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## Lewis acid-catalysed nucleophilic opening of a bicyclic hemiaminal followed by ring contraction: Access to functionalized L-idonojirimycin derivatives

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- **Title:** Lewis acid-catalysed nucleophilic opening of a bicyclic hemiaminal followed by ring contraction: Access to functionalized L-idonojirimycin derivatives

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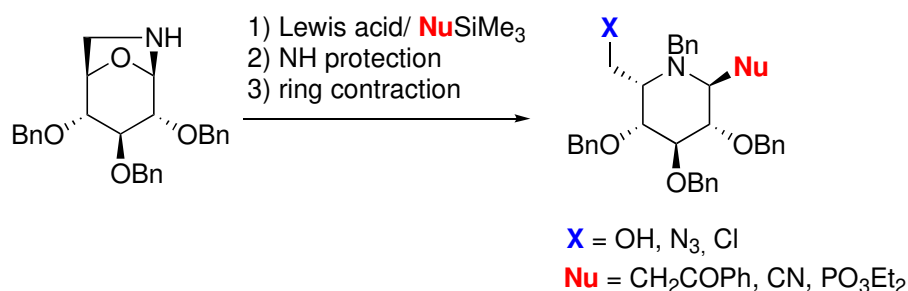
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- **Abstract:** The Lewis acid-catalyzed nucleophilic opening of a *D-gluco*-configured bicyclic hemiaminal has been examined. Several Lewis acids and silylated nucleophiles have been screened allowing the introduction of acetophenone, phosphonate or nitrile at the pseudoanomeric position in satisfactory yields and high 1,2 trans stereoselectivities. Their skeletal rearrangement triggered by the *N*-benzyl anchimeric assistance provided the corresponding *L-ido*-configured piperidines displaying various functional groups at C-6 position in good yield.

**Graphical abstract:**



**Highlights:**

- ◆ Lewis acid-catalyzed nucleophilic opening of a *D-gluco*-configured bicyclic hemiaminal
- ◆ Ring contraction of the resulting azepane functionalized at C-1
- ◆ Access to L-idonojirimycin derivatives with orthogonal functions at C-1 and C-6

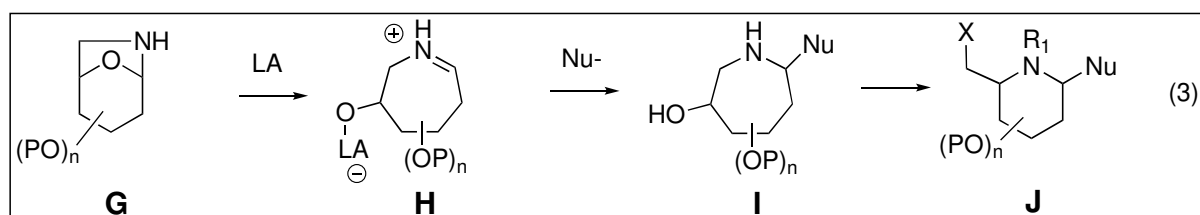
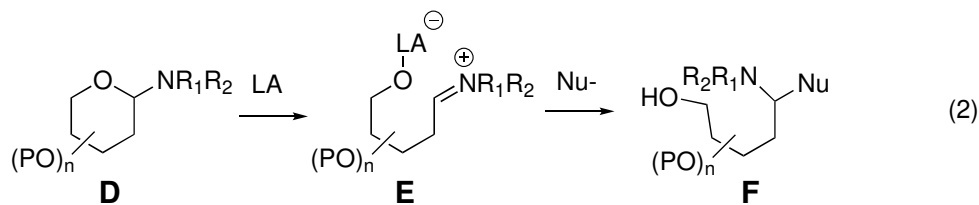
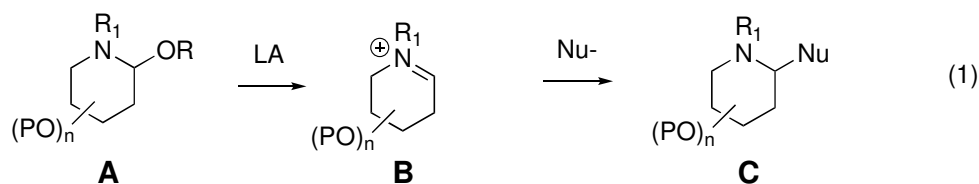
**Keywords:** hemiaminal; iminosugar; skeletal rearrangement; bicycle opening

**Lewis acid-catalysed nucleophilic opening of a bicyclic hemiaminal followed by ring contraction: Access to functionalized L-idonojirimycin derivatives**

*N. Auburger,\* B. Onfroy, N. Fontelle, Q. Foucart, Y. Blériot\**

**Introduction**

Iminosugars, sugars in which the ring oxygen has been substituted for a nitrogen atom, are considered to be one of the most potent classes of glycomimetics.<sup>1,2</sup> These compounds are active towards some carbohydrate processing enzymes by virtue of their analogy with positively charged transition state of the enzyme. Their inhibitory potency has suggested their use in a wide range of potential therapeutic strategies including viral infections,<sup>3,4</sup> cancer,<sup>5</sup> diabetes,<sup>6</sup> lysosomal storage diseases<sup>7</sup> and contraception.<sup>8</sup> The tuning of their biological activities toward a specific function or pathology requires the development of efficient routes both for the synthesis of the iminosugar skeleton and for its subsequent decoration. In this context, introduction of a pseudoanomeric substituent in a stereoselective manner to generate chemically and enzymatically stable iminosugar C-glycosides<sup>9</sup> is one of the available strategies to increase the selectivity and potency of this class of compounds. The group introduced at C-1 mimicks the aglycon moiety of the parent glycoside and generally leads to an increased affinity and specificity toward the targeted enzyme. Amongst the numerous ways to access such derivatives,<sup>10</sup> one consists in exploiting the Lewis acid mediated activation of hemiaminals followed by trapping of the resulting iminium ion with a carbon nucleophile.<sup>11,12</sup> Indeed, in the presence of a Lewis acid, sugar-derived semicyclic N,O-acetals of type **A** provide nitrogen-containing cyclic compounds **C** via cyclic iminium ion intermediates **B** (Scheme 1, eq. 1).<sup>13</sup> When the positions of nitrogen and oxygen of **A** are inverted as in **D**, the reactions proceeds via formation of acyclic iminium ion intermediates **E** to afford ring-opened products **F** that require an extra cyclization step to complete the synthesis (Scheme 1, eq. 2).<sup>14,15,16</sup> Our group<sup>17,18,19,20,21</sup> and colleagues<sup>22,23</sup> have exploited transient bicyclic sugar hemiaminals as iminoglycosyl donors to generate polyhydroxylated azepanes. More recently, we disclosed the introduction of structural diversity at C-1 via the use of Grignard reagents and obtained six- and seven-membered iminosugar C-glycosides displaying aryl or alkyl substituents at the pseudoanomeric position.<sup>24,25</sup> Opening of bicyclic sugar hemiaminals in the presence of a Lewis acids with silylated nucleophiles is scarce<sup>26,27</sup> but might lead to iminosugar scaffolds of interest. Herein, we have studied the reactivity of sugar-derived bicyclic hemiaminal of type **G** to afford seven-membered products **I** via a cyclic iminium ion intermediate **H** (Scheme 1, eq. 3). Furthermore, activation of the resulting free OH in derivative **I** has been performed to access six-membered iminosugar derivatives of type **J** displaying orthogonal functions at C-1 and C-6 available for further derivatization.



**Scheme 1:** Lewis acid-mediated strategies to access iminosugar C-glycosides (eq. 1 and 2) and aim of this work (eq. 3)

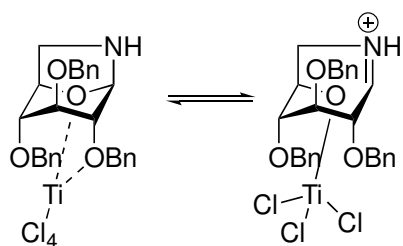
## Results

The starting hemiaminal **1** derived from D-glucopyranose was prepared according to the literature.<sup>24</sup> To define the best ring opening reaction conditions, **1** was first submitted to the Lewis acid-catalyzed reaction with trimethylsilyl cyanide. Introduction of a pseudoanomeric CN group is of interest as it can give access to other functions including amines, amides and acids and they are several examples related to iminosugars in the literature.<sup>28,29,30,31,32</sup> After investigation on the nature and amount of the Lewis acid (Table 1) it was found that TiCl<sub>4</sub> was the best reagent both in terms of yield and diastereoselectivity. One equiv. of TiCl<sub>4</sub> and 5 equiv. of trimethylsilyl cyanide (TMSCN) gave the best results (entry 5) leading to azepane **2a** in 50% isolated yield and with high diastereoselectivity (96:4). Use of other Lewis acids (TMSOTf, BF<sub>3</sub>.OEt<sub>2</sub> and SnCl<sub>4</sub>) did not improve this transformation both in terms of yields and stereoselectivities (entries 7-9).

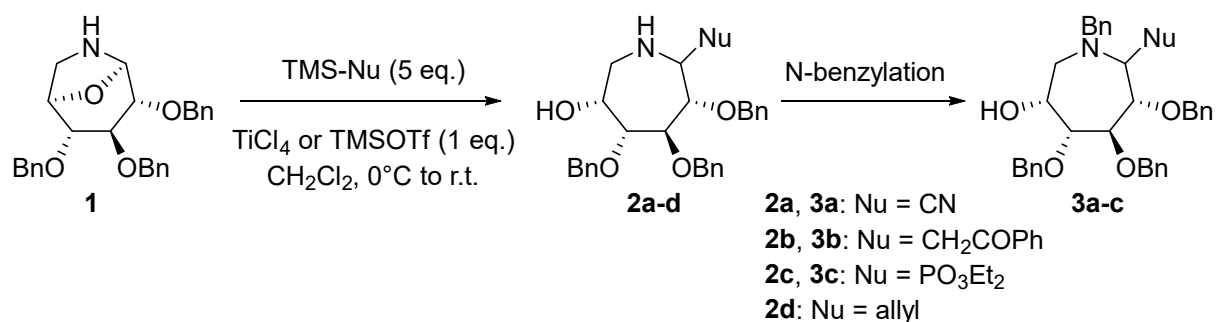
Entry	Lewis acid	Eq.	Eq. TMSCN	Yield
1	TiCl <sub>4</sub>	0.05	2	17%
2	TiCl <sub>4</sub>	0.5	2	24%
3	TiCl <sub>4</sub>	0.5	5	29%
4	TiCl <sub>4</sub>	0.5	10	23%
5	<b>TiCl<sub>4</sub></b>	<b>1</b>	<b>5</b>	<b>50% (96:4)</b>
6	TiCl <sub>4</sub>	2	5	42%
7	TMSOTf	1	5	40% (58:42)
8	BF <sub>3</sub> .OEt <sub>2</sub>	1	5	36% (80:20)
9	SnCl <sub>4</sub>	1	5	0%

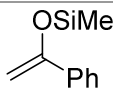
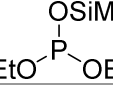
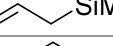
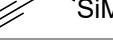
**Table 1:** Lewis-acid mediated pseudoanomeric cyanation of hemiaminal **1**

As a consequence,  $\text{TiCl}_4$  (1 eq.) was selected to both scale up the synthesis of **2a** that was obtained in 66% yield on a gram scale and introduce other silylated nucleophiles at the pseudoanomeric position (Table 2). A couple of other functionalities were next successfully introduced while others failed with the optimized conditions used. With the silyl enol ether of acetophenone, a benzoylmethyl group was appended to yield compound **2b** in 46% yield (entry 3). Through the use of diethyl trimethylsilyl phosphite, it was possible to obtain the protected iminosugar phosphonate **2c** in 42% yield (entry 5).<sup>33</sup> Introduction of unsaturated alkyl chains through the use of allyltrimethylsilane and propargyltrimethylsilane failed as allyl derivative was only obtained in 9% yield while propargyl derivative could not be isolated (entries 7-8). Noteworthy, all successful addition reactions, leading to the formation of a C-C or C-P bond, proceeded with a high degree of stereoselectivity leading to one single or major diastereoisomer. As NMR analysis of these azepanes can be problematic due to their ring flexibility and unusual conformation<sup>34,35,36</sup> the stereochemistries were firmly established by analyzing the NMR coupling constants of the related piperidine compounds obtained after ring contraction (see Scheme 2 for their synthesis and Table 3 for NMR data). All piperidines adopt a  ${}^4C_1$  conformation and display a 1,2 trans relationship (sugar numbering). Purification by flash chromatography of the resulting aminoalcohols proved sometimes difficult. Therefore, chemoselective *N*-benzylation of the crude addition products **2a-c** was performed and furnished compounds **3a-c** (entries 2, 4 and 6). Interestingly, switching to trimethylsilyl triflate (TMSOTf) as the Lewis acid to evaluate the impact of the nature of the Lewis acid on the stereochemical outcome of the reaction, gave much lower diastereoselectivities with the silyl cyanide and the silyl enol ether (entries 9 and 10) while the 1,2 *cis* diastereoisomer of **2c** was preferentially obtained with diethyl trimethylsilyl phosphite (entry 11). A tentative explanation for this result is the strong oxygen chelation ability of  $\text{TiCl}_4$  that could lead to a complex in which the lower face of the hemiaminal or iminium ion is hindered<sup>37</sup> favouring the attack of the nucleophile on the upper face (Figure 1).



**Figure 1:** Tentative explanation for the high diastereoselectivity observed with  $\text{TiCl}_4$  during the Lewis-acid mediated nucleophilic opening of hemiaminal **1**



Entry	Lewis acid	TMS-Nu	Product	Yield	1,2 <i>trans</i> : <i>cis</i> d.r.
1	TiCl <sub>4</sub>	TMSCN	2a	50% <sup>a</sup> 66% <sup>a</sup> (1g)	96:4
2			3a	36% <sup>b</sup>	
3			2b	46% <sup>a</sup>	100:0
4			3b	45% <sup>b</sup>	
5			2c	42% <sup>a</sup>	96:4
6			3c	52% <sup>b</sup>	
7			2d	9% <sup>a</sup>	
8			/	0%	
9	TMSOTf	TMSCN	2a	40% <sup>a</sup>	58 : 42
10			2b	52% <sup>a</sup>	
11		2c	32% <sup>a</sup>	17:83	

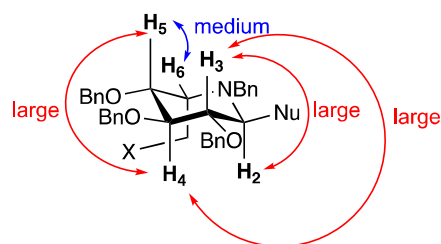
<sup>a</sup> isolated yield of purified unseparable azepane mixture; <sup>b</sup> isolated yield of purified compound after N-benylation of the crude azepane mixture. d.r. were determined by <sup>1</sup>H-NMR of azepane mixtures

**Table 2:** Scope of the opening of bicyclic hemiaminal **1** with silylated nucleophiles

**Table 3:** NMR coupling constants of piperidines **6b-c**, **7a-c**, **9a,c**

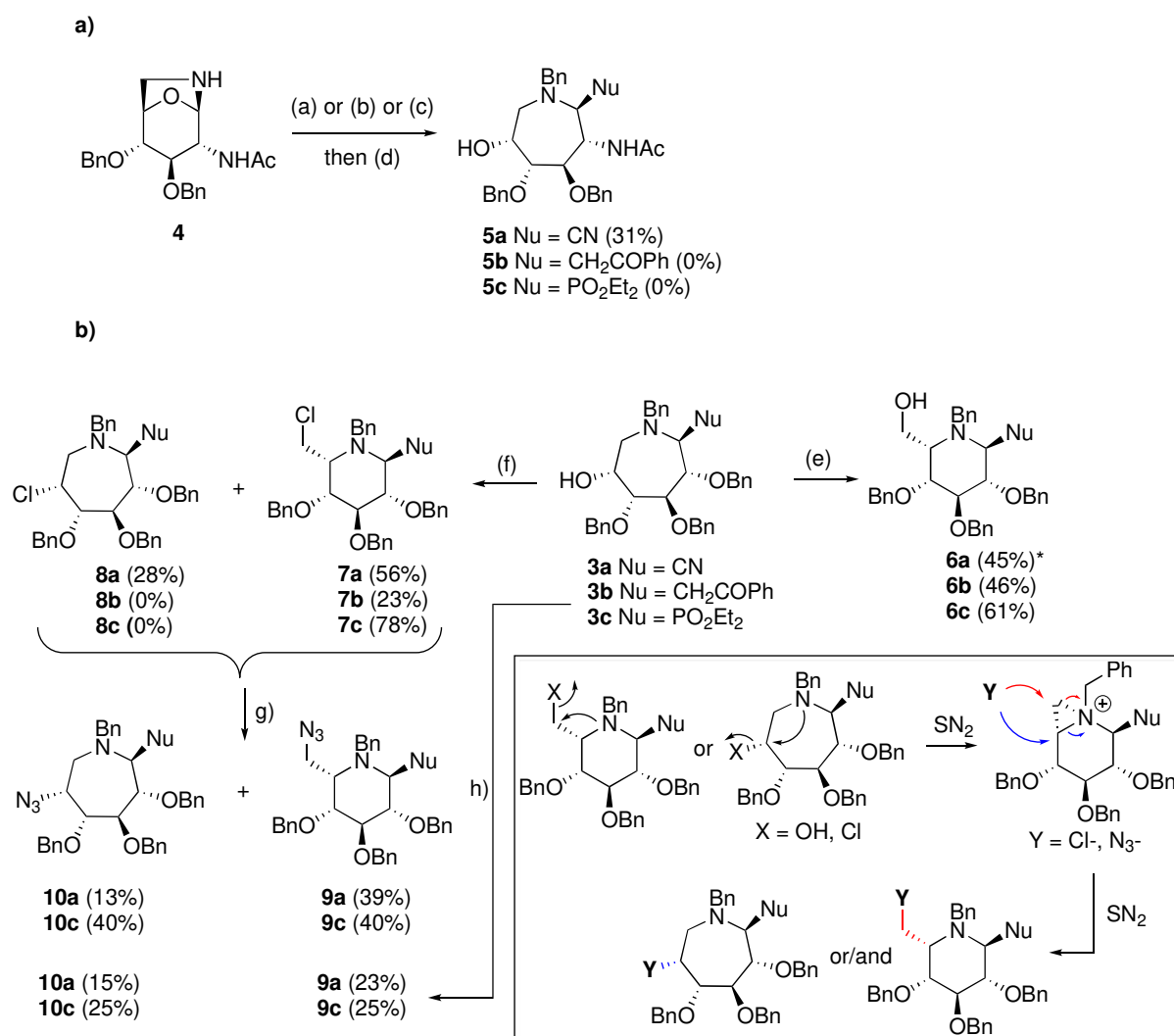
Piperidine	Nu	X	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
6b	CH <sub>2</sub> COPh	OH	ND*	8.0	9.6	6.1
6c	PO <sub>3</sub> Et <sub>2</sub>	OH	10,7	9.1	9.0	ND*
7a	CN	Cl	7.6	7.9	6.3	5.0
7b	CH <sub>2</sub> COPh	Cl	7.7	7.7	8.8	5.5
7c	PO <sub>3</sub> Et <sub>2</sub>	Cl	9.8	8.0	8.7	5.8
9a	CN	N <sub>3</sub>	8.1	7.3	8.6	4.7
9c	PO <sub>3</sub> Et <sub>2</sub>	N <sub>3</sub>	10.0	8.4	8.9	5.7

ND\* : not determined



This reaction was next applied to the recently reported hemiaminal **4** that displays an acetamide group at C-2.<sup>25</sup> While introduction of a nitrile moiety was successful yielding azepane **5a** albeit in low yield (31%) the reactions with trimethylsilyl phosphite and the silyl enol ether of acetophenone led to unstable products that decomposed during purification and that could not be isolated (Scheme 2a).

With the 5-hydroxyazepanes **3a-c** in hand, their ring contraction towards piperidines with concomitant introduction of functional groups at C-6 was next examined (Scheme 2b). Our group<sup>38,39</sup> and others<sup>40,41,42</sup> have reported the anchimeric assistance of the *N*-benzyl group to assist the skeletal rearrangement of sugar-derived seven-membered azacycles triggered by the activation of the leaving group  $\beta$  to the nitrogen atom to provide polysubstituted piperidines. This transformation can be coupled to the introduction of a new function replacing the leaving group with overall retention of configuration, the result of two successive  $S_N2$  reactions. To this end, treatment of azepanes **3a-c** with trifluoroacetic anhydride (TFAA; 1.5 eq.) and triethylamine ( $Et_3N$ , 2 eq.) in toluene furnished the corresponding L-configured hydroxymethylpiperidines **6a-c** in satisfactory yields (46-61%) after ester hydrolysis along with recovered starting material resulting from the attack of the nucleophile at the methine carbon of the transient fused piperidine-aziridinium ion. In parallel, reaction of azepanes **3a-c** with mesyl chloride ( $MsCl$ , 1.5 eq.) and  $Et_3N$  (2 eq.) at 0°C in dichloromethane furnished an inseparable mixture (84% yield) of the chloromethylpiperidine **7a** and the chloroazepane **8a** in a 2:1 ratio, while only the chloromethylpiperidine **7b** (23%) and the chloromethylpiperidine **7c** (78%) could be respectively isolated from the reaction mixture with no trace of the corresponding azepanes **8b** and **8c**. The low yield obtained for **7b** can be explained by the poor chemical stability of this derivative that partially decomposed during chromatography purification. Further treatment of the mixture of azepane **8a** and piperidine **7a** with  $NaN_3$  in DMF at 80°C overnight provided the major six-membered and minor seven-membered azidonitriles **9a** and **10a** in 52% yield and in a 3:1 ratio. Under the same reaction conditions, chloromethylpiperidine **7c** furnished an inseparable mixture of the six- and seven-membered azidophosphonates **9c** and **10c** respectively in 81% yield in a 1:1 ratio. These compounds were in parallel directly obtained from azepanes **3a** and **3c** by treatment with diphenylphosphorazide ( $dppa$ , 2 eq.), triphenylphosphine ( $PPh_3$ , 2 eq.) and diethylazodicarboxylate (DEAD, 1.6 eq.) in THF albeit in modest yield.



(a) TMSCN, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to r.t.; (b) CH<sub>2</sub>C(OSiMe<sub>3</sub>)Ph, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to r.t.; (c) P(OEt)<sub>2</sub>(OSiMe<sub>3</sub>), TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to r.t.; (d) BnBr, K<sub>2</sub>CO<sub>3</sub>, KI cat., THF; (e) TFAA, NEt<sub>3</sub>, toluene, reflux then 15% NaOH; (f) MsCl, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to r.t.; (g) NaN<sub>3</sub>, DMF, 80°C; (h) dppa, PPh<sub>3</sub>, DEAD, THF.

\* piperidine **6a** and azepane **3a** could not be separated by column chromatography; the indicated yield is therefore based on NMR analysis of the crude piperidine-azepane mixture.

## Scheme 2: Ring isomerization of azepanes **3a-c** to furnish piperidines **6a-c**, **7a-c** and **9a,c**

In conclusion, we have exploited the in house bicyclic hemiaminal **1** and its TiCl<sub>4</sub>-promoted ring opening to introduce new functionalities, namely CN, CH<sub>2</sub>COPh and PO<sub>3</sub>Et<sub>2</sub>, on the ring of tetrahydroxylated azepanes. The reaction proceeds in satisfactory yield and high 1,2 trans diastereoselectivity. These derivatives were further converted into the corresponding piperidines through a skeletal rearrangement that takes place with overall retention of configuration and that allowed concomitant introduction of an additional functional group at C-6 position. The resulting piperidine derivatives **6a-c**,



**7a-c, 9a and 9c** constitute useful precursors to introduce structural diversity at the C-1 and C-6 positions of L-idonojirimycin, an iminosugar with biological potential.<sup>43,44</sup>

## Experimental section

### General information

All commercial reagents and solvents were used as supplied. Air and water sensitive reactions were performed in dried glassware under Ar atmosphere. TLC plates (Merck silica gel 60 F<sub>254</sub>) were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 3 g of phosphomolybdic acid in 100 mL of ethanol followed by heating with a heat gun. After washing steps, organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Flash chromatography columns were performed using Macherey-Nagel silica gel 60 (15–40 μm). NMR experiments were recorded with a Bruker AM-400 spectrometer at 400 MHz for <sup>1</sup>H nuclei, at 100 MHz for <sup>13</sup>C nuclei and at 162 MHz for <sup>31</sup>P nuclei. The chemical shifts are expressed in part per million (ppm) using residual CHCl<sub>3</sub> signal as internal reference ( $\delta(^1\text{H})=7.26$  ppm and  $\delta(^{13}\text{C})=77.16$  ppm) and H<sub>3</sub>PO<sub>4</sub> signal as external reference ( $\delta(^{31}\text{P})=0.00$  ppm). The coupling constant values (J) are given in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: b=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet. HRMS were obtained with a Bruker LC-QTOF MaXis Impact spectrometer. Optical rotations were measured at 20°C using an Anton Paar MCP100 polarimeter. Compounds names and numbering in the experimental section are given according to IUPAC nomenclature.

### General procedure A for nucleophilic opening of bicyclic hemiaminal

To a solution of hemiaminal in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) at 0°C was added the silylated nucleophile (5.0 eq.) followed by 1M TiCl<sub>4</sub> solution in CH<sub>2</sub>Cl<sub>2</sub> (1.0 eq.). The reaction mixture was stirred for 2h at 0°C and for 5h at r.t. The reaction was quenched by addition of aqueous saturated NaHCO<sub>3</sub> solution at 0°C. The organic phase was washed with water and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>.

### General procedure B for hydroxyazepane ring contraction

To a solution of hydroxyazepane in anhydrous toluene (0.1 M) were added Et<sub>3</sub>N (2.0 eq.) and TFAA (1.5 eq.) at 0°C. The solution was stirred for 5h at reflux. After cooling at r.t., aqueous 15% NaOH solution was added and the mixture was stirred at r.t. for 1h. The organic phase was washed with water and the aqueous phase was extracted with EtOAc.

### General procedure C for hydroxyazepane chlorination

To a solution of hydroxyazepane in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.07 M) were added Et<sub>3</sub>N (2.0 eq.) and MsCl (1.5 eq.) at 0°C. After stirring at 0°C for 3h and at r.t. for 2h, the solvent was removed under reduced pressure.

## General procedure D for azidation of chloromethylpiperidine/chloroazepane

To a solution of chloromethylpiperidine/chloroazepane in anhydrous DMF (0.1M) was added  $\text{NaN}_3$  (2.0 eq.). The solution was stirred overnight at  $80^\circ\text{C}$ .  $\text{H}_2\text{O}$  was added and the aqueous phase was extracted with  $\text{Et}_2\text{O}$ .

### (2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-hydroxyazepane-2-carbonitrile **2a**

Following general procedure A, bicyclic hemiaminal **1** (1 g, 2.3 mmol) was treated with TMSCN (1.4 mL, 11.5 mmol). Azepane **2a** was obtained (flash chromatography PE:EtOAc 5:5) as a light yellow oil (705 mg, 50%):  $[\alpha]_{\text{D}}^{20} +13$  (*c* 0.1,  $\text{CHCl}_3$ );  $R_f$  0.45 (PE:EtOAc 5:5);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.41-7.25 (m, 15H, H-ar), 4.75, 4.50 (2d, 2H,  $^2J$  11.2 Hz,  $\text{CH}_2\text{Ph}$ ), 4.66, 4.63 (ABq, 2H,  $J_{\text{AB}}$  11.2 Hz,  $\text{CH}_2\text{Ph}$ ), 4.58, 4.54 (ABq, 2H,  $J_{\text{AB}}$  11.7 Hz,  $\text{CH}_2\text{Ph}$ ), 4.13 (d, 1H,  $J_{2,3}$  9.0 Hz, H-2), 4.01-3.97 (m, 1H, H-6), 3.99 (dd, 1H,  $J_{4,3}$  3.0,  $J_{4,5}$  7.0 Hz, H-4), 3.90 (dd, 1H,  $J_{5,4}$  7.0,  $J_{5,6}$  2.1 Hz, H-5), 3.76 (dd, 1H,  $J_{3,2}$  9.0,  $J_{3,4}$  3.0 Hz, H-3), 3.10 (dd, 1H,  $J_{7a,6}$  4.3,  $J_{7a,7b}$  14.2 Hz, H-7a), 2.89 (dd, 1H,  $J_{7b,6}$  8.8,  $J_{7b,7a}$  14.2 Hz, H-7b);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  137.7, 137.5, 137.0 (Cq-ar), 128.7, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0 (C-ar), 119.8 (CN), 82.6 (C-3), 82.0 (C-5), 78.7 (C-4), 74.0, 73.5, 73.4 (3x $\text{CH}_2\text{Ph}$ ), 69.6 (C-6), 52.5 (C-2), 49.6 (C-7); HR-ESI-MS positive mode (*m/z*): calcd. for  $\text{C}_{28}\text{H}_{30}\text{N}_2\text{NaO}_4$  [ $\text{M}+\text{Na}$ ] $^+$ : 481.2098; found: 481.2110.

### 2-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-hydroxyazepan-2-yl)-1-phenylethan-1-one **2b**

Following general procedure A, bicyclic hemiaminal **1** (100 mg, 0.23 mmol) was treated with 1-phenyl-1-trimethylsiloxyethylene (240  $\mu\text{L}$ , 1.15 mmol). Azepane **2b** was obtained (flash chromatography PE:EtOAc 15:85) as a yellow oil (58.7 mg, 46%):  $[\alpha]_{\text{D}}^{20} -12$  (*c* 0.1,  $\text{CHCl}_3$ );  $R_f$  0.35 (PE:EtOAc 15:85);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.86 (dd, 2H,  $J_{o,m}$  8.3,  $J_{o,p}$  1.2 Hz, H-ortho PhCO), 7.53 (tt, 1H,  $J_{p,m}$  7.4,  $J_{p,o}$  1.2 Hz, H-para PhCO), 7.39 (dd, 2H,  $J_{m,o}$  8.3,  $J_{m,p}$  7.4 Hz, H-meta PhCO), 7.35-7.23 (m, 15H, H-ar), 4.74, 4.53 (2d, 2H,  $^2J$  11.4 Hz,  $\text{CH}_2\text{Ph}$ ), 4.65, 4.44 (2d, 2H,  $^2J$  11.5 Hz,  $\text{CH}_2\text{Ph}$ ), 4.64, 4.61 (ABq, 2H,  $J_{\text{AB}}$  12.3 Hz,  $\text{CH}_2\text{Ph}$ ), 4.08-4.02 (m, 2H, H-4, H-6), 3.93 (dd, 1H,  $^3J$  6.6,  $^3J$  2.2 Hz, H-5), 3.65-3.57 (m, 2H, H-2, H-3), 3.37 (dd, 1H,  $^2J$  16.2,  $J_{\text{CHCO},2}$  3.8 Hz, CHCO), 3.06 (dd, 1H,  $J_{7a,6}$  4.4,  $J_{7a,7b}$  13.8 Hz, H-7a), 2.94-2.85 (m, 1H, CHCO), 2.85 (dd, 1H,  $J_{7b,6}$  8.8,  $J_{7b,7a}$  13.8 Hz, H-7b);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  199.2 (CO), 138.2, 138.0, 137.8, 136.9 (Cq-ar), 133.0 (C-para PhCO), 128.5, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.7 (C-ar), 84.2 (C-3), 83.0 (C-5), 79.5 (C-4), 73.0, 72.9, 72.8 (3x $\text{CH}_2\text{Ph}$ ), 70.3 (C-6), 57.0 (C-2), 50.1 (C-7), 41.9 ( $\text{CH}_2\text{CO}$ ); HR-ESI-MS positive mode (*m/z*): calcd. for  $\text{C}_{35}\text{H}_{38}\text{NO}_5$  [ $\text{M}+\text{H}$ ] $^+$ : 552.2744; found: 552.2753.

### Diethyl ((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-hydroxyazepan-2-yl) phosphonate **2c**

Following general procedure A, bicyclic hemiaminal **1** (100 mg, 0.23 mmol) was treated with diethyl trimethylsilyl phosphite (270  $\mu\text{L}$ , 1.15 mmol). Azepane **2c** was obtained (flash chromatography EtOAc 100%) as a colorless oil (56.4 mg, 42%):  $[\alpha]_{\text{D}}^{20} -20$  (*c* 0.15,  $\text{CHCl}_3$ );  $R_f$  0.5 (EtOAc);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.38-7.20 (m, 15H, H-ar), 4.76, 4.39

(2d, 2H,  $^2J$  11.1 Hz, CH<sub>2</sub>Ph), 4.65, 4.57 (2d, 2H,  $^2J$  11.0 Hz, CH<sub>2</sub>Ph), 4.64, 4.54 (2d, 2H,  $^2J$  11.8 Hz, CH<sub>2</sub>Ph), 4.20-4.01 (m, 6H, 2xOCH<sub>2</sub>CH<sub>3</sub>, H-4, H-6), 3.96 (dd, 1H,  $^3J$  7.4,  $^3J$  2.7 Hz, H-5), 3.92 (ddd, 1H,  $J_{3,2}$  9.4,  $J_{3,4}$  2.8,  $J_{H,P}$  13.7 Hz, H-3), 3.43 (dd, 1H,  $J_{2,3}$  9.4,  $J_{H,P}$  18.7 Hz, H-2), 3.24 (dd, 1H,  $J_{7a,6}$  5.1,  $J_{7a,7b}$  13.8 Hz, H-7a), 2.76 (dd, 1H,  $J_{7b,6}$  9.8,  $J_{7b,7a}$  13.8 Hz, H-7b), 2.33 (bd, 1H,  $J_{OH,6}$  7.4 Hz, OH), 1.31-1.24 (m, 6H, 2xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 138.2, 138.1, 137.8 (Cq-ar), 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6 (C-ar), 81.6 (C-5), 81.4 (d,  $J_{C,P}$  3.8 Hz, C-3), 78.0 (d,  $J_{C,P}$  14.6 Hz, C-4), 73.1, 73.1, 72.9 (3xCH<sub>2</sub>Ph), 70.0 (C-6), 63.1, 62.0 (2d,  $J_{C,P}$  6.9 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 59.1 (d,  $J_{C,P}$  156.8 Hz, C-2), 52.0 (d,  $J_{C,P}$  14.5 Hz, C-7), 16.5, 16.5 (2d,  $J_{C,P}$  6.3 Hz, 2xCH<sub>3</sub>); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz): δ 26.4; HR-ESI-MS positive mode (m/z): calcd. for C<sub>31</sub>H<sub>41</sub>NO<sub>7</sub>P [M+H]<sup>+</sup>: 570.2615; found: 570.2636.

### **(2*S*,3*S*,4*R*,5*R*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-hydroxyazepane-2-carbonitrile 3a**

Following general procedure A, bicyclic hemiaminal **1** (500 mg, 1.16 mmol) was treated with TMSCN (0.7 mL, 5.8 mmol). To a solution of crude azepane **2a** in anhydrous THF (15 mL) were added K<sub>2</sub>CO<sub>3</sub> (320 mg, 2.3 mmol, 2 eq.), KI (34 mg, cat.) and BnBr (0.22 mL, 1.8 mmol, 1.5 eq.). The reaction mixture was stirred for 72h at 70°C. Filtration over Dicalite, concentration under reduced pressure and purification by flash chromatography (PE:EtOAc 85:15) afforded azepane **3a** as a light yellow oil (230 mg, 36% over two steps): [ $\alpha$ ]<sub>D</sub><sup>20</sup> +9 (*c* 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.35 (PE:EtOAc 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.41-7.28 (m, 18H, H-ar), 7.17-7.13 (m, 2H, H-ar), 4.75, 4.67 (2d, 2H,  $^2J$  11.5 Hz, OCH<sub>2</sub>Ph), 4.66, 4.62 (2d, 2H,  $^2J$  11.8 Hz, OCH<sub>2</sub>Ph), 4.39 (s, 2H, OCH<sub>2</sub>Ph), 4.10-4.04 (m, 1H, H-6), 4.06 (dd, 1H,  $J_{4,3}$  3.5,  $J_{4,5}$  7.2 Hz, H-4), 4.00 (d, 1H,  $J_{2,3}$  7.0 Hz, H-2), 3.89 (dd, 1H,  $J_{5,4}$  7.2,  $J_{5,6}$  5.2 Hz, H-5), 3.88, 3.75 (2d, 2H,  $^2J$  13.3 Hz, NCH<sub>2</sub>Ph), 3.71 (dd, 1H,  $J_{3,2}$  7.0,  $J_{3,4}$  3.5 Hz, H-3), 3.32 (d, 1H,  $J_{OH,6}$  9.8 Hz, OH), 3.09 (dd, 1H,  $J_{7a,6}$  6.7,  $J_{7a,7b}$  13.6 Hz, H-7a), 2.90 (dd, 1H,  $J_{7b,6}$  2.0,  $J_{7b,7a}$  13.6 Hz, H-7b); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 138.1, 138.0, 136.9, 136.5 (Cq-ar), 129.4, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8 (C-ar), 115.7 (CN), 84.9 (C-5), 81.9 (C-4), 78.8 (C-3), 73.7, 73.3, 72.9 (3xOCH<sub>2</sub>Ph), 68.9 (C-6), 59.8 (NCH<sub>2</sub>Ph), 54.9 (C-7), 54.6 (C-2); HR-ESI-MS positive mode (m/z): calcd. for C<sub>35</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 571.2567; found: 571.2572.

### **2-((2*S*,3*S*,4*R*,5*R*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-hydroxyazepan-2-yl)-1-phenylethan-1-one 3b**

Following general procedure A, bicyclic hemiaminal **1** (200 mg, 0.46 mmol) was treated with 1-phenyl-1-trimethylsiloxyethylene (480 μL, 2.3 mmol). To a solution of crude azepane **2b** in anhydrous DMF (10 mL) were added K<sub>2</sub>CO<sub>3</sub> (150 mg, 1.1 mmol, 2.3 eq.) and BnBr (65 μL, 0.58 mmol, 1.25 eq.). The reaction mixture was stirred at r.t. overnight, diluted with water and extracted with Et<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash chromatography (PE:EtOAc 8:2) afforded azepane **3b** as a yellow oil (134 mg, 45% over two steps): [ $\alpha$ ]<sub>D</sub><sup>20</sup> -4 (*c* 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.4 (PE:EtOAc 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.94-7.90 (m, 2H, H-ortho PhCO), 7.61-7.55 (tt, 1H,  $J_{p,m}$  7.4,  $J_{p,o}$  1.2 Hz, H-para PhCO), 7.47-7.14 (m, 27H, H-

ar), 4.77, 4.71 (ABq, 2H,  $J_{AB}$  11.7 Hz, OCH<sub>2</sub>Ph), 4.58, 4.53 (ABq, 2H,  $J_{AB}$  11.5 Hz, OCH<sub>2</sub>Ph), 4.54, 4.51 (ABq, 2H,  $J_{AB}$  11.5 Hz, OCH<sub>2</sub>Ph), 4.25-4.17 (m, 1H, H-2), 4.17-4.12 (m, 1H, H-6), 4.16 (dd, 1H,  $J_{4,3}$  1.9,  $J_{4,5}$  6.6 Hz, H-4), 3.93 (dd, 1H,  $J_{5,4}$  6.6,  $J_{5,6}$  1.4 Hz, H-5), 3.92, 3.82 (2d, 2H,  $^2J$  13.9 Hz, NCH<sub>2</sub>Ph), 3.86 (dd, 1H,  $J_{3,2}$  6.9,  $J_{3,4}$  1.9 Hz, H-3), 3.51 (dd, 1H,  $^2J$  16.5,  $J_{CHCO,2}$  8.2 Hz, CHCO), 3.14 (dd, 1H,  $^2J$  16.5,  $J_{CHCO,2}$  5.2 Hz, CHCO), 2.99 (dd, 1H,  $J_{7a,6}$  7.5,  $J_{7a,7b}$  13.5 Hz, H-7a), 2.85 (dd, 1H,  $J_{7b,6}$  2.1,  $J_{7b,7a}$  13.5 Hz, H-7b); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 199.0 (CO), 139.3, 138.4, 137.8, 137.6, 137.1 (Cq-ar), 132.9 (C-para PhCO), 128.8, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.9, 127.9, 127.8, 127.6, 127.6, 127.1 (C-ar), 85.8 (C-5), 83.6 (C-4), 79.6 (C-3), 72.9, 72.3, 71.5 (3xOCH<sub>2</sub>Ph), 68.9 (C-6), 58.0 (NCH<sub>2</sub>Ph), 57.9 (C-2), 53.5 (C-7), 34.9 (CH<sub>2</sub>CO); HR-ESI-MS positive mode (m/z): calcd. for C<sub>42</sub>H<sub>44</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 642.3214; found: 642.3225.

### Diethyl ((2*S*,3*R*,4*S*,5*R*,6*R*)-1-benzyl-3,4,5-tris(benzyloxy)-6-hydroxyazepan-2-yl)phosphonate **3c**

Following general procedure A, bicyclic hemiaminal **1** (300 mg, 0.7 mmol) was treated with diethyl trimethylsilyl phosphite (0.8 mL, 3.5 mmol). To a solution of crude azepane **2c** in anhydrous THF (7 mL) were added K<sub>2</sub>CO<sub>3</sub> (192 mg, 1.4 mmol, 2 eq.), KI (8 mg, cat.) and BnBr (100 μL, 0.83 mmol, 1.2 eq.). The reaction mixture was stirred for 48h at 70°C. Filtration over Dicalite, concentration under reduced pressure and purification by flash chromatography (PE:EtOAc 6:4) afforded azepane **3c** as a colorless oil (240 mg, 52% over two steps): [α]<sub>D</sub><sup>20</sup> +11 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.75 (EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.45-7.41 (m, 2H, H-ar), 7.38-7.24 (m, 18H, H-ar), 4.86, 4.64 (2d, 2H,  $^2J$  11.5 Hz, OCH<sub>2</sub>Ph), 4.79, 4.71 (2d, 2H,  $^2J$  11.2 Hz, OCH<sub>2</sub>Ph), 4.68, 4.63 (ABq, 2H,  $J_{AB}$  10.8 Hz, OCH<sub>2</sub>Ph), 4.29 (dd, 1H,  $^3J$  6.6,  $^3J$  5.2 Hz, H-4), 4.23-3.99 (m, 9H, 2xOCH<sub>2</sub>CH<sub>3</sub>, NCH<sub>2</sub>Ph, H-3, H-5, H-6), 3.70 (dd, 1H,  $J_{2,3}$  7.1,  $J_{H,P}$  19.9 Hz, H-2), 3.17 (ddd, 1H,  $J_{7a,6}$  3.6,  $J_{7a,7b}$  13.3,  $J_{H,P}$  3.6 Hz, H-7a), 2.88 (dd, 1H,  $J_{7b,6}$  8.5,  $J_{7b,7a}$  13.3 Hz, H-7b), 1.34, 1.23 (2t, 6H,  $J_{CH_3,CH_2}$  7.1 Hz, 2xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 139.2, 138.5, 138.4, 138.2 (Cq-ar), 129.1, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.2 (C-ar), 83.6 (C-5), 81.63 (C-4), 80.3 (d,  $J_{C,P}$  12.0 Hz, C-3), 73.8, 73.3, 73.1 (3xOCH<sub>2</sub>Ph), 68.3 (C-6), 62.1 (d,  $J_{C,P}$  139.3 Hz, C-2), 61.8, 61.6 (2d,  $J_{C,P}$  7.3 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 58.5 (NCH<sub>2</sub>Ph), 53.3 (d,  $J_{C,P}$  8.0 Hz, C-7), 16.6, 16.4 (2d,  $J_{C,P}$  5.9 Hz, 2xCH<sub>3</sub>); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz): δ 26.8; HR-ESI-MS positive mode (m/z): calcd. for C<sub>38</sub>H<sub>46</sub>NNaO<sub>7</sub>P [M+Na]<sup>+</sup>: 682.2904; found: 682.2901.

### *N*-((2*R*,3*S*,4*R*,5*R*,6*R*)-1-Benzyl-4,5-bis(benzyloxy)-2-cyano-6-hydroxyazepan-3-yl)acetamide **5a**

Following general procedure A, bicyclic hemiaminal **4** (93 mg, 0.24 mmol) was treated with TMSCN (0.15 mL, 1.2 mmol). To a solution of crude azepane in anhydrous THF (3 mL) were added K<sub>2</sub>CO<sub>3</sub> (67 mg, 0.48 mmol, 2 eq.), KI (12 mg, cat.) and BnBr (44 μL, 0.36 mmol, 1.5 eq.). The reaction mixture was stirred for 15h at r.t. Filtration over Dicalite, concentration under reduced pressure and purification by flash chromatography (PE to PE:EtOAc 5:5) afforded azepane **5a** as a yellow oil (38 mg, 31% over two steps): [α]<sub>D</sub><sup>20</sup> -1 (c 2.9, CHCl<sub>3</sub>); R<sub>f</sub> 0.30 (PE:EtOAc 6:4); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.39-7.23 (m, 15H, H-

ar), 7.14 (d, 1H,  $J_{\text{NH},3}$  9.7 Hz, NH), 4.88 (d, 1H,  $^2J$  12.0 Hz, OCHPh), 4.63, 4.59 (ABq, 2H,  $J_{\text{AB}}$  11.2 Hz, OCH<sub>2</sub>Ph), 4.58-4.54 (m, 1H, H-3), 4.56 (d, 1H,  $^2J$  12.0 Hz, OCHPh), 4.23-4.18 (m, 1H, H-6), 3.97 (dd, 1H,  $J_{5,4}$  6.5,  $J_{5,6}$  1.6 Hz, H-5), 3.81 (d, 1H,  $J_{2,3}$  5.8 Hz, H-2), 3.80 (d, 1H,  $^2J$  13.3 Hz, NCHPh), 3.70 (dd, 1H,  $J_{4,3}$  1.1,  $J_{4,5}$  6.5 Hz, H-4), 3.60 (d, 1H,  $^2J$  13.3 Hz, NCHPh), 3.12 (dd, 1H,  $J_{7a,6}$  6.1,  $J_{7a,7b}$  13.3 Hz, H-7a), 2.97 (bd, 1H,  $J_{7b,7a}$  13.3 Hz, H-7b), 2.88-2.70 (m, 1H, OH), 1.83 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.7 (CONH), 137.9, 137.8, 136.8 (C<sub>q</sub>-ar), 129.1, 128.9, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.7 (C-ar), 114.8 (CN), 85.1 (C-5), 83.5 (C-4), 73.9, 72.0 (2xOCH<sub>2</sub>Ph), 70.1 (C-6), 61.4 (NCH<sub>2</sub>Ph), 55.0 (C-7), 53.0 (C-2), 49.7 (C-3), 23.3 (CH<sub>3</sub>); HR-ESI-MS positive mode (m/z): calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 500.2544; found: 500.2557.

### **2-((2S,3S,4R,5R,6S)-1-Benzyl-3,4,5-tris(benzyloxy)-6-(hydroxymethyl)piperidin-2-yl)-1-phenylethan-1-one 6b**

Following general procedure B, hydroxyazepane **3b** (120 mg, 0.19 mmol) was converted to hydroxypiperidine **6b**. Purification by flash chromatography (PE:EtOAc 8:2) afforded **6b** as a light brown oil (55 mg, 46%): [ $\alpha$ ]<sub>D</sub><sup>20</sup> -74 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.33 (PE:EtOAc 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.77-7.73 (m, 2H, H-ortho PhCO), 7.56-7.50 (bt, 1H,  $J_{p,m}$  7.4 Hz, H-para PhCO), 7.43-7.27 (m, 17H, H-ar), 7.18-7.12 (m, 2H, H-ar), 7.11-7.05 (m, 1H, H-ar), 7.03-6.99 (m, 2H, H-ar), 5.02, 4.70 (2d, 2H,  $^2J$  11.4 Hz, OCH<sub>2</sub>Ph), 4.99, 4.85 (2d, 2H,  $^2J$  10.7 Hz, OCH<sub>2</sub>Ph), 4.59 (s, 2H, OCH<sub>2</sub>Ph), 4.01 (dd, 1H,  $J_{5,4}$  6.1,  $J_{5,6}$  9.6 Hz, H-5), 3.93 (d, 1H,  $^2J$  13.7 Hz, NCHPh), 3.92-3.85 (m, 1H, H-7a), 3.86 (dd, 1H,  $J_{4,3}$  9.6,  $J_{4,5}$  8.0 Hz, H-4), 3.77-3.63 (m, 3H, H-2, H-3, H-7b), 3.48 (d, 1H,  $^2J$  13.7 Hz, NCHPh), 3.31 (dd, 1H,  $^2J$  17.3,  $J_{\text{CHCO},2}$  3.0 Hz, CHCO), 3.24-3.16 (m, 2H, H-6, OH), 3.01 (dd, 1H,  $^2J$  17.3,  $J_{\text{CHCO},2}$  10.1 Hz, CHCO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  198.4 (CO), 138.8, 138.7, 138.2, 137.9, 136.8 (C<sub>q</sub>-ar), 133.3 (C-para PhCO), 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.3 (C-ar), 85.2 (C-4), 78.5 (C-3), 77.4 (C-5), 76.0, 75.4, 72.8 (3xOCH<sub>2</sub>Ph), 57.9 (C-6), 57.1 (C-7), 52.2 (C-2), 51.2 (NCH<sub>2</sub>Ph), 37.1 (CH<sub>2</sub>CO); HR-ESI-MS positive mode (m/z): calcd. for C<sub>42</sub>H<sub>44</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 642.3214; found: 642.3234.

### **Diethyl ((2S,3R,4S,5R,6S)-1-benzyl-3,4,5-tris(benzyloxy)-6-(hydroxymethyl)piperidin-2-yl) phosphonate 6c**

Following general procedure B, hydroxyazepane **3c** (560 mg, 0.85 mmol) was converted to hydroxypiperidine **6c**. Purification by flash chromatography (PE:EtOAc 6:4) afforded **6c** as a yellow oil (345 mg, 61%): [ $\alpha$ ]<sub>D</sub><sup>20</sup> -2 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.85 (PE:EtOAc 6:4); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.44-7.24 (m, 20H, H-ar), 5.03, 4.94 (2d, 2H,  $^2J$  10.5 Hz, OCH<sub>2</sub>Ph), 4.95, 4.87 (2d, 2H,  $^2J$  10.7 Hz, OCH<sub>2</sub>Ph), 4.64, 4.58 (ABq, 2H,  $J_{\text{AB}}$  11.6 Hz, OCH<sub>2</sub>Ph), 4.46 (d, 1H,  $^2J$  13.4 Hz, NCHPh), 4.24-3.89 (m, 6H, 2xOCH<sub>2</sub>CH<sub>3</sub>, H-3, H-5), 3.85 (dd, 1H,  $^3J$  9.1,  $^3J$  9.0 Hz, H-4), 3.73 (d, 1H,  $^2J$  13.4 Hz, NCHPh), 3.74-3.65 (m, 2H, H-7), 3.43 (dd, 1H,  $J_{2,3}$  10.7 Hz,  $J_{\text{H,P}}$  23.2 Hz, H-2), 3.23-3.13 (m, 1H, H-6), 1.37, 1.18 (2t, 6H,  $J_{\text{CH}_3,\text{CH}_2}$  7.1 Hz, 2xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  138.5, 138.4, 138.4, 137.7 (C<sub>q</sub>-ar), 128.8, 128.7, 128.6, 128.6, 128.3, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7 (C-ar), 85.0 (d,  $J_{\text{C,P}}$  7.0 Hz, C-4), 76.5 (C-3), 76.2 (d,  $J_{\text{C,P}}$  1.3 Hz, C-5), 75.9, 75.2, 73.2 (3xOCH<sub>2</sub>Ph), 62.3, 62.0 (2d,

$J_{C,P}$  7.0 Hz,  $2 \times OCH_2CH_3$ ), 57.2 (C-7), 56.8 (d,  $J_{C,P}$  14.5 Hz, C-6), 55.6 (d,  $J_{C,P}$  159.9 Hz, C-2), 54.2 (NCH<sub>2</sub>Ph), 16.5, 16.3 (2d,  $J_{C,P}$  6.3 Hz,  $2 \times CH_3$ ); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz):  $\delta$  24.2; HR-ESI-MS positive mode (m/z): calcd. for C<sub>38</sub>H<sub>46</sub>NNaO<sub>7</sub>P [M+Na]<sup>+</sup>: 682.2904; found: 682.2900.

**(2S,3S,4R,5R,6R)-1-Benzyl-3,4,5-tris(benzyloxy)-6-(chloromethyl)piperidine-2-carbonitrile 7a and (2S,3S,4R,5S,6R)-1-Benzyl-3,4,5-tris(benzyloxy)-6-chloroazepane-2-carbonitrile 8a**

Chlorination of hydroxyazepane **3a** (111 mg, 0.20 mmol) was carried out according to general procedure C. Purification by flash chromatography (PE:EtOAc 95:5) afforded a 2:1 mixture of chloromethylpiperidine **7a** and chloroazepane **8a** (97 mg, 84%). A small fraction of each compound was isolated for analysis. **7a**: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -7 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.49 (PE:EtOAc 95:5); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.39-7.22 (m, 20H, H-ar), 4.76, 4.70 (ABq, 2H,  $J_{AB}$  11.2 Hz, OCH<sub>2</sub>Ph), 4.73, 4.67 (ABq, 2H,  $J_{AB}$  11.0 Hz, OCH<sub>2</sub>Ph), 4.59, 4.52 (ABq, 2H,  $J_{AB}$  11.5 Hz, OCH<sub>2</sub>Ph), 4.17, 4.04 (2d, 2H, <sup>2</sup>J 13.5 Hz, NCH<sub>2</sub>Ph), 4.02 (d, 1H,  $J_{2,3}$  7.6 Hz, H-2), 3.84 (m, 3H, H-3, H-5, H-7a), 3.72 (dd, 1H, <sup>3</sup>J 7.9, <sup>3</sup>J 6.3 Hz, H-4), 3.65 (dd, 1H,  $J_{7b,6}$  6.6,  $J_{7b,7a}$  11.8 Hz, H-7b), 3.33 (ddd, 1H,  $J_{6,7b}$  6.6, <sup>3</sup>J 5.1, <sup>3</sup>J 5.0 Hz, H-6); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  138.0, 137.6, 137.2, 137.1 (Cq-ar), 128.9, 128.7, 128.7, 128.6, 128.6, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9 (C-ar), 117.6 (CN), 79.2 (C-4), 78.3 (C-3), 76.6 (C-5), 74.7, 73.2 (3xOCH<sub>2</sub>Ph), 58.2 (C-6), 55.3 (NCH<sub>2</sub>Ph), 52.3 (C-2), 40.2 (C-7); HR-ESI-MS positive mode (m/z): calcd. for C<sub>35</sub>H<sub>35</sub>ClN<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 589.2228; found: 589.2234; **8a**: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -47 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.5 (PE:EtOAc 95:5); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.43-7.24 (m, 20H, H-ar), 4.69 (s, 2H, OCH<sub>2</sub>Ph), 4.64, 4.50 (2d, 2H, <sup>2</sup>J 11.2 Hz, OCH<sub>2</sub>Ph), 4.59 (d, 1H,  $J_{2,3}$  9.9 Hz, H-2), 4.56-4.50 (m, 1H, H-6), 4.51, 4.46 (ABq, 2H,  $J_{AB}$  11.7 Hz, OCH<sub>2</sub>Ph), 4.11 (bd, 1H,  $J_{5,4}$  6.5 Hz, H-5), 4.06, 3.89 (2d, 2H, <sup>2</sup>J 13.8 Hz, NCH<sub>2</sub>Ph), 3.97 (dd, 1H,  $J_{3,2}$  9.9,  $J_{3,4}$  1.6 Hz, H-3), 3.90 (dd, 1H,  $J_{4,3}$  1.6,  $J_{4,5}$  6.5 Hz, H-4), 3.17 (dd, 1H,  $J_{7a,6}$  11.4,  $J_{7a,7b}$  14.6 Hz, H-7a), 2.90 (dd, 1H,  $J_{7b,6}$  4.4,  $J_{7b,7a}$  14.6 Hz, H-7b); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  137.6, 137.6, 137.2, 137.1 (Cq-ar), 128.8, 128.7, 128.7, 128.7, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.8 (C-ar), 119.7 (CN), 83.2 (C-3), 81.6 (C-5), 78.4 (C-4), 74.5, 73.8, 72.8 (3xOCH<sub>2</sub>Ph), 58.3 (C-2), 54.9 (C-6), 52.2 (C-7, NCH<sub>2</sub>Ph); HR-ESI-MS positive mode (m/z): calcd. for C<sub>35</sub>H<sub>35</sub>ClN<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 589.2228; found: 589.2239.

**2-((2S,3S,4R,5R,6R)-1-Benzyl-3,4,5-tris(benzyloxy)-6-(chloromethyl)piperidin-2-yl)-1-phenylethan-1-one 7b**

Chlorination of hydroxyazepane **3b** (130 mg, 0.20 mmol) was carried out according to general procedure C. Purification by flash chromatography (PE:EtOAc 96:4 to 94:6) afforded chloromethylpiperidine **7b** as a pale yellow oil (32 mg, 23%): [ $\alpha$ ]<sub>D</sub><sup>20</sup> -73 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.3 (PE:EtOAc 96:4); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.82 (bd, 2H,  $J_{o,m}$  7.7 Hz, H-ortho PhCO), 7.54 (bt, 1H,  $J_{p,m}$  7.4 Hz, H-para PhCO), 7.42 (dd, 2H,  $J_{m,o}$  7.7,  $J_{m,p}$  7.4 Hz, H-meta PhCO), 7.38-7.19 (m, 20H, H-ar), 4.92, 4.67 (2d, 2H, <sup>2</sup>J 11.3 Hz, OCH<sub>2</sub>Ph), 4.91, 4.77 (2d, 2H, <sup>2</sup>J 10.8 Hz, OCH<sub>2</sub>Ph), 4.57 (s, 2H, OCH<sub>2</sub>Ph), 4.07 (d, 1H, <sup>2</sup>J 14.1 Hz, NCHPh), 3.87 (dd, 1H, <sup>3</sup>J 8.8, <sup>3</sup>J 5.5 Hz, H-5), 3.82 (dd, 1H,  $J_{7a,6}$  4.8,  $J_{7a,7b}$  11.7 Hz, H-7a), 3.78-3.71 (m, 3H,

H-2, H-4, H-7b), 3.66 (d, 1H,  $^2J$  14.1 Hz, NCHPh), 3.57 (dd, 1H,  $^3J$  9.3,  $^3J$  7.7 Hz, H-3), 3.41 (dd, 1H,  $^2J$  16.2,  $J_{\text{CHCO}_2}$  4.8 Hz, CHCO), 3.34-3.28 (m, 1H, H-6), 3.02 (dd, 1H,  $^2J$  16.2,  $J_{\text{CHCO}_2}$  8.1 Hz, CHCO);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  198.5 (CO), 139.5, 138.5, 138.3, 138.0, 136.9 (Cq-ar), 133.0 (C-para PhCO), 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 127.9, 127.8, 127.2 (C-ar), 83.1 (C-4), 80.1 (C-3), 77.8 (C-5), 75.3, 74.7, 72.7 (3xOCH<sub>2</sub>Ph), 59.3 (C-6), 54.1 (C-2), 52.5 (NCH<sub>2</sub>Ph), 40.6 (C-7), 40.1 (CH<sub>2</sub>CO); HR-ESI-MS positive mode (m/z): calcd. for C<sub>42</sub>H<sub>43</sub>ClNO<sub>4</sub> [M+H]<sup>+</sup>: 660.2875; found: 660.2893.

**Diethyl ((2S,3R,4S,5R,6R)-1-benzyl-3,4,5-tris(benzyloxy)-6-(chloromethyl)piperidin-2-yl)phosphonate 7c**

Chlorination of hydroxyazepane **3c** (84 mg, 0.13 mmol) was carried out according to general procedure C. Purification by flash chromatography (PE:EtOAc 75:25) afforded chloromethylpiperidine **7c** as a colorless oil (67 mg, 78%):  $[\alpha]_{\text{D}}^{20}$  -22 ( $c$  0.1,  $\text{CHCl}_3$ );  $R_f$  0.45 (PE:EtOAc 75:25);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.45-7.25 (m, 20H, H-ar), 4.93 (s, 2H, OCH<sub>2</sub>Ph), 4.87, 4.83 (ABq, 2H,  $J_{\text{AB}}$  11.1 Hz, OCH<sub>2</sub>Ph), 4.65, 4.54 (2d, 2H,  $^2J$  11.5 Hz, OCH<sub>2</sub>Ph), 4.44 (d, 1H,  $^2J$  14.0 Hz, NCHPh), 4.36-4.26 (m, 1H, OCHCH<sub>3</sub>), 4.26-4.05 (m, 3H, H-3, 2xOCHCH<sub>3</sub>), 4.04 (dd, 1H,  $J_{5,4}$  8.7,  $J_{5,6}$  5.8 Hz, H-5), 4.01-3.92 (m, 1H, OCHCH<sub>3</sub>), 3.90 (d, 1H,  $^2J$  14.0 Hz, NCHPh), 3.86 (dd, 1H,  $J_{7a,6}$  5.4,  $J_{7a,7b}$  11.7 Hz, H-7a), 3.86-3.80 (m, 1H, H-4), 3.67 (dd, 1H,  $J_{7b,6}$  10.2,  $J_{7b,7a}$  11.7 Hz, H-7b), 3.56 (dd, 1H,  $J_{2,3}$  9.8,  $J_{\text{H-P}}$  23.7 Hz, H-2), 3.40-3.32 (m, 1H, H-6), 1.33, 1.19 (2t, 6H,  $J_{\text{CH}_3, \text{CH}_2}$  7.1 Hz, 2xCH<sub>3</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  138.6, 138.4, 138.3, 137.8 (Cq-ar), 129.0, 128.5, 128.3, 128.3, 128.0, 128.0, 127.9, 127.8, 127.6, 127.3 (C-ar), 82.6 (d,  $J_{\text{C-P}}$  14.8 Hz, C-4), 76.4 (d,  $J_{\text{C-P}}$  2.3 Hz, C-3), 75.9 (C-5), 75.1, 74.5, 73.2 (3xOCH<sub>2</sub>Ph), 62.6, 61.9 (2d,  $J_{\text{C,P}}$  6.9 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 58.1 (d,  $J_{\text{C-P}}$  13.3 Hz, C-6), 55.5 (d,  $J_{\text{C-P}}$  158.1 Hz, C-2), 54.5 (d,  $J_{\text{C-P}}$  3.5 Hz, NCH<sub>2</sub>Ph), 41.3 (C-7), 16.4, 16.3 (d,  $J_{\text{C-P}}$  6.6 Hz, 2xCH<sub>3</sub>);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 162 MHz):  $\delta$  24.2; HR-ESI-MS positive mode (m/z): calcd. for C<sub>38</sub>H<sub>45</sub>ClNNaO<sub>6</sub>P [M+Na]<sup>+</sup>: 700.2565; found: 700.2585.

**((2S,3S,4S,5R,6S)-6-(Azidomethyl)-1-benzyl-3,4,5-tris(benzyloxy)piperidine-2-carbonitrile 9a**

Azidation of **7a-8a** mixture (82 mg, 0.15 mmol) was carried out according to general procedure D. Purification by flash chromatography (PE:EtOAc 95:5) afforded a 3:1 mixture of azidomethylpiperidine **9a** and azidoazepane **10a** (44 mg, 52%). A small fraction of **9a** was isolated for analysis:  $R_f$  0.4 (PE:EtOAc 95:5);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.40-7.21 (m, 20H, H-ar), 4.83, 4.78 (ABq, 2H,  $J_{\text{AB}}$  11.2 Hz, OCH<sub>2</sub>Ph), 4.80, 4.75 (ABq, 2H,  $J_{\text{AB}}$  10.6 Hz, OCH<sub>2</sub>Ph), 4.63, 4.50 (2d, 2H,  $^2J$  11.7 Hz, OCH<sub>2</sub>Ph), 4.13, 3.96 (2d, 2H,  $^2J$  13.4 Hz, NCH<sub>2</sub>Ph), 4.06 (d, 1H,  $J_{2,3}$  8.1 Hz, H-2), 3.84 (dd, 1H,  $J_{3,2}$  8.1,  $J_{3,4}$  7.3 Hz, H-3), 3.76 (dd, 1H,  $J_{4,3}$  7.3,  $J_{4,5}$  8.6 Hz, H-4), 3.73 (dd, 1H,  $J_{5,4}$  8.6,  $J_{5,6}$  4.7 Hz, H-5), 3.57 (dd, 1H,  $J_{7a,6}$  4.2,  $J_{7a,7b}$  13.2 Hz, H-7a), 3.50 (dd, 1H,  $J_{7b,6}$  6.4,  $J_{7b,7a}$  13.2 Hz, H-7b), 3.10 (ddd, 1H,  $J_{6,5}$  4.7,  $J_{6,7a}$  4.2,  $J_{6,7b}$  6.4 Hz, H-6);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  138.1, 137.6, 137.2, 137.0 (Cq-ar), 128.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9 (C-ar), 117.6 (CN), 80.5 (C-4), 78.9 (C-3), 76.7 (C-5), 75.2, 75.1, 73.4 (3xOCH<sub>2</sub>Ph), 55.9 (C-6), 55.1 (NCH<sub>2</sub>Ph), 52.8 (C-2), 47.4 (C-7).

**Diethyl((2*S*,3*R*,4*S*,5*R*,6*S*)-6-(azidomethyl)-1-benzyl-3,4,5-tris(benzyloxy) piperidin-2-yl)phosphonate **9c** and diethyl ((2*S*,3*R*,4*S*,5*R*,6*R*)-6-azido-1-benzyl-3,4,5-tris(benzyloxy)azepan-2-yl)phosphonate **10c****

Azidation of chloromethylpiperidine **7c** (85 mg, 0.12 mmol) was carried out according to general procedure D. Purification by flash chromatography (PE:EtOAc 75:25) afforded a 1:1 mixture of azidomethylpiperidine **9c** and azidoazepane **10c** (70 mg, 81%). A small fraction of each compound was isolated for analysis. **9c**: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -5 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.48 (PE:EtOAc 75:25); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.41-7.36 (m, 2H, H-ar), 7.35-7.20 (m, 18H, H-ar), 4.94, 4.90 (ABq, 2H, J<sub>AB</sub> 10.7 Hz, OCH<sub>2</sub>Ph), 4.86, 4.82 (ABq, 2H, J<sub>AB</sub> 10.8 Hz, OCH<sub>2</sub>Ph), 4.62, 4.49 (2d, 2H, <sup>2</sup>J 11.6 Hz, OCH<sub>2</sub>Ph), 4.39 (d, 1H, <sup>2</sup>J 13.9 Hz, NCHPh), 4.23-3.99 (m, 4H, H-3, 3xOCH<sub>2</sub>CH<sub>3</sub>), 3.96 (dd, 1H, J<sub>5,4</sub> 8.9, J<sub>5,6</sub> 5.7 Hz, H-5), 3.92-3.83 (m, 1H, OCH<sub>2</sub>CH<sub>3</sub>), 3.79 (d, 1H, <sup>2</sup>J 13.9 Hz, NCHPh), 3.77 (dd, 1H, J<sub>4,3</sub> 8.4, J<sub>4,5</sub> 8.9 Hz, H-4), 3.52 (dd, 1H, J<sub>2,3</sub> 10.0 Hz, J<sub>H,P</sub> 23.7 Hz, H-2), 3.46, 3.41 (AB from ABX, 2H, J<sub>AB</sub> 13.3, J<sub>AX</sub> 9.3, J<sub>BX</sub> 4.8 Hz, H-7), 3.23-3.15 (m, 1H, H-6), 1.30, 1.14 (2t, 6H, J<sub>CH<sub>3</sub>,CH<sub>2</sub></sub> 7.1 Hz, 2xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  138.8, 138.5, 138.4, 137.8 (Cq-ar), 128.8, 128.6, 128.6, 128.4, 128.4, 128.0, 128.0, 127.9, 127.6, 127.5 (C-ar), 83.7 (d, J<sub>C,P</sub> 15.8 Hz, C-4), 76.6 (C-3), 75.6 (C-5), 75.5, 74.9, 73.3 (3xOCH<sub>2</sub>Ph), 62.2, 62.1 (2d, J<sub>C,P</sub> 6.5 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 56.7 (d, J<sub>C,P</sub> 14.0 Hz, C-6), 56.1 (d, J<sub>C,P</sub> 159.1 Hz, C-2), 54.6 (d, J<sub>C,P</sub> 3.0 Hz, NCH<sub>2</sub>Ph), 48.0 (C-7), 16.4, 16.3 (2d, J<sub>C,P</sub> 6.4 Hz, 2xCH<sub>3</sub>); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz):  $\delta$  24.2; HR-ESI-MS positive mode (m/z): calcd. for C<sub>38</sub>H<sub>45</sub>N<sub>4</sub>NaO<sub>6</sub>P [M+Na]<sup>+</sup>: 707.2969; found: 707.2992; **10c**: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -52 (c 0.1, CHCl<sub>3</sub>); R<sub>f</sub> 0.47 (PE:EtOAc 75:25); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.39-7.21 (m, 20H, H-ar), 4.77-4.58 (m, 6H, 3xOCH<sub>2</sub>Ph), 4.26-3.82 (m, 11H, NCH<sub>2</sub>Ph, 2xOCH<sub>2</sub>CH<sub>3</sub>, H-2, H-3, H-4, H-5, H-6), 3.10-2.95 (m, 2H, H-7), 1.30, 1.15 (2t, 6H, J<sub>CH<sub>3</sub>,CH<sub>2</sub></sub> 7.1 Hz, 2xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  138.9, 138.3, 137.9, 137.8 (Cq-ar), 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.3 (C-ar), 81.5, 81.4, 81.2 (C-3, C-4, C-5), 73.2 (3xOCH<sub>2</sub>Ph), 62.4 (d, J<sub>C,P</sub> 148.9 Hz, C-2), 61.9, 61.7 (2d, J<sub>C,P</sub> 7.0 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 56.7 (C-6), 49.8 (d, J<sub>C,P</sub> 13.8 Hz, C-7), 16.6, 16.4 (2d, J<sub>C,P</sub> 6.3 Hz, 2xCH<sub>3</sub>); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz):  $\delta$  27.0; HR-ESI-MS positive mode (m/z): calcd. for C<sub>38</sub>H<sub>45</sub>N<sub>4</sub>NaO<sub>6</sub>P [M+Na]<sup>+</sup>: 707.2969; found: 707.3001.

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