Synthesis of Functionalized Pentalenes via Carbonyl-Ene Reaction and Enzymatic Kinetic Resolution

Timo Anderl, Marc Emo, Sabine Laschat,* Angelika Baro, Wolfgang Frey
Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax +49(711)68564285; E-mail: sabine.laschat@oc.uni-stuttgart.de
Received 5 February 2008
Dedicated to Prof. Larry E. Overman on the occasion of his 65th birthday

Abstract: The synthesis of functionalized pentalene derivatives is described. Bicyclo[3.3.0]octane-3,7-dione (Weiss diketone) was converted in six steps into the silyl-protected 3-methylbicyclo[3.3.0]octenol, which was submitted to Lewis acid catalyzed carbonyl ene reactions with trioxane yielding the primary alcohol with exocyclic double bond in high yield. By subsequent kinetic resolution with lipases compound was enantiomerically enriched (up to 94% ee). It was also demonstrated that compound could be functionalized by hydroboration and oxidative workup to give the trihydroxy pentalene as well as by chain extension to the pentalene.

Key words: bicyclo[3.3.0]octanedione, hydroboration, lipases, primary alcohols, pentalene

A variety of natural products and pharmaceutical compounds contain a substituted pentalene, in the form of a bicyclo[3.3.0]octane system, as a common structural feature. Typical examples are carbacyclin (1), triquinanes such as silphiperfolene (2) and hirsutane (3), and the macrolactam cylindramide (4) (Figure 1).1,2

Consequently, several different synthetic routes to the pentalene system were reported: cationic, anionic, radical or metal-mediated cyclizations,3–5 Diels–Alder reactions6 as well as intermolecular Pauson–Khand reactions.7 Although the last reaction opens access to different substitution patterns,8,9 the use of stoichiometric amounts of Co₂(CO)₈ is a major limitation. Thus, we considered the readily available Weiss diketone as a suitable precursor to functionalized pentalenes (Scheme 1).

Diketone may be converted into the alkene, followed by Lewis acid catalyzed carbonyl-ene reaction as the key step towards pentalene derivative, which should then be further functionalized to the pentalene.

The carbonyl-ene reaction of the regioisomer of with exocyclic double bond and glyoxylate was performed by Mikami in a highly stereoselective manner,12 and White-sell reported an auxiliary-controlled ene reaction of glyoxylate with bicyclo[3.3.0]octa-1,5-diene.13 However, to the best of our knowledge, the ene reaction of endocyclic alkene with aldehydes has not been reported. It was particularly envisaged to utilize the exocyclic double bond in derivative for hydroboration and enzymatic resolution, and furthermore, to use the alcohol side chain for chain extension. The results towards this goal are reported below.

The synthesis of the ene component commenced with the diketone (Scheme 2), which was prepared in 69% yield from dimethyl acetone-1,3-dicarboxylate (9) and glyoxal according to the procedure by Weiss.10 Following a method by Piers,14 diketone was treated with 2,2-dimethylpropane-1,3-diol in the presence of TsOH to yield the monoacetal in 32% yield. In this manner, the total yield of 10 was isolated in 32% yield. In this manner, the total yield of 10
was improved to 84%. Reduction of 10 with NaBH₄ in MeOH gave the alcohol 12 as a diastereomeric mixture (dr 97:3) in 99% yield. Cleavage of the acetal 12 with PPTS in aqueous acetone afforded the ketone 13. The major diastereomer of 13 could be separated by recrystallisation from Et₂O. An X-ray crystal structure analysis confirmed the \textit{endo}-configuration of the alcohol moiety (Figure 2).¹⁶

Compound 13 was protected with TBSCI in the presence of imidazole in DMF to give the silyl ether 14 in 99% yield. Wittig reaction of the derivative 14 with methyltriphenylphosphonium bromide gave the enolic alcohol 15 in 99% yield. TsOH, toluene reflux, 3 h

The carbonyl-ene reaction of the alkene 6 with 1,3,5-trioxane (1 equiv) and Lewis acids¹⁹ (3 equiv) in CH₂Cl₂ was performed under various conditions, and after aqueous workup, the regioisomeric products \textit{rac}-7 and \textit{rac}-15 were isolated (Table 1).

**Table 1** Carbonyl-Ene Reaction of Pentalene 6 with 1,3,5-Trioxane in the Presence of Various Lewis Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)¹</th>
<th>7:15²</th>
<th>Yield (%)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·OEt₂</td>
<td>0</td>
<td>8</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>0</td>
<td>8</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>–78</td>
<td>5</td>
<td>95</td>
<td>1:99</td>
<td>3 (15)</td>
</tr>
<tr>
<td>4</td>
<td>AlMe₂Cl</td>
<td>20</td>
<td>24</td>
<td>82</td>
<td>8:92</td>
<td>10 (15)</td>
</tr>
<tr>
<td>5</td>
<td>AlMe₃</td>
<td>20</td>
<td>96</td>
<td>89</td>
<td>20:80</td>
<td>47⁷ (7 + 15)</td>
</tr>
<tr>
<td>6</td>
<td>MAPH</td>
<td>–78</td>
<td>3</td>
<td>100</td>
<td>99:1</td>
<td>91 (7)</td>
</tr>
</tbody>
</table>

¹ Determined by capillary GC.
² Isolated yield.
³ Combined yield.

Despite complete consumption, no trace of the desired products \textit{rac}-7 and \textit{rac}-15 were found with BF₃·OEt₂ and SnCl₄ (entries 1 and 2). With AlCl₃, AlMe₂Cl, and AlMe₃, the formation of product \textit{rac}-15 clearly dominated (entries 3–5). However, by using the sterically demanding Lewis acid methylaluminum bis(2,6-diphenylphenoxy) (MAPH) originally developed by Maruoka and Yamamoto,²⁰ the desired regioisomer \textit{rac}-7 was strongly favored (entry 6), and on a preparative scale we succeeded in isolating \textit{rac}-7 in 91% yield.

In order to obtain enantiomerically pure pentalenes, the alcohol \textit{rac}-7 was submitted to lipase-catalyzed kinetic resolution (Scheme 3). An empirical primary alcohol rule by Kazlauskas is based on the size of substituents, and the general structure 16 represents the favored enantiomer that is acylated by the lipase.²¹ We anticipated that the (1R,3aR,5S,6aS)-pentalene isomer 7 with comparable shape should fit this rule. The first screening of various lipases and solvents at 40 °C is summarized in Table 2.

As shown in Table 2, most lipases were active in various solvents, however, with regard to selectivity (E-value) and activity, that is, short reaction times, lipase PS-D in n-hexane seemed to work best (entry 9). Thus, this system was chosen for further optimization (Table 3).
As can be seen from Table 3, upon decreasing the reaction temperature the E-value increased, and the best result was obtained at −20 °C with 94% ee and an E-value of 70, albeit with long reaction time (entry 4). Unfortunately, scaling up resulted in a dramatic reduction of the enantioselectivity, and on a 2 mmol scale, 48% of the acetate \( (1R,3aR,5S,6aS)\)-17 and 46% of alcohol \( (1S,3aS,5R,6aR)\)-7 were obtained with only 70% ee each (E = 12). The enantiomeric excess of the acetate \( (1R,3aR,5S,6aS)\)-17 was determined after saponification with \( \text{K}_2\text{CO}_3\) in MeOH–H\(_2\)O to give the corresponding alcohol \( (1R,3aR,5S,6aS)\)-7 and subsequent GC analysis. Next, the functionalization of the exocyclic methylene group in \( \text{rac}-7\) was explored (Scheme 4). Following a method by Maezaki and Tanaka,\(^2\) the racemic pentalene \( 7\) was converted into the MOM-protected derivative \( 18\),
which was submitted to hydroboration.\textsuperscript{23} Final oxidative workup gave the terminal alcohols 8a and 8b as a diastereomeric mixture (dr 81:19), which was separated by chromatography on SiO\textsubscript{2} to yield 8a as the major diastereomer (66\%) and 18\% of a diastereomeric mixture (dr 95:5) (Scheme 4).

In order to probe the versatility of rac-7 as a building block for chain extension, it was converted into bromide 19 in 48\% yield by Mukaiyama redox condensation\textsuperscript{24} with Ph\textsubscript{3}PBr\textsubscript{2} and imidazole in CH\textsubscript{2}Cl\textsubscript{2} at \(-40{\degree}\text{C}\) (Scheme 5, Method A). The yield could be improved to 82\% by using a method developed by Iranpoor,\textsuperscript{25} utilizing Ph\textsubscript{3}P, DDQ, and tetrabutylammonium bromide in CH\textsubscript{2}Cl\textsubscript{2} at room temperature (Scheme 5, Method B).

As chain elongation of bromide 19 by treatment of the corresponding Grignard reagent with formaldehyde was insufficient, an alternative route was developed (Scheme 5). Tosylation\textsuperscript{26} of rac-7 gave derivative 20 in 74\% yield. Subsequent Kolbe synthesis\textsuperscript{27} provided the nitrite 21 in 60\% yield without any problem. Nitrile 21 was converted into aldehyde 22 by reaction with DIBAL-H in CH\textsubscript{2}Cl\textsubscript{2} followed by hydrolysis. Finally, aldehyde 22 was reduced with NaBH\textsubscript{4} in MeOH to yield the desired alcohol 23 in 79\%.

In conclusion, Weiss diketone 5 was found to be a useful precursor for the formation of functionalized pentalene derivatives such as 7 by utilizing a Lewis acid catalyzed carbonyl-ene reaction as a key step. Enantiomerically enriched pentalenes (1,3,5a,5R,6aR)- and (1R,3aR,5S,6aS)-7 were available by lipase-catalyzed kinetic resolution. The primary alcohol moiety and the exocyclic double bond in compound 7 provided entries into further functionalization such as chain elongation to alcohol 23 and hydroboration to derivative 8, respectively. Progress towards the use of pentalenes in natural product synthesis is currently under way.

Melting points were measured on a Mettler-Toledo DSC822e calorimeter and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker Avance 300 or a Bruker Avance 500 spectrometer with TMS as an internal standard. Mass spectra were obtained using a Finnigan MAT 95 or a Varian MAT 711 spectrometer. Optical rotations were measured using a Perkin-Elmer Polarimeter 241 at 20 °C. Flash chromatography was performed using Kieselgel 60, 40–63 \(\mu\text{m}\) (Fluka). GC was performed on a Thermo-Finnigan Trace GC Ultra using an Optima-5 column (30 m \(\times\) 0.25 mm) (Macherey-Nagel) with H\textsubscript{2} as carrier gas: temperature program: 16 °C min\(^{-1}\) gradient from 80 to 300 °C. All solvents were dried, and reactions were performed in dried glassware. PE = hexanes (bp 30–75 °C).

The following compounds were prepared according to literature procedures: 5,\textsuperscript{10} 10,\textsuperscript{11} 14 and 12,\textsuperscript{15}

\((3aR,5r,6aS)-5\text{-Hydroxyhexahydropentalen-2(1\text{H})-one}\) (13)

PTPS (2.28 g, 9.10 mmol) was added to a solution of the acetal 12 (8.20 g, 36.2 mmol) in acetone (400 mL), and the mixture was heated at reflux for 4 h. After cooling to r.t., the mixture was hydrolyzed with aq sat NaHCO\textsubscript{3} (200 mL). The aqueous layer was separated and extracted with CH\textsubscript{2}Cl\textsubscript{2} (5 \(\times\) 40 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), and the solvent removed under vacuum to give a colorless solid (4.80 g). Recrystallization from hexane–Et\textsubscript{2}O (2:1) gave 13 as colorless plates; yield: 4.13 g (81\%); mp 47 °C; \(\delta\) = 0.28 (PE–EtOAc, 1:2). The spectroscopic data were in accordance with those given in the literature.\textsuperscript{17}

Anal. Calcd for C\textsubscript{2}H\textsubscript{2}O\textsubscript{2}: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.66.

\((3aR,5r,6aS)-5\text{-[(\text{tert-Butyl}(dimethyl)silyl)oxy]hexahydropentalen-2(1\text{H})-one}\) (14)

A solution of 13 (3.04 g, 21.7 mmol), TBSCI (3.92 g, 26.0 mmol), and imidazole (3.69 g, 54.2 mmol) in DMF (30 mL) was stirred at r.t. for 1 h. The solvent was removed and the residue was purified by flash chromatography on SiO\textsubscript{2} with PE–EtOAc (10:1) to give 14 as a colorless oil; yield: 5.48 g (99\%); \(\delta\) = 0.52 (PE–EtOAc, 10:1).

FT-IR (ATR): 2951 (m), 2928 (m), 2856 (m), 1739 (s), 1252 (m), 1029 (m), 831 (s), 772 cm\(^{-1}\) (s).

\(\text{MS (CI)}: [\text{M}+\text{NH}_4]+ = 272.2 (12, [M + \text{NH}_4]^+)\), 255.2 (20, [MH\textsuperscript{+}]), 197.1 (100, [M\textsuperscript{+} – \text{t-Bu}]), 105 (11), 75 (10), [HOSiMe\textsubscript{3}]\textsuperscript{+}.

---

Scheme 4

Scheme 5
Anal. Calcd for C_{6}H_{12}O_{5}Si: C, 66.09; H, 10.30. Found: C, 66.07; H, 10.34.

tert-Butyl(dimethyl)((3aR,6aS)-5-methyleneoctahydropentalen-2-yl)oxy)silane (6a)

r-ButOK (0.23 g, 2.00 mmol) was added in one portion to a solution of methyltriphenylphosphonium bromide (0.72 g, 2.00 mmol) in freshly distilled THF (10 mL), and the mixture was stirred for 30 min. Then a solution of 14 (0.20 g, 1.00 mmol) in THF (10 mL) was slowly added. After stirring for 2.5 h, the mixture was diluted with H_{2}O (10 mL). The layers were separated, and the aqueous layer was extracted with PE (4 × 15 mL). The combined organic layers were dried (MgSO_{4}) and concentrated. The crude product was purified by flash chromatography on PE to give 6a as a colorless oil; yield: 0.23 g (92%); R_{f} = 0.27 (PE).

1H NMR (300 MHz, CDCl_{3}): δ = 0.00 [s, 6 H, Si(CH_{3})_{2}], 0.84 [s, 9 H, SiC(CH_{3})_{2}], 1.17–1.27 (m, 2 H, CH-2, H-6), 1.93–2.03 (m, 2 H, CH-3, H-4), 2.40 (s, 3 H, CH(=O)), 2.73–2.79 (m, 2 H, CH-1), 3.30 (d, 1 H, H-3), 3.37 (s, 3 H, CH(=O)), 3.46 (s, 3 H, CH(=O)), 4.05 (tt, J = 8.4, 6.1 Hz, 1 H, H-5), 4.74–4.77 (m, 2 H, CH(=O)).

13C NMR (125 MHz, CDCl_{3}): δ = 1.17 (C-6), 1.26 (C-5), 10.3 (C-2), 12.1 (C-3), 16.2 (C-1), 21.6 (C-4), 25.9 (C-1a), 38.3 (C-3a), 40.2 (C-1, C-3), 42.5 (C-4), 74.6 (C-5), 105.7 (CH=O), 152.8 (C-2).

Carbonyl-Ene Reaction of 6 to Alcohols 7 and 15; General Procedure

A solution of 6a (4.90 g, 19.4 mmol) and TsOH hydrolysis (0.18 g, 1.00 mmol) in toluene (400 mL) was heated at reflux for 1 h. After cooling to r.t.,aq. sat. NaHCO_{3} (40 mL). The aqueous layer was separated and extracted with PE (3 × 40 mL). The combined extracts were dried (MgSO_{4}) and concentrated. The residue was chromatographed on SiO_{2} with PE to give 6b as a colorless oil; yield: 4.27 g (87%); R_{f} = 0.19 (PE).

FT-IR (ATR): 2951 (s), 2928 (s), 2885 (m), 2856 (m), 1252 (s), 1107 (vs), 1036 (s), 987 (s), 833 (vs), 771 cm^{-1} (vs).

1H NMR (500 MHz, CDCl_{3}): δ = 0.03 [s, 6 H, Si(CH_{3})_{2}], 0.86 [s, 9 H, SiC(CH_{3})_{2}], 1.27 (ddd, J = 12.1, 8.0, 6.8 Hz, 1 H, H-1), 1.32 (ddd, J = 11.9, 8.8, 8.6 Hz, 1 H, H-3), 1.66 (ddd, J = 1.8, 1.7, 13 Hz, 1.3 Hz, 1 H, CH at C-5), 1.98–2.05 (m, 3 H, H-1, H-3, H-4), 2.48 (dd, J = 16.0, 9.2 Hz, 1 H, H-4), 2.55 (ddd, J = 9.1, 9.0, 8.6, 8.5, 2.8 Hz, 1 H, H-3a), 2.93–3.00 (m, 1 H, H-6a), 4.07 (ddd, J = 8.6, 8.0, 6.0, 5.7 Hz, 1 H, H-2), 5.22 (ddq, J = 1.8, 1.8, 1.7, 17 Hz, 1 H, H-6).

13C NMR (125 MHz, CDCl_{3}): δ = 47.4–47.8 [Si(CH_{3})_{2}], 16.5 (CH), 18.1 (Si(CH_{3})_{2}), 25.9 (Si(CH_{3})_{2}), 38.6 (C-3a), 41.1 (C-1), 43.5 (C-3), 44.2 (C-4), 48.0 (C-6a), 74.4 (C-2), 128.8 (C-6), 137.4 (C-5).

MS (Cl): m/z (%) = 253.2 (39, [M^{+}], 237.2 (26), 212.1 (46), 195.1 (100, [M - r-But]), 121.1 (28, [M^{+} - OSiMe_{3}-r-Bu]), 119.1 (34), 75 (22, [HOSiMe_{3}^{+}]).

Anal. Calcd for C_{6}H_{12}O_{5}Si: C, 71.36; H, 11.18. Found: C, 71.59; H, 11.03.

Carbonyl-Ene Reaction of 6 to Alcohols 7 and 15; General Procedure

A solution of 1,3,5-trioxane (36 mg, 0.40 mmol) in anhyd CH_{2}Cl_{2} (1 mL) was added dropwise to a solution of the appropriate Lewis acid (3 equiv) in anhyd CH_{2}Cl_{2} (5 mL) in a Schlenk flask at 0 °C under N_{2} and the mixture stirred for 1 h. At the given temperature (Table 1), a solution of 6 (100 mg, 0.40 mmol) in anhyd CH_{2}Cl_{2} (1 mL) was added dropwise, and the mixture was stirred for the given time. After warming to r.t.,aq. sat. NaHCO_{3} (10 mL) was added, the aqueous layer separated and extracted with CH_{2}Cl_{2} (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO_{4}), and concentrated. The crude product was purified by chromatography on SiO_{2} with PE to give 7a (50:1 → 10:1) to give the alcohols 7 and 15 as colorless oils.
chromatography with PE–EtOAc (10:1) to give rac-7 as a colorless oil; yield: 0.51 g (91%).

**Lipase Screening of rac-7: General Procedure**

Vinyl acetate (4.0 mL, 3.7 mg, 42 μmol), molecular sieves (4 Å, 4 beads) and the respective lipase Chirazym I-1 (0.1 mg), Novozym 435 (2 mg), AY Amano (5 mg), PS-D Amano I (0.3–2 mg), or AK Amano 20 (1–2.5 mg) were added to a solution of rac-7 (4.0 mg, 14 μmol) in the appropriate solvent (1 mL) at the given temperature (Tables 2, 3). The mixture was stirred for the given time (Tables 2, 3), and the reaction was followed by TLC to almost identical intensities of rac-7 [Rf = 0.22 (PE–EtOAc)] and product 17 [Rf = 0.57 (PE–EtOAc)]. Then aliquots (50 μL) were taken in intervals of 30 min and filtered through SiO2 with CH2Cl2 (10 mL) as eluent. Conversion and enantioselectivity of alcohol 7 was directly determined from the filtrate by GC. This procedure was repeated until the conversion exceeded 50%.

**Enzymatic Kinetic Resolution of rac-7 on a Preparative Scale**

Vinyl acetate (0.50 mL, 0.46 g, 5.31 mol), molecular sieves (4 Å, 0.05 g) and Lipase PS-D Amano I (0.07 g) were added to a solution of rac-7 (0.49 g, 1.77 mmol, 20 mL) in n-hexane (88 mL) at -20 °C, and the mixture was stirred for 12 h (conversion determined as described above). Then the mixture was filtered through SiO2 with CH2Cl2 (300 mL) as eluent and the filtrate concentrated. The residue was purified by chromatography on SiO2 with PE–EtOAc (50:1 → 5:1) to give rac-7 [Rf = 0.57 (PE–EtOAc; 10:1)] as a colorless oil (0.28 g, 48%), and the alcohol (15.3 μL, 5.6 μL) in the second fraction [Rf = 0.22 (PE–EtOAc, 10:1)] as a colorless oil (0.23 g, 46%); [α]D = +48 (c 1.00, CH2Cl2).

(1R,3α,5S,6αS)-5-[[tert-Butyl(dimethyl)silyloxy)-2-methyl-eneocyclohexa-1-yl]methyl Acetate (17)

[α]D = +0.4 (c 1.00, CH2Cl2).

**FT-IR (ATR):** 2951 (m), 2929 (m), 2856 (m), 1741 (vs), 1462 (m), 1381 (s), 1228 (m), 892 (s), 773 cm–1 (vs).

**1H NMR (500 MHz, CDCl3):** δ = 0.03 [s, 6 H, Si(CH3)2], 0.87 [s, 9 H, Si(CH3)3], 1.34 (dd, d = 12.6, 7.9 Hz, 1 H, H-1H4), 1.42 (ddd, d = 12.8, 6.7, 6.7 Hz, 1 H, H-1H5), 1.97–2.06 (m, 2 H, H-2H-4H6), 2.05 (s, 3 H, CH3), 2.14–2.20 (m, 1 H, H-6a), 2.23 (ddd, J = 15.6, 4.7, 1.9 Hz, 1 H, H-3H4), 2.42 (ddddd, J = 8.9, 8.7, 8.7, 7.9, 4.7 Hz, 1 H, H3a), 2.57 (ddddd, J = 15.6, 8.9, 2.0, 2.0, 1.3 Hz, 1 H, H-1H3), 2.64 (m, 1 H, H-1), 3.99 (ddd, J = 10.8, 7.4 Hz, 1 H, CH2CH2O), 4.11 (dd, J = 10.8, 6.8 Hz, 1 H, CH2CH2O), 4.14 (ddd, J = 7.4, 7.2, 6.7 Hz, 1 H, H-5), 4.82 (dd, J = 2.0, 2.0, 1.9, 1.3 Hz, 1 H, H-6), 4.88 (dd, J = 1.9, 1.9, 1.3 Hz, 1 H, H-6).

**13C NMR (125 MHz, CDCl3):** δ = 18.1 [Si(CH3)3], 21.0 [Si(CH3)3], 25.9 [Si(CH3)3], 39.0 (C-3a), 39.8 (C-3), 41.9 (C-6), 42.4 (C-4), 46.6 (C-6a), 50.4 (C-1), 66.6 (CH2O), 74.9 (C-5), 106.9 (CH3), 171.2 (C-2).

**MS (CI):** m/z (%) = 325.2 (10, [MH]+), 307.2 (10, [MH]+ – H2O), 265.2 (84), 207.1 (20), 133.1 (100, [CH3H]+), 117 (18).


(1R,3α,5S,6αS)-5-[[tert-Butyl(dimethyl)silyloxy)-2-methyl-eneocyclohexa-1-yl]methyl Acetate (17)

Analogous to a literature procedure, 2-9-BBN (112 mg, 0.92 mmol) was added with caution to a solution of 18 (60 mg, 0.18 mmol) in anhyd THF (1 mL) at 0 °C, and the mixture was warmed slowly to r.t. and then stirred for 4 h. At 0 °C, aq 2 M NaOH (0.5 mL) and H2O (30 wt%, 0.5 mL) were slowly added. After sonification at r.t. for 20 min, the mixture was acidified with aq 2 M HCl, diluted with H2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were concentrated under vacuum (dried with MgSO4 and concentrated). The residue with dr 81:19 (determined by GC) was chromatographed on SiO2 with PE–EtOAc (5:1) as eluent to give 8a in the first fraction [Rf = 0.71 (PE–EtOAc, 1:1)] as a colorless oil (41 mg, 66%), and 8b in the second fraction [Rf = 0.68 (PE–EtOAc, 1:1)] as a colorless oil (11 mg, 18%, dr = 5:95).

**Alcohol 8a**

**FT-IR (ATR):** 3433 (s), 2927 (s), 2856 (s), 2363 (m), 1463 (m), 1252 (s), 1106 (s), 1037 cm–1 (vs).

**1H NMR (500 MHz, CDCl3):** δ = 0.04 [s, 6 H, Si(CH3)2], 0.87 [s, 9 H, Si(CH3)3], 1.38 (dd, J = 12.1, 12.1, 9.3 Hz, 1 H, H-3), 1.47 (dd, J = 13.1, 4.5, 1.7 Hz, 1 H, H-4H5), 1.53 (dd, J = 13.1, 4.3, 4.0, 1.7 Hz, 1 H, H-6), 1.80–1.88 (m, 3 H, H-2H-4H-6, H-2), 1.92 (dddd, J = 9.4, 9.0, 8.9, 3.7 Hz, 1 H, H-1), 1.98 (dddd, J = 12.1, 8.5, 6.3 Hz, 1 H, H-3H4), 2.05 (ddddd, J = 10.4, 8.9, 8.8, 4.1 Hz, 1 H, H-6a), 2.41 (ddddd, J = 10.4, 9.3, 8.8, 4.3 Hz, 1 H, H-1H3a), 3.36–3.40 (m, 1 H, CH2CH2O), 3.38 (s, 3 H, OCH3), 3.43 (dd, J = 11.1, 8.6 Hz, 1 H, CH2CH2O), 3.62 (dd, J = 11.1, 10.2, 3.5 Hz, 1 H, CH2CH2O), 3.69 (dd, J = 9.7, 3.8 Hz, 1 H, CH2CH2O), 3.81 (br d, J = 10.2 Hz, 1 H, OCH3), 4.26 (dddd, J = 5.2, 5.2, 4.3, 4.3 Hz, 1 H, H-5), 4.67 (s, 2 H, OCH2O).

**13C NMR (125 MHz, CDCl3):** δ = -4.85, -4.88 [Si(CH3)3], 18.0 [Si(CH3)3], 25.9 [Si(CH3)3], 38.2 (C-3), 39.7 (C-3a), 41.2 (C-6), 42.2 (C-4), 46.5 (C-6a), 51.2 (C-2), 53.2 (C-1), 55.6 (OCH2), 66.5 (CH2O), 71.3 (CH2OCH2O), 76.4 (C-5), 96.3 (OCH2O).

**MS (CI):** m/z (%) = 345.2 (52, [M]+), 313.2 (32), 225.1 (44), 133.1 (100).

Anal. Calcd for C_{19}H_{24}O_{4}Si: C, 62.74; H, 10.53. Found: C, 62.90; H, 10.50.

Alcohol 8b

FT-IR (ATR): 3429 (m), 2972 (s), 2856 (s), 2362 (m), 1462 (m), 1253 (m), 1107 (vs), 1042 cm\(^{-1}\) (vs).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.04\) [s, 6 H, Si(CH\(_3\))\(_3\)], 0.87 [s, 9 H, Si(CH\(_3\))\(_2\)CH\(_3\)], 1.25–1.36 (m, 2 H, H-1, H-3), 1.51 (ddd, \(J = 12.6, 6.9, 3.8\) Hz, 1 H, H-6), 1.58–1.62 (m, 1 H, H-6), 1.97–2.10 (m, 3 H, H-1, H-3, H-5), 2.22 (dddd, \(J = 10.1, 8.2, 4.5, 2.0\) Hz, 1 H, H-4), 2.37 (dddd, \(J = 8.6, 8.6, 8.6, 3.8\) Hz, 1 H, H-6a), 2.52 (m, 1 H, H-3a), 2.73 (br s, 1 H, OH), 3.38 (s, 3 H, OCH\(_3\)), 3.45 (dd, \(J = 9.5, 4.5\) Hz, 1 H, CH\(_2\)OHCH\(_3\)), 3.54 (dd, \(J = 10.1, 9.7, 1\) H, CH\(_2\)OHCH\(_3\)), 3.61 (br d, \(J = 7.9\) Hz, 2 H, CH\(_2\)OH), 4.04 (dddd, \(J = 7.9, 7.9, 5.7, 5.7\) Hz, 1 H, H-2), 4.63 (s, 2 H, OCH\(_2\)OMe).

\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 13.9, 7.0, 6.2, 1.3\) Hz, 1 H, H-4), 2.00 (dddd, \(J = 13.9, 7.0, 6.2, 1.3\) Hz, 1 H, H-4), 2.22 (dddd, \(J = 15.1, 4.8, 2.0, 1.9\) Hz, 1 H, H-3), 2.28 (dddd, \(J = 8.8, 7.9, 6.2, 5.0\) Hz, 1 H, H-6a), 2.39 (dddd, \(J = 8.8, 8.7, 8.4, 8.0\) Hz, 1 H, H-3a), 2.55 (dddd, \(J = 15.1, 8.7, 2.1, 2.0, 1.4\) Hz, 1 H, H-3), 2.69–2.75 (m, 1 H, H-1), 3.29 (dd, \(J = 9.8, 8.6\) Hz, 1 H, CH\(_2\)Br), 3.47 (dd, \(J = 9.8, 5.5\) Hz, 1 H, CH\(_2\)Br), 4.12 (dddd, \(J = 7.0, 6.9, 5.8, 5.8\) Hz, 1 H, H-5), 4.82 (dddd, \(J = 2.0, 2.0, 2.0, 0.9\) Hz, 1 H, =CH\(_2\)H), 4.89 (dddd, \(J = 2.1, 1.9, 1.9, 0.9\) Hz, 1 H, =CH\(_2\)H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 34.3\) [s, 21.7 (Ar-H), 37.4 (CHBr), 38.9 (C-3a), 39.8 (C-3), 42.3 (C-4), 42.3 (C-6), 46.9 (C-6a), 53.5 (C-1), 74.8 (C-5), 107.6 (=CH\(_2\)H), 153.2 (C-5).

MS (Cl): \(m/z\) (%) = 347.1 (12, [M\(^+\)]), 345.1 (12, [M\(^+\)]), 289.0 (5, [M – t-Bu\(^+\)]), 287.5 (5, [M – t-Bu\(^+\)]), 265.2 (14, [M* – Br]), 133.1 (100), 105.1 (13), 91.1 (16).

Anal. Calcd for C\(_{19}\)H\(_{24}\)BrO\(_4\)Si: C, 55.64; H, 8.46; Br, 23.13. Found: C, 55.71; H, 8.49; Br, 22.90.

\[(1\text{RS,3a\text{SR,5S,6a\text{SR}}}\text{-5-\)-(Butyl(dimethyl)silyl)oxy)-2-methyleneoctahydronaphthalen-1-ylmethyl-4-methylbenzenesulfonate (20)]\)

A solution of rac-7 (74 mg, 0.26 mmol), Et\(_3\)N (56 mg, 0.08 mL, 0.55 mmol) and DMAP (4 mg, 0.03 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was stirred at r.t. for 15 min prior to the addition of TsCl (106 mg, 0.56 mmol) in small portions. The mixture was stirred at r.t. for 7 h and then quenched with H\(_2\)O (2 mL). The layers were separated, and the aqueous layer was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO\(_4\)), and concentrated. The residue was purified by flash chromatography with PE–EtOAc (10:1) to give 20 as a colorless solid; yield: 94 mg (83%); mp 59–60 °C; \(R_f = 0.19\) (PE–EtOAc, 30:1).

FT-IR (ATR): 2951 (m), 2926 (m), 1357 (s), 1250 (m), 1189 (m), 1166 (s), 1096 (s), 1031 (s), 1006 (m), 952 (s), 891 (s), 829 (s), 769 cm\(^{-1}\) (s).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.00\) [s, 6 H, Si(CH\(_3\))\(_3\)], 0.83 [s, 9 H, Si(CH\(_3\))\(_2\)CH\(_3\)], 1.26–1.33 (m, 1 H, H-4), 1.33–1.39 (m, 1 H, H-6), 1.90–1.99 (m, 2 H, H-4, H-6), 2.14–2.23 (m, 2 H, H-3, H-6a), 2.31–2.40 (m, 1 H, H-3a), 2.43–2.49 (m, 1 H, H-3), 4.04 (dddd, \(J = 0.9\) Hz, 3 H, Ar-H), 2.60–2.66 (m, 1 H, H-1), 3.89 (dd, \(J = 9.5, 7.9\) Hz, 1 H, CH\(_2\)OHOTs), 4.02 (dd, \(J = 9.5, 6.0\) Hz, 1 H, CH\(_2\)OHOTs), 4.10 (dddd, \(J = 6.7, 6.7, 6.0, 6.0\) Hz, 1 H, H-5), 4.70 (dddd, \(J = 1.9, 1.9, 1.8, 0.8\) Hz, 1 H, \(\text{CH}_2\)H), 7.31–7.34 (m, 2 H, Ar-H\(_{\text{Ar}}\)), 7.76–7.79 (m, 2 H, Ar-H\(_{\text{Ar}}\)).

UV–Vis (hexane, 5–10 \text{mg L}^{-1}): \(\lambda_{\text{max}}\) (log e) = 273 (0.15), 222 nm (0.19).

(ddddd, J = 5.6, 5.6, 5.6, 5.6 Hz, 1 H, H-5), 4.75 (dddd, J = 1.9, 1.9, 1.9 Hz, 1 H, =CH₂H₆), 4.87 (dddd, J = 1.9, 1.9, 1.9 Hz, 1 H, =CH₂H₆).

1^1^1^NMR (125 MHz, CDCl₃): δ = 48.8 [Si(CH₃)₃], 18.1 [Si(CH₃)₃], 21.1 (CH₂CN), 25.9 [Si(CH₂CH₃)₃], 39.2 (C-3a), 39.8 (C-3), 41.5 (C-6), 42.3 (C-4), 46.8 (C-1), 47.7 (C-6a), 75.3 (C-5), 106.1 (=CH₂), 118.9 (CN), 153.3 (C-2).

Anal. Calcd for C₈H₂₃O₅Si: C, 68.86; H, 10.88. Found: C, 68.78; H, 10.80.

Acknowledgment

We gratefully acknowledge the Deutsche Forschungsgemeinschaft, the Ministerium für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg, the European Union (ERASMUS/Sokrates fellowship for M.E.), and the Fonds der Chemischen Industrie for generous financial support. We would like to thank Dr. Michael Schwarm (Degussa AG) for kind donation of lipases.

References


(b) Brummond, K. M.; Kent, J. L. Tetrahedron 2000, 56, 1626
(16) CCDC-676656 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ; Fax: +44 1223 336 033; or E-mail: deposit@ccdc.cam.ac.uk.