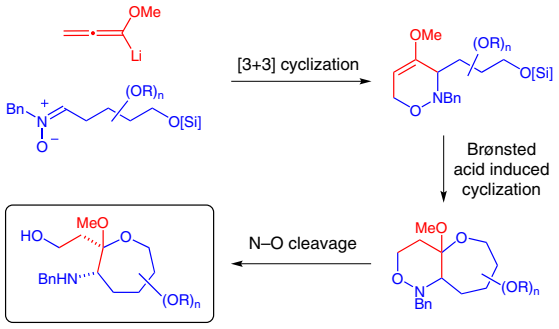
Synthesis M. Jasiński et al. Paper

Three-Step Synthesis of 3-Aminoseptanoside Derivatives by Using Lithiated Methoxyallene and δ-Siloxynitrones

Marcin Jasiński[*a]
Greta Utecht[a]
Andrzej Fruziński[b,1]
Hans-Ulrich Reissig[c]

[a] Department of Organic and Applied Chemistry, University of Łódź, Tamka 12, 91-403 Łódź, Poland
mjasinski@uni.lodz.pl
[b] Institute of General and Ecological Chemistry, Łódź University of Technology, Żeromskiego 115, 90-924 Łódź, Poland
[c] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
hans.reissig@chemie.fu-berlin.de

Dedicated to Professor Grzegorz Mlostoń on the occasion of his 65th birthday

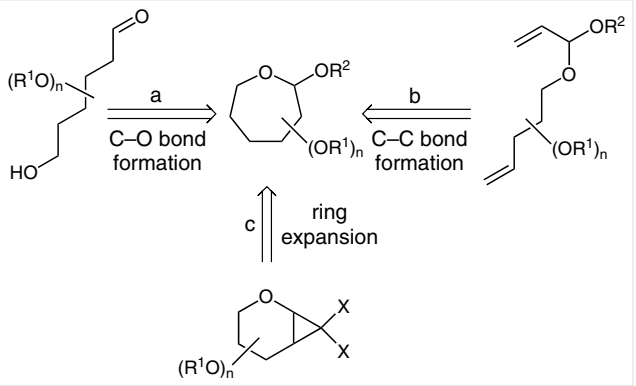


Received: 24.09.2015
Accepted after revision: 04.11.2015
Published online: 04.01.2016
DOI: 10.1055/s-0035-1560398; Art ID: ss-2015-t0558-op

Abstract A three-step approach to enantiomerically pure 3-aminoseptanoside derivatives by addition of lithiated methoxyallene to δ-silylated aldopentose-derived nitrones, followed by Brønsted acid mediated cyclization and chemoselective N–O bond scission is presented. For the addition of the methoxyallene anion leading to 3,6-dihydro-1,2-oxazines, excellent *syn*-diastereoselectivities were observed in the case of D-xylose- and L-arabinose-derived nitrones, whereas the D-ribose analogue provided *syn*- and *anti*-configured products in an approximately 2:1 ratio. Subsequent proton-induced reactions provided the corresponding dimethyl ketals as kinetic products, which slowly converted into bicyclic oxepanoides formed in a highly *cis*-selective manner. The final reductive ring opening was performed in good yields by using an excess of samarium(II) iodide. With a selected compound it was demonstrated that this type of product is a suitable precursor for the preparation of polyfunctionalized oxepanopyrrolidine derivatives.

Key words allenes, nitrones, heterocycles, 1,2-oxazines, oxepanes, septanosides

Over the last decades, enantiomerically pure seven-membered oxacycles have attracted great attention as synthetic targets, mainly due to their presence in a variety of natural products and pharmaceutical applications.[2] Apart from naturally occurring compounds, numerous oxepane-based carbohydrate mimetics, particularly septanoses and septanoside derivatives, are of biological importance.[3] Several synthetic approaches towards these compounds have been developed to date, including expansion of smaller rings and the formation of new C–C or C–O bonds by cyclization of open-chain precursors as key steps.[4–10] For example, the formation of hemiacetal or acetal moieties by cyclization of polyfunctionalized linear hydroxy aldehydes or equivalents thereof,[4] ring-closing metathesis of appropriately installed dienes,[5] and ring expansion reactions of 1,2-cyclopropanated carbohydrates[6] are the most often used strategies (Scheme 1). Alternative methods leading to septanoside derivatives have also been reported, including Grignard reactions with suitably protected hexose derivatives,[7] metal-catalyzed cycloisomerization of alkynyl alcohols,[8] electrophile-induced cyclization of alkenyl sulfides,[9] and Baeyer–Villiger oxidation of inositol derivatives.[10]



Scheme 1 Selected strategies towards septanoside derivatives: (a) (hemi)acetal formation; (b) ring-closing metathesis; (c) ring-expansion of (dihalo)cyclopropanated carbohydrate derivatives

On the other hand, it has been demonstrated that readily available lithiated alkoxyallenes are very useful nucleophiles in reactions with carbonyl compounds and related electrophiles, e.g. imines, nitriles, thioketones, and nitrones.[11] Special attention has been paid to the latter enantiopure substrates leading via formal [3+3] cyclizations to 3,6-dihydro-1,2-oxazines, which have been extensively applied in the preparation of various polyfunctionalized O-

and N-heterocycles.[12] For example, 1,2-oxazines bearing carbohydrate-derived side chains are suitable precursors of pyran- and oxepane-based carbohydrate mimetics of types **1** and **2** (Figure 1), which are easily available by Lewis acid mediated cyclizations.[13] Additionally, Brønsted acid mediated cyclization of carbohydrate-derived 1,2-oxazines opened up an easy access to enantiopure furanoside- and pyranoside-like compounds such as **3**–**5** (Figure 1).[14]

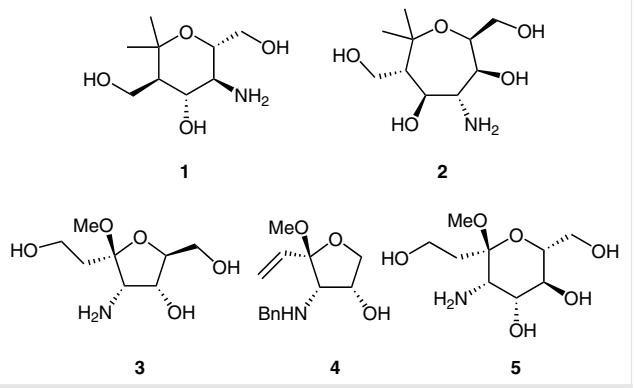
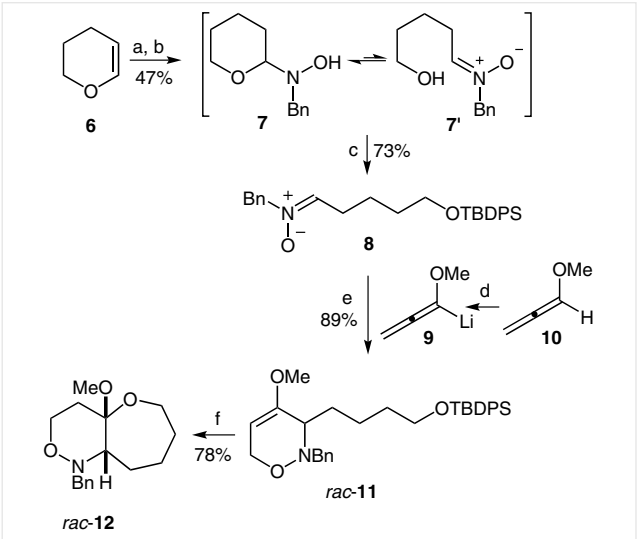


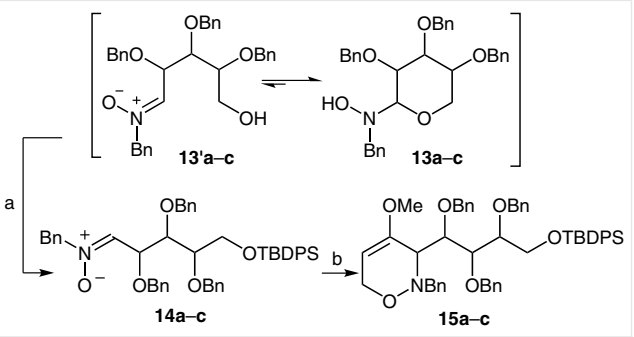
Figure 1 Examples of polyfunctionalized oxacycles **1**–**5** available from 1,2-oxazine derivatives by Lewis acid (**1** and **2**) or Brønsted acid induced cyclizations (**3**–**5**)

In continuation of the latter results, we envisioned the possible use of δ-*O*-silylated nitrones, particularly derived from aldopentoses, as key substrates for the preparation of the title compounds. To test this hypothesis, nitrone **8** depicted in Scheme 2 was selected as a model compound for the reaction with lithiated methoxyallene. We assumed that addition of *N*-benzylhydroxylamine by the more nucleophilic nitrogen atom to 2*H*-3,4-dihydropyran (**6**) would lead to *N*-(tetrahydropyran-2-yl)hydroxylamine derivative **7**, but this attempted acid-catalyzed reaction under standard reaction conditions [e.g., cat. PTSA, CH_2Cl_2 or neat, temperature up to 70 °C (closed ampule)], as well as reaction in an ionic liquid ([bmim]BF_4, up to 60 °C)[15] typically either provided unconsumed substrates or led to complex mixtures. Thus, the desired **7** was prepared in two steps, by addition of water to **6**, followed by solvent-free condensation[16] of the resulting hemiacetal with *N*-benzylhydroxylamine. By following the protocol described in our earlier work for the lower homologue of the L-erythrose series,[14c] compound **7** (existing as a mixture with its open-chain tautomer **7′** in a ca. 55:45 ratio) was trapped with the silylating agent *tert*-butyldiphenylsilyl chloride to give the desired nitrone **8** in an acceptable 34% overall yield (Scheme 2). The reaction of **8** with lithiated methoxyallene **9**, generated in situ by treatment of the parent allene **10** with *n*-butyllithium at low temperature (THF, –40 °C),[17] provided, after three hours at –78 °C and subsequent aqueous workup, the corresponding 3,6-dihydro-1,2-oxazine derivative *rac*-**11** as the only product. As anticipated, its subsequent reaction with an excess of hydrogen chloride in methanol resulted in deprotection of the silyl ether, followed by spontaneous cyclization to afford the bicyclic oxepane derivative *rac*-**12**, isolated after chromatography as a single diastereomer (78% yield, *cis*/*trans* >99:1). The *cis*-fusion in **12** was tentatively proposed on the basis of NOE (GOESY-NMR) measurements, which indicated correlation of the bridgehead hydrogen atom located at C-9a with the protons of the methoxy group.



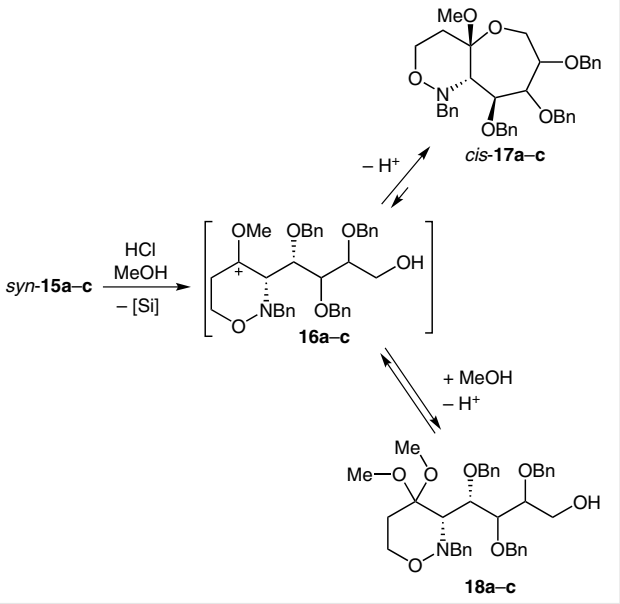
Scheme 2 Synthesis of oxepane derivative *rac*-**12**. *Reagents and conditions*: (a) H_2O, concd aq HCl, r.t., 1.5 h; (b) BnNHOH, 110 °C (neat), 4 h; (c) TBDPSCl, imidazole, DMAP, CH_2Cl_2, r.t., 72 h; (d) *n*-BuLi, THF, –40 °C, 5 min; (e) 1. THF, –78 °C (acetone/dry ice bath), 3 h; then H_2O; 2. Et_2O, $MgSO_4$, 16 h; (f) 0.3% HCl in MeOH, r.t., 3 d.

Next, we turned our attention to enantiopure nitrones derived from D-xylose (**14a**), L-arabinose (**14b**), and D-ribose (**14c**),[18] which were prepared in a similar manner as described for **8**, by silylation of the corresponding *N*-glycosylhydroxylamines **13**/**13′a**–**c** with *tert*-butyldiphenylsilyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine and imidazole, and were isolated exclusively as *Z*-isomers (Scheme 3). As evidenced by thin-layer chromatography monitoring, crude mixtures obtained by the addition of **9** to **14a**–**c** consisted mainly of the primarily formed allenylhydroxylamines[12] (not shown), which, after stirring with the drying agent overnight, smoothly cyclized to the desired 1,2-oxazines **15a**–**c** in high yields (Scheme 3, Table 1). Whereas excellent diastereoselectivity was observed for substrate **14b**, with matching configuration (dr 98:2), and high diastereoselectivity for **14a** (dr 91:9), the D-ribose-derived analogue **14c** provided a mixture of products in an approximately 2:1 ratio, indicating that the stereogenic centers of **14c** are apparently in a mismatching arrangement. Analytically pure major *syn*-configured diastereomers were easily isolated by purification after additional chromatography.



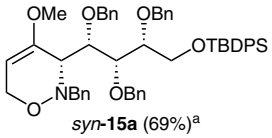
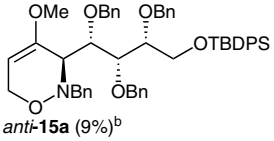
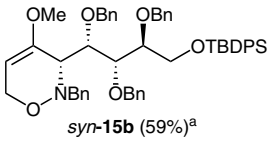
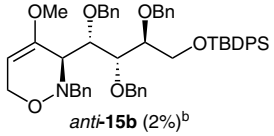
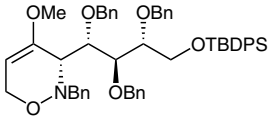
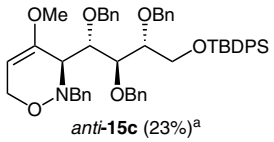
Scheme 3 Synthesis of aldopentose-derived 1,2-oxazines **15a–c** from nitrones **14a–c**. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMAP, CH_2Cl_2, r.t., 4 d; (b) 1. lithiated methoxyallene **9**, THF, –78 °C, 3 h; then H_2O; 2. Et_2O, $MgSO_4$, 16 h.

In analogy to the synthesis of *rac*-**12**, treatment of *syn*-1,2-oxazines **15** with Brønsted acid was assumed to provide the intermediate carbenium ions **16**, which after cyclization would be expected to lead to oxepane[3,2-*c*][1,2]oxazine derivatives **17**, as depicted in Scheme 4. The reaction of D-xylose-derived 1,2-oxazine **15a** with methanolic hydrogen chloride resulted in deprotection of the terminal hydroxyl group, however, in comparison to the smooth conversion of model compound *rac*-**11**; thus, the expected product **17a** formed significantly more slowly, along with the formation of an additional compound identified as ketal **18a** (both isolated after 48 h in 52% and 27% yield, respectively). In a separate experiment, the reaction mixture was monitored (TLC) for a longer time, showing gradual consumption of **18a**; after five days the desired bicyclic product **17a** was isolated solely, as a mixture of *cis*- and *trans*-fused compounds (75% yield, *cis*/*trans* 88:12). Additional chromatographic purification enabled the isolation of the major isomer *cis*-**17a** in 55% yield. These observations clearly reveal that ketal **18a** is a kinetic byproduct reversibly formed under the applied reaction conditions, whereas oxepane derivative **17a** is considered to be the thermodynamically more stable product.



Scheme 4 Acid-induced formation of intermediates **16** and their competitive transformations into oxepane derivatives *cis*-**17** and ketals **18**

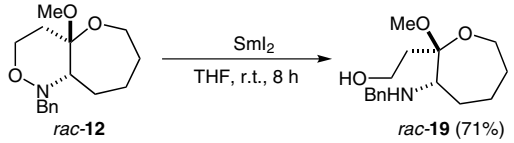
Table 1 1,2-Oxazine Derivatives **15a–c** Obtained from Aldopentose-Derived Nitrones **14a–c**

Series	Products (yield)	
D-xylose	 *syn*-**15a** (69%)[a]	 *anti*-**15a** (9%)[b]
L-arabinose	 *syn*-**15b** (59%)[a]	 *anti*-**15b** (2%)[b]
D-ribose	 *syn*-**15c** (48%)[a]	 *anti*-**15c** (23%)[a]

[a] Yield of isolated purified material.
[b] Yield estimated by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

In continuation, 1,2-oxazines **15b**,**c** were also converted into the respective bicyclic oxepane derivatives in high yields and diastereoselectivities (**17b**: 87% yield, *cis*/*trans* 84:16; **17c**: 79% yield, *cis*/*trans* >99:1) (Scheme 4); however, in the latter case of the D-ribose-derived **17c** a much longer reaction time of eight days was necessary for the conversion to go to completion. Hence, whereas in the case of *rac*-**11** the *tert*-butyldiphenylsilyl removal seems to be a crucial step in the reaction progress, the ring-closure in **16a**–**c** is slowed down, very likely for steric reasons (substitution with three bulky benzyloxy groups), and competitive intermolecular ketal formation is observed.

With new oxepane derivatives in hand, model compound *rac*-**12** as well as D-xylose-derived product *cis*-**17a** were tested for simultaneous reductive debenzylation and ring opening under standard hydrogenolysis conditions (MeOH, *i*-PrOH, EtOAc, r.t., up to 3 atm) in the presence of palladium on carbon (10% Pd) as catalyst; all attempts led to complex mixtures of products. To attain more control over the planned deprotection, we decided to cleave the N–O bond first. As in previous reports on chemoselective bond scissions in 1,2-oxazines and also other N–O-heterocyclic systems,[19] samarium(II) iodide was found to be a superior reducing agent in this context, but a remarkably longer reaction time (up to 16 h) was required. Thus, treatment of *rac*-**12** with an excess of samarium(II) iodide provided the fairly stable oxepane derivative *rac*-**19** in 71% yield, after eight hours (Scheme 5). Similar results were obtained for the carbohydrate-derived analogues *cis*-**17a**–**c**, which gave the expected products **20a**–**c** in high yields of 63–87% (Table 2). Similarly to the *syn*-**15a**–**c** series (Scheme 4), the cyclization of *anti*-**15c** provided the corresponding bicyclic product *cis*-**21c** exclusively (87%), which after samarium(II) iodide mediated ring opening led to the desired oxepane derivative **22c** (Table 2). In this case, consumption of the substrate was very slow, leading after 48 hours to **22c** (49%), which was accompanied by significant amounts (26%) of a side product identified as the corresponding oxepanopyrrolidine derivative **23c** (Figure 2).[20]

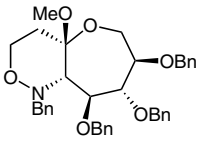
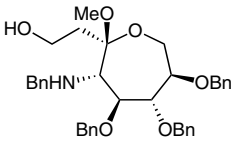
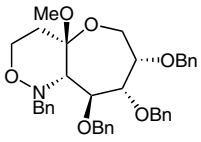
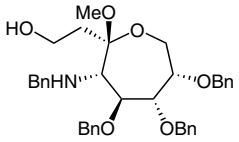
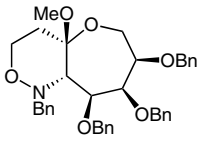
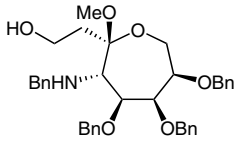
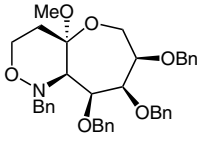
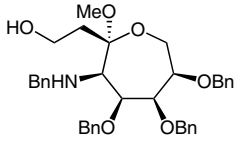


rac-**12** *rac*-**19** (71%)

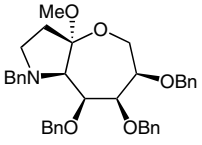
Scheme 5 Samarium(II) iodide mediated ring opening of *rac*-**12** leading to oxepane derivative *rac*-**19**

The absolute configurations of the newly generated stereogenic centers of the aldopentose-derived products in the **a**–**c** series were established on the basis of NOE (NOESY, GOESY) analysis (see Supporting Information). These measurements provided evidence that in all cases addition of methoxyallene anion **9** to nitrones **14** preferentially yield *syn*-configured products **15**, whereas subsequent ring closure leading to bicyclic oxepane derivatives **17** and **21** proceeded in highly *cis*-selective fashion. The observed stereochemical outcomes nicely match our previous observations on additions of lithiated alkoxyallenes to nitrones,[12,14c] and Brønsted acid promoted cyclizations of 1,2-oxazine derivatives leading to smaller rings.[14]

Table 2 Synthesis of Oxepane Derivatives *cis*-**17a**–**c** and *cis*-**21c** and Septanose Derivatives **20a**–**c** and **22c**

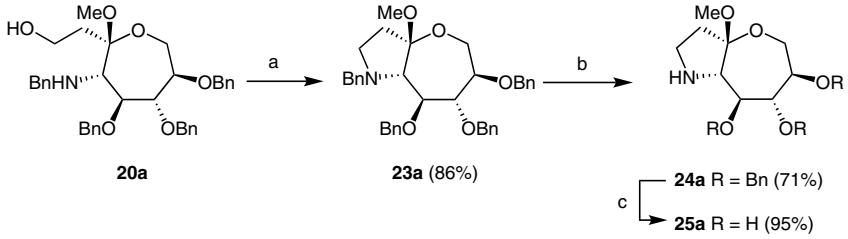
Series	Oxepane (yield)[a]	Septanose (yield)[b]
syn-**15a**		
	cis-**17a** (55%)	**20a** (78%)
syn-**15b**		
	cis-**17b** (68%)	**20b** (63%)
syn-**15c**		
	cis-**17c** (60%)	**20c** (87%)
anti-**15c**		
	cis-**21c** (87%)	**22c** (49%)

[a] Yield of isolated purified material, obtained as shown in Scheme 4.
[b] Yield of isolated purified material, obtained as shown in Scheme 5.



23c

Figure 2 Proposed structure of byproduct oxepanopyrrolidine derivative **23c** isolated from the reaction of *cis*-**21c** with samarium(II) iodide



20a **23a** (86%)

Scheme 6 Synthesis of D-xylose-derived oxepanopyrrolidine derivative **23a** and its stepwise deprotection: *Reagents and conditions*: (a) MsCl, pyridine, 0 °C to r.t., 16 h; (b) H_2 (balloon pressure), Pd/C (10%), *i*-PrOH–EtOAc (4:1), r.t., 7 h; (c) H_2 (4 atm), Pd/C (10%), *i*-PrOH, r.t., 3 d.

The debenzylation reaction of *rac*-**19** under mild conditions (10% Pd/C, r.t., balloon pressure) proceeded smoothly (15 min), but provided a mixture of two unstable products accompanied by a set of more polar compounds. Similar decomposition was observed for the septanose derivatives **20a**–**c**. It is noteworthy that, in the series of ^{1}H NMR spectra taken of crude reaction mixtures, gradual loss of the diagnostic signal attributed to the methoxy groups was observed. It appears that the presence of the primary amino group in the initially formed 3-aminooxepanes affect the acetal moiety. It is also worth noting that decomposition observed for **20** under hydrogenation conditions has not been reported for the lower α-aminoketal homologues (furan and pyran) such as **3** and **5** (Figure 1).

To overcome difficulties in the deprotection steps, we tried to reduce the nucleophilicity of the amino group of septanose derivatives **20** by its conversion into an amide. For this purpose, compound **20a** was treated with an excess of acetyl chloride under various reaction conditions; in all attempts this led exclusively to the corresponding mono-O-acylated derivative. Neither higher loadings of the electrophile nor harsh reaction conditions (refluxing triethylamine) provided the desired product. The observed remarkable inertness of the benzylamino moiety probably results from the steric hindrance caused by the neighboring groups. For this reason, we exploited the presence of the pendant 2-hydroxyethyl moiety in **20a** for the intramolecular trapping of the amino group. Thus, activation of the hydroxyl group with methanesulfonyl chloride resulted in spontaneous ring closure to give oxepino[3,2-*b*]pyrrolidine derivative **23a** in a high yield of 86% (Scheme 6). Deprotection of **23a** was then smoothly performed in two steps. The use of primary alcohols (MeOH, EtOH) as solvents for hydrogenolysis under standard conditions (Pd/C, balloon pressure) provided the desired N-debenzylated compound **24a** contaminated with a significant amount (up to 30%) of the corresponding N-methylated or N-ethylated products. These byproducts are very likely formed by trapping of the in situ generated formaldehyde or acetaldehyde, respectively, by reductive amination.[13d,21] The formation of side products was easily suppressed when the hydrogenolysis was performed in an isopropyl alcohol–ethyl acetate mixture to give compound **24a** in 71% yield. Subsequent exhaustive deprotection of the three hydroxyl groups in **24a** under medium pressure (4 atm) afforded **25a** in excellent yield (58% overall yield over 3 steps).

The structure of D-xylose-derived oxepanopyrrolidine **23a** was unambiguously confirmed by a single-crystal X-ray analysis (Figure 3).

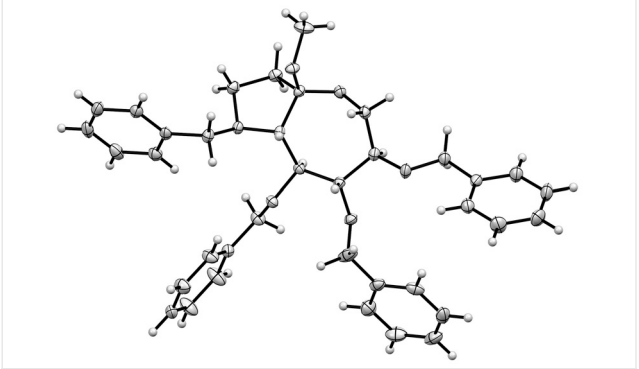


Figure 3 Single-crystal X-ray analysis of compound **23a** (displacement ellipsoids are drawn at a 50% probability level)

In summary, it was demonstrated that a series of three δ-siloxyaldopentose-derived nitrones could serve as suitable starting materials for the preparation of highly functionalized enantiopure oxepane derivatives. The simple protocol comprises a [3+3] cyclization employing lithiated methoxyallene followed by hydrogen chloride induced cyclization. With the exception of the D-ribose-derived nitrone, the key addition of lithiated methoxyallene as well as subsequent ring closure reactions of the resulting 1,2-oxazines proceeded in a highly stereoselective fashion. The synthesis of the desired 3-aminoseptanose analogues was accomplished by chemoselective samarium(II) iodide mediated ring opening of the corresponding bicyclic oxepane derivatives. As demonstrated for a selected example, decomposition of the resulting septanosides during attempted deprotection under hydrogenolysis conditions could be easily overcome by intramolecular trapping of the amino functionality, to give the polyhydroxylated oxepanopyrrolidine derivative in high overall yield. Nevertheless, new conditions should be examined to allow the deprotection of compounds **20** and **22** to afford monocyclic polyhydroxylat-

ed oxepane derivatives, for example reduction with alkali metals in liquid ammonia.[22] The presented approach supplements alkoxyallene strategies towards oxepane derivatives developed thus far,[13,23] and opens up new possibilities in the synthesis of (bicyclic) aminocarbohydrate-like compounds. Further work on the synthesis and evaluation of the biological activity of oxepanopyrrolidines such as **25** is underway.

Solvents and reagents were purchased and used as received without further purification. Products were purified by flash column chromatography on silica gel (230–400 mesh, Merck or Fluka). NMR spectra were recorded on a Bruker AVIII 600 instrument. Chemical shifts are reported relative to solvent residual peaks [^{1}H NMR: δ = 2.50 (DMSO-d_6), 3.31 (CD_3OD), 7.26 ($CDCl_3$); ^{13}C NMR: δ = 39.5 (DMSO-d_6), 49.0 (CD_3OD), 77.0 ($CDCl_3$)].[24] Substitution patterns of the carbon atoms were determined by 2D NMR spectroscopy (COSY, HMQC, HMBC) and are indicated as ^{13}C NMR peak multiplicity. IR spectra were measured of samples prepared as KBr pellets or thin films. Mass spectrometry was performed on a Finnigan MAT-95 or a Varian 500-MS LC Ion Trap instrument. Melting points of samples in capillaries were determined on a MEL-TEMP II apparatus (Aldrich) or with a polarizing optical microscope (POM, Opta-Tech) and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at the temperatures indicated. Elemental analyses were obtained on a Vario EL III (Elementar Analysensysteme GmbH) instrument. Medium pressure hydrogenolyses were run in a 3911 Shaker Hydrogenation Apparatus (Parr Instrument Company). If not stated otherwise, reactions were carried out under argon in flame-dried flasks with addition of the reactants by syringes; subsequent manipulations were conducted in air. Single-crystal X-ray data were collected on a Bruker SMART APEX II CCD diffractometer (Cu Kα radiation, λ = 1.54178 Å, 30W Incoatec Microfocus Source IμS with Montel optics); the structure solution and refinement was performed using SHELXS-97[25] and SHELXL-2014.[26] CCDC 1426022 contains 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.

(*Z*)-*N*-Benzyl[5-(*tert*-butyldiphenylsiloxy)pentylidene]amine *N*-Oxide (8)

Concd aq HCl (0.25 mL, 3.0 mmol) was added at r.t. to a solution of 2*H*-3,4-dihydropyran (**6**; 0.84 g, 10.0 mmol) in H_2O (10 mL), and the mixture was stirred for 1.5 h. The reaction was quenched with sat. aq $NaHCO_3$ solution and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was removed in vacuo to afford the crude hemiacetal[27] as a colorless oil, which was used for the next step without further purification; yield: 0.75 g (73%). A mixture of this crude product (0.75 g, 7.3 mmol) and BnNHOH (1.23 g, 10.0 mmol) was heated in an open flask (neat) at 110 °C for 4 h. The resulting mixture was cooled to r.t., and purified by column chromatography (silica gel, EtOAc) to give **7** as a thick yellow oil; yield: 0.97 g (63%). Imidazole (640 mg, 9.4 mmol) and DMAP (110 mg, 0.90 mmol), followed by TBDPSCl (1.54 g, 1.46 mL, 5.62 mmol) were added at 0 °C to a solution of this 'masked nitrone' **7** (0.97 g, 4.68 mmol) in anhydrous CH_2Cl_2 (50 mL). The mixture was allowed to reach r.t. and was stirred for 72 h. The resulting mixture was diluted with CH_2Cl_2 (30 mL), H_2O was added (40 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 1:1) to give **8**.

Yield: 1.53 g (73%); thick colorless oil.

IR (neat): 3085–2860 (=C–H, C–H), 1590 (C=N), 1110 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 1.56–1.61 (m, 4 H, 2 CH_2), 2.47–2.52 (m, 2 H, NCH_2), 3.66–3.69 (m, 2 H, OCH_2), 4.87 (s, 2 H, CH_2Ph), 6.61 (t, *J* = 5.8 Hz, 1 H, N=CH), 7.35–7.43, 7.64–7.67 (2 m, 11 H, 4 H, 3 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.8 (s, q, *t*-Bu), 21.9, 26.4, 32.3, 63.3 (4 t, 4 CH_2), 69.2 (t, CH_2Ph), 127.6*, 128.78, 128.83, 129.1, 129.5*, 133.0, 133.9*, 135.5* (5 d, 2 s, d, 3 Ph), 139.1 (d, N=CH); * higher intensity.

ESI-MS: *m*/*z* (%) = 468 (28) [M + Na]$^+$, 446 (100) [M + H]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{35}NO_2Si$: 445.2437; found: 445.2433.

Reaction of Lithiated Methoxyallene 9 with Nitrones; Typical Procedure

Lithiated methoxyallene **9** was generated under an inert atmosphere by treating a solution of methoxyallene (217 mg, 0.24 mL, 3.10 mmol) in anhydrous THF (15 mL) with 2.5 M *n*-BuLi in hexane (1.2 mL, 3.00 mmol) at –40 °C. After ca. 5 min, a solution of nitrone **8** (445 mg, 1.00 mmol) or **14a–c** (764 mg, 1.00 mmol) in THF (10 mL) was added dropwise at –78 °C, and the mixture was stirred for 3 h at this temperature. The mixture was quenched with H_2O, allowed to reach r.t. and extracted with Et_2O (3 × 20 mL). The combined extracts were stirred with the drying agent ($MgSO_4$) overnight until the cyclization of the primarily formed allenyl adduct was complete (16 h, TLC monitoring, hexane–EtOAc, 6:1, permanganate stain). The solvents were removed in vacuo, and the crude product was purified by column chromatography.

2-Benzyl-3-[4′-(*tert*-butyldiphenylsiloxy)butyl]-4-methoxy-3,6-dihydro-2*H*-[1,2]oxazine (*rac*-11)

Column chromatography (silica gel, PE–EtOAc, 5:1); thick colorless oil; yield: 459 mg (89%).

IR (neat): 3070–2855 (=C–H, C–H), 1675 (C=C), 1470, 1455, 1220, 1175, 1110 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*-Bu), 1.48–1.57 (m, 4 H, 2′-H_2, 3′-H_2), 1.62–1.67, 1.83–1.89 (2 m, 1 H each, 1′-H_2), 3.15 (t, *J* = 5.0 Hz, 1 H, 3-H), 3.54 (s, 3 H, OMe), 3.65 (t, *J* = 6.1 Hz, 2 H, 4′-H_2), 3.88, 4.05 (AB system, J_{AB} = 14.0 Hz, 2 H, CH_2Ph), 4.23–4.31 (m, 2 H, 6-H_2), 4.71 (pseudo-t, *J* ≈ 2.8 Hz, 1 H, 5-H), 7.22–7.42, 7.66–7.68 (2 m, 11 H, 4 H, 3 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.9 (s, q, *t*-Bu), 21.9, 32.9 (2 t, C-2′, C-3′), 29.6 (t, C-1′), 54.2 (q, OMe), 58.0 (t, CH_2Ph), 62.2 (d, C-3), 64.0 (t, C-4′), 64.2 (t, C-6), 91.2 (d, C-5), 127.0, 127.5*, 128.2, 128.5*, 129.4, 134.3, 135.6*, 138.0* (5 d, s, d, s, 3 Ph), 154.4 (s, C-4); * higher intensity.

ESI-MS: *m*/*z* (%) = 554 (63) [M + K]$^+$, 538 (7) [M + Na]$^+$, 516 (100) [M + H]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{32}H_{41}NO_3Si$: 515.2856; found: 515.2850.

(3*S*,1′*S*,2′*R*,3′*R*)-2-Benzyl-3-[1′,2′,3′-tris(benzyloxy)-4′-(*tert*-butyldiphenylsiloxy)butyl]-4-methoxy-3,6-dihydro-2*H*-[1,2]oxazine (*syn*-15a)

Column chromatography (silica gel, hexane–EtOAc, 7:1); colorless glassy semisolid; yield: 676 mg (81%); dr 91:9; the pure major diastereomer was isolated after additional column chromatography (silica gel, hexane–EtOAc, 7:1); yield: 575 mg (69%); $[\alpha]_D^{22}$ +26.9 (*c* 1.45, $CHCl_3$).

IR (KBr): 3090–2750 (=C–H, C–H), 1675 (C=C), 1450, 1430, 1210, 1115, 1080 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*-Bu), 3.38 (br d, *J* ≈ 6.0 Hz, 1 H, 3-H), 3.52 (s, 3 H, OMe), 3.61 (td, *J* ≈ 3.8, 5.1 Hz, 1 H, 3′-H), 3.70 (dd, *J* = 5.2, 11.1 Hz, 1 H, 4′-H), 3.78 (AB system, J_{AB} = 13.5 Hz, 1 H, NCH_2Ph), 3.79 (dd, *J* = 3.7, 11.1 Hz, 1 H, 4′-H), 4.05 (t, *J* ≈ 5.1 Hz, 1 H, 2′-H), 4.14 (dd, *J* = 5.1, 6.0 Hz, 1 H, 1′-H), 4.15 (AB system, J_{AB} = 13.5 Hz, 1 H, NCH_2Ph), 4.24 (dd, *J* = 3.2, 15.1 Hz, 1 H, 6-H), 4.36 (AB system, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.48 (dt, *J* ≈ 1.7, 15.1 Hz, 1 H, 6-H), 4.59 (AB system, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.67 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 4.74 (s, 2 H, OCH_2Ph), 4.80 (dd, *J* = 2.2, 3.2 Hz, 1 H, 5-H), 4.89 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 7.15–7.43, 7.64–7.66 (2 m, 26 H, 4 H, 6 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.9 (s, q, *t*-Bu), 53.6 (q, OMe), 56.9 (t, NCH_2Ph), 56.0 (t, C-6), 62.0 (d, C-3), 63.8 (t, C-4′), 72.6, 74.5, 74.7 (3 t, 3 OCH_2Ph), 79.3 (d, C-1′), 79.8 (d, C-2′), 80.4 (d, C-3′), 91.5 (d, C-5), 126.9, 127.0, 127.2, 127.3, 127.60, 127.64, 127.9, 128.0*, 128.07, 128.11, 128.3, 128.9, 129.5, 129.6, 133.4, 133.5, 135.66, 135.69, 137.3, 138.8, 139.4, 139.5 (14 d, 2 s, 2 d, 4 s, 6 Ph), 150.1 (s, C-4); * higher intensity.

ESI-MS: *m*/*z* (%) = 835 (62) $[M + H]^+$, 834 (100) $[M]^+$.

Anal. Calcd for $C_{53}H_{59}NO_6Si$ (834.4): C, 76.32; H, 7.13; N, 1.68. Found: C, 76.13; H, 6.84; N, 1.46.

***anti*-15a**

^1H NMR (600 MHz, $CDCl_3$): δ (selected signals) = 3.51 (s, 3 H, OMe), 3.82–3.86, 3.89–3.92 (2 m, 2 H each), 4.21 (br t, *J* ≈ 4.5 Hz, 1 H), 4.53, 4.54 (2 d, *J* = 8.9 Hz, 1 H each), 4.55 (m_c, 1 H), 4.84 (pseudo-t, *J* ≈ 2.8 Hz, 1 H, 5-H); other signals overlap with those of *syn*-**15a**.

(3*S*,1′*S*,2′*R*,3′*S*)-2-Benzyl-3-[1′,2′,3′-tris(benzyloxy)-4′-(*tert*-butyldiphenylsiloxy)butyl]-4-methoxy-3,6-dihydro-2*H*-[1,2]oxazine (*syn*-15b)

Column chromatography (silica gel, hexane–EtOAc, 7:1) provided a thick yellow oil, which was used for the next step without further purification.

Yield: 492 mg (59%); dr 98:2; $[\alpha]_D^{22}$ +34.0 (*c* 0.73, $CHCl_3$).

IR (KBr): 3090–2835 (=C–H, C–H), 1675 (C=C), 1450, 1210, 1115, 1070 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*-Bu), 3.51 (br d, *J* ≈ 6.9 Hz, 1 H, 3-H), 3.55 (s, 3 H, OMe), 3.68 (ddd, *J* = 3.1, 4.9, 6.3 Hz, 1 H, 3′-H), 3.88 (dd, *J* = 4.9, 11.3 Hz, 1 H, 4′-H), 3.92 (AB system, J_{AB} = 13.9 Hz, 1 H, NCH_2Ph), 4.03–4.06 (m, 2 H, 2′-H, 4′-H), 4.16 (dd, *J* = 3.7, 6.9 Hz, 1 H, 1′-H), 4.18 (AB system, J_{AB} = 13.9 Hz, 1 H, NCH_2Ph), 4.23 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 4.26 (dd, *J* = 3.3, 15.2 Hz, 1 H, 6-H), 4.47 (dt, *J* ≈ 1.2, 15.2 Hz, 1 H, 6-H), 4.50 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 4.65 (AB system, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.72, 4.76 (AB system, J_{AB} = 11.4 Hz, 2 H, OCH_2Ph), 4.83 (t, *J* ≈ 2.6 Hz, 1 H, 5-H), 4.98 (AB system, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 7.14–7.42, 7.64–7.67 (2 m, 26 H, 4 H, 6 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.9 (s, q, *t*-Bu), 53.6 (q, OMe), 57.0 (t, NCH_2Ph), 60.2 (t, C-6), 63.0 (t, C-4′), 63.1 (d, C-3), 71.8, 73.9, 74.6 (3 t, 3 OCH_2Ph), 79.2 (d, C-2′), 79.3 (d, C-1′), 80.5 (d, C-3′), 91.5 (d, C-5), 126.8, 126.9, 127.07, 127.13, 127.3, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 128.7, 129.51, 129.53, 133.4, 133.6, 135.7, 135.8, 137.5, 139.0, 139.5, 139.9 (14 d, 2 s, 2 d, 4 s, 6 Ph), 150.4 (s, C-4).

ESI-MS: *m*/*z* (%) = 857 (100) $[M + Na]^+$, 835 (74) $[M + H]^+$.

Anal. Calcd for $C_{53}H_{59}NO_6Si$ (834.4): C, 76.32; H, 7.13; N, 1.68. Found: C, 76.11; H, 7.05; N, 1.55.

***anti*-15b**

^1H NMR (600 MHz, $CDCl_3$): δ (selected signals) = 1.07 (s, 9 H, *t*-Bu), 3.53 (s, 3 H, OMe), 3.64 (br d, *J* ≈ 3.9 Hz, 1 H, 3-H), 4.36 (br d, *J* ≈ 8.5 Hz, 1 H), 4.45 (d, *J* = 11.8 Hz, 1 H, CH_2Ph); other signals overlap with those of *syn*-**15b**.

Reaction of 14c with Lithiated Methoxyallene 9

The crude reaction mixture obtained according to the general procedure was pre-purified by filtration through a short pad of silica gel (hexane–EtOAc, 10:1 to 8:1) to give *syn*-**15c** and *anti*-**15c** (dr 67:33) as a colorless oil; yield: 659 mg (79%). Pure diastereomers were isolated after additional column chromatography (silica gel, hexane–EtOAc, 6:1).

(3*S*,1′*S*,2′*S*,3′*R*)-2-Benzyl-3-[1′,2′,3′-tris(benzyloxy)-4′-(*tert*-butyldiphenylsiloxy)butyl]-4-methoxy-3,6-dihydro-2*H*-[1,2]oxazine (*syn*-15c)

Thick colorless oil; yield: 402 mg (48%, second eluted); $[\alpha]_D^{22}$ +41.5 (*c* 1.30, $CHCl_3$).

IR (KBr): 3090–2790 (=C–H, C–H), 1685 (C=C), 1495, 1455, 1430, 1210, 1110, 1070 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, *t*-Bu), 3.38 (br s, 1 H, 3-H), 3.49 (s, 3 H, OMe), 3.72 (d, *J* = 14.0 Hz, 1 H, NCH_2Ph), 3.91 (dd, *J* = 6.7, 11.0 Hz, 1 H, 4′-H), 3.99 (dd, *J* = 3.8, 11.0 Hz, 1 H, 4′-H), 4.05–4.15 (m, 5 H, 6-H, 1′-H, 2′-H, 3′-H, NCH_2Ph), 4.23 (AB system, J_{AB} = 11.5 Hz, 1 H, OCH_2Ph), 4.42 (br d, *J* ≈ 15.2 Hz, 1 H, 6-H), 4.56 (AB system, J_{AB} = 11.3 Hz, 1 H, OCH_2Ph), 4.62 (AB system, J_{AB} = 11.5 Hz, 1 H, OCH_2Ph), 4.68 (AB system, J_{AB} = 11.3 Hz, 1 H, OCH_2Ph), 4.70, 4.72 (AB system, J_{AB} = 11.8 Hz, 2 H, OCH_2Ph), 4.77 (dd, *J* = 1.6, 3.1 Hz, 1 H, 5-H), 7.08–7.40, 7.63–7.67 (2 m, 26 H, 4 H, 6 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.9 (s, q, *t*-Bu), 53.6 (q, OMe), 57.3 (t, NCH_2Ph), 59.7 (t, C-6), 61.3 (d, C-3), 64.7 (t, C-4′), 72.6, 72.8, 74.1 (3 t, 3 OCH_2Ph), 78.9, 79.1, 81.3 (3 d, C-1′, C-2′, C-3′), 91.7 (d, C-5), 127.00*, 127.05, 127.1, 127.51*, 127.53*, 127.7, 127.98, 128.05*, 128.16, 128.19, 128.7, 129.4, 133.66, 133.72, 135.72, 135.75, 137.7, 138.9, 139.2, 139.4 (12 d, 2 s, 2 d, 4 s, 6 Ph), 150.8 (s, C-4); * higher intensity.

ESI-MS: *m*/*z* (%) = 835 (100) $[M + H]^+$.

Anal. Calcd for $C_{53}H_{59}NO_6Si$ (834.4): C, 76.32; H, 7.13; N, 1.68. Found: C, 76.15; H, 7.20; N, 1.58.

(3*R*,1′*S*,2′*S*,3′*R*)-2-Benzyl-3-[1′,2′,3′-tris(benzyloxy)-4′-(*tert*-butyldiphenylsiloxy)butyl]-4-methoxy-3,6-dihydro-2*H*-[1,2]oxazine (*anti*-15c)

Thick colorless oil; yield: 192 mg (23%, first eluted); $[\alpha]_D^{22}$ –47.9 (*c* 0.33, $CHCl_3$).

IR (KBr): 3090–2830 (=C–H, C–H), 1675 (C=C), 1455, 1430, 1220, 1115 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, *t*-Bu), 3.48 (s, 3 H, OMe), 3.76 (br d, *J* ≈ 3.4 Hz, 1 H, 3-H), 3.86–3.90 (m, 2 H, NCH_2Ph, 4′-H), 3.97 (dd, *J* = 3.7, 10.9 Hz, 1 H, 4′-H), 4.04–4.11 (m, 3 H, NCH_2Ph, 2′-H, 3′-H), 4.19 (dd, *J* = 3.4, 6.4 Hz, 1 H, 1′-H), 4.23 (br dd, *J* ≈ 1.7, 14.5 Hz, 1 H, 6-H), 4.30 (br d, *J* ≈ 14.5 Hz, 1 H, 6-H), 4.49 (AB system, J_{AB} = 11.4 Hz, 1 H, OCH_2Ph), 4.65, 4.66 (AB system, J_{AB} = 11.5 Hz, 2 H, OCH_2Ph), 4.69 (br t, *J* ≈ 2.8 Hz, 1 H, 5-H), 4.696, 4.704 (AB system, J_{AB} = 12.5 Hz, 2 H, OCH_2Ph), 4.74 (AB system, J_{AB} = 11.4 Hz, 1 H, OCH_2Ph), 7.18–7.39, 7.61–7.67 (2 m, 26 H, 4 H, 6 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.2, 26.9 (s, q, *t*-Bu), 54.1 (q, OMe), 58.2 (t, NCH_2Ph), 63.4 (t, C-6), 63.6 (d, C-3), 64.7 (t, C-4′), 72.8, 72.9, 73.1 (3 t, 3 OCH_2Ph), 79.1 (d, C-1′) 79.9, 81.0 (2 d, C-2′, C-3′), 91.3 (d, C-5), 126.9, 127.0, 127.07, 127.14, 127.5*, 127.67, 127.68, 128.0, 128.06*, 128.07, 128.1, 128.4*, 129.4, 133.7, 133.8, 135.7*, 138.0, 138.9, 139.0, 139.3 (13 d, 2 s, d, 4 s, 6 Ph), 152.8 (s, C-4); * higher intensity.

ESI-MS: *m*/*z* (%) = 857 (29) $[M + Na]^+$, 835 (100) $[M + H]^+$.

Anal. Calcd for $C_{53}H_{59}NO_6Si$ (834.4): C, 76.32; H, 7.13; N, 1.68. Found: C, 76.49; H, 6.99; N, 1.54.

Cyclization of 1,2-Oxazine Derivatives *rac*-11 and *syn*-15a–c; General Procedure

A solution of 1,2-oxazine derivative *rac*-**11** (257 mg, 0.50 mmol) or *syn*-**15a–c** (417 mg, 0.50 mmol) in ca. 0.3% HCl in MeOH (25 mL) was stirred at r.t. for the required time. The resulting mixture was treated with an excess of solid $NaHCO_3$, diluted with CH_2Cl_2 (50 mL), and filtered through a short pad of Celite. The crude mixture was pre-purified by filtration through a short pad of silica gel (PE–EtOAc, 6:1) to give a mixture of *cis*- and *trans*-products. The major *cis*-fused diastereomers were isolated by additional column chromatography.

cis-1-Benzyl-4a-methoxyoxepano[3,2-*c*][1,2]oxazine (*rac*-12)

Reaction time 3 d; partially purified product (126 mg, 91%, *cis*/*trans* >99:1) was subjected to column chromatography (silica gel, PE–EtOAc, 6:1) to yield *rac*-**12** as thick colorless oil; yield: 108 mg (78%).

IR (neat): 3070–2855 (=C–H, C–H), 1590, 1430, 1110 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.18–1.26 (m, 1 H, 8-H), 1.61–1.71 (m, 3 H, 7-H_2, 9-H), 1.80 (ddd, *J* = 5.7, 12.4, 14.4 Hz, 1 H, 4-H), 1.89–1.95 (m, 2 H, 4-H, 8-H), 2.05 (ddd, *J* = 2.6, 5.8, 14.2 Hz, 1 H, 9-H), 2.88 (d, *J* = 9.7 Hz, 1 H, 9a-H), 3.27 (s, 3 H, OMe), 3.57 (dtd, *J* ≈ 1.6, 3.2, 12.7 Hz, 1 H, 6-H), 3.70 (AB system, J_{AB} = 14.0 Hz, 1 H, CH_2Ph), 3.70–3.77 (m, 2 H, 3-H, 6-H), 3.88 (ddd, *J* = 3.0, 11.2, 12.3 Hz, 1 H, 3-H), 4.09 (AB system, J_{AB} = 14.0 Hz, 1 H, CH_2Ph), 7.22–7.25, 7.29–7.32, 7.37–7.40 (3 m, 1 H, 2 H, 2 H, Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.1 (t, C-9), 27.0 (t, C-8), 28.5 (t, C-4), 29.9 (t, C-7), 48.0 (q, OMe), 58.5 (t, CH_2Ph), 60.9 (t, C-6), 66.0 (t, C-3), 71.0 (d, C-9a), 99.9 (s, C-4a), 126.9, 128.1, 128.5, 138.0 (3 d, s, Ph).

ESI-MS: *m*/*z* (%) = 278 (62) $[M + H]^+$, 246 (100) $[M – OMe]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1678.

(4a*S*,7*R*,8*R*,9*S*,9a*S*)-1-Benzyl-7,8,9-tris(benzyloxy)-4a-methoxyoxepano[3,2-*c*][1,2]oxazine (*cis*-17a)

Reaction time 5 d; partially purified **17a** (223 mg, 75%, *cis*/*trans* 88:12) was subjected to column chromatography (silica gel, hexane–EtOAc, 6:1) to yield the major *cis*-isomer as thick colorless oil; yield: 164 mg (55%); $[\alpha]_D^{22}$ +34.1 (*c* 0.67, $CHCl_3$).

IR (KBr): 3090–2830 (=C–H, C–H), 1455, 1355, 1125, 1075 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.84 (ddd, *J* = 5.8, 12.9, 14.7 Hz, 1 H, 4-H), 2.00 (br d, *J* ≈ 14.7 Hz, 1 H, 4-H), 2.99 (d, *J* = 9.1 Hz, 1 H, 9a-H), 3.26 (s, 3 H, OMe), 3.49–3.55 (m, 2 H, 6-H, 8-H), 3.61–3.68 (m, 2 H, 6-H, 7-H), 3.77 (br dd, *J* ≈ 5.5, 11.1 Hz, 1 H, 3-H), 3.93–3.98 (m, 2 H, 3-H, 9-H), 4.18, 4.59 (AB system, J_{AB} = 14.9 Hz, 2 H, NCH_2Ph), 4.63, 4.71 (AB system, J_{AB} = 14.9 Hz, 2 H, OCH_2Ph), 4.82, 5.00 (AB system, J_{AB} = 10.2 Hz, 2 H, OCH_2Ph), 4.83, 5.02 (AB system, J_{AB} = 10.8 Hz, 2 H, OCH_2Ph), 7.19–7.22, 7.25–7.33, 7.39–7.41 (3 m, 1 H, 17 H, 2 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.3 (t, C-4), 48.0 (q, OMe), 57.6 (t, C-6), 59.6 (t, NCH_2Ph), 64.4 (t, C-3), 67.3 (d, C-9a), 73.7, 75.8, 76.3 (3 t, 3 OCH_2Ph), 79.9 (d, C-9), 80.5 (d, C-7), 88.8 (d, C-8), 98.3 (s, C-4a), 126.7, 127.36, 127.37, 127.7*, 127.8, 128.0, 128.18, 128.23, 128.3, 128.4, 128.5, 138.3, 138.8, 139.1, 139.6 (11 d, 4 s, 4 Ph); * higher intensity.

ESI-MS: *m*/*z* (%) = 618 (73) $[M + Na]^+$, 596 (100) $[M + H]^+$.

Anal. Calcd for $C_{37}H_{41}NO_6$ (595.3): C, 74.60; H, 6.94; N, 2.35. Found: C, 74.61; H, 6.93; N, 2.39.

trans-17a

^{1}H NMR (600 MHz, $CDCl_3$): δ (selected signals) = 1.81 (ddd, *J* = 5.3, 13.2, 14.1 Hz, 1 H, 4-H), 2.19 (br dt, *J* ≈ 2.3, 14.1 Hz, 1 H, 4-H), 3.34 (s, 3 H, OMe), 3.70 (ddd, *J* = 1.4, 5.3, 12.0 Hz, 1 H, 3-H), 4.49 (dd, *J* = 8.1, 8.9 Hz, 1 H), 4.84 (d, *J* = 11.3 Hz, 1 H, CH_2Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ (selected signals) = 32.1 (t, C-4), 48.0 (q, OMe), 96.4 (s, C-4a).

(4a*S*,7*S*,8*R*,9*S*,9a*S*)-1-Benzyl-7,8,9-tris(benzyloxy)-4a-methoxyoxepano[3,2-*c*][1,2]oxazine (*cis*-17b)

Reaction time 5 d; partially purified **17b** (259 mg, 87%, *cis*/*trans* 84:16) was subjected to column chromatography (silica gel, hexane–EtOAc, 5:1) to yield the major *cis* isomer as thick colorless oil.

Yield: 203 mg (68%); $[\alpha]_D^{22}$ +9.3 (*c* 0.77, $CHCl_3$).

IR (KBr): 3090–2830 (=C–H, C–H), 1455, 1350, 1115, 1075, 1030 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.92 (ddd, *J* = 5.6, 12.0, 14.5 Hz, 1 H, 4-H), 1.97 (br d, *J* ≈ 14.5 Hz, 1 H, 4-H), 2.80 (d, J = 9.2 Hz, 1 H, 9a-H), 3.19 (s, 3 H, OMe), 3.60–3.67 (m, 3 H, 6-H, 7-H, 8-H), 3.69 (br ddd, *J* ≈ 1.2, 5.2, 10.9 Hz, 1 H, 3-H), 3.77 (dd, *J* = 3.3, 12.7 Hz, 1 H, 6-H), 3.88 (br td, *J* ≈ 3.4, 11.5 Hz, 1 H, 3-H), 4.08 (AB system, J_{AB} = 14.9 Hz, 1 H, NCH_2Ph), 4.16 (dd, *J* = 5.2, 9.2 Hz, 1 H, 9-H), 4.30 (AB system, J_{AB} = 14.9 Hz, 1 H, NCH_2Ph), 4.52, 4.55 (AB system, J_{AB} = 12.2 Hz, 2 H, OCH_2Ph), 4.57 (AB system, J_{AB} = 10.7 Hz, 1 H, OCH_2Ph), 4.65 (AB system, J_{AB} = 12.3 Hz, 1 H, OCH_2Ph), 4.72 (AB system, J_{AB} = 10.7 Hz, 1 H, OCH_2Ph), 4.73 (AB system, J_{AB} = 12.3 Hz, 1 H, OCH_2Ph), 7.10–7.14, 7.17–7.28, 7.29–7.32 (3 m, 1 H, 17 H, 2 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.9 (t, C-4), 48.0 (q, OMe), 59.5 (t, NCH_2Ph), 60.4 (t, C-6), 63.9 (t, C-3), 70.5 (d, C-9a), 71.7, 73.7, 74.2 (3 t, 3 OCH_2Ph), 75.5 (d, C-7), 78.2 (d, C-9), 83.1 (d, C-8), 97.8 (s, C-4a), 126.6, 127.4, 127.49, 127.51, 127.7, 127.98, 127.99, 128.19, 128.21, 128.28, 128.29, 128.33, 138.5, 138.7, 138.9, 139.6 (12 d, 4 s, 4 Ph).

ESI-MS: *m*/*z* (%) = 618 (100) $[M + Na]^+$, 596 (13) $[M + H]^+$.

Anal. Calcd for $C_{37}H_{41}NO_6$ (595.3): C, 74.60; H, 6.94; N, 2.35. Found: C, 74.45; H, 6.92; N, 2.37.

trans-17b

^{1}H NMR (600 MHz, $CDCl_3$): δ (selected signals) = 1.89 (br d, *J* ≈ 14.2 Hz, 1 H, 4-H), 2.15 (br ddd, *J* = 5.9, 13.5, 14.2 Hz, 1 H, 4-H), 3.26 (s, 3 H, OMe), 4.34 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.77 (d, *J* = 11.8 Hz, 1 H, CH_2Ph).

(4a*S*,7*R*,8*S*,9*S*,9a*S*)-1-Benzyl-7,8,9-tris(benzyloxy)-4a-methoxyoxepano[3,2-*c*][1,2]oxazine (*cis*-17c)

Reaction time 8 d; the crude mixture (247 mg) containing **17c** (*cis*/*trans* >99:1) contaminated with small amounts of ketal **18c** (ca. 4%) was subjected to column chromatography (silica gel, hexane–EtOAc, 6:1 to 4:1) and then filtered through a short silica gel pad (CH_2Cl_2) to yield *cis*-**17c** as thick colorless oil.

Yield: 179 mg (60%); $[\alpha]_D^{22}$ +13.7 (*c* 1.27, $CHCl_3$).

IR (neat): 3090–2810 (=C–H, C–H), 1495, 1455, 1360, 1145, 1065, 1030 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.71 (br td, *J* ≈ 5.8, 14.6 Hz, 1 H, 4-H), 2.00 (br d, *J* ≈ 14.6 Hz, 1 H, 4-H), 3.25 (s, 3 H, OMe), 3.36–3.41 (m, 2 H, 6-H, 8-H), 3.74 (dd, *J* = 5.5, 10.8 Hz, 1 H, 3-H), 3.86–3.94 (m, 3 H, 3-H, 9-H, 9a-H), 4.01 (dd, *J* = 11.3, 12.6 Hz, 1 H, 6-H), 4.09 (AB system, J_{AB} = 15.4 Hz, 1 H, NCH_2Ph), 4.09–4.11 (m, 1 H, 7-H), 4.49, 4.50 (AB system, J_{AB} = 12.1 Hz, 2 H, OCH_2Ph), 4.62 (AB system, J_{AB} = 11.5 Hz, 1 H, OCH_2Ph), 4.68 (AB system, J_{AB} = 15.4 Hz, 1 H, NCH_2Ph), 4.79, 4.81 (AB system, J_{AB} = 11.8 Hz, 2 H, OCH_2Ph), 4.87 (AB system, J_{AB} = 11.5 Hz, 1 H, OCH_2Ph), 7.16–7.18, 7.22–7.35, 7.38–7.42 (3 m, 1 H, 17 H, 2 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.5 (t, C-4), 48.0 (q, OMe), 57.4 (t, C-6), 59.9 (t, NCH_2Ph), 63.8 (d, C-9a), 64.7 (t, C-3), 71.2, 73.6, 74.2 (3 t, 3 OCH_2Ph), 77.6 (d, C-8), 77.8 (d, C-7), 79.1 (d, C-9), 99.0 (s, C-4a), 126.5, 127.2, 127.4, 127.5, 127.6, 127.97, 128.00, 128.05, 128.07, 128.1, 128.2, 128.4, 138.3, 138.8, 139.1, 140.2 (12 d, 4 s, 4 Ph).

ESI-MS: *m*/*z* (%) = 634 (49) $[M + K]^+$, 618 (11) $[M + Na]^+$, 596 (100) $[M + H]^+$.

Anal. Calcd for $C_{37}H_{41}NO_6$ (595.3): C, 74.60; H, 6.94; N, 2.35. Found: C, 74.75; H, 7.12; N, 2.12.

Ketal 18c

According to the general procedure, the reaction of 1,2-oxazine *syn*-**15c** was quenched with excess solid $NaHCO_3$ after 48 h. Partially purified ketal **18c** was isolated by column chromatography (silica gel, PE–EtOAc, 3:1) as a yellow oil; yield: 154 mg (49%, ca. 90% purity).

IR (neat): 3090–2815 (=C–H, C–H), 1495, 1455, 1355, 1265, 1210, 1100–1060 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.79 (br d, *J* ≈ 13.0 Hz, 1 H, 5-H), 1.94 (br td, *J* ≈ 5.7, 13.0 Hz, 1 H, 5-H), 2.59 (br s, 1 H, OH), 3.11, 3.18 (2 s, 3 H each, 2 OMe), 3.39 (br d, *J* ≈ 6.0 Hz, 1 H, 3-H), 3.73 (dd, *J* = 5.5, 11.7 Hz, 1 H, 6-H), 3.84–3.88 (m, 1 H, 4′-H), 3.91–3.95 (m, 2 H, 3′-H, 4′-H), 4.09 (td, *J* ≈ 2.7, 11.7 Hz, 1 H, 6-H), 4.14–4.22 (m, 3 H, 1′-H, NCH_2Ph), 4.34 (*pseudo*-t, *J* ≈ 3.8 Hz, 1 H, 2′-H), 4.51 (AB system, J_{AB} = 11.6 Hz, 1 H, OCH_2Ph), 4.57, 4.60 (AB system, J_{AB} = 11.7 Hz, 2 H, OCH_2Ph), 4.73 (AB system, J_{AB} = 11.6 Hz, 1 H, OCH_2Ph), 4.81, 4.87 (AB system, J_{AB} = 10.9 Hz, 2 H, OCH_2Ph), 7.17–7.45 (m, 20 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.6 (t, C-5), 47.3, 47.6 (2 q, 2 OMe), 58.7 (t, NCH_2Ph), 61.3 (d, C-3), 61.7 (t, C-4′), 63.2 (t, C-6), 71.6, 72.8, 74.9 (3 t, 3 OCH_2Ph), 79.7 (d, C-3′), 79.9 (d, C-1′), 81.4 (d, C-2′), 98.6 (s, C-4), 126.7, 127.4, 127.53, 127.58, 127.65, 127.67, 128.02, 128.09, 128.16, 128.2, 128.3*, 138.4, 138.66, 138.69, 139.6 (11 d, 4 s, 4 Ph); * higher intensity.

ESI-MS: *m*/*z* (%) = 628 (26) $[M + H]^+$, 627 (100) $[M]^+$.

(4a*R*,7*R*,8*S*,9*S*,9a*R*)-1-Benzyl-7,8,9-tris(benzyloxy)-4a-methoxyoxepano[3,2-*c*][1,2]oxazine (*cis*-21c)

By a procedure analogous to that described for the synthesis of *cis*-**17a–c** from *syn*-**15a–c**, 1,2-oxazine derivative *anti*-**15c** (346 mg, 0.41 mmol) was cyclized to give bicyclic product *cis*-**21c**, isolated by standard column chromatography (silica gel, PE–EtOAc, 6:1) as a thick colorless oil; yield: 212 mg (87%); $[\alpha]_D^{22}$ +8.5 (*c* 0.21, $CHCl_3$).

IR (KBr): 3090–2785 (=C–H, C–H), 1495, 1455, 1360, 1205, 1110, 1065, 1030 (C–O) cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6, 403 K):[28] δ = 1.72 (br dt, *J* ≈ 4.4, 9.2 Hz, 1 H), 2.20 (br ddd, *J* ≈ 4.6, 8.6, 13.3 Hz, 1 H), 3.11 (br s, 1 H), 3.19 (s, 3 H, OMe), 3.70–3.77 (m, 4 H), 3.80 (ddd, *J* = 4.2, 8.8, 11.2 Hz, 1 H), 3.84–3.86 (m, 1 H), 4.24 (m_c, 1 H), 4.42 (m_c, 1 H), 4.44 (br d, *J* ≈ 15.6 Hz, 1 H, NCH_2Ph), 4.63, 4.67 (2 br d, *J* ≈ 11.9 Hz, 1 H each, OCH_2Ph), 4.65, 4.69 (2 br d, *J* ≈ 12.3 Hz, 1 H each, OCH_2Ph), 4.75, 4.81 (2 br d, *J* ≈ 11.7 Hz, 1 H each, OCH_2Ph), 7.15–7.32, 7.35–7.40 (2 m, 16 H, 4 H, 4 Ph).

ESI-MS: *m*/*z* (%) = 618 (100) $[M + Na]^+$, 596 (29) $[M + H]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{42}NO_6$: 596.3012; found: 596.3001.

Anal. Calcd for $C_{37}H_{41}NO_6$ (595.3): C, 74.60; H, 6.94; N, 2.35. Found: C, 74.35; H, 7.16; N, 2.27.

Synthesis of *rac*-19 and 20a–c by Samarium(II) Iodide Induced Ring Opening of *rac*-12 and *cis*-17a–c; General Procedure

To a solution of SmI_2 (ca. 0.1 M in THF, 10 mL, ca. 1.0 mmol),[29] a solution of *rac*-**12** (91 mg, 0.33 mmol) or *cis*-**17** (197 mg, 0.33 mmol) in THF (4 mL) was added dropwise at r.t. The mixture was stirred until the starting materials were fully consumed (TLC monitoring), then quenched with sat. aq sodium potassium tartrate solution (10 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvents were removed under reduced pressure. The resulting crude product was filtered through a short pad of silica gel (PE–EtOAc, 1:1) and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 40:1) to afford the pure product as sticky colorless oil.

***cis*-3-Benzylamino-2-(2′-hydroxyethyl)-2-methoxyoxepane (*rac*-19)**

Reaction time 8 h; yield: 65 mg (71%).

IR (neat): 3320–3130 (O–H, N–H), 3060–2830 (=C–H, C–H), 1455, 1360, 1225, 1115, 1065, 1050 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.32–1.40 (m, 1 H, 5-H), 1.36–1.71 (m, 3 H, 4-H, 6-H_2), 1.81–1.90 (m, 2 H, 4-H, 5-H), 1.97–2.04 (m, 2 H, 2-CH_2), 2.97 (br d, *J* ≈ 9.5 Hz, 1 H, 3-H), 3.17 (s, 3 H, OMe), 3.59–3.63 (m, 2 H, 7-H, CH_2-OH), 3.71 (AB system, J_{AB} = 13.1 Hz, 1 H, CH_2Ph), 3.71–3.74 (m, 1 H, CH_2-OH), 3.75–3.80 (m, 1 H, 7-H), 3.92 (AB system, J_{AB} = 13.1 Hz, 1 H, CH_2Ph), 7.25–7.28, 7.29–7.35 (2 m, 1 H, 4 H, Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 26.8 (t, C-5), 28.0 (t, C-4), 29.8 (t, C-6), 37.0 (t, 2-CH_2), 47.8 (q, OMe), 52.2 (t, CH_2Ph), 57.2 (t, CH_2-OH), 61.9 (t, C-7), 66.5 (d, C-3), 105.0 (s, C-2), 127.3, 128.3, 128.6, 139.2 (3 d, s, Ph).

ESI-MS: *m*/*z* (%) = 318 (25) $[M + K]^+$, 302 (22) $[M + Na]^+$, 280 (100) $[M + H]^+$, 248 (98) $[M - OMe]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{25}NO_3$: 279.1834; found: 279.1834.

Anal. Calcd for $C_{16}H_{25}NO_3$ (279.2): C, 68.79; H, 9.02; N, 5.01. Found: C, 68.58; H, 8.96; N, 4.86.

(2*S*,3*S*,4*S*,5*R*,6*R*)-3-Benzylamino-4,5,6-tris(benzyloxy)-2-(2′-hydroxyethyl)-2-methoxyoxepane (20a)

Reaction time 8 h; yield: 155 mg (78%); $[\alpha]_D^{22}$ +34.5 (*c* 0.58, $CHCl_3$).

IR (neat): 3360–3170 (O–H, N–H), 3110–2845 (=C–H, C–H), 1455, 1360, 1210, 1105, 1070, 1040 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.94 (ddd, *J* = 1.9, 8.5, 15.9 Hz, 1 H, 2-CH_2), 1.94 (ddd, *J* = 1.4, 6.8, 15.9 Hz, 1 H, 2-CH_2), 2.90 (d, *J* = 8.8 Hz, 1 H, 3-H), 3.20 (s, 3 H, OMe), 3.41–3.45 (m, 1 H, 5-H), 3.55 (dd, *J* = 2.9, 10.7 Hz, 1 H, 7-H), 3.62 (pseudo-t, *J* ≈ 9.1 Hz, 1 H, 4-H), 3.64–3.73 (m, 4 H, 6-H, 7-H, CH_2OH), 3.66, 4.06 (AB system, J_{AB} = 13.2 Hz, 2 H, NCH_2Ph), 4.60, 4.86 (AB system, J_{AB} = 10.5 Hz, 2 H, OCH_2Ph), 4.63, 4.71 (AB system, J_{AB} = 11.3 Hz, 2 H, OCH_2Ph), 4.80, 4.91 (AB system, J_{AB} = 10.9 Hz, 2 H, OCH_2Ph), 7.11–7.13, 7.19–7.32 (2 m, 2 H, 18 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 36.8 (t, 2-CH_2), 48.1 (q, OMe), 53.6 (t, NCH_2Ph), 56.6 (t, CH_2OH), 58.6 (t, C-7), 63.5 (d, C-3), 73.9, 76.1, 76.3 (3 t, 3 OCH_2Ph), 77.7 (d, C-4), 80.5 (d, C-6), 88.9 (d, C-5), 105.5 (s, C-2), 127.2, 127.5, 127.6, 127.81, 127.85, 127.9, 128.2, 128.26, 128.33, 128.45, 128.46, 128.54, 137.4, 138.2, 138.8, 139.2 (12 d, 4 s, 4 Ph).

ESI-MS: *m*/*z* (%) = 620 (38) $[M + Na]^+$, 598 (100) $[M + H]^+$, 566 (29) $[M - OMe]^+$.

Anal. Calcd for $C_{37}H_{43}NO_6$ (597.3): C, 74.35; H, 7.25; N, 2.34. Found: C, 74.41; H, 7.12; N, 2.31.

(2*S*,3*S*,4*S*,5*R*,6*S*)-3-Benzylamino-4,5,6-tris(benzyloxy)-2-(2′-hydroxyethyl)-2-methoxyoxepane (20b)

Reaction time 8 h; yield: 124 mg (63%); $[\alpha]_D^{22}$ +31.1 (*c* 0.91, $CHCl_3$).

IR (KBr): 3425–3300 (O–H, N–H), 3090–2805 (=C–H, C–H), 1455, 1130, 1090, 1070, 1030 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.97 (ddd, *J* = 2.5, 8.4, 15.2 Hz, 1 H, 2-CH_2), 2.05 (ddd, *J* = 2.3, 7.0, 15.2 Hz, 1 H, 2-CH_2), 2.75 (d, *J* = 5.0 Hz, 1 H, 3-H), 3.17 (s, 3 H, OMe), 3.49–3.58 (m, 6 H, 6-H, 7-H, NCH_2Ph, CH_2OH), 3.69 (dd, *J* = 3.9, 14.4 Hz, 1 H, 7-H), 3.77 (br d, *J* ≈ 7.5 Hz, 1 H, 5-H), 3.98 (dd, *J* = 5.0, 7.5 Hz, 1 H, 4-H), 4.54 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 4.59 (AB system, J_{AB} = 11.3 Hz, 1 H, OCH_2Ph), 4.62, 4.63 (AB system, J_{AB} = 12.4 Hz, 2 H, OCH_2Ph), 4.66 (AB system, J_{AB} = 11.7 Hz, 1 H, OCH_2Ph), 4.74 (AB system, J_{AB} = 11.3 Hz, 1 H, OCH_2Ph), 7.05–7.08, 7.12–7.27 (2 m, 2 H, 18 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 38.2 (t, 2-CH_2), 48.8 (q, OMe), 52.3 (t, NCH_2Ph), 57.3 (t, CH_2OH), 61.0 (t, C-7), 65.6 (d, C-3), 72.1, 73.4, 74.3 (3 t, 3 OCH_2Ph), 76.3 (d, C-6), 79.4 (d, C-4), 86.2 (d, C-5), 104.6 (s, C-2), 127.0, 127.6, 127.67, 127.69, 127.8, 127.9, 128.2, 128.3*, 128.36, 128.38, 128.4, 138.1, 138.3, 138.6, 139.3 (11 d, 4 s, 4 Ph); * higher intensity.

ESI-MS: *m*/*z* (%) = 620 (45) $[M + Na]^+$, 598 (100) $[M + H]^+$, 566 (43) $[M - OMe]^+$.

Anal. Calcd for $C_{37}H_{43}NO_6$ (597.3): C, 74.35; H, 7.25; N, 2.34. Found: C, 74.11; H, 7.31; N, 2.27.

(2*S*,3*S*,4*S*,5*S*,6*R*)-3-Benzylamino-4,5,6-tris(benzyloxy)-2-(2′-hydroxyethyl)-2-methoxyoxepane (20c)

Reaction time 16 h; yield: 171 mg (87%); $[\alpha]_D^{22}$ +7.1 (*c* 1.12, $CHCl_3$).

IR (neat): 3340–3305 (O–H, N–H), 3090–2850 (=C–H, C–H), 1455, 1370, 1205, 1100, 1065 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.88 (ddd, *J* = 1.7, 8.0, 15.9 Hz, 1 H, 2-CH_2), 1.94 (ddd, *J* = 1.5, 7.7, 15.9 Hz, 1 H, 2-CH_2), 3.20 (s, 3 H, OMe), 3.40–3.44 (m, 2 H, 6-H, 7-H), 3.56 (br d, *J* ≈ 8.9 Hz, 1 H, 4-H), 3.66 (ddd, *J* = 1.7, 7.7, 11.5 Hz, 1 H, CH_2OH), 3.71 (ddd, *J* = 1.5, 8.0, 11.5 Hz, 1 H, CH_2OH), 3.74 (AB system, J_{AB} = 13.2 Hz, 1 H, NCH_2Ph), 3.77 (d, *J* = 8.9 Hz, 1 H, 3-H), 4.02 (AB system, J_{AB} = 13.2 Hz, 1 H, NCH_2Ph), 4.03 (m_c, 1 H, 5-H), 4.09 (dd, *J* = 11.7, 12.8 Hz, 1 H, 7-H), 4.50, 4.51 (AB system, J_{AB} = 12.8 Hz, 2 H, OCH_2Ph), 4.53 (s, 2 H, OCH_2Ph), 4.62, 4.68 (AB system, J_{AB} = 12.0 Hz, 2 H, OCH_2Ph), 7.19–7.23, 7.25–7.31, 7.32–7.35 (3 m, 3 H, 15 H, 2 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 37.0 (t, 2-CH_2), 48.0 (q, OMe), 53.4 (t, NCH_2Ph), 56.8 (t, CH_2OH), 58.2 (t, C-7), 59.3 (d, C-3), 71.3, 73.3, 74.0 (3 t, 3 OCH_2Ph), 76.1 (d, C-6), 76.7 (d, C-4), 77.8 (d, C-5), 106.2 (s, C-2), 127.1, 127.3, 127.4, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4*, 128.48, 128.49, 137.3, 138.2, 139.0, 139.5 (11 d, 4 s, 4 Ph); * higher intensity.

ESI-MS: *m*/*z* (%) = 598 (46) $[M + H]^+$, 566 (100) $[M - OMe]^+$.

Anal. Calcd for $C_{37}H_{43}NO_6$ (597.3): C, 74.35; H, 7.25; N, 2.34. Found: C, 74.19; H, 7.09; N, 2.29.

Compounds 23c and 22c by Reaction of *cis*-21c with Samarium(II) Iodide

A sample of oxepane derivative *cis*-**21c** (59 mg, 0.10 mmol) was reacted with SmI_2 (ca. 0.1 M in THF, 4 mL, ca. 0.4 mmol, reaction time 48 h) to give after purification by column chromatography (silica gel, CH_2Cl_2–MeOH, 40:1) compounds **23c** (15 mg, 26%, first eluted) and **22c** (29 mg, 49%, second eluted).

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-Benzylamino-4,5,6-tris(benzyloxy)-2-(2′-hydroxyethyl)-2-methoxyoxepane (22c)

Thick colorless oil; $[\alpha]_D^{22}$ –6.8 (*c* 0.21, $CHCl_3$).

IR (neat): 3370–3315 (O–H, N–H), 3090–2865 (=C–H, C–H), 1455, 1360, 1140, 1090, 1065 (C–O) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.84 (ddd, *J* = 3.8, 9.1, 14.9 Hz, 1 H, 2-CH_2), 2.20 (ddd, *J* = 3.1, 5.7, 14.9 Hz, 1 H, 2-CH_2), 3.12 (s, 3 H, OMe), 3.14 (br d, *J* ≈ 1.7 Hz, 1 H, 3-H), 3.49 (ddd, *J* = 3.8, 5.7, 12.0 Hz, 1 H, CH_2OH), 3.64 (ddd, *J* = 3.1, 9.1, 12.0 Hz, 1 H, CH_2OH), 3.71 (dd, *J* = 3.7, 12.1 Hz, 1 H, 7-H), 3.74 (AB system, J_{AB} = 11.9 Hz, 1 H, NCH_2Ph), 3.86 (ddd, *J* = 2.0, 3.7, 9.5 Hz, 1 H, 6-H), 4.08 (pseudo-t, *J* ≈ 2.9 Hz, 1 H, 4-H), 4.16 (dd, *J* = 9.5, 12.1 Hz, 1 H, 7-H), 4.27 (m_c, 1 H, 5-H), 4.39 (AB system, J_{AB} = 11.9 Hz, 1 H, NCH_2Ph), 4.56, 4.57 (AB system, J_{AB} = 12.4 Hz, 2 H, OCH_2Ph), 4.60, 4.63 (AB system, J_{AB} = 11.8 Hz, 2 H, OCH_2Ph), 4.74, 4.87 (AB system, J_{AB} = 11.5 Hz, 2 H, OCH_2Ph), 7.11–7.17, 7.25–7.40 (2 m, 4 H, 16 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 38.6 (t, 2-CH_2), 48.5 (q, OMe), 54.4 (t, NCH_2Ph), 57.7 (t, CH_2OH), 62.6 (t, C-7), 65.3 (d, C-3), 71.8*, 74.9 (2 t, 3 OCH_2Ph), 76.1 (d, C-6), 78.3 (d, C-4), 81.0 (d, C-5), 104.2 (s, C-2), 126.8, 127.4, 127.52, 127.54, 127.6, 127.7, 128.1, 128.19, 128.22, 128.38, 128.42, 128.8, 138.1, 138.5, 138.6, 139.9 (12 d, 4 s, 4 Ph); * higher intensity.

ESI-MS: *m*/*z* (%) = 620 (21) $[M + Na]^+$, 598 (100) $[M + H]^+$, 566 (33) $[M - OMe]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{44}NO_5$: 598.3169; found: 598.3157.

Anal. Calcd for $C_{37}H_{43}NO_6$ (597.3): C, 74.35; H, 7.25; N, 2.34. Found: C, 74.08; H, 7.47; N, 2.28.

(3a*R*,6*R*,7*S*,8*S*,8a*R*)-1-Benzyl-6,7,8-tris(benzyloxy)-3a-methoxyoxepano[3,2-*b*]pyrrolidine (23c)

Thick colorless oil; $[\alpha]_D^{22}$ –27.3 (*c* 0.10, $CHCl_3$).

IR (neat): 3090–2855 (=C–H, C–H), 1495, 1455, 1115, 1090, 1075, 1030 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.04 (br dd, *J* ≈ 5.4, 12.6 Hz, 1 H, 3-H), 2.28 (br td, *J* ≈ 7.4, 12.6 Hz, 1 H, 3-H), 2.43 (ddd, *J* = 5.4, 8.1, 12.4 Hz, 1 H, 2-H), 2.52 (br s, 1 H, 8a-H), 3.06 (br dd, *J* ≈ 7.7, 12.4 Hz, 1 H, 2-H), 3.16 (m_c, 1 H, 6-H), 3.17 (s, 3 H, OMe), 3.59 (m_c, 1 H, 8-H), 3.67–3.76 (m, 5 H, 5-H_2, 7-H, NCH_2Ph), 4.10, 4.21 (AB system, J_{AB} = 12.1 Hz, 2 H, OCH_2Ph), 4.77, 4.88 (AB system, J_{AB} = 12.6 Hz, 2 H, OCH_2Ph), 4.79, 5.04 (AB system, J_{AB} = 12.3 Hz, 2 H, OCH_2Ph), 7.13–7.29, 7.37–7.48 (m, 16 H, 4 H 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 31.4 (t, C-3), 47.4 (q, OMe), 51.2 (t, C-2), 61.1 (t, C-5), 61.3 (t, NCH_2Ph), 70.8, 72.7 (2 t, 2 OCH_2Ph), 72.9 (d, C-8a), 74.1 (t, OCH_2Ph), 76.6 (d, C-7), 80.7 (d, C-8), 82.8 (d, C-6), 110.5 (s, C-3a), 126.6, 126.9, 127.2, 127.3, 127.4, 127.7, 127.79, 128.03, 128.1, 128.2, 128.3, 129.1, 138.4, 139.2, 139.9, 140.5 (12 d, 4 s, 4 Ph).

ESI-MS: *m*/*z* (%) = 602 (62) $[M + Na]^+$, 580 (100) $[M + H]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{42}NO_5$: 580.3063; found: 580.3068.

Anal. Calcd for $C_{37}H_{41}NO_5$ (579.3): C, 76.66; H, 7.13; N, 2.42. Found: C, 76.47; H, 7.23; N, 2.14.

(3a*S*,6*R*,7*R*,8*S*,8a*S*)-1-Benzyl-6,7,8-tris(benzyloxy)-3a-methoxyoxepano[3,2-*b*]pyrrolidine (23a)

A solution of MsCl (92 mg, 0.80 mmol, 62 μL) in anhydrous pyridine (2 mL) was added dropwise at 0 °C to a solution of **20a** (420 mg, 0.70 mmol) in anhydrous pyridine (15 mL). After stirring of the mixture at ambient temperature overnight, 5% aq $CuSO_4$ solution (15 mL) was added. The mixture was extracted with Et_2O (3 × 15 mL), the combined extracts were dried ($MgSO_4$), and the solvents were removed in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 3:1) to give **23a** as a colorless solid; yield: 349 mg (86%). Suitable crystals for an X-ray crystal structure determination were obtained from CH_2Cl_2–hexane solution by slow evaporation of the solvents.

Mp 126–128 °C; $[\alpha]_D^{22}$ +22.9 (*c* 0.53, $CHCl_3$).

IR (KBr): 3090–2810 (=C–H, C–H), 1495, 1455, 1115, 1090, 1070, 1040 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.72 (ddd, *J* = 7.0, 12.9, 13.4 Hz, 1 H, 3-H), 2.08 (dd, *J* = 4.9, 12.9 Hz, 1 H, 3-H), 2.22 (ddd, *J* = 4.9, 8.7, 13.4 Hz, 1 H, 2-H), 2.76 (dd, *J* = 7.0, 8.7 Hz, 1 H, 2-H), 2.78 (d, *J* = 10.1 Hz, 1 H, 8a-H), 3.18 (s, 3 H, OMe), 3.44 (pseudo-t, *J* ≈ 9.7 Hz, 1 H, 8-H), 3.52–3.58 (m, 2 H, 5-H, 7-H), 3.55 (AB system, J_{AB} = 12.8 Hz, 1 H, NCH_2Ph), 3.65 (ddd, *J* = 4.2, 8.5, 11.2 Hz, 1 H, 6-H), 3.72 (dd, *J* = 11.2, 11.9 Hz, 1 H, 7-H), 4.47 (AB system, J_{AB} = 12.8 Hz, 1 H, NCH_2Ph), 4.65, 4.77 (AB system, J_{AB} = 11.4 Hz, 2 H, OCH_2Ph), 4.78, 4.90 (AB system, J_{AB} = 10.6 Hz, 2 H, OCH_2Ph), 4.94, 5.14 (AB system, J_{AB} = 11.0 Hz, 2 H, OCH_2Ph), 7.13–7.33 (m, 20 H, 4 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.5 (t, C-3), 47.5 (q, OMe), 49.3 (t, C-2), 60.1 (t, C-5), 62.7 (t, NCH_2Ph), 72.9 (d, C-8a), 73.9, 76.2, 76.4 (3 t, 3 OCH_2Ph), 79.7 (d, C-6), 83.5 (d, C-8), 87.9 (d, C-7), 108.7 (s, C-3a), 126.5, 126.9, 127.0, 127.2, 127.7, 127.83, 127.87, 127.93, 128.0, 128.1, 128.4, 128.7, 138.5, 139.1, 139.3, 139.6 (12 d, 4 s, 4 Ph).

ESI-MS: *m*/*z* (%) = 580 (100) $[M + H]^+$.

Anal. Calcd for $C_{37}H_{41}NO_5$ (579.3): C, 76.66; H, 7.13; N, 2.42. Found: C, 76.44; H, 6.98; N, 2.25.

(3a*S*,6*R*,7*R*,8*S*,8a*S*)-6,7,8-Tris(benzyloxy)-3a-methoxyoxepano[3,2-*b*]pyrrolidine (24a)

H_2 was bubbled through a stirred suspension of Pd/C (10% Pd, 150 mg) in *i*-PrOH (8 mL) for 30 min. A solution of **23a** (116 mg, 0.2 mmol) in EtOAc (2 mL) was added, and the mixture was stirred at r.t. at normal pressure (hydrogen balloon). After 7 h, the solution was filtered through a short pad of Celite, and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (silica gel, PE–EtOAc, 1:1) to give **24a** as a colorless solid; yield: 69 mg (71%).

Mp 123–124 °C; $[\alpha]_D^{22}$ –12.3 (*c* 0.65, $CHCl_3$).

IR (KBr): 3430 (N–H), 3090–2850 (=C–H, C–H), 1115, 1095, 1075, 1045 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.60 (ddd, *J* = 7.4, 8.7, 13.3 Hz, 1 H, 3-H), 1.82 (br s, 1 H, NH), 2.13–2.18 (m, 1 H, 3-H), 2.65 (td, *J* ≈ 4.9, 9.1 Hz, 1 H, 2-H), 2.79–2.85 (m, 1 H, 2-H), 3.03 (d, *J* = 9.8 Hz, 1 H, 8a-H), 3.19 (s, 3 H, OMe), 3.43 (pseudo-t, *J* ≈ 9.6 Hz, 1 H, 8-H), 3.50–3.57 (m, 2 H, 5-H, 7-H), 3.62–3.71 (m, 2 H, 5-H, 6-H), 4.65 (AB system, J_{AB} = 11.4 Hz, 1 H, CH_2Ph), 4.67 (AB system, J_{AB} = 11.2 Hz, 1 H, CH_2Ph), 4.76 (AB system, J_{AB} = 11.4 Hz, 1 H, CH_2Ph), 4.85, 4.91 (AB system, J_{AB} = 10.7 Hz, 2 H, CH_2Ph), 5.00 (AB system, J_{AB} = 11.2 Hz, 1 H, CH_2Ph), 7.25–7.35 (m, 15 H, 3 Ph).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 31.9 (t, C-3), 42.4 (t, C-2), 48.3 (q, OMe), 60.4 (t, C-5), 66.8 (d, C-8a), 73.8, 76.0, 76.1 (3 t, 3 CH_2Ph), 78.4 (d, C-8), 79.7 (d, C-6), 88.2 (d, C-7), 110.4 (s, C-3a), 127.4, 127.7, 127.78, 127.80, 127.9, 128.2, 128.3, 128.4, 128.5, 138.4, 138.6, 138.9 (9 d, 3 s, 3 Ph).

ESI-MS: *m*/*z* (%) = 490 (100) $[M + H]^+$, 458 (77) $[M – OMe]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{30}H_{35}NO_5$: 489.2515; found: 489.2515.

(3a*S*,6*R*,7*R*,8*S*,8a*S*)-6,7,8-Tris(hydroxy)-3a-methoxyoxepano[3,2-*b*]pyrrolidine (25a)

A solution of **24a** (260 mg, 0.45 mmol) in *i*-PrOH (6 mL) was added to a suspension of 10% Pd/C (300 mg) in *i*-PrOH (15 mL), and the resulting mixture was hydrogenated at 4 atm for 3 d at r.t. The solution was filtered through a short pad of Celite, and the solvent was removed under reduced pressure. The crude mixture was filtered through a short silica gel pad (CH_2Cl_2–MeOH, 5:1) to give **25a** as a colorless solid; yield: 94 mg (95%).

Mp 167–168 °C; $[\alpha]_D^{22}$ +34.4 (*c* 0.24, MeOH).

IR (KBr): 3495, 3405, 3315, 3235 (O–H, N–H), 2980–2870 (C–H), 1325, 1130, 1070, 1035 (C–O) cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.80 (ddd, *J* = 8.7, 10.0, 13.8 Hz, 1 H, 3-H), 2.36 (ddd, *J* = 3.4, 7.1, 13.8 Hz, 1 H, 3-H), 3.02 (ddd, *J* = 7.1, 10.0, 10.7 Hz, 1 H, 2-H), 3.08 (d, *J* = 10.4, 1 H, 8a-H), 3.18 (ddd, *J* = 3.4, 8.7, 10.7 Hz, 1 H, 2-H), 3.20 (dd, *J* = 8.3, 9.3 Hz, 1 H, 7-H), 3.24 (s, 3 H, OMe), 3.37 (dd, *J* = 9.3, 10.4 Hz, 1 H, 8-H), 3.49–3.54 (m, 2 H, 5-H, 6-H), 3.59–3.64 (m, 1 H, 5-H).

^{13}C NMR (151 MHz, CD_3OD): δ = 32.2 (t, C-3), 43.3 (t, C-2), 48.9 (q, OMe), 64.2 (t, C-5), 68.4 (d, C-8a), 69.8 (d, C-8), 72.6 (d, C-6), 80.4 (d, C-7), 110.7 (s, C-3a).

ESI-MS: *m*/*z* (%) = 220 (100) $[M + H]^+$, 188 (52) $[M – OMe]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_9H_{18}NO_5$: 220.1185; found: 220.1182.

Anal. Calcd $C_9H_{17}NO_5$ (219.2): C, 49.31; H, 7.82; N, 6.39. Found: C, 49.35; H, 7.91; N, 6.26.

Acknowledgement

Financial support by the Ministry of Science and Higher Education (Republic of Poland, grant Iuventus Plus no. IP2014 017173) and by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560398.

References

(1) Responsible for X-ray crystal-structure determination.
(2) (a) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631. (b) Belen'kii, L. I. *Oxepanes and Oxepines*, In *Comprehensive Heterocyclic Chemistry III*; Vol. 13; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**, Chap. 13.02, 45. (c) Piva, O. *Synthesis of Seven-Membered Ring Ethers and Lactones*, In *Synthesis of Saturated Oxygenated Heterocycles II*; Cossy, J., Ed.; Springer: Berlin, **2014**, 283.
(3) (a) Bozó, E.; Boros, S.; Párkányi, L.; Kuszmann, J. *Carbohydr. Res.* **2000**, *329*, 269. (b) Castro, S.; Duff, M.; Snyder, N. L.; Morton, M.; Kumar, C. V.; Peczuh, M. W. *Org. Biomol. Chem.* **2005**, *3*, 3869. (c) Pakulski, Z. *Pol. J. Chem.* **2006**, *80*, 1293. (d) Sabatino, D.; Damha, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8259. (e) Duff, M. R. Jr.; Fyvie, W. S.; Markad, S. D.; Frankel, A. E.; Kumar, C. V.; Gascón, J. A.; Peczuh, M. W. *Org. Biomol. Chem.* **2011**, *9*, 154. (f) Saha, J.; Peczuh, M. W. *Adv. Carbohydr. Chem. Biochem.* **2011**, *66*, 121.
(4) (a) Contour, M. O.; Fayet, C.; Gelas, J. *Carbohydr. Res.* **1990**, *201*, 150. (b) Ng, C. J.; Stevens, J. D. *Carbohydr. Res.* **1996**, *284*, 241. (c) Castro, S.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 3312. (d) Tauss, A.; Steiner, A. J.; Stütz, A. E.; Tarling, C. A.; Withers, S. G.; Wrodnigg, T. M. *Tetrahedron: Asymmetry* **2006**, *17*, 234. (e) Sizun, G.; Dukhan, D.; Griffon, J.-F.; Griffe, L.; Meillon, J.-C.; Leroy, F.; Storer, R.; Sommadossi, J.-P.; Gosselin, G. *Carbohydr. Res.* **2009**, *344*, 448. (f) Venukumar, P.; Sudharani, C.; Sridhar, P. R. *Chem. Commun.* **2014**, *50*, 2218.
(5) (a) Ovaa, H.; Leeuvenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. A. *Tetrahedron Lett.* **1998**, *39*, 3025. (b) Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057. (c) Schmidt, B.; Biernat, A. *Chem. Eur. J.* **2008**, *14*, 6135. (d) Schmidt, B.; Biernat, A. *Org. Lett.* **2008**, *10*, 105.
(6) (a) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831. (b) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165. (c) Ganesh, N. V.; Jayaraman, N. *J. Org. Chem.* **2007**, *72*, 5500. (d) Batchelor, R.; Harvey, J. E.; Northcote, P. T.; Teesdale-Spittle, P.; Hoberg, J. O. *J. Org. Chem.* **2009**, *74*, 7627. (e) Ganesh, N. V.; Jayaraman, N. *J. Org. Chem.* **2009**, *74*, 739. (f) Hewitt, R. J.; Harvey, J. E. *J. Org. Chem.* **2010**, *75*, 955. (g) Ganesh, N. V.; Raghothama, S.; Sonti, R.; Jayaraman, N. *J. Org. Chem.* **2010**, *75*, 215. (h) Dey, S.; Jayaraman, N. *Beilstein J. Org. Chem.* **2012**, *8*, 522. (i) Dey, S.; Jayaraman, N. *Carbohydr. Res.* **2014**, *399*, 49.
(7) (a) Saha, J.; Peczuh, M. W. *Org. Lett.* **2009**, *11*, 4482. (b) Vannam, R.; Peczuh, M. W. *Org. Lett.* **2013**, *15*, 4122.
(8) (a) Alcázar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877. (b) Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851.
(9) Köver, A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *ARKIVOC* **2007**, *(iv)*, 364.
(10) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.
(11) For selected recent examples, see: (a) Schmiedel, V. M.; Stefani, S.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2013**, *9*, 2564. (b) Bera, M. K.; Domínguez, M.; Hommes, P.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2014**, *10*, 394. (c) Jasiński, M.; Mlostoń, G.; Stolarski, M.; Costa, W.; Domínguez, M.; Reissig, H.-U. *Chem. Asian J.* **2014**, *9*, 2641. For reviews, see: (d) Zimmer, R.; Reissig, H.-U. *Chem. Soc. Rev.* **2014**, *43*, 2888. (e) Zimmer, R.; Reissig, H.-U. *Allenes in Multicomponent Synthesis of Heterocycles*, In *Multicomponent Reactions in Organic Synthesis*; Zhu, J.; Wang, Q.; Wang, M.-X., Eds.; Wiley-VCH: Weinheim, **2015**, 301.
(12) (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. (b) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153. (c) Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2005**, 1152. (d) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003. (e) Dekaris, V.; Reissig, H.-U. *Synlett* **2010**, 42. (f) Jasiński, M.; Lentz, D.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2012**, *8*, 662. (g) Parmeggiani, C.; Cardona, F.; Giusti, L.; Reissig, H.-U.; Goti, A. *Chem. Eur. J.* **2013**, *19*, 10595. (h) Jasiński, M.; Moreno-Clavijo, E.; Reissig, H.-U. *Eur. J. Org. Chem.* **2014**, 442.
(13) (a) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2005**, *44*, 6227; *Angew. Chem.* **2005**, *117*, 6383. (b) Al-Harrasi, A.; Pfrengle, F.; Prisyazhnyuk, V.; Yekta, S.; Kooš, P.; Reissig, H.-U. *Chem. Eur. J.* **2009**, *15*, 11632. (c) Pfrengle, F.; Reissig, H.-U. *Chem. Eur. J.* **2010**, *16*, 11915. (d) Bouché, L.; Kandziora, M.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2014**, *10*, 213. (e) Salta, J.; Dernedde, J.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2015**, *11*, 638. (f) Salta, J.; Reissig, H.-U. *Synthesis* **2015**, *47*, 1893. (g) Kandziora, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2015**, 370. (h) Kandziora, M.; Mucha, E.; Zucker, S. P.; Reissig, H.-U. *Synlett* **2015**, *26*, 367.
(14) (a) Bressel, B.; Egart, B.; Al-Harrasi, A.; Pulz, R.; Reissig, H.-U.; Brüdgam, I. *Eur. J. Org. Chem.* **2008**, 467. (b) Dekaris, V.; Bressel, B.; Reissig, H.-U. *Synlett* **2010**, 47. (c) Jasiński, M.; Lentz, D.; Moreno-Clavijo, E.; Reissig, H.-U. *Eur. J. Org. Chem.* **2012**, 3304.
(15) (a) Chakraborty, B.; Sharma, P. K.; Rai, N.; Sharma, C. D. *J. Chem. Sci.* **2012**, *124*, 679. (b) Chakraborty, B.; Sharma, C. D. *Tetrahedron Lett.* **2013**, *54*, 5532.
(16) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261.
(17) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(18) Maciaszczyk, J.; Jasiński, M. *Tetrahedron: Asymmetry* **2015**, *26*, 510.
(19) (a) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359. (b) Jung, S. H.; Lee, J. E.; Koh, H. Y. *Bull. Korean Chem. Soc.* **1998**, *19*, 33. (c) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755. (d) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353. (e) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 8375. (f) Bressel, B.; Reissig, H.-U. *Org. Lett.* **2009**, *11*, 527. (g) Dekaris, V.; Pulz, R.; Al-Harrasi, A.; Lentz, D.; Reissig, H.-U. *Eur. J. Org. Chem.* **2011**, 3210. (h) Jasiński, M.; Watanabe, T.; Reissig, H.-U. *Eur. J. Org. Chem.* **2013**, 605.
(20) Compound **23c** is probably formed as a result of Sm(III) activation of the free hydroxyl group of **22c**, followed by spontaneous S_N2 ring closure, rather than via redox processes. For SmI_2-mediated ring contraction in 3,6-dihydro-2*H*-1,2-oxazines, see ref. 19h.
(21) For reports on the dehydrogenation of alcohols, see: (a) Smith, G. V.; Notheisz, F. *Hydrogenolysis of Benzyl–Nitrogen Bonds*, In *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: San Diego, **1999**, Chap. 4.2.1.1, 161. (b) Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6910. (c) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661.
(22) (a) Stick, R. V.; Williams, S. J. *Synthesis and Protecting Groups In Carbohydrates: The Essential Molecules of Life*; Elsevier: Amsterdam, **2009**, Chap. 2, 35. For selected examples of Birch-type debenzylations, see: (b) Iserloh, U.; Dudkin, V.; Wang, Z.-G.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 7027. (c) Werz, D.

B.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6315; *Angew. Chem.* **2005**, *117*, 6474. (d) Cumpstey, I.; Ramstadius, C.; Akhtar, T.; Goldstein, I. J.; Winter, H. C. *Eur. J. Org. Chem.* **2010**, 1951. (e) Liu, Z.; Bittman, R. *Org. Lett.* **2012**, *14*, 620.

(23) (a) Fall, Y.; Gomez, G.; Fernandez, C. *Tetrahedron Lett.* **1999**, *40*, 8307. (b) Pérez, M.; Canoa, P.; Gomez, G.; Teijeira, M.; Fall, Y. *Synthesis* **2005**, 411.

(24) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

(25) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

(26) Sheldrick, G. M. *Acta Crystallogr., Sect. C* **2015**, *71*, 3.

(27) Nishiyama, K.; Kamiya, A.; Hammam, M. A. S.; Kinoshita, H.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1309.

(28) The ^{1}H NMR spectrum of *cis*-**21c** taken at room temperature showed a series of very broad signals, which could be resolved at 403 K (DMSO-d_6); however, partial decomposition of the material was observed at this temperature. In the case of longer-time experiments (e.g., ^{13}C NMR, HMQC), the appearance of a new set of signals made correct assignments difficult.

(29) (a) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501. (b) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049.