Chain-Elongation of Sugar Aldehydes by Asymmetric Homoaldol Reaction: Introduction of a Functionalized 3-Methyl-Substituted Three-Carbon Unit

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Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday

Abstract: O-Protected aldehydo-sugars reacted with α-titanated crotyl N,N-diisopropylcarbamate to furnish chain-elongated alk-1-enyl carbamates. These were further functionalized by epoxidation of the double bond and subsequent methanolysis to form methyl 3-C-methyl-3-deoxy-furanosides. Mukaiyama-type addition of benzaldehyde led to tetrasubstituted tetrahydrofurans. All reactions proceeded with high diastereoselectivities and allow for a broad application.

Key words: homoaldol reaction, epoxides, (–)-sparteine-mediated metalation, stereoselective synthesis, branched carbohydrates

Partially protected aldehydo-sugars frequently have been chain-elongated by an unsubstituted or substituted C3-unit by means of allylmetals.2 As we have demonstrated for simpler substrates, enantioselective deprotonation of (E)-but-2-enyl N,N-diisopropylcarbamate (1) with n-butyl-lithium/(–)-sparteine (3) affords the chiral lithium complex 2. Delithiotitanation to form the titanium complex 4 and subsequent homoaldol reaction4,5 yield (Z)-anti-4-hydroxyalk-2-enyl carbamates 6 with >90% ee (Scheme 1).

The decisive step is a 1,3-chirality transfer during the Zimmerman–Traxler transition state (TS A). As a consequence, with achiral aldehydes 5, the enantiomers 6 and ent-6 are produced from rac-4, and chiral aldehydes give rise to two enantiomerically pure diastereomers with the reagent rac-4.

Enol carbamates 6 are stable, protected γ-hydroxy aldehydes and are easily converted into γ-lactol ethers 7 and γ-lactones 8 (Scheme 2). Among various transformations, proceeding with essentially complete substrate-induced stereoselectivity, the epoxidation to afford highly reactive oxiranes 9 and subsequent methanolysis to form methyl furanosides 10, and as well, the Mukaiyama-type condensation with aldehydes for the synthesis of tetrahydrofuran-3-carbaldehydes 11, are of great interest in synthesis.

The homoaldol reaction occasionally has been employed in natural product synthesis.11 Starting from O-protected (R)-lactaldehyde, both key intermediates of the Kinoshita rifamycin S12 synthesis were constructed within few steps, by utilization of homoenolate reagent rac-4.

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We now investigated four additional complex \(O,\overline{O}\)-isopropylidene-protected aldehydes 2,3-\(O\)-isopropylidene-\(D\)-glyceraldehyde (12),\(^{14}\) 1,2:3,4-di-\(O\)-isopropylidene-\(D\)-galacto-hexodialdo-1,5-pyranose (13),\(^{15}\) 2,3:4,6-di-\(O\)-isopropylidene-\(D\)-xylo-hex-2-ulofuranose (14),\(^{16}\) and 2,3:4,5-di-\(O\)-isopropylidene-\(D\)-ribose (15)\(^{17}\) in the asymmetric homoaldol reaction and subsequent transformations (Figure 1). Compounds 12–15 were prepared by the published standard procedures.\(^{14–17}\)

First, the aldehydes 12–15 were added to a solution of racemic titanium reagent rac-4, prepared by deprotonation of 1 with \(n\)-butyllithium/\(N,\overline{N},\overline{N},\overline{N}\)tetramethylethylenediamine (TMEDA) and addition of three equivalents of tetraisopropoxytitanium in diethyl ether. Workup after stirring for 5.5 hours at \(-78\,^\circ\text{C}\) afforded mixtures of the 4,5-anti and the 4,5-syn addition products 16a–d and 17a–d, respectively (Scheme 3, Table 1). Since (\(R\))-4 and

![Scheme 3](image-url)

**Table 1** Homoaldol Reaction of Titanium Complex 4 with \(\alpha\)-Chiral Aldehydes 12–15

<table>
<thead>
<tr>
<th>Substrate/Intermediate</th>
<th>Product 16(^{a})</th>
<th>Yield (%)</th>
<th>([\alpha])(^{b})_D</th>
<th>Product 17(^{a})</th>
<th>Yield (%)</th>
<th>([\alpha])(^{b})_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 + rac-4</td>
<td>16a</td>
<td>45</td>
<td>0.55(^{b})</td>
<td>17a</td>
<td>31</td>
<td>0.62(^{b})</td>
</tr>
<tr>
<td>12 + ((R))-4</td>
<td>16b</td>
<td>55</td>
<td>+30.8(^{c})</td>
<td></td>
<td>&lt;1</td>
<td>+9.1(^{c})</td>
</tr>
<tr>
<td>13 + rac-4</td>
<td>16c</td>
<td>41</td>
<td>0.31(^{c})</td>
<td>17b</td>
<td>29</td>
<td>-13.1(^{d})</td>
</tr>
<tr>
<td>13 + ((R))-4</td>
<td>16d</td>
<td>72</td>
<td>-13.1(^{d})</td>
<td></td>
<td>&lt;2</td>
<td>-70.0(^{d})</td>
</tr>
<tr>
<td>14 + rac-4</td>
<td>16e</td>
<td>33</td>
<td>0.29(^{c})</td>
<td>17c</td>
<td>28</td>
<td>0.43(^{c})</td>
</tr>
<tr>
<td>14 + ((R))-4</td>
<td>16f</td>
<td>50</td>
<td>+27.6(^{d})</td>
<td></td>
<td>&lt;1</td>
<td>+18.2(^{e})</td>
</tr>
<tr>
<td>15 + rac-4</td>
<td>16g</td>
<td>50</td>
<td>0.56(^{c})</td>
<td>17d</td>
<td>30</td>
<td>0.40(^{e})</td>
</tr>
<tr>
<td>15 + ((R))-4</td>
<td></td>
<td>47</td>
<td>+55.8(^{c})</td>
<td></td>
<td>&lt;1</td>
<td>-10.4(^{e})</td>
</tr>
</tbody>
</table>

\(^{a}\)Numbering of compounds 16a–d and 17a–d are for the assignment of the \(^1\)H and \(^1\)C NMR data.

\(^{b}\)EtOAc–cyclohexane (10:1).

\(^{c}\)\(c = 2\) (CHCl\(_3\)).

\(^{d}\)\(c = 1\) (CHCl\(_3\)).

\(^{e}\)Et\(_2\)O–\(n\)-pentane (2:1).

Figure 1  Applied sugar aldehydes for homoaldol reaction.
(S)-4 do not interconvert under the reaction conditions, both starting materials follow their independent reaction pathway.

Nevertheless, the 4,5-anti-diastereomer in all examples is produced in slight excess, demonstrating that (R)-4 and aldehydes 12–15 form the ‘matched pair’. 4,5-anti-Diastereomers 16 and 4,5-syn-diastereomers 17 are readily separable by silica gel chromatography, since 17 has a higher tendency for intramolecular hydrogen bonding and is consequently less polar. All compounds 16 and 17 were obtained after chromatographic separation in analytically pure form. Once again, the high hydrolytic stability of enol carbamates turned out to be a great advantage. When (R)-4 (>90% ee), prepared by (−)-sparteine-mediated lithiation was used, only 4,5-syn-diastereomers 17 were formed in traces.

The 1-CH-2-CH coupling constants of 6.4–6.6 Hz in all compounds 16 and 17 provide evidence for the expected 1-Z configuration. More polar diastereomer 16d gave suitable crystals for an X-ray crystal structure analysis (Figure 2) which proved the assumed configuration. It is seen from the conformation that (at least in the solid state) a hydrogen bridge between the 4-OH group and the 5-O is disfavored. The stereochemical assignments of the further compounds are mainly based on their polarity. The correct assignment of 16c is supported by an X-ray crystal structure analysis of tetrahydrofuran 26c, obtained from enol carbamate 16c (see below).

During the epoxidation/methanolysis, two new stereocenters at C-2 and C-1 are created. The 1H NMR coupling constants in 20a and 20b ($^3J_{2,3} = \sim 4$ Hz, $^3J_{3,4} = \sim 8$ Hz, $^3J_{4,5} = \sim 6$ Hz) match well with those of simple methyl furanosides and are typical for a 1,2-cis,2,3-cis,3,4-trans configuration. Further, a coupling between 2-H and 2-OH of 7.9 Hz is a good indication for the cis-relation between 1-OMe and 2-OH, caused by a slowly exchanging hydrogen and the 2-OH group. Furanosides 20a and 20b correspond to 3-deoxy-3-C-methyl-D-altrose (21) and 3-deoxy-3-C-methyl-D-lyxose (22), respectively (Figure 3).

Figure 2 X-ray crystal structure of 16d.

The substructure in enol carbamates 16, similar to Z-homoaliphatic alcohols allows for a highly diastereoselective, vanadyl-catalyzed epoxidation of the double bond by means of tert-butyl hydroperoxide, directed by the hydroxyl group (Scheme 4). In most cases, the 2-carbamoyloxoyxiranes 18 formed are stable enough for chromatographic purification but are highly reactive in the presence of acids. The oxiranes 18 have some relation-
A further, very versatile chain-extension is given by the BF$_3$-catalyzed condensation of the homoaldol products with aldehydes or ketones, which we discovered several years ago (Scheme 5). The $E$-oxonium ion 23, formed from the 4-hydroxyalk-1-enyl carbamate 16 and aldehydes, undergoes cyclization from the least hindered conformation to deliver finally $cis$,trans,$cis$-configured tetrahydrofuran-3-carbaldehydes with essentially perfect diastereoselectivity.

Homoaldol products 16a–c were stirred separately with 1.1 equivalents each of benzaldehyde and BF$_3$·OEt$_2$ at 0 °C. After aqueous workup, tetrahydrofurans 26a–c were isolated with 56–71% yield as pure diastereomers (Scheme 5, Table 3). Compound 26c provided suitable crystals for an X-ray crystal structure analysis (Figure 4).30,31

**Table 2** Epoxidation and Subsequent Methanolysis of Homoaldol Adducts 16

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Epoxide 18$^a$</th>
<th>Yield (%)</th>
<th>$[\alpha]_D^{20}$</th>
<th>Furanoside 20$^a$</th>
<th>Yield (%)</th>
<th>$[\alpha]_D^{20}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>18a</td>
<td>84</td>
<td>-9.8$^b$</td>
<td>20a</td>
<td>84</td>
<td>+138.3$^b$</td>
</tr>
<tr>
<td>16b</td>
<td>18b</td>
<td>38$^c$</td>
<td>-45.0$^d$</td>
<td>20b</td>
<td>81</td>
<td>-12.0$^d$</td>
</tr>
<tr>
<td>16c</td>
<td>18c</td>
<td>24$^e$</td>
<td>-6.7$^d$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Numbering of compounds 18a–c and 20a.b are for the assignment of the $^1$H and $^{13}$C NMR data.

$^b$ $c$ = 2 (CHCl$_3$).

$^c$ 25% recovered starting material 16b.

$^d$ $c$ = 1 (CHCl$_3$).

$^e$ 28% recovered starting material 16c.

**Scheme 5** Synthesis of tetrahydrofuran-3-carbaldehydes 26 by Mukiyama-type cyclization of homoaldol adducts 16. Reagents and conditions: a) BF$_3$·OEt$_2$, R$^\*$CHO, CH$_2$Cl$_2$, 0 °C, 30 min; b) H$_2$O, 0 °C.
Due to the mild reaction conditions five- and six-membered acetonide ring units survive the Lewis-acidic reaction conditions. Taking into consideration the great versatility in the homoaldol part and the aldehyde (or ketone) unit, a vast variety of sugar-like compounds of variable chain-length are accessible with few highly stereoselective steps.

All moisture-sensitive reactions were carried out under argon in flame-dried glassware sealed by rubber septa. Unless otherwise specified, materials were obtained from commercial sources and used without purification. All solvents (n-pentane, Et₂O, CH₃Cl₂) were dried according to standard procedures and purified by distillation prior to use. Addition of chemicals was performed by using disposable plastic syringes. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) at a pressure of about 1.5 bar and monitored by TLC. Solvents for chromatography (Et₂O, n-pentane, cyclohexane, EtOAc) were distilled prior to use. For analytical TLC, Merck plastic sheets (60 F254 silica gel) were used. Visualization was accomplished with permanganate solution and vanillin solution. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer. Optical rotations were measured at 20 °C with a PerkinElmer 341 polarimeter at the sodium D line. The IR spectra were recorded using a Varian 3100 Excalibur series spectrometer. Elemental analyses were performed at the Chemistry Department of the University of Münster. ESI (exact mass determination) was carried out with a Quattro LCZ (Waters-Micromass, Manchester, UK) with nanospray inlet.

Table 3  Tetrahydrofuran Synthesis from Homoaaldol Adducts 16a–c

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Tetrahydrofuran 26</th>
<th>Yield (%)</th>
<th>[α]D²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>26a</td>
<td>56</td>
<td>+80.6b</td>
</tr>
<tr>
<td>16b</td>
<td>26b</td>
<td>61</td>
<td>-59.0b</td>
</tr>
<tr>
<td>16c</td>
<td>26c</td>
<td>71</td>
<td>+33.9c</td>
</tr>
</tbody>
</table>

[a Numbers for 26a–c are given for the assignment of the ¹H and ¹³C NMR data.
 b c = 1 (CHCl₃).
 c c = 2 (CHCl₃).]

Figure 4  X-ray crystal structure of 26c.

Tetrahydrofuran Synthesis from Homoaldol Adducts 16a–d and 17a–d; General Procedure

(6)-Crotyl carbamate 1 (1.0 equiv) and TMEDA (1.1 equiv) were dissolved in Et₂O (2 mL/mmol) and cooled to −78 °C under argon. A soln of 1.6 M n-BuLi in n-hexane (1.1 equiv) was added dropwise within 3 min. The mixture was stirred for 30 min at −78 °C and a precooled solution of Ti(Oi-Pr)₃ (3.0 equiv) in Et₂O (1 mL/mmol) was added. After a transmetalation time of 40 min, a soln of the aldehyde 12, 13, 14 or 15 (1.1 equiv) in Et₂O (1 mL/mmol) was added and stirring was continued for 5.5 h. The reaction was stopped by addition of sat. NH₄Cl at −78 °C, warmed to r.t. and washed with sat. K/Na tartrate solution (10 mL/mmol). The aqueous layer was separated and extracted with Et₂O (3 × 10 mL/mmol). The combined organic extracts were dried (Na₂SO₄) and the solvent was evaporated. The residue was purified by column chromatography on silica gel (EtO₂-n-pentane, 1:2 → 2:1).

[Z,3S,4S,5R]- and [Z,3R,4R,5R]-4,5,6-Trihydroxy-5,6-O-isopropylidene-3-methylhex-1-enyl N,N-Diisopropylcarbamate (16a and 17a)

According to the General Procedure, the reaction of 1 (1.19 g, 6.00 mmol) with aldehyde 12 (0.83 g, 6.35 mmol) gave 0.89 g (45%) of 16a and 0.62 g (31%) of 17a, both as colorless oils.

16a

[α]D²⁰ +30.8 (c = 2.40, CHCl₃); R₉ = 0.55 (EtOAc-cyclohexane, 10:1).

IR (ATR): 3567, 2965, 2932, 2874, 1680, 1442, 1370, 1209, 1151, 1054, 976, 887 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.10 [d, ³J₃,CH₃ = 7.1 Hz, 3 H, 3-CH₃], 1.25 (br s, 12 H, 2'-CH₃), 1.32, 1.39 [s each, 6 H, C(CH₃)₂], 1.86 (d, ³J₂,COH = 3.7 Hz, 1 H, OH), 2.92 (ddd, ³J₂,3 = 10.0 Hz, ³J₂,4 = 4.6 Hz, ³J₂,5 = 0.7 Hz, 1 H, 3-H₂), 3.65 (ddd, ³J₃,4 = 8.6 Hz, 1 H, 4-H₁), 3.82, 3.97 (br s each, 2 H, 1'-H₂), 3.91–4.07 (m, 3 H, 5-H₁, 6-H₂, 6-H₃), 4.73 (dd, ³J₂,3 = 6.6 Hz, 1 H, 2'-H₂), 7.09 (dd, 1 H, 1'-H₂).

Synthesis 2007, No. 6, 883–892 © Thieme Stuttgart · New York
13C NMR (75 MHz, CDCl3): δ = 17.9 (3-CH3), 20.9 (2'-C), 25.4, 26.6 (C(3')H3), 33.0 (C-3), 46.2 (C-1'), 65.5 (C-6), 75.1 (C-4), 77.5 (C-5), 108.5 [C(CH3)2], 111.1 (C-2), 135.9 (C-1), 152.8 (NC=O).


17a

[13C]NMR (75 MHz, CDCl3): δ = 1.12 [d, J3,3(CH3) = 6.9 Hz, 3 H, 3-CH3], 1.25 [br s, 12 H, 2'CH2], 1.35, 1.42 [s each, 6 H, C(3')CH3], 2.29 [d, J3,7CH3 = 3.6 Hz, 1 H, OH], 2.75 [ddq, J3,3(CH3) = 10.0 Hz, 3J4,2 = 4.1 Hz, 1 H, 3-H3], 3.42 [dd, J3,4 = 6.5 Hz, 1 H, 4-H1], 3.73 [d, J3,5,6 = 6.5 Hz, J3,6,7 = 8.0 Hz, 1 H, 1-H, 6-H1], 3.81, 4.02 [br s each 2 H, 1'-H, 2'-H], 3.95-4.21 (m, 2 H, 5-H, 6-Ha), 4.83 [dd, J1,2 = 6.5 Hz, 1 H, 2-H], 7.06 (d, 1 H, 1-H).

13C NMR (75 MHz, CDCl3): δ = 17.8 (3-CH3), 21.0 (2'-C), 25.4, 26.7 [C(3')H3], 32.9 (C-3), 46.2 (C-1'), 66.1 (C-6), 75.6 (C-4), 77.3 (C-5), 109.2 [C(CH3)2], 111.1 (C-2), 135.1 (C-1), 152.6 (NC=O).


[2,3,3S,4S(2R,3S,4S,5R)-]- and [Z,3R,4R(2S,3R,4R,5R)-]-4-(3,4,5,6-Tetrahydroxy-3,4,5,6-di-o-isopropylidene-2-tetrahydropyranyl)-4-hydroxy-3-methylbut-1-enyl N,N-Diisopropycarbamate (16b and 17b)

According to the General Procedure, the reaction of 1 (0.59 g, 3.00 mmol) with aldehyde 14 (0.80 g, 3.10 mmol) gave 0.45 g (33%) of 16b as a colorless solid and 0.40 g (29%) of 17b as a yellow oil.

Mp 50 °C; [α]D20 +27.6 (c = 1.29, CHCl3); Rf = 0.29 (EtO-oted-pete-nane, 2:1).

IR (ATR): 3533, 2984, 2393, 1933, 1684, 1432, 1370, 1190, 1158, 1135, 672 cm-1.

1H NMR (300 MHz, CDCl3): δ = 1.17 [d, J3,3(CH3) = 6.9 Hz, 3 H, 3-CH3], 1.25 [br s, 12 H, 2'CH2], 1.33, 1.37, 1.44, 1.47 [s each, 12 H, 2(C(3')H3)], 1.66, 2.47 (d, J3,7CH3 = 7.7 Hz, 1 H, OH), 2.51 (m, 1 H, 3-H3), 3.06 (dd, J3,4 = 5.0 Hz, 1 H, 4-H1), 4.38, 4.60 [br s each 2 H, 1'-H, 2'-H], 4.02-4.11 (m, 3 H, 5-H, 6-Ha), 4.54 [br s, 1 H, 6-Ha], 4.93 (dd, J3,4 = 6.4 Hz, J3,5,6 = 9.7 Hz, 1 H, 1-H, 6-H1), 7.03 (d, J3,6 = 0.6 Hz, 1 H, 1-H).

13C NMR (75 MHz, CDCl3): δ = 18.6 (3-CH3), 20.9 (2'-C), 23.7, 26.6, 27.2, 28.9 [C(3')H3], 32.9 (C-3), 46.3 (C-6), 60.3 (C-4), 72.9 (C-7), 73.3 (C-8), 77.3 (C-4), 87.7 (C-6), 97.7, 111.7 [C(CH3)2], 113.2 (C-5), 115.5 (C-2), 134.2 (C-1), 152.4 (NC=O).

Anal. Calcd for C19H30NO6: C, 60.37; H, 8.59; N, 3.06. Found: C, 60.21; H, 8.59; N, 2.97.

17c

[α]D20 +18.2 (c = 2.30, CHCl3); Rf = 0.43 (EtO-oted-pete-nane, 2:1).

IR (ATR): 3530, 2994, 2938, 1700, 1437, 1372, 1138, 1121, 1065, 762 cm-1.

1H NMR (400 MHz, CDCl3): δ = 1.23 [d, J3,3(CH3) = 6.8 Hz, 3 H, 3-CH3], 1.25 [br s, 12 H, 2'CH2], 1.35, 1.38, 1.43, 1.47 [s each, 12 H, 2(C(3')H3)], 2.50 (d, J3,7CH3 = 6.1 Hz, 1 H, OH), 3.22 (m, 1 H, 3-H3), 3.77 (dd, J3,4 = 3.7 Hz, 1 H, 4-H1), 3.95, 4.02 (br s each 2 H, 1'-H, 2'-H), 4.02-4.11 (m, 3 H, 5-H, 6-Ha, 6-Ha), 4.93 (dd, J3,4 = 6.5 Hz, J3,5,6 = 9.4 Hz, 1 H, 1-H, 6-H1), 7.04 (d, J3,6 = 0.8 Hz, 1 H, 1-H).

13C NMR (100 MHz, CDCl3): δ = 18.7 (3-CH3), 21.5 (2'-C), 21.5, 27.0, 27.9, 28.8 [C(3')H3], 31.8 (C-3), 45.6 (C-6), 60.6 (C-4), 72.9 (C-7), 73.1 (C-8), 74.1 (C-4), 84.9 (C-6), 97.5, 112.1 [C(CH3)2], 116.4 (C-5), 122.8 (C-2), 135.4 (C-1), 152.7 (NC=O).

Anal. Calcd for C19H30NO6: C, 60.37; H, 8.59; N, 3.06. Found: C, 60.18; H, 8.55; N, 3.04.

[2,3,3S,4S(5S,6R,7R)-]- and [Z,3R,4R(5S,6S,7R)-]-4-(3,4,5,6-Pentahydroxy-5,6-di-o-isopropylidene-3-methylbut-1-enyl N,N-Diisopropycarbamate (16d and 17d)

According to the General Procedure, the reaction of 1 (0.59 g, 3.00 mmol) with aldehyde 15 (0.80 g, 3.10 mmol) gave 0.22 g (50%) of 16d as a colorless solid and 0.13 g (30%) of 17d as a colorless oil.
16d Mp 78 °C; [α]D20 20 455.8 (c = 2.91, CHCl3); Rf = 0.56 (Et2O–n-pentane, 2:1).

IR (ATR): 3505, 2985, 2935, 2878, 1702, 1457, 1371, 1214, 1135, 1061, 761 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.18 [d, J₁₃₂,CH₋₃ = 6.9 Hz, 3 H, 3-CH₋₃], 1.25 (br s, 12 H, 2-CH₃), 1.32, 1.39, 1.43 [s each, 12 H, 2 C(CH₃)₂], 3.19 (m, 1 H, 1-H1), 3.60–4.21 (m, 6 H, 4-H1, 5-H1, 6-H1, 7-H₁, 8-H₂, 8-H₃), 3.96, 4.06 (br s each, 2 H, 1-H₂, 1-H₃), 7.12 (dd, J₁₃₂ = 0.6 Hz, 1 H, 1-H₁).

13C NMR (100 MHz, CDCl₃): δ = 18.0 (3-CH₃), 25.3, 26.5, 28.1 [C(CH₃)₂], 32.4 (C-3), 47.3 (C-1′), 68.1 (C-8), 71.7 (C-7), 73.2 (C-6), 78.5 (C-4), 78.6 (C-5), 108.3, 110.2 [C(CH₃)₂], 111.1 (C-2), 135.5 (C-1), 152.8 (NC=O).


The combined organic phases were dried (Na₂SO₄), the solvent was evaporated, and the residue was purified by column chromatography on silica gel (Et₂O–n-pentane, 1:2 → 2:1).

16b According to the General Procedure, the reaction of 1 (0.59 g, 3.00 mmol) with aldehyde 13 (0.85 g, 3.30 mmol) gave 0.99 g (72%) of 16b as a colorless solid. For analytical data, see above.

16c According to the General Procedure, the reaction of 1 (0.59 g, 3.00 mmol) with aldehyde 14 (0.87 g, 3.37 mmol) gave 0.73 g (50%) of 16c as a colorless solid. For analytical data, see above.

16d According to the General Procedure, the reaction of 1 (0.59 g, 3.00 mmol) with aldehyde 15 (0.76 g, 3.30 mmol) gave 0.60 g (47%) of 16d as a colorless oil. For analytical data, see above.

1.2-Epoxy-4-hydroxyalkyl Carbamates 18a–c; General Procedure

Homoalcohol adduct 16 (1.0 equiv) was dissolved in anhyd CH₂Cl₂ (3 ml/mmol) under argon. VO(acac)₂ (2 mol%, 0.05 mmol) and t-BuOOH (1.5 equiv) were added at r.t. and the mixture was allowed to stir for 15 h. The reaction was stopped by addition of Me₂S (0.7 equiv) and was stirred for additional 30 min. The mixture was washed with sat. NaHCO₃ soln (7 ml/mmol) and the combined organic extracts were dried (MgSO₄). The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (Et₂O–n-pentane, 1:1 → 2:1).

15[1,2R,3R,4S,5R]-1,2-Epoxy-4,5,6-trihydroxy-5,6-isopropylidene-3-methylhexyl N,N-Diisopropylcarbamate (18a)

According to the General Procedure, 16a (0.89 g, 2.70 mmol) was converted with VO(acac)₂ (13.5 mg, 0.05 mmol) and t-BuOOH (0.5 ml, 4.05 mmol) into the product 18a (0.78 g, 94%) as a light yellow oil; [α]D20 20 9.8 (c = 1.82, CHCl₃); Rf = 0.41 (EtOAc–cyclohexane, 3:1).

IR (ATR): 3471, 2974, 2936, 2878, 1691, 1602, 1434, 1301, 1212, 897, 813, 1054 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.1 (d, J₁₃₂,CH₋₃ = 7.2 Hz, 3 H, 3-CH₋₃), 1.24 (br s, 12 H, 2-CH₃), 1.35, 1.42 [s each, 6 H, C(CH₃)₂], 1.86 (ddq, J₁₃₂ = 0.41, CHCl₃); 2.05 (s, 1 H, OH), 3.04 (dd, J₁₃₂ = 3.0 Hz, 1 H, 1-H₂), 3.89 (dd, J₁₃₂ = 3.0 Hz, 1 H, 1-H₃), 4.06 (br s each, 2 H, 1-H₁), 4.09 (dd, J₁₃₂ = 13.9 Hz, 1 H, 3-H₁), 4.16 (dd, J₁₃₂ = 5.6 Hz, 1 H, 4-H₁), 4.17 (dd, J₁₃₂ = 5.6 Hz, 1 H, 5-H₁), 4.23 (dd, J₁₃₂ = 4.5 Hz, 1 H, 6-H₁), 5.61 (d, 1 H, 1-H₁).

13C NMR (75 MHz, CDCl₃): δ = 13.3 (3-CH₃), 21.0 (C-2′), 25.1, 26.6, 28.4 [C(CH₃)₂], 35.8 (C-3), 47.9 (C-1′), 56.5 (C-2′), 65.2 (C-5), 74.6 (C-4), 75.2 (C-1), 77.8 (C-5), 108.6 [C(CH₃)₂], 154.0 (NC=O).

Anal. Calcd for C₁₉H₂₇NO₄: C, 59.11; H, 9.05; N, 4.05; Found: C, 58.39; H, 9.05; N 3.92.

15[1,2R,3R,4S,5R]-1,2-Epoxy-4,5,6-trihydroxy-5,6-di-O-isopropylidene-2-tetrahydropyran-4-hydroxy-3-methylbutyl N,N-Diisopropylcarbamate (18b)

According to the General Procedure, 16b (0.16 g, 0.35 mmol) was converted with VO(acac)₂ (1.9 mg, 0.01 mmol) and t-BuOOH (0.06 ml, 0.49 mmol) into the product 18b (0.064 g, 38%) as a colorless solid; mp 76 °C; [α]D20 20 45.0 (c = 1.20, CHCl₃); Rf = 0.17 (EtOAc–n-pentane, 1:1).

IR (ATR): 3456, 2975, 2937, 1698, 1549, 1437, 1372, 1211, 1065, 899, 770 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.11 [d, J₁₃₂,CH₋₃ = 7.1 Hz, 3 H, 3-CH₋₃], 1.22 (br s, 12 H, 2-CH₃), 1.32, 1.33, 1.46, 1.51 [s each, 12 H, 2 C(CH₃)₂], 1.34 (d, J₁₃₂ = 5.6 Hz, 1 H, OH), 2.07 (ddq, J₁₃₂ = 3.0 Hz, 1 H, 1-H₁), 2.39 (dd, J₁₃₂ = 19.2 Hz, 1 H, 1-H₂), 3.72, 3.84 (br s each, 2 H, 1-H₁), 3.87 (dd, J₁₃₂ = 7.5 Hz, 1J₁₃₂ = 2.0 Hz, 1 H, 1-H₂), 4.02 (dd, 1 H, 4-H₁), 4.32
(dd, $J_{2,3} = 2.4$ Hz, $J_{3,4} = 5.2$ Hz, 1 H, 8-H1), 4.52 (dd, $J_{2,3} = 8.0$ Hz, 1 H, 6-H4), 4.63 (dd, 1 H, 7-H5), 5.53 (d, 1 H, 9-H1), 5.68 (d, 1 H, 1-H1). $^{13}$C NMR (75 MHz, CDCl3); $\delta = 15.2$ (C-3), 21.0 (C-2), 24.4, 24.9, 25.9, 26.0 (C(CH3)2), 34.3 (C-3), 44.2 (C-1), 57.8 (C-2), 66.9 (C-4), 70.4 (C-6), 70.5 (C-8), 71.5 (C-7), 76.2 (C-5), 96.6 (C-9), 108.5, 109.3 (C(CH3)2), 154.2 (NC=O).

Anal. Calcd for C19H31NO4: C, 70.83; H, 9.50; N, 3.55. Found: C, 70.79; H, 9.52; N, 3.60.

($S,S,20$)-(2R,3R,4S,5S)-2,3-Epoxy-4-(2,3,4,5-tetrahydroxy-3-oxo-2-methoxy-4-methyltetrahydrofuran-3-yl)2-methoxy-5-methyltetrahydrofuran-3-ol (20b)

According to the General Procedure, 18b (0.081 g, 0.16 mmol) was converted with MeOH (0.50 mL, 12.29 mmol) and MeSO2H (0.01 mL, 0.16 mmol) into the product 20b (45 mg, 81%); light yellow solid; mp 125 °C; $[a]_{D}^{20} = -12.0$ (c = 1.00, CHCl3); $R_{f} = 0.26$ (EtO–O–pentane, 2:1).

IR (ATR): 3593, 2963, 2928, 2870, 1716, 1495, 1454, 1371, 1258, 1151, 1101, 759, 698 cm–1.

$^{1}H$ NMR (400 MHz, CDCl3): $\delta = 1.12$ (d, $J_{1,2} = 6.7$ Hz, 3 H, 4-H1), 3.94 (dd, $J_{1,2} = 5.7$ Hz, 1 H, 1-H1), 4.36 (dd, $J_{1,2} = 9.9$ Hz, 1 H, 2-H1), 4.64 (d, $J_{1,2} = 5.4$ Hz, 1 H, 3-H1), 5.18 (s, 1 H, 9-H1), 5.83 (d, $J_{1,2} = 9.8$ Hz, 1 H, 8-H1), 7.82 (d, $J_{1,2} = 9.8$ Hz, 1 H, 5-H1), 8.87 (d, $J_{1,2} = 10.0$ Hz, 1 H, 6-H1), 4.47 (dd, 1 H, 7-H1), 4.66 (dd, 1 H, 8-H1), 4.87 (d, 1 H, 2-H1), 5.52 (d, 1 H, 10-H1).

$^{13}$C NMR (100 MHz, CDCl3): $\delta = 35.6$ (C-20), 37.2 (C-21), 39.6 (C-22), 43.5 (C-23), 50.6 (C-24), 53.7 (C-25), 55.3 (C-26), 67.4 (C-27), 72.7 (C-28), 76.8 (C-29), 115.6 (C-7), 118.2 (C-8), 120.8 (C-9), 122.7 (C-10), 127.8 (C-11), 130.4 (C-12), 135.1 (C-13), 139.3 (C-14), 152.7 (C-15), 154.2 (C-16), 168.8 (C-17).

ESI (EM): $m/z$ calcd for [C19H31O5Na+]: 383.1684; found: 383.1676.

Mukaiyama-Type Cyclization of Homoolaldol Adducts 16a–c; General Procedure

A soln of homoolaldol adduct 16 (1.0 equiv) and benzaldehyde (1.1 equiv) in CH2Cl2 (9 mL/mmol) at 0 °C was treated dropwise with BF3·OEt2 (1.1 equiv). The mixture was allowed to stir for 30 min at 0 °C. The reaction was stopped by addition of H2O (10 mL/mmol), diluted with EtO (10 mL/mmol), and warmed to r.t. The organic layer was separated and neutralized with NaHCO3. The aqueous layer was extracted with EtO (20 mL/mmol) and the combined organic extracts were dried (MgSO4). The solvent was evaporated and the residue was purified by column chromatography on silica gel (EtO–O–pentane, 1:3–2:1).

($2,3,4,5,6$)-($2,3,4,5,6$)-Tetrahydroxy-3,4,5,6-di-O-isopropylidene-2-tetrahydrofuran-3-ol (26a)

According to the General Procedure, the reaction of homoolaldol adduct 16a (0.2 g, 0.56 mmol) with benzaldehyde (0.09 g, 0.84 mmol) and BF3·OEt2 (0.12 mL, 0.84 mmol) gave 0.12 g (56%) of 26a; colorless solid; mp 35 °C; $[a]_{D}^{20} = +80.6$ (c = 1.07, CHCl3); $R_{f} = 0.61$ (EtOAc–cyclohexane, 3:1).

IR (ATR): 3036, 2984, 2878, 1716, 1495, 1454, 1371, 1258, 1151, 1101, 759, 698 cm–1.

$^{1}H$ NMR (300 MHz, CDCl3): $\delta = 1.24$ [d, $J_{1,2} = 6.9$ Hz, 3 H, 4-H1], 1.40, 1.45 [s each, 6 H, C(CH3)2], 2.65 [ddq, $J_{1,2} = 5.6$ Hz, 1 H, 1-H1], 4.53 ($J_{1,2} = 5.4$ Hz, 1 H, 2-H1), 8.57 (d, $J_{1,2} = 3.5$ Hz, 1 H, 3-H1), 4.31 ($J_{1,2} = 7.2$ Hz, 1 H, 8-H1), 4.16–4.31 (m, 2 H, 6-H1, 7-H1), 5.25 (d, 1 H, 2-H2), 7.23–7.42 (m, 5 H, ArH), 9.07 (d, 1 H, CHO).

$^{13}$C NMR (75 MHz, CDCl3); $\delta = 17.8$ (C-4), 25.4, 26.7 (C(CH3)2), 38.4 (C-4), 64.0 (C-3), 67.5 (C-7), 77.8 (C-6), 80.6 (C-2), 86.4 (C-5), 109.5 (C(CH3)2), 126.0, 128.0, 128.7, 137.0 (Ar-C), 200.9 (CHO).

Anal. Calcd for C17H20O5: C, 70.23; H, 7.64. Found: C, 70.11; H, 7.51.
According to the General Procedure, the reaction of homoolald adduct 16b (0.25 g, 0.54 mmol) with benzaldehyde (0.06 g, 0.59 mmol) and BF₃·OEt₂ (0.09 mL, 0.59 mmol) gave 0.14 g (61%) of 26b; colorless solid; mp 121 °C; [α]D₂₀ +1.04, CHCl₃); ν (CH₃) 2.97, 2.92, 2.90, 2.85, 2.80, 2.70, 2.68, 2.65, 2.63, 2.60, 2.58; ν (CHO) 3.47, 3.45, 3.43, 3.41, 3.39, 3.37, 3.35, 3.33, 3.31, 3.29; δ (CH₃) 1.33, 1.31, 1.29, 1.27, 1.25, 1.23, 1.21, 1.19, 1.17, 1.15; δ (C₆H₅) 7.38, 7.36, 7.34, 7.32, 7.30, 7.28, 7.26, 7.24, 7.22, 7.20.

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References

(1) X-ray crystal structure analysis.


(21) X-ray crystal structure analysis for 16d: Formula C₈₈H₆₈O₇, M = 429.54, colorless crystal 0.40 × 0.30 × 0.30 mm, a = 10.239 (1), b = 12.544 (1), c = 10.305 (1) Å, β = 115.42 (1), V = 1195.4 (2) Å³, ρcalc = 1.193 g cm⁻³, μ = 0.088 mm⁻¹, empirical absorption correction (0.966 ≤ T ≤ 0.974), Z = 2, monoclinic, space group P2₁ (No. 4), λ = 0.71073 Å, T = 198 K, ω and φ scans, 11178 reflections collected (h, k, l), ω = 0.67 Å⁻¹, 5221 independent (Rint = 0.063) and 3783 observed reflections [I ≥ 2σ(I)], R = 0.045, wR² = 0.104, Flack parameter +0.1 (8), max. residual electron density 0.19 (-0.17) e Å⁻³, hydrogen atoms calculated and refined as riding atoms.


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(25) We isolated and characterized this type of intermediate previously.₄

(26) Carbohydrate numbering which matches with those of the open-chain precursor 16.


(30) X-ray crystal structure analysis for 26c: Formula C₁₈₂H₁₉₂O₇, M = 418.47, colorless crystal 0.30 × 0.20 × 0.15 mm, a = 10.573 (1), b = 10.872 (1), c = 19723 (1) Å, V = 2267.2 (3) Å³, ρcalc = 1.226 g cm⁻³, μ = 0.744 mm⁻¹, empirical absorption correction (0.808 ≤ T ≤ 0.897), Z = 4, orthorhombic, space group P2₁2₁2₁ (No. 19), λ = 1.54178 Å, T = 293 K, ω and φ scans, 22050 reflections collected (h, k, l), [(sin θ)/λ] = 0.60 Å⁻¹, 4065 independent (Rint = 0.039) and 3861 observed reflections [I ≥ 2σ(I)], 276 refined parameters, R = 0.033, wR² = 0.089, Flack parameter 0.07 (15), max. residual electron density 0.17 (-0.12) e Å⁻³, hydrogen atoms calculated and refined as riding atoms.

(31) Data sets were collected with Nonius KappaCCD diffractometers, in case of Mo-radiation equipped with a rotating anode generator. Programs used: data collection COLLECT, data reduction Denzo-SMN, absorption correction SORTEAV and Denzo-SMN structure solution SHELXS-97, structure refinement SHELXL-97, and graphics SCHAKAL. CCD 621679 & 621680 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033, E-mail: deposit@ccdc.cam.ac.uk].


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