Synthesis of β-Hydroxy O-Alkyl Hydroxylamines from Epoxides Using a Convenient and Versatile Two-Step Procedure

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Abstract: A simple and convenient synthetic method was developed to prepare β-hydroxy O-alkyl hydroxylamines in which base-mediated ring opening of epoxides with acetophenone oxime followed by cleavage of the oxime with 2,4-dinitrophenylhydrazine in acidic media furnished the hydroxylamine, which can be protected in situ with various N-protecting groups.

Key words: hydroxylamines, epoxides, ring opening, oxime cleavage, protecting groups

O-Alkyl hydroxylamines (or aminooxy compounds), which are non-basic substitutes for amines,1 are found in various natural products such as L-canaline2 and in various synthetic products displaying interesting biological activities.2,3 Along with their β-hydroxy congeners,4 these compounds predominantly show enzyme inhibition activities whereby the aminooxy moiety forms a stable oxime with an aldehyde group present on the cofactor. In preparative chemistry these reactive species usually serve as starting material for the preparation of functionalized O-alkyl oximes by simple condensation with aldehydes or ketones, often with quantitative yields and with almost complete functional group compatibility. This classical reaction has undergone a renaissance as a chemoselective ligation strategy and has emerged as a powerful means for the assembly of biomolecules.5

In connection with ongoing projects in our laboratory,6 we required a variety of β-hydroxy O-alkyl hydroxylamines 2 and conceived that these might be accessed by the opening of epoxides 1 by N-protected hydroxylamines followed by deprotection of the nitrogen atom (Scheme 1). Toward this end, the most efficient approach leading to 2 seemed to be a direct opening of epoxide 1 by an N-protected hydroxylamine (i.e., N-Fmoc-hydroxylamine7 or commercially available N-Boc-hydroxylamine). Surprisingly, such protocols are scarcely documented in the literature. In most reports, N-Boc-hydroxylamine is used under basic conditions, which leads to the expected β-hydroxy O-alkyl hydroxylamines in low to modest yields.4b,c,8 The successful employment of N-hydroxyphthalimide in this context was also described by Porco and co-workers9 with promotion by a Co-oligosalen catalyst.10 In pursuit of our goal, we initially looked for viable conditions on commercially available cyclopentene oxide (3h; see Table 1). Because the use of potassium carbonate with N-Fmoc-hydroxylamine under Plenikiewicz’s conditions8b showed no discernible conversion (Table 1, entry 1), we decided to leave basic conditions aside and investigate the ring opening of epoxide 3h under Lewis acid catalysis conditions (Table 1, entries 2–15), which is a method usually used for the insertion of alcohols and/or amines but not yet employed with hydroxylamines as the nucleophile component. The ring opening of epoxide 3h with N-Fmoc-hydroxylamine was first investigated with BF3·Et2O in dichloromethane (Table 1, entry 2), conditions that are known to be efficient for the reaction of benzyl alcohol with a similar epoxide,6a but this approach was unsuccessful in this case. The use of lanthanide-based Lewis acids [i.e., Sc(OTf)3 and Yb(OTf)3] also failed (Table 1, entries 3–6). Changing the nucleophile to N-Boc hydroxylamine or N-hydroxypiperidine, presumably more nucleophilic species, was also unproductive with numerous types of Lewis acid [LiBr, InCl3, ZrCl4, Cu(OTf)2, or Ti(OiPr)4; Table 1, entries 7–15]. Finally, we envisaged an alternative two-step procedure based on the intermediate introduction of an oxime under basic conditions as a hydroxylamine precursor, followed by its acid-mediated cleavage to give the expected β-hydroxy O-alkyl hydroxylamine. Oximes are more nucleophilic than hydroxylamines under basic conditions and their high-yield ring-opening of epoxides has been described.11 Thus, the group of Soltani Rad recently described the aqueous-mediated ring opening of various epoxides with a range of oximes.12 Their protocol involved the use of a slight excess of potassium hydroxide (1.3 equiv) to deprotonate the oxime (1 equiv) in a mixture of water–dimethyl sulfoxide (DMSO) (7:3) at room temperature, followed by the addition of an excess of epoxide (1.5 equiv). Similar conditions were evaluated on cyclopentene oxide (3h) but with a slight excess of acetophenone oxime, as it would ultimately represent the least precious component in reactions employing more complex epoxides (Table 1, entry

Scheme 1

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Surprisingly, the solvent system used by Soltani Rad et al. was not efficient for our model epoxide and only traces of the expected compound were obtained. Heating to 90 °C led to formation of the desired oxime in 73% yield. Unfortunately, the presence of an epoxide was not compatible with 2,4-dinitrophenylhydrazine-mediated cleavage of the oxime (Table 2, entry 5). Thus, epoxide 4e was opened with a second equivalent of acetophenone oxime to give 4f in good yield (Table 2, entry 6). Highly functionalized Cerny’s epoxide 3j was converted into its β-hydroxy O-alkyl hydroxylamine derivative 5j in 76% over two steps (Table 2, entry 9). Protection as carbamates in situ was also successful, and 5–8j were obtained in high yields (Table 2, entry 9). Finally, the cyclopentene-derived epoxide 1a was opened with acetophenone oxime at 90 °C and converted into the Fmoc-protected targeted skeleton in good yield (73%) over two steps (Table 2, entry 10).

In conclusion, we have established a convenient two-step procedure for the synthesis of β-hydroxy O-alkyl hydroxylamines by oxime-mediated regioselective opening of epoxides under basic conditions, followed by cleavage of the resulting oxime by 2,4-dinitrophenylhydrazine. We showed that various protecting groups could be introduced for protection of the highly polar resulting O-alkyl hydroxylamines in situ. The scope of the reaction revealed its good tolerance for alkenes, halogens, and alcohols.

Reactions were performed under an atmosphere of argon and monitored by thin-layer chromatography on Merck silica gel plates (60 F254 aluminum sheets). All separations were carried out under flash-chromatographic conditions on silica gel (Redi Sep prepacked column, 230–400 mesh) with the use of a CombiFlash Companion. N,N-Dimethylformamide (DMF) was purified by filtration through an activated alumina column under argon. MeOH was purchased from Acros Organics at the highest commercial quality and used without further purification. Reagent-grade chemicals were ob-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>LA (cat.) or base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>HONHfmoC</td>
<td>K2CO3</td>
<td>EtOH</td>
<td>60</td>
<td>NR</td>
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<tr>
<td>2</td>
<td>HONHfmoC</td>
<td>BF3Et2O</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>NR</td>
</tr>
<tr>
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<td>Sc(OtO)3</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>NR</td>
<td></td>
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<tr>
<td>4</td>
<td>Sc(OtO)3</td>
<td>MeCN</td>
<td>r.t.</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Sc(OtO)3</td>
<td>THF</td>
<td>r.t.</td>
<td>NR</td>
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</tr>
<tr>
<td>6</td>
<td>Yb(OtO)3</td>
<td>THF</td>
<td>r.t.</td>
<td>NR</td>
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<td>7</td>
<td>HONHBoc</td>
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<td>Yb(OtO)3</td>
<td>CH2Cl2</td>
<td>r.t.</td>
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<td>9</td>
<td>Sc(OtO)3</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>NR</td>
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<tr>
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<td>Yb(OtO)3</td>
<td>CH2Cl2</td>
<td>r.t.</td>
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<td>r.t.</td>
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<tr>
<td>13</td>
<td>Ti(OiPr)4</td>
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<td>r.t.</td>
<td>NR</td>
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<tr>
<td>14</td>
<td>Cu(OtO)2</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>NR</td>
<td></td>
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<tr>
<td>15</td>
<td>ZrCl4</td>
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<td>r.t.</td>
<td>NR</td>
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<td>H2O–DMSO</td>
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<td>trace</td>
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<tr>
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<td>H2O–DMSO</td>
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<td>23</td>
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<tr>
<td>18</td>
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<td>DMF</td>
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<td>trace</td>
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<td>19</td>
<td>KOH</td>
<td>DMF</td>
<td>90</td>
<td>73</td>
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</tr>
</tbody>
</table>

* Isolated yield.
* NR = no reaction.
* In a 7:3 ratio.

Table 1 Ring Opening of Cyclopentene Oxide with Hydroxylamine-Derived Nucleophiles

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**Table 2** Scope of the Two-Step Procedure; Synthesis of β-Hydroxy O-Alkyl Hydroxylamines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide 3</th>
<th>O-Alkyl oxime 4</th>
<th>Product (Yield)</th>
<th>O-Alkyl hydroxylamine 5–8</th>
<th>R³</th>
<th>Product (Yield)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>OPMP</td>
<td>PhN=O</td>
<td>4a⁵ 83</td>
<td>H 5a 77</td>
<td></td>
<td>Fmoc 6a 81⁴</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>4b 74³</td>
<td>Fmoc 6b 95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>4c 84³</td>
<td>Fmoc 6c 69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>4d 46⁶</td>
<td>Fmoc 6d 93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>4e 73</td>
<td>H 5e 0⁶</td>
<td></td>
<td>Fmoc 6e 0⁶</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>4f 86</td>
<td>Fmoc 6f _³⁸</td>
<td></td>
<td>Alloc 8f 61</td>
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<tr>
<td>7</td>
<td></td>
<td></td>
<td>4h 73⁵</td>
<td>H 5h _³⁸</td>
<td></td>
<td>Fmoc 6h 99</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>4i 89⁴</td>
<td>Fmoc 6i _³⁸</td>
<td></td>
<td>Alloc 8i 81</td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td>4j 89³</td>
<td>H 5j 76</td>
<td></td>
<td>Fmoc 6j 76</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>4k 84³</td>
<td>Fmoc 2a 87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Isolated yield.
* PMP = p-methoxyphenyl.
* The yield dropped to 54% when only 2 equiv of H₂SO₄ were used.
* Reaction performed at 50 °C.
* Reaction performed at 90 °C.
* Formation of the expected product was not observed.
* Formation of the expected product was observed by ¹H NMR spectroscopic analysis, but its isolation was troublesome.
* The expected product was obtained as an inseparable mixture with Fmoc-protected 2,4-dinitrophénylhydrazine.
tained from Sigma–Aldrich or Acros Organics chemical companies and were used as received. Optical rotations were measured with an Anton Paar MCP 300 polarimeter at 589 nm and are expressed in deg cm\(^{-1}\) g\(^{-1}\). IR spectra were recorded with a Perkin–Elmer FT-IR system using a diamond window Dura SamplIR II and the data are reported in reciprocal centimeters (cm\(^{-1}\)). \(^1\)H (500 or 300 MHz) and \(^13\)C (125 or 75 MHz) NMR spectra were recorded with Bruker Avance spectrometers. Chemical shifts are given in ppm (d) and are referenced to the internal solvent signal or to TMS used as an internal standard. High-resolution mass spectra (HRMS) were recorded with a Micromass LCT Premier XE instrument (Waters) and were determined by electrospray ionization (ESI).

**Epoxide Opening: General Procedure A**

Acetophenone oxime (1.5 equiv) and KOH (3 equiv) were dissolved in anhydrous DMF (0.15 M in epoxide) and the solution was stirred at r.t. for 30 min. A solution of epoxide (1 equiv) in anhydrous DMF (0.3 M in epoxide) was then added and the mixture was stirred at the indicated temperature for 16 h. After addition of H\(_2\)O, aq HCl (1 M) was added dropwise until pH 1–2. The mixture was extracted with MTBE (3×) and the combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo.

**Acetophenone Oxime O-[2-Hydroxy-3-(4-methoxyphenyl)pro- pyl] Oxime (4a)**

The reaction was carried out according to General Procedure A with glycidyl 4-methoxyphenyl ether (90 mg, 0.5 mmol), acetophenone oxime (101 mg, 0.75 mmol) and KOH (84 mg, 1.5 mmol) in DMF (5 mL). The mixture was stirred at r.t. for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 95:5–9:1) to give 4a.

Yield: 131 mg (0.415 mmol, 83%); colorless oil; \(R_f = 0.19\) (heptane–MTBE, 4:1).

**Acetophenone O-[2-Hydroxyoctyl] Oxime (4b)**

The reaction was carried out according to General Procedure A with 1,2-epoxyoctane (128 mg, 1 mmol), acetophenone oxime (203 mg, 1.5 mmol), and KOH (168 mg, 3 mmol) in DMF (10 mL). The mixture was stirred at 90 °C for 16 h and worked up as described. The crude product was purified by preparative HPLC (NW50 column, Merck; heptane–EtOAc, 10:0–8:2 over 35 min; 100 mL/min; UV detection at 254 nm) to give 4b.

Yield: 92 mg (0.420 mmol, 84%); colorless oil; \(R_f = 0.24\) (heptane–MTBE, 4:1).

**Acetophenone O-[2-Hydroxy-3-(3-en-1-yl) Oxime (4c)**

The reaction was carried out according to General Procedure A with 2-methyl-2-vinylloxirane (84 mg, 1 mmol), acetophenone oxime (203 mg, 1.5 mmol) and KOH (168 mg, 3 mmol) in DMF (10 mL). The mixture was stirred at 50 °C for 16 h and worked up as described. The crude product was purified by preparative HPLC (NW50 column, Merck; heptane–EtOAc, 10:0–8:2 over 35 min; 100 mL/min; UV detection at 254 nm) to give 4c.

Yield: 197 mg (0.464 mmol, 46%); pale-yellow oil; \([\alpha]_D^{24} = -12.6 (c 0.89, CHCl_3)\); \(R_f = 0.22\) (heptane–EtOAc, 3:7).

**Acetophenone O-[2-(3-Dihydroxypropyl) Oxime (4d)**

The reaction was carried out according to General Procedure A with (S)-glycidol (74 mg, 1 mmol), acetophenone oxime (203 mg, 1.5 mmol) and KOH (168 mg, 3 mmol) in DMF (10 mL). The mixture was stirred at 90 °C for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 1:1) to give 4d.

Yield: 97 mg (0.464 mmol, 46%); pale-yellow oil; \([\alpha]_D^{24} = -12.6 (c 0.89, CHCl_3)\); \(R_f = 0.22\) (heptane–EtOAc, 3:7).

**Acetophenone O-[2-Oxiran-2-ylmethyl Oxime (4e)**

The reaction was carried out according to General Procedure A with epichlorohydrin (234 µL, 3 mmol), acetophenone oxime (405 mg, 3 mmol) and KOH (336 mg, 6 mmol) in DMF (20 mL). The mixture was stirred at r.t. for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 4:1) to give 4e.

Yield: 420 mg (2.2 mmol, 73%); colorless oil; \(R_f = 0.48\) (heptane–EtOAc, 7:3).

**Acetophenone O-Oxiran-2-ylmethyl Oxime (4e)**

The reaction was carried out according to General Procedure A with epichlorohydrin (234 µL, 3 mmol), acetophenone oxime (405 mg, 3 mmol) and KOH (336 mg, 6 mmol) in DMF (20 mL). The mixture was stirred at r.t. for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 4:1) to give 4e.
(1E,1′E)-Acetophenone O-(2-Hydroxy-3-[(E)-1-phenylethylidenecarbonyl]oxy)propyl) Oxime (4f)

The reaction was carried out according to General Procedure A with 4c (100 mg, 0.52 mmol), acetophenone oxime (106.1 mg, 0.78 mmol) and KOH (88 mg, 1.6 mmol) in DMF (5 mL). The mixture was stirred at r.t. for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 7:3) to give 4f.

Yield: 147.5 mg (0.45 mmol, 86%); colorless oil; Rf = 0.63 (heptane–EtOAc, 3:2).

IR (neat): 3411, 2925, 2854, 1650, 1601, 1581, 1503, 1460, 1438, 1375, 1318, 1197, 1104, 1059, 1039, 972, 905, 886, 760, 690 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.28 (s, 3 H, Me), 2.46–4.42 (m, 5 H, H-1, H-2), 7.32–7.41 (m, 6 H, Ph-H), 7.59–7.69 (m, 4 H, Ph-H).

13C NMR (75 MHz, CDCl₃): δ = 12.7 (CH₃), 44.8 (C-3), 50.2 (C-2), 74.8 (C-1), 126.0 (CH-Ph), 128.3 (CH-Ph), 129.1 (CH-Ph), 136.3 (C₆H₅Ph), 155.3 (C₆H₅N=).


Compound 4j

The reaction was carried out according to General Procedure A with NAP-protected Cerny’s epoxide (142 mg, 0.4 mmol), acetophenone oxime (101 mg, 0.75 mmol) and KOH (84 mg, 1.5 mmol) in DMF (5 mL). The mixture was stirred at 90 °C for 16 h and worked up as described. The crude product was purified by column chromatography (heptane–EtOAc, 8.2:7.3) to give 4j.

Yield: 187 mg (0.446 mmol, 89%); pale-yellow foam; [α]D24 = −7.6 (c 1.09, CHCl₃); Rf = 0.47 (heptane–EtOAc, 1:1).

IR (neat): 3411, 2925, 2905, 1445, 1359, 1318, 1304, 1039, 972, 918, 905, 886, 760, 690 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.23 (s, 3 H, Me), 3.23 (br s, 1 H, OH), 3.43 (s, 1 H, H-2), 3.64 (dd, J = 6.4 Hz, 1 H, H-6), 3.84 (d, J = 7.3 Hz, 1 H, H-6), 4.07–4.14 (m, 2 H, H-3, H-4), 4.60 (d, J = 4.9 Hz, 1 H, H-5), 4.77 and 4.84 (AB, JAB = 12.2 Hz, 2 H, CH₂-NAP), 5.63 (s, 1 H, H-1), 7.28–7.36 (m, 3 H, ArH), 7.39–7.51 (m, 3 H, ArH), 7.56–7.63 (m, 2 H, ArH), 7.73–7.82 (m, 2 H, ArH).

13C NMR (75 MHz, CDCl₃): δ = 13.0 (CH₃), 66.5 (C-6), 71.0 (C-3), 71.8 (CH₂-NAP), 75.6 (C-5), 79.9 (C-2), 83.3 (C-4), 100.6 (C-1), 125.7 (CH-Ar), 125.9 (CH-Ar), 126.1 (CH-Ar), 126.1 (CH-Ar), 127.6 (CH-Ar), 127.8 (CH-Ar), 128.2 (CH-Ar), 128.4 (CH-Ar), 129.4 (CH-Ar), 132.9 (C₆H₅NAP), 133.1 (C₆H₅NAP), 135.3 (C₆H₅NAP), 136.0 (C₆H₅NAP), 156.8 (C₆H₅N=).

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C₁₂H₁₀N₂O₂Na: 442.1630; found: 442.1631.

(1R,2S,3R,5S)-2-[(Benzyloxy)methyl]-3-(naphthalen-2-ylmethoxy)-6-oxacyclohexyl[3.1.0]hexane (1a)

To a solution of (1R,2S,3R,5S)-2-[(benzyloxy)methyl]-6-oxacyclohexyl[3.1.0]hexane-3-ol (205 mg, 0.931 mmol, 1 equiv) in anhydrous DMF (10 mL) were added NaH (60% in mineral oil, 67 mg, 1.68 mmol, 1.8 equiv) and 2-bromomethylnaphthalene (309 mg, 1.40 mmol, 1.5 equiv) and the mixture was stirred at r.t. for 4 h. After addition of crushed ice, the mixture was extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and concentrated in vacuo. Purification by column chromatography (heptane–EtOAc, 7:3) gave 1a.

Yield: 322 mg (0.893 mmol, 96%); pale-yellow oil; [α]D24 = −48.0 (c 0.089, CHCl₃); Rf = 0.43 (heptane–EtOAc, 3:2).

IR (neat): 2925, 2856, 1362, 1121, 1084, 1027, 839, 815, 737, 697 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 2.04 (dd, J = 0.9, 7.6, 15.3 Hz, 1 H, H-5), 2.18 (d, J = 15.3 Hz, 1 H, H-5), 2.65 (J = 5.8 Hz, 1 H, H-2), 3.37 and 3.40 (ABX, JAB = 9.5 Hz, JAX = 6.1 Hz, JBX = 6.1 Hz, 2 H, CH₂-ObN), 3.46 (d, J = 2.1 Hz, 1 H, H-4), 3.54 (br s, 1 H, H-3), 3.93 (d, J = 7.6 Hz, 1 H, H-1), 4.45 (s, 2 H, CH₂-ObN), 4.61 and 4.68 (AB, JAB = 12.8 Hz, 2 H, CH₂-NAP), 7.20–7.33 (m, 5 H, ArH), 7.40–7.50 (m, 3 H, ArH), 7.69–7.84 (m, 4 H, ArH).

13C NMR (75 MHz, CDCl₃): δ = 34.8 (C-5), 47.4 (C-2), 57.9 (C-3), 59.7 (C-4), 69.2 (CH₂-ObN), 70.9 (CH₂-NAP), 73.2 (CH₂-ObN), 80.9 (C₆H₅N=).
(C-1), 125.7 (CH-Ar), 125.9 (CH-Ar), 126.0 (CH-Ar), 126.4 (CH-Ar), 127.4 (CH-Ar), 127.6 (CH-Ar), 127.8 (CH-Ar), 128.0 (CH-Ar), 128.3 (CH-Ar), 132.9 (Cq-NAP), 133.2 (Cq-NAP), 135.9 (Cq-NAP), 138.0 (Cq-Bn).


(9H-Fluoren-9-yl)methyl 2-Hydroxy-3-(4-methoxyphenox)propanoylcarbamate (6a)

The reaction was carried out according to General Procedure B with 4a (79 mg, 0.25 mmol, 2,4-dinitrophenylhydrazine (99 mg, 0.05 mmol), H₂SO₄ (135 µL, 2.5 mmol) in MeOH (2 mL), and then with NaHCO₃ (420 mg, 5 mmol) and FmocCl (323 mg, 1.25 mmol) in MeOH (10 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 8:2 → 7.3) to give 6a.

Yield: 88 mg (0.202 mmol, 81%); pale-yellow amorphous solid; Rf = 0.16 (heptane–EtOAc, 1.6:1).


Synthesis of N-Protected γ-Alkyl Hydroxylamine: General Procedure B

To a solution of β-hydroxy oxime O-ether (1 equiv) in anhydrous MeOH (0.13 M) were added H₂SO₄ (10 equiv) and 2,4-dinitrophenylhydrazine (2 equiv) and the mixture was stirred at r.t. for 16 h. After dilution with MeOH (4 × initial volume), powdered NaHCO₃ (20 equiv) was added slowly at 0 °C, followed by protecting reagent (5 equiv). The reaction mixture was stirred for 3 h at r.t. and then treated with EtOAc (2 × volume of MeOH). The organic layer was washed with H₂O (2), brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by column chromatography (heptane–EtOAc, 1:1) gave 5a.

Yield: 41 mg (0.192 mmol, 77%); pale-yellow amorphous solid; Rf = 0.10 (heptane–EtOAc, 1:4).

IR (neat): 3301, 3249, 2935, 1513, 1240, 1046, 1033, 825 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 3.76 (s, 3 H, OMe), 3.83 and 3.90 (ABX, JAX = 11.7 Hz, JXX = 3.1 Hz, JAB = 6.5 Hz, H-1, H-1), 3.96 (d, J = 5.6 Hz, 2 H, H-3), 4.22–4.30 (m, 1 H, H-2), 6.79–6.89 (m, 4 H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 55.7 (OCH₃), 68.5 (C-2), 68.1 (CH₂-Bn), 69.1 (C-3), 79.0 (C-1), 114.7 (CH-Ar), 115.6 (CH-Ar), 123.8 (CH-Ar), 127.2 (CH-Ar), 127.9 (CH-Ar), 131.5 (Cq-Bn), 152.6 (Cq-CO), 154.1 (Cq-OMe), 158.6 (CO).


Benzyl 2-Hydroxy-3-(4-methoxyphenox)propanoylcarbamate (7a)

The reaction was carried out according to General Procedure B with 4a (79 mg, 0.25 mmol, 2,4-dinitrophenylhydrazine (99 mg, 0.05 mmol), H₂SO₄ (135 µL, 2.5 mmol) in MeOH (2 mL), and then with NaHCO₃ (420 mg, 5 mmol) and CbzCl (188 µL, 1.25 mmol) in MeOH (10 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 8:2 → 7.3) to give 7a.

Yield: 69 mg (0.199 mmol, 80%); yellow amorphous solid; Rf = 0.24 (heptane–EtOAc, 3:2).

IR (neat): 3406, 3160, 2954, 1724, 1506, 1266, 1232, 1129, 1109, 1041, 823, 739, 696 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 3.76 (s, 3 H, OMe), 3.92–4.02 (m, 4 H, H-1, H-3), 4.28–4.29 (m, 1 H, H-2), 5.19 (s, 2 H, CH₂-Bn), 6.78–6.78 (m, 4 H, ArH), 7.33–7.40 (m, 5 H, ArH), 7.63 (s, 1 H, ArH).
The reaction was carried out according to General Procedure B with 4b (70 mg, 0.266 mmol), 2,4-dinitrophenylhydrazine (105 mg, 0.532 mmol), and H₂SO₄ (143 µL, 2.66 mmol) in MeOH (2 mL), and then with NaHCO₃ (447 mg, 5.32 mmol) and FmocCl (344 mg, 1.33 mmol) in MeOH (10 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 7:3) to give 6b.

Yield: 97 mg (0.253 mmol, 95%); pale-yellow crystals; Rₛ = 0.27 (heptane–EtOAc, 7:3).

IR (neat): 3262, 2975, 2924, 2855, 1698, 1495, 1479, 1465, 1447, 1218, 1176, 756, 736 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 9.57 (s, 1 H, OH), 5.94 (s, 1 H, ArH), 5.31 (d, J = 9.8, 11.3 Hz, 1 H, H-1), 4.40 (d, J = 6.7 Hz, 1 H, CH-Fmoc), 4.05 and 4.04 (ABX, Jₓᵧ = 7.3 Hz, 2 H, ArH), 4.32 (t, J = 7.3 Hz, 2 H, ArH), 7.67 (s, 1 H, NH), 7.82 (d, J = 7.3 Hz, 2 H, ArH).

1C NMR (75 MHz, CDCl₃): δ = 141.1 (C=O), 22.6 (C-7), 25.5 (C-4 or C-5), 29.3 (C-4 or C-5), 31.7 (C-6), 32.1 (C-3), 46.9 (CH-Fmoc), 67.6 (CH₂-Fmoc), 68.1 (C-1), 81.8 (C-1), 120.0 (CH₂-CH₂), 124.9 (CH₂-CH₂), 127.9 (CH₂-CH₂), 141.3 (C₁-C₇), 143.3 (C₃-Fmoc), 143.3 (C₇-Fmoc), 158.7 (C=O).


(9H-Fluoren-9-yl)methyl (2-Hydroxyoctyl)oxycarbamate (6b)

The reaction was carried out according to General Procedure B with 4c (70 mg, 0.266 mmol), 2,4-dinitrophenylhydrazine (105 mg, 0.532 mmol), and H₂SO₄ (143 µL, 2.66 mmol) in MeOH (2 mL), and then with NaHCO₃ (447 mg, 5.32 mmol) and FmocCl (344 mg, 1.33 mmol) in MeOH (10 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 7:3) to give 6b.

Yield: 97 mg (0.253 mmol, 95%); pale-yellow crystals; Rₛ = 0.27 (heptane–EtOAc, 7:3).

IR (neat): 3262, 2975, 2924, 2855, 1698, 1495, 1479, 1465, 1447, 1218, 1176, 756, 736 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 8.08±0.04 (m, 3 H, H-8), 1.18±1.54 (m, 10 H, H₃–H₇), 3.62 (dd, J = 9.8, 11.3 Hz, 1 H, H-1), 4.40 (d, J = 6.7 Hz, 1 H, CH-Fmoc), 4.05 and 4.04 (ABX, Jₓᵧ = 7.3 Hz, 2 H, ArH), 4.32 (t, J = 7.3 Hz, 2 H, ArH), 7.67 (s, 1 H, NH), 7.82 (d, J = 7.3 Hz, 2 H, ArH).

1C NMR (75 MHz, CDCl₃): δ = 141.1 (C=O), 22.6 (C-7), 25.5 (C-4 or C-5), 29.3 (C-4 or C-5), 31.7 (C-6), 32.1 (C-3), 46.9 (CH-Fmoc), 67.6 (CH₂-Fmoc), 68.1 (C-1), 81.8 (C-1), 120.0 (CH₂-CH₂), 124.9 (CH₂-CH₂), 127.9 (CH₂-CH₂), 141.3 (C₁-C₇), 143.3 (C₃-Fmoc), 143.3 (C₇-Fmoc), 158.7 (C=O).


Synthesis of β-Hydroxy O-Alkyl Hydroxylamines
Yield: 152.8 mg (0.451 mmol, 99%); pale-yellow oil; \( R_f = 0.13 \) (heptane–EtOAc, 7:3).

(1H NMR (500 MHz, CDCl3); \( \delta = 1.49–1.58 \) (m, 1 H, H-3), 1.59–1.73 (m, 3 H, H-4, H-5), 1.89–2.00 (m, 2 H, H-3, H-5), 2.36 (br s, 1 H, OH), 4.04–4.09 (m, 1 H, H-1), 4.13–4.18 (m, 1 H, H-2), 4.20 (t, \( J = 6.7 \) Hz, 1 H, CH-Fmoc), 4.50 (d, \( J = 6.7 \) Hz, 2 H, CH2-Fmoc), 7.29 (td, \( J = 0.9, 7.6 \) Hz, 2 ArH), 7.38 (t, \( J = 7.3 \) Hz, 2 ArH), 7.55 (br s, 1 H, NH), 7.56 (d, \( J = 7.3 \) Hz, 2 ArH), 7.74 (d, \( J = 7.6 \) Hz, 2 ArH).

(13C NMR (75 MHz, CDCl3); \( \delta = 20.5 (C-4), 27.9 (C-5), 31.7 (C-3), 47.3 (CH-Fmoc), 67.6 (CH2-Fmoc), 75.8 (C-2), 93.5 (C-1), 120.2 (CH-2Ar), 125.1 (CH-Ar), 127.3 (CH-Ar), 128.0 (CH-Ar), 141.5 (Cq-Fmoc), 143.6 (Cq-Fmoc), 158.3 (Cq-O).

HRMS (ESI-TOF): \( m/z \) [M + H]+ calcd for C17H20NO5: 318.1350; found: 318.1350.

Fluorenylmethyl [(1R,2R,3S,4R,5R)-3-Hydroxy-2-(naphthalen-2-ylmethoxy)-6,8-dioxabicyclo[3.2.1]octan-4-yl] oxycarbamate (6j)

To a solution of \( 6j \) (100 mg, 0.238 mmol), 2,4-dinitrophenylhydrazine (94 mg, 0.477 mmol), and H2SO4 (128 μL, 2.38 mmol) in MeOH (2 mL). THF (100 μL) was added to improve the solubility of the starting material. After 16 h at r.t., 2,4-dinitrophenylhydrazine (47 mg, 0.238 mmol, 1 equiv) was added to complete the reaction and the mixture was stirred for 2 h before being diluted with MeOH (8 mL).

The reaction was carried out according to General Procedure B with \( 6j \) (100 mg, 0.238 mmol), 2,4-dinitrophenylhydrazine (94 mg, 0.477 mmol), and H2SO4 (128 μL, 2.38 mmol) in MeOH (2 mL). THF (100 μL) was added to improve the solubility of the starting material. After 16 h at r.t., 2,4-dinitrophenylhydrazine (47 mg, 0.238 mmol, 1 equiv) was added to complete the reaction and the mixture was stirred for 2 h before being diluted with MeOH (8 mL). H2SO4 (400 mg, 4.76 mmol) and FmocCl (308 mg, 1.19 mmol) were added, and the reaction mixture was stirred at r.t. for 4 h. Addition of NaHCO3 (200 mg, 2.38 mmol) and FmocCl (154 mg, 0.759 mmol) were necessary to complete the reaction. The mixture was then stirred overnight and worked up as described. Purification by column chromatography (heptane–EtOAc, 4:1–3:2) afforded \( 6j \).

Yield: 98 mg (0.182 mmol, 76%); pale-yellow amorphous solid; \( R_{f} = 0.21 \) (heptane–EtOAc, 1:1; visualized by KMnO4 only).

IR (neat): 3384, 3209, 1721, 1513, 1269, 1101, 1076, 1011, 909, 577, 545 cm–1.

HRMS (ESI-TOF): \( m/z \) [M + H]+ calcd for C21H22N2O7: 369.1561; found: 369.1561.

Fluorenylmethyl [(1R,2R,3S,4R,5R)-3-Hydroxy-2-(naphthalen- 2-ylmethoxy)-6,8-dioxabicyclo[3.2.1]octan-4-yl] oxycarbamate (7)

The reaction was carried out according to General Procedure B with \( 7 \) (100 mg, 0.238 mmol), 2,4-dinitrophenylhydrazine (94 mg, 0.477 mmol), and H2SO4 (128 μL, 2.38 mmol) in MeOH (2 mL). THF (100 μL) was added to improve the solubility of the starting material. After 16 h at r.t., 1,4-dinitrophenylhydrazine (47 mg, 0.238 mmol, 1 equiv) was added to complete the reaction and the mixture was stirred for 2 h before being diluted with MeOH (8 mL).

The reaction was carried out according to General Procedure B with \( 7 \) (100 mg, 0.238 mmol), 2,4-dinitrophenylhydrazine (94 mg, 0.477 mmol), and H2SO4 (128 μL, 2.38 mmol) in MeOH (2 mL). THF (100 μL) was added to improve the solubility of the starting material and then with NaHCO3 (400 mg, 4.76 mmol) and CbzlCl (179 μL, 1.19 mmol) in MeOH (8 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 8:2→6:4 to give 7).

Yield: 95 mg (0.210 mmol, 88%); pale-yellow oil; \( R_{f} = 0.3 \) (c 1.02, CHCl3); \( R_{f} = 0.15 \) (heptane–EtOAc, 3:2).

IR (neat): 3384, 3129, 1721, 1511, 1269, 1110, 1076, 1011, 993, 973, 877, 826, 751, 735 cm–1.
with NaHCO$_3$ (126 mg, 1.5 mmol) and FmocCl (97 mg, 0.375 mmol) in MeOH (2 mL) and then, with NaHCO$_3$ (400 mg, 4.76 mmol) and AlCl$_3$ (0.714 mmol, 3 equiv), and H$_2$SO$_4$ (128 μL, 1.5 mmol), and H$_2$SO$_4$ (40 μL, 0.5 mmol), and H$_2$SO$_4$ (100 mg, 0.238 mmol), 2,4-dinitrophenylhydrazine (141 mg, 0.750 mmol) in MeOH (8 mL). The mixture was worked up as described and the crude product was purified by column chromatography (heptane–EtOAc, 3:2) to give 8j.

Yield: 71 mg (0.177 mmol, 74%); pale-yellow solid; [α]$_D$ = −1.1 (c 0.92, CHCl$_3$); $R_f$ = 0.15 (heptane–EtOAc, 3:2).

IR (neat): 3381, 3217, 1714, 1507, 1258, 1099, 819, 749 cm$^{-1}$.

HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for C$_{39}$H$_{37}$NNaO$_6$: 638.2519; found: 638.2529.

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Supporting Information

For this article is available online on http://www.thieme-connect.com/ejournals/toc/synthesis.

References

