraene-2,13-dione (**35**). Compound **35** was synthesized according to the synthetic route for **28a**, using compound **24b** instead of **24a** and compound **8** instead of **19**, and was collected as a white solid. [α]<sub>D</sub><sup>+92</sup> (c 0.1, MeOH). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.24 (d, *J* = 6.9 Hz, 6H), 1.77-1.98 (m, 2H), 2.11-2.31 (m, 2H), 2.48 (s, 3H), 2.74-2.82 (m, 2H), 2.84-2.92 (m, 2H), 2.94-3.04 (m, 1H), 3.59 (dd, *J* = 3.9, 9.0 Hz, 1H), 3.73-3.79 (m, 1H), 3.84 (d, *J* = 3.3 Hz, 2H), 3.90 (dd, *J* = 4.5, 12.6 Hz, 1H), 4.06-4.13 (m, 1H), 4.22 (dd, *J* = 2.7, 9.0 Hz, 1H), 4.25-4.31 (m, 1H), 5.80-5.98 (m, 2H), 7.09-7.14 (m, 2H), 7.19 (s, 1H), 7.22-7.23 (m, 1H), 7.91 (s, 1H), 7.98 (s, 1H), 8.00 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 21.4, 24.1, 24.2, 26.9, 31.0, 34.2, 36.9, 51.1, 52.3, 54.1, 69.0, 69.6, 71.4, 124.0, 125.4, 125.8, 126.6, 128.6, 128.9, 131.9, 133.2, 134.0, 134.4, 136.2, 139.4, 140.3, 149.3, 166.7, 200.5. HRMS calcd (M+H)<sup>+</sup>: 479.2910; found 479.2925. LC-MS Purity System A: *t*<sub>R</sub> = 2.71 min, 98%; System B: *t*<sub>R</sub> = 1.67 min, 99%.

(*E*)-(*S*)-4-[(*R*)-1-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-17-methyl-3-aza-bicyclo[13.3.1]nonadeca-1(18),9,15(19),16-tetraene-2,14-dione (**36**). Compound **36** was synthesized according to the synthetic route for **28b**, using compound **18b** instead of **18a**, and was collected as a white solid. [α]<sub>D</sub><sup>+2.7</sup> (c 0.1, MeOH). <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz): δ 1.23 (d, *J* = 6.9 Hz, 6H), 1.29-1.50 (m, 2H), 1.56-1.74 (m, 4H), 1.78-1.89 (m, 2H), 2.02-2.23 (m, 4H), 2.44 (s, 3H),

2.54-2.64 (m, 1H), 2.77 (dd, *J* = 8.1, 12.6 Hz, 1H), 2.82-2.94 (m, 2H), 3.28-3.38 (m, overlapped of solvent peak, 1H), 3.71 (dt, *J* = 3.3, 7.8 Hz, 1H), 3.86 (d, *J* = 4.8 Hz, 2H), 3.88-3.95 (m, 1H), 5.43 (dt, *J* = 6.5, 15.2 Hz, 1H), 5.60 (dt, *J* = 6.9, 15.2 Hz, 1H), 7.15-7.19 (m, 2H), 7.23-7.28 (m, 2H), 7.70 (s, 1H), 7.90 (s, 1H), 8.06 (s, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>OD, 75.5 MHz): δ 21.3, 24.4, 25.7, 27.8, 29.2, 31.2, 32.5, 32.8, 35.4, 38.2, 52.6, 54.2, 55.2, 73.3, 126.8, 127.0, 127.4, 128.0, 129.7, 130.8, 131.8, 133.4, 134.1, 137.2, 137.4, 138.8, 141.0, 150.6, 171.2, 202.8. HRMS calcd (M+H)<sup>+</sup>: 491.3274; found 491.3274. LC-MS Purity System A: *t*<sub>R</sub> = 2.96 min, 98%; System B: *t*<sub>R</sub> = 1.78 min, 100%.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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## SUPPLEMENTARY MATERIALS

Supplementary material is available on the publishers web site along with the published article.

## PATIENT'S CONSENT

Declared none.

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