Stereoselective Synthesis of Highly Substituted Bicyclic γ-Lactones Using Homoa aldol Addition of 1-(1-Cycloalkenyl)methyl Carbamates

Mustafa Özlügedik, Jesper Kristensen, Jenny Reuber, Roland Fröhlich, Dieter Hoppe

Abstract: Stereoselective addition of aldehydes 4 to metallated 1-(1-cycloalkenyl)methyl N,N-diisopropylcarbamates 1 gave cyclic homoaal dol adducts 6. By applying the (-)-sparteine method, enantio-merically enriched products were obtained. These were oxidatively cyclized to diastereomerically pure γ-lactones 8 via the γ-lactol ethers 7. After deprotonation of γ-lactones 8 with lithium hexamethyldisilazide, a further substitution was achieved. By trapping the lactone enolates stereomers of the lactone enolates adducts 11 with β-naphthylmethyl bromide, single diastero-eromers of γ-lactones 12 were produced.

Key words: asymmetric synthesis, 1-alkenyl carbamates, homoa-ldol addition, (-)-sparteine, bicyclic lactones

A few enantio-merically enriched 1-heterosubstituted allylithium compounds are readily accessible by (-)-sparteine-induced deprotonation of achiral precursors. After lithium-titanium exchange, a chiral homoenolate is produced, which adds stereoselectively to aldehydes and ketones.

We recently published the generation of enantioenriched (1-lithiomethyl)-1-cycloalkenylmethyl N,N-diisopropylcarbamates D and their asymmetric homoaal dol reaction with p-bromobenzaldehyde to serve as equivalents for homoenolate synthons B (Scheme 1). The application of this methodology to the synthesis of bicyclic γ-lactones A from aldehydes C and their further elaboration to highly substituted lactones of type E through introduction of a further residue R1 by means of enolate chemistry are reported in this paper. For the synthesis of the racemic adducts 6 (Scheme 2), the deprotonation of (cycloalkenyl)methyl diisopropylcarbamates 1a–1f (Cb = diisopropylcarbamate) was carried out by treatment with n-butyllithium–N,N,N',N'-tetramethylethlenediamine (TMEDA) in toluene (Conditions A). The intermediate lithium compound rac-2·TMEDA was converted to the (triisopropoxy)titanium derivative rac-3 with three equivalents of Ti(Oi-Pr)4; aldehyde 4 was then added. According to the Zimmerman-Traxler transition state TS5 the Z-anti-diastereomers rac-6 were formed with diastereoselectivities greater than 95:5. When n-butyllithium–(-)-sparteine was used for the deprotonation of 1 (Conditions B), the pro-S proton was removed to form (S)-2·(-)-sparteine with selectivities exceeding 90:10. However, with the exception of the configurationally stable γ-methyl-substituted derivatives 2b and 2d, an epimerisation to form substantial amounts of (R)-2·(-)-sparteine competes with the lithium-titanium exchange, which proceeds stereospecifically with inversion of configuration. Since the reaction of Ti(Oi-Pr)4 was sluggish, we applied the more reactive CI4Ti(Oi-Pr)3. Although the yields of adducts 6 were quite low, a reasonable degree of chirality transfer was maintained (Table 1).

Methanalysis of 6 in the presence of catalytic mercuric acetate provided the γ-lactol ethers 7 as anomeric mixtures. Grieco oxidation then furnished the bicyclic γ-lactones 8. Substrates with annulated five- and six-membered rings gave products as essentially pure diasteromers (Table 2). Larger rings, such as cycloheptane and cyclooctane gave rise to mixtures of cis- and trans-fused bicycles (rac-8ei and rac-8f), entries 13 and 14. The relative configuration could be unambiguously assigned due to NOE effects in 1H NMR between the bridgehead proton and the CH3 group.

The vinyl carbamate 6df (82% ee), bearing a mercuric salt-sensitive unsaturated side chain, required a more elaborate strategy previously applied by us in the synthesis of the pheromone (+)-eldanolide. Conversion of 6df to the silyl ether 9, vinyl deprotonation and subsequent quenching of the vinyllithium intermediate with dimethylsulfide, afforded the monothioacetol 10. Compound 10 was solvolized by aqueous MeOH–methanesulfonic acid to yield in 56% lactone 8df with 82% ee (Scheme 3).
Table 1  Prepared Homoaldol Products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Conditions</th>
<th>Ti-Reagent</th>
<th>Productab</th>
<th>Yield (%)</th>
<th>erc</th>
<th>([\alpha]_{b}d)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a + 4a</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6aa</td>
<td>83</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1a + 4b</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6ab</td>
<td>79</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1a + 4c</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6ac</td>
<td>69</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1a + 4d</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6ad</td>
<td>71</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>1b + 4b</td>
<td>B</td>
<td>Ti(Oi-Pr)₄</td>
<td>6bb</td>
<td>79</td>
<td>87:13</td>
<td>+29.6</td>
</tr>
<tr>
<td>6</td>
<td>1b + 4b</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6bb</td>
<td>77</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>1b + 4e</td>
<td>B</td>
<td>Ti(Oi-Pr)₄</td>
<td>6be</td>
<td>70</td>
<td>86:14</td>
<td>+82.7</td>
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<tr>
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<td>1b + 4e</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6be</td>
<td>77</td>
<td>–</td>
<td>–</td>
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<td>9</td>
<td>1b + 4f</td>
<td>B</td>
<td>Ti(Oi-Pr)₄</td>
<td>6bf</td>
<td>57</td>
<td>85:15</td>
<td>+70.1</td>
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<tr>
<td>10</td>
<td>1b + 4f</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6bf</td>
<td>59</td>
<td>–</td>
<td>–</td>
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<td>11</td>
<td>1b + 4i</td>
<td>B</td>
<td>C(Ti(Oi-Pr)₃)</td>
<td>6bf</td>
<td>29</td>
<td>96:4</td>
<td>+113</td>
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<tr>
<td>12</td>
<td>1b + 4i</td>
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<td>Ti(Oi-Pr)₄</td>
<td>rac-6bi</td>
<td>79</td>
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<td>–</td>
</tr>
<tr>
<td>13</td>
<td>1c + 4b</td>
<td>B</td>
<td>Ti(Oi-Pr)₄</td>
<td>6cb</td>
<td>70</td>
<td>77:23</td>
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<td>14</td>
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<td>A</td>
<td>Ti(Oi-Pr)₄</td>
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<td>68</td>
<td>–</td>
<td>–</td>
</tr>
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<td>15</td>
<td>1c + 4e</td>
<td>B</td>
<td>Ti(Oi-Pr)₄</td>
<td>6ce</td>
<td>82</td>
<td>76:24</td>
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<td>1c + 4e</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6ce</td>
<td>88</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>1d + 4b</td>
<td>B</td>
<td>C(Ti(Oi-Pr)₃)</td>
<td>6db</td>
<td>40</td>
<td>94:6</td>
<td>+48.1</td>
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<tr>
<td>18</td>
<td>1d + 4b</td>
<td>A</td>
<td>Ti(Oi-Pr)₄</td>
<td>rac-6db</td>
<td>80</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>19</td>
<td>1d + 4c</td>
<td>B</td>
<td>C(Ti(Oi-Pr)₃)</td>
<td>6dc</td>
<td>25</td>
<td>89:11</td>
<td>+61.7</td>
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</tbody>
</table>

Scheme 2  Reagents and conditions: a) s-BuLi, TMEDA, toluene, –78 °C for racemates (Conditions A) or n-BuLi, (–)-sparteine, toluene, –78 °C for enantioenriched products (Conditions B). b) Ti(Oi-Pr)₄ or C(Ti(Oi-Pr)₃), 3 equiv c) 1. R'CCHO (4), ii. 2 N HCl. d) Hg(OAc)₂ (5–10 mol%), MeSO₃H (2 equiv) in MeOH. e) m-ClC₆H₄CO₃H–BF₃·OEt₂.
The lactones 8bi and 8di, containing bromine as a heavy atom, were crystalline. These were subjected to X-ray crystal structure analysis with anomalous diffraction (Figures 1 and 2) in order to elucidate their absolute configurations. These structures correlated well with those predicted and therefore confirm the proposed configurations of the intermediates and related derivatives reported in this paper.

In order to demonstrate the further synthetic diversity offered by the bicyclic lactones 8, we investigated the preparation and alkylation of a selection of examples (Scheme 4, Table 3). Lactones rac-8 were converted with lithium hexamethyldisilazide (LiHMDS) into the lactone-enolates 11 and alkylated by treatment with 2-(bromomethyl)naphthalene to furnish the unpolar products 12a–f as single diastereomers. Exemplary, a $^1$H NMR investigation of compound 12f revealed the cis-configuration by an NOE effect between the 3a-CH$_3$ and the 7a-CH$_2$ groups. As predicted, the bicyclic enolate 11 is attacked exclusively from the convex face.$^{13}$

In conclusion, the asymmetric deprotonation of achiral 2-substituted (1-cycloalkenyl)methyl carbamates, with subsequent homoaldol reaction and enolate alkylation provides a versatile brick-box system for the synthesis of highly substituted bicyclic lactones. Some examples for more complex elaboration will be found in ref.$^{14}$

**Scheme 3** *Reagents and conditions:* a) ClSiMe$_3$, Et$_3$N, CH$_2$Cl$_2$, 0 °C → r.t., 15 h. b) i. n-BuLi. ii. MeSSMe, THF, 3 h, –78 °C. c) MeSO$_3$H, MeOH, 15 h, 50 °C.

**Scheme 4** *Reagents and conditions:* a) LiHMDS, THF, 1 h, –78 °C. b) 2-(bromomethyl)naphthalene, THF, –78 °C → r.t., 15 h.

**Table 3** Prepared γ-Lactones 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>n</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>rac-8aa</td>
<td>rac-12a</td>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>rac-8ab</td>
<td>rac-12b</td>
<td>1</td>
<td>H</td>
<td>i-Pr</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>rac-8ac</td>
<td>rac-12c</td>
<td>1</td>
<td>H</td>
<td>n-Pr</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>rac-8ad</td>
<td>rac-12d</td>
<td>1</td>
<td>H</td>
<td>n-Oct</td>
<td>48</td>
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<tr>
<td>5</td>
<td>rac-8ae</td>
<td>rac-12e</td>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>46</td>
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<tr>
<td>6</td>
<td>rac-8bc</td>
<td>rac-12f</td>
<td>2</td>
<td>Me</td>
<td>n-Pr</td>
<td>52</td>
</tr>
</tbody>
</table>

n-BuLi (1.6 M in hexane) and s-BuLi [1.4 M in hexane–cyclohexane (92:8)] were used. Aldehydes were distilled prior to use. (−)-Sparteine was kept under Ar in a refrigerator after the original bottles had been opened. All reactions, which are sensitive to moisture or air, were carried out under Ar using the septum-and-syringe techniques. All solvents were purified by distillation or dried (toluene, Et$_2$O ether) prior to use. Flash chromatography was carried out with silica gel (40–63 μm) using an Ar pressure of 1.2–1.4 bar. Chiral GC was carried out with a Beta-Dex$^{18}$ 120 capillary column, 30 m, Supelco. $^1$H and $^{13}$C NMR spectra were recorded on ARX 300, Bruker.
Homooldal Reaction of Allyl Carbamates 1; General Procedure (GP1)

To a solution of allyl carbamate 1 (1.0 mmol) and diamine (1.1–1.2 mmol) in toluene (3–10 mL) at –78 °C was added dropwise n-BuLi (1.6 M in hexane) or s-BuLi (0.97–1.20 M in hexane) (1.1–1.2 mmol) under vigorous stirring. The reaction mixture was stirred at this temperature for 10–120 min and then a precooled (–78 °C) solution of tetraisopropoxytitanium (TiPT) or chlorotriisopropoxytitanium (CI-TiPT) or chlorotrisopropoxytitanium (Cl-TiPT) (1 M in hexane, 1.1–3.6 mmol) was added. The reaction mixture was stirred for 1 h at –78 °C and then, the aldehyde (1.5–3.0 mmol), dissolved in toluene (1 mL), was added. Finally, the reaction mixture was stirred for 1 h at –78 °C before it was allowed to warm to r.t. The solution was poured into ice-cooled mixture of Et2O (15 mL) and aq 2 N HCl (15 mL). The aqueous layer was allowed to warm to r.t. The solution was poured into ice-cooled mixture of Et2O (15 mL) and aq 2 N HCl (15 mL). The aqueous layer was extracted with Et2O (3 × 15 mL). The combined organic extracts were dried over anhyd MgSO4 and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

rac-[1Z,1 Rajasthan,2(1SR)]-1-[2-(1-Hydroxybutylo)cyclopentylidene]methyl N,N-Diisopropylcarbamate (rac-6ac)

According to GP1, allyl carbamate 1a (1.13 g, 5.00 mmol) and TMEDA (640 mg, 5.50 mmol) were dissolved in toluene (15 mL) and cooled to –78 °C before 1.2 M s-BuLi (4.6 mL, 5.50 mmol) was added. The reaction mixture was stirred for 30 min after which TiPT (4.27 g, 15.0 mmol) was added. The orange-coloured solution was stirred for 1 h at –78 °C then ethanal (4.27 g, 15.0 mmol) was added. The reaction mixture was stirred for 30 min after which TiPT (4.27 g, 15.0 mmol) was added. The orange-coloured solution was stirred for 1 h at –78 °C then butanal (4e, 450 mg, 6.25 mmol), dissolved in toluene (1.0 mL), was added. After workup and flash chromatography (petroleum ether–EtOAc, 4:1) 6ac (1.28 g, 69%) was obtained as a colourless oil; Rf 0.39 (petroleum ether–EtOAc, 4:1).

IR (film): 3491 (OH), 1703 (C=O) cm–1.

1H NMR (300 MHz, CDCl3): δ = 0.90 (t, J = 6.9 Hz, 3 H), 1.23 [1.23] (d, J = 6.9 Hz, 12 H), 1.28–1.36 (m, 2 H), 2.80–2.90 (m, 1 H), 3.75 (dt, J = 2.5, 8.0 Hz, 1 H), 3.91 (sept, J = 6.9 Hz, 2 H), 7.02 (m, 1 H).

13C NMR (75 MHz, CDCl3): δ = 14.2 (CH3), 20.8 (CH3), 22.6 (CH3), 28.8 (CH2), 29.5 (CH2), 36.3 (CH3), 46.3 (CH), 46.5 (CH), 73.3 (CH), 126.4 (Cq), 130.3 (CH), 152.7 (C=O).


rac-[1Z,1 Rajasthan,2(1SR)]-1-[2-(1-Hydroxypropyl)cyclopentylidene]methyl N,N-Diisopropylcarbamate (rac-6ab)

According to GP1, allyl carbamate 1a (225 mg, 1.00 mmol) and TMEDA (128 mg, 1.10 mmol) were dissolved in toluene (3 mL) and cooled to –78 °C before 1.30 M s-BuLi (0.85 mL, 1.10 mmol) was added. The reaction mixture was stirred for 30 min after which TiPT (835 mg, 3.00 mmol) was added. The orange-coloured solution was stirred for 1 h at –78 °C and then 2-methylpropanal (4.27 g, 15.0 mmol) was added. The reaction mixture was stirred for 30 min after which TiPT (835 mg, 3.00 mmol) was added. The orange-coloured solution was stirred for 1 h at –78 °C and then 2-methylpropanal (4b, 144 mg, 2.00 mmol), dissolved in toluene (1.0 mL), was added.

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sparteine (1.18 g, 5.00 mmol) were dissolved in toluene (20 mL) and cooled to –78 °C before 1.6 M (–)-sparteine (188 mg, 0.80 mmol) were dissolved in toluene (5 mL). Cyclopentylidene methyl Et2O, 6:1) to give the residue was purified by flash chromatography (petroleum ether–EtOAc, 6:1). After workup, the residue was purified by flash chromatography (petroleum ether–EtOAc, 5:1) to give the residue was purified by flash chromatography (petroleum ether–EtOAc, 4:1) to give 6bb (247 mg, 79%) as a colourless solid; Rf 0.39 (petroleum ether–EtOAc: 4:1); mp 56 °C (petroleum ether–EtOAc); [α]D20 = +29.6 (c = 0.26, CHCl3); 73% ee.15

IR (KBr): 3493 (OH), 1695 (C=O) cm–1. Anal. Calcd for C21H31NO3 (345.48): C, 73.01; H, 9.04; N, 4.05. Found: C, 73.51; H, 9.06; N, 4.05.

Carbamate rac-6bb was prepared by applying the analogous procedure with sec-BuLi–TMEDA (1.2 equiv). Allyl carbamate 1b (239 mg, 1.00 mmol) gave rac-6bb (240 mg, 77%).

1H NMR (300 MHz, CDCl3): δ = 1.16–1.28 (m, 12 H), 1.30 (s, 3 H), 1.33–1.84 (m, 4 H), 2.02 (ddddd, J = 2.4, 4.1, 8.4, 13.7 Hz, 4 H), 3.40–4.25 (br s, 2 H), 4.41 (m, 1 H), 5.14 (dddd, J = 1.7, 1.7, 10.6 Hz, 1 H), 5.24 (ddd, J = 17.2, 1.7 Hz, 1 H), 5.93 (ddd, J = 5.0, 10.6, 17.3 Hz, 1 H), 6.91 (dd, J = 1.6, 2.3 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 20.7 (CH3), 22.6 (CH3), 24.0 (CH3), 32.0 (CH), 36.1 (CH). GC, 49.6 (C) 77.1 (CH), 115.3 (CH2), 129.2 (CH), 130.8 (Cq) 151.9 (C=O).

Anal. Calcd for C32H56NO3 (495.89): C, 76.46; H, 10.31; N, 4.57. Found: C, 76.65; H, 10.38; N, 4.65.

Carbamate rac-6bf was prepared by applying the analogous procedure with s-BuLi–TMEDA (1.2 equiv). Allyl carbamate 1b (239 mg, 1.00 mmol) gave rac-6bf (174 mg, 59%).

1H NMR (300 MHz, CDCl3): δ = 1.16–1.28 (m, 12 H), 1.30 (s, 3 H), 1.33–1.84 (m, 4 H), 2.02 (ddddd, J = 2.4, 4.1, 7.9, 15.1 Hz, 4 H), 2.34 (ddddd, J = 1.4, 1.4, 4.1, 8.4, 13.7 Hz, 4 H), 3.40–4.25 (br s, 2 H), 4.41 (m, 1 H), 5.14 (dddd, J = 1.7, 1.7, 10.6 Hz, 1 H), 5.24 (ddd, J = 17.2, 1.7 Hz, 1 H), 5.93 (ddd, J = 5.0, 10.6, 17.3 Hz, 1 H), 6.91 (dd, J = 1.6, 2.3 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 20.7 (CH3), 22.6 (CH3), 24.0 (CH3), 32.0 (CH), 36.1 (CH). GC, 49.6 (C) 77.1 (CH), 115.3 (CH2), 129.2 (CH), 130.8 (Cq) 151.9 (C=O).

Anal. Calcd for C32H56NO3 (495.89): C, 76.46; H, 10.31; N, 4.57. Found: C, 76.65; H, 10.38; N, 4.65.

Carbamate rac-6bf was prepared by applying the analogous procedure with s-BuLi–TMEDA (1.2 equiv). Allyl carbamate 1b (239 mg, 1.00 mmol) gave rac-6bf (174 mg, 59%).
According to GP1, allyl carbamate 1d (92% ee). 

Diisopropylcarbamate (6de) 

Diisopropylcarbamate (6dc) 

Diisopropylcarbamate (6dd) 

Diisopropylcarbamate (6df) 

Diisopropylcarbamate (6de) 

Diisopropylcarbamate (6dc) 

Diisopropylcarbamate (6dd) 

Diisopropylcarbamate (6df) 

Diisopropylcarbamate (6de) 

Diisopropylcarbamate (6dc) 

Diisopropylcarbamate (6dd) 

Diisopropylcarbamate (6df)
and cooled to –78 °C before 1.6 M (–)-sparteine (212 mg, 0.91 mmol) were dissolved in toluene (5 mL) according to GP1, allyl carbamate TiPT (710 mg, 2.73 mmol), dissolved in toluene (1 mL), was added. The reaction mixture was stirred for 1 h after which Cl− was added. The dark solution was stirred for 1 h at –78 °C and then naphthalene-1-
benzaldehyde (197 mg, 0.70 mmol) and (–)-sparteine (0.64 mL, 0.84 mmol) were dissolved in toluene (5 mL) and cooled to –78 °C before 1.0 M Cl-TiPT solution in toluene (4.7 mL, 4.7 mmol) was added. The reaction mixture was stirred for 15 min after which Cl-TiPT (657 mg, 2.52 mmol), dissolved in toluene (1 mL), was added. The dark solution was stirred for 1 h at –78 °C and then p-bromobenzaldehyde (4i, 194 mg, 1.05 mmol), dissolved in toluene (1 mL), was added. After workup, the residue was purified by flash chromatography (petroleum ether–Et2O, 40:1) to give 6ei (87 mg, 27%); as a colourless oil; Rf 0.40, CHCl3). Shift experiment: er = 68.3:31.7 (50% ee). 6df was prepared by applying the analogous procedure with s-BuLi–TMEDA (1.2 equiv.). Allyl carbamate 1d (700 mg, 3.0 mmol) gave rac-6df (529 mg, 57%).

{[1Z,1S,2(1R)]-1-[2-(1-Hydroxy-1-ferrocenylmethyl)-2-methylcyclohexylidene]methyl N,N-Diisopropylcarbamate (6ei)} According to GP1, allyl carbamate 1e (188 mg, 0.70 mmol) and (–)-sparteine (196 mg, 0.84 mmol) were dissolved in toluene (5 mL) and cooled to –78 °C before 1.32 M s-BuLi (0.64 mL, 0.84 mmol) was added. The reaction mixture was stirred for 15 min after which Cl-TiPT (657 mg, 2.52 mmol), dissolved in toluene (1 mL), was added. The dark solution was stirred for 1 h at –78 °C and then p-bromobenzaldehyde (4i, 194 mg, 1.05 mmol), dissolved in toluene (1 mL), was added. After workup, the residue was purified by flash chromatography (petroleum ether−Et2O, 40:1) to give 6ei (87 mg, 27%); as a colourless oil; Rf 0.40, CHCl3). Shift experiment: er = 68.3:31.7 (50% ee). 6df was prepared by applying the analogous procedure with s-BuLi–TMEDA (1.2 equiv.). Allyl carbamate 1e (294 mg, 1.1 mmol) gave rac-6ei (323 mg, 71%).

1H NMR (300 MHz, CDCl3): δ = 0.98–1.75 (m, 20 H), 1.75–2.88 (m, 1 H), 1.94–2.07 (m, 1 H), 2.25 (s, 1 H), 3.68 [4.11] (br s, 2 H), 4.64 (s, 1 H), 6.94 (s, 1 H), 7.20 (m, 2 H), 7.38 (m, 2 H).

13C NMR (75 MHz, CDCl3): δ = 20.8 (2 CH3), 22.3 (CH2), 23.6 (CH3), 30.1 (CH3), 37.4 (CH), 45.5 (Cq), 73.4 (CH), 124.4 (Cq), 124.6 (Cq), 125.9 (CH), 125.9 (CH2), 126.8 (CH), 128.0 (CH), 132.4 (CH2), 132.4 (CH2), 132.4 (Cq), 133.9 (Cq), 152.0 (C=O).


Found: C, 76.25; H, 8.61; N, 3.42.

Carbamate rac-6ei was prepared by applying the analogous procedure with s-BuLi–TMEDA (1.2 equiv.). Allyl carbamate 1e (294 mg, 1.1 mmol) gave rac-6ei (323 mg, 71%).
Hg(OAc)₂ (242 mg, 0.76 mmol) and MeSO₃H (730 mg, 7.60 mmol) in CH₂Cl₂ (5 mL), BF₃·OEt₂ (255 mg, 1.82 mmol) was oxidized with m-CPBA (1.5–2.0 mmol, ca 60 proc.) and BF₃·OEt₂ (199 µL, 1.42 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–EtOAc, 1:2) to yield rac-8aa (138 mg, 69%) as a colourless oil; Rf 0.44 (petroleum ether–EtOAc, 1:2).

IR (film): 2957, 2870, 2833 (CH₃aliph) cm⁻¹.

rac-(3RS,3aSR,6aRS)-3-Methylhexahydrocyclopenta[c]furan-1-one (rac-8aa)

According to GP3, rac-β-7aa (211 mg, 1.42 mmol) was oxidized with m-CPBA (384 mg, 1.56 mmol, ca 60 proc.) and BF₃·OEt₂ (199 µL, 1.42 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–EtOAc, 1:2) to yield rac-8aa (138 mg, 69%) as a colourless oil; Rf 0.44 (petroleum ether–EtOAc, 1:2).

IR (film): 1767 (CeO) cm⁻¹.

Hg(OAc)₂ (300 MHz, CDCl₃): δ = 1.03–1.95 (m, 23 H), 1.27 (s, 3 H), 2.08–2.22 (m, 1 H), 2.22 (br s, 1 H, OH), 3.65 [4.08] (br s, 2 H), 4.40 (s, 1 H), 6.93 (s, 1 H), 7.19 (m, 2 H), 7.38 (m, 2 H).

1³C NMR (75 MHz, CDCl₃): δ = 19.5 (CH₃), 20.8 (2 × CH₃), 23.7 (CH₃), 25.0 (CH₃), 26.3 (CH₃), 29.4 (CH₃), 31.3 (CH₃), 33.9 (CH₃), 46.1 (C), 46.5 (CH), 79.2 (CH), 121.2 (C), 126.9 (C), 130.0 (CH), 130.4 (CH), 136.6 (C), 139.6 (C), 152.3 (CeO).

Anal. Calcd for C₂₄H₃₆BrNO₃ (466.45): C, 61.80; H, 7.78; N, 3.00.

1H NMR (300 MHz, CDCl3): δ = 0.86 (t, J = 6.9 Hz, 3 H), 1.18–1.91 (m, 20 H), 2.22 (m, 1 H), 2.73 (dd, d = 2.9, 6.1, 9.1, 10.5 Hz, 1 H), 3.40–3.49 (m, 1 H), 4.86 (d, J = 6.1 Hz, 1 H).

rac-(3RS,3aSR)-3-Propylhexahydrocyclopenta[ac]furan-1-one (rac-8ac)

According to GP3, a mixture of rac-α- and α-7ac (478 mg, 2.60 mmol) was oxidized with m-CuPB (704 mg, 2.86 mmol, ca 60 proc.) and BF3·OEt2 (728 μL, 5.20 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–EtOAc, 1:2) to yield rac-8ac (311 mg, 71%) as a colourless oil; RI = 0.54 (petroleum ether–EtOAc, 1:2).

IR (film): 1776 (C=O) cm–1.

rac-(3SR,3aSR,6aRS)-3-Octylhexahydrocyclopenta[ac]furan-1-one (rac-7ad)

According to GP2, rac-7ad (1.31 g, 3.56 mmol) was cyclized with Hg(OAc)2 (20 mg, 0.06 mmol) and MeSO3H (117 mg, 0.67 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–EtOAc, 1:2) to yield 7ad (262 mg (29%); RI = 0.43 (petroleum ether–EtOAc, 4:1)) and rac-7ad (354 mg (39%); RI = 0.52 (petroleum ether–EtOAc, 4:1)) as colourless oils.

rac-α-7ad

1H NMR (300 MHz, CDCl3): δ = 0.86 (t, J = 6.9 Hz, 3 H), 1.18–1.91 (m, 20 H), 2.22 (m, 1 H), 2.73 (dd, d = 2.9, 6.1, 9.1, 10.5 Hz, 1 H), 3.40–3.49 (m, 1 H), 4.86 (d, J = 6.1 Hz, 1 H).

IR (film): 1776 (C=O) cm–1.

rac-β-7ad

1H NMR (300 MHz, CDCl3): δ = 0.85 (t, J = 6.6 Hz, 3 H), 1.16–1.81 (m, 20 H), 2.36–2.46 (m, 1 H), 2.56 (m, 1 H), 3.30 (s, 3 H), 3.63 (dd, d = 4.5, 5.9, 7.7 Hz, 1 H), 4.64 (d, J = 1.0 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 14.1 (CH3), 22.6 (CH2), 25.8 (CH3), 26.5 (CH2), 29.3 (CH2), 29.6 (CH3), 30.4 (CH2), 31.9 (CH3), 32.9 (CH2), 38.0 (CH2), 48.4 (CH), 51.5 (CH), 54.5 (CH3), 88.3 (CH), 111.9 (CH).

EI-MS (782.541): m/z (%): 254 (1.1) [M]+, 223 (8) [M – OCH3]+, 194 (7), 141 (100), 112 (17), 95 (8), 49 (49), 69 (19), 55 (11).

rac-(3SR,3aSR,6aRS)-3-Octylhexahydrocyclopenta[ac]furan-1-one (rac-8ad)

According to GP3, a mixture of rac-α- and β-7ad and (491 mg, 2.60 mmol) was oxidized with m-CuPB (523 mg, 2.12 mmol, content ca 60 proc.) and BF3·OEt2 (540 μL, 3.86 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–EtOAc, 1:2) to yield rac-8ad (380 mg, 83%) as a colourless oil; RI = 0.53 (petroleum ether–EtOAc, 1:2).

IR (film): 1770 (C=O) cm–1.

rac-(3RS,3aSR,6aRS)-3-Phenylhexahydrocyclopenta[ec]furan-1-one (rac-8ae)

According to GP2, rac-8ae (1.19 g, 3.60 mmol) was oxidized with Hg(OAc)2 (229 mg, 0.72 mmol) and MeSO3H (692 mg, 7.20 mmol). The crude mixture of anomeric lactol ethers rac-7ae (316 mg (1.45 mmol) of the crude product (609 mg)) was oxidized (GP3) with m-CuPB (394 mg, 1.60 mmol, content ca 60 proc.) and BF3·OEt2 (406 μL, 2.90 mmol). After purification by silica gel chromatography (petroleum ether–Et2O, 1:2) lactone rac-8ae (186 mg, 63%) was isolated as a colourless oil; RI = 0.18 (petroleum ether–Et2O, 4:1).

IR (film): 1765 (C=O) cm–1.

rac-(3RS,3aSR,6aRS)-3-Isopropyl-3a-methylhexahydrocyclopenta[c]furan-1-one (8bb)

According to GP2, 6bb (189 mg, 0.61 mmol, [α]20D = +29.6) was cyclized with Hg(OAc)2 (20 mg, 0.06 mmol) and MeSO3H (117 mg, 1.22 mmol). The crude mixture of 7bb was oxidized according to GP3 with m-CuPB (165 mg, 0.67 mmol, content ca 60 proc.) and BF3·OEt2 (94 μL, 0.67 mmol). After flash chromatography (petroleum ether–Et2O, 1:2) of the crude product, 8bb was yielded (60 mg, 54%) as a colourless oil; RI = 0.67 (petroleum ether–Et2O, 1:2); [α]20D = +21.3 (c = 0.15, CHCl3).

IR (film): 1771 (C=O) cm–1.

rac-(3RS,3aSR,6aSR)-3-Methyl-3-phenylhexahydrocyclopenta[c]furan-1-one (8be)

According to GP2, 6be (139 mg, 0.42 mmol, 70% ee) was cyclized with Hg(OAc)2 (13 mg, 0.04 mmol) and MeSO3H (81 mg, 0.84 mmol). After workup, the crude mixture of 7be was used without further purification. According to GP3, 7be was oxidized with m-CuPB (242 mg, 0.84 mmol, content ca 60 proc.) and BF3·OEt2 (118 μL, 0.84 mmol). After workup, the crude products were purified by flash chromatography (petroleum ether–Et2O, 4:1) to yield 8be (51 mg, 56% based on 6be) as a solid; RI = 0.21 (petroleum ether–Et2O, 4:1); [α]20D = −6.2 (c = 1.34, CHCl3); mp 58 °C (petroleum ether–Et2O).

IR (KBr): 1771 (C=O) cm–1.
IR (KBr): 1766 (C=O) cm–1.

HRMS: m/z calcd C_{17}H_{20}O_{2} (280.36): 280.22662; found: C, 81.60; H, 7.09.

rac-(3S,3aSR,7aRS)-3a-Methyl-3-propylhexahydrobenzo[c]furan-1-one (8dc)

rac-(3S,3aSR,7aRS)-3a-Methyl-3-propylhexahydrobenzo[c]furan-1-one (8dc) was oxidized according to GP3 with m-CPBA (148 mg, 0.60 mmol, content ca 60% proc.) and BF₃·OEt₂ (84 μL, 0.60 mmol). Purification by flash chromatography (petroleum ether–Et₂O, 8:1) yielded 7dd (81 mg, 62%); [α]$_D^{20} = -85.5$ (c = 0.40, CHCl₃).

IR (KBr): 1787 (C=O) cm–1.

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8dg)

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8dg) was cyclized with Hg(OAc)$_2$ (10 mg, 0.03 mmol) and MeSO$_3$H (50 mg, 0.52 mmol). The crude mixture of 7dd was oxidized according to GP3 with m-CPBA (96 mg, 0.34 mmol, content ca 60% proc.) and BF$_3$·OEt$_2$ (48 μL, 0.34 mmol). Purification by flash chromatography (petroleum ether–Et₂O, 4:1) yielded 8dd (54 mg, 78%); as a colourless oil; R$_f$ 0.38 (petroleum ether–Et₂O, 4:1); [α]$_D^{20} = +25.4$ (c = 0.34, CHCl₃).

IR (film): 1777 (C=O) cm–1.

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8di)

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8di) was oxidized according to GP3 with Hg(OAc)$_2$ (10 mg, 0.03 mmol) and MeSO$_3$H (50 mg, 0.56 mmol). The crude mixture of 7di was oxidized according to GP3 with m-CPBA (148 mg, 0.60 mmol, content ca 60% proc.) and BF$_3$·OEt$_2$ (84 μL, 0.60 mmol). Purification by flash chromatography (petroleum ether–Et₂O, 8:1) yielded 8dd (63 mg, 80%); as a colourless oil; R$_f$ = 0.44 (petroleum ether–Et₂O, 4:1); [α]$_D^{20} = -85.5$ (c = 0.40, CHCl₃).

IR (KBr): 1798 (C=O) cm–1.

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8gg)

rac-(2S,3aSR,7aRS)-3a-Methyl-3-(1-naphthyl)hexahydrobenzo[c]furan-1-one (8gg) was oxidized according to GP3 with Hg(OAc)$_2$ (10 mg, 0.03 mmol) and MeSO$_3$H (50 mg, 0.56 mmol). The crude mixture of 7gg was oxidized according to GP3 with m-CPBA (148 mg, 0.60 mmol, content ca 60% proc.) and BF$_3$·OEt$_2$ (84 μL, 0.60 mmol). Purification by flash chromatography (petroleum ether–Et₂O, 8:1) yielded 8dd (63 mg, 80%) as a colourless oil; R$_f$ = 0.44 (petroleum ether–Et₂O, 4:1); [α]$_D^{20} = -85.5$ (c = 0.40, CHCl₃).

IR (KBr): 1798 (C=O) cm–1.
flections collected (a-h, -k, +l), [sin(θ/λ) = 1.02 Å⁻¹, 3065 independent (R_{free} = 0.025) and 2873 observed reflections I ≥ 2σ(I)], 328 refined parameters, R1 = 0.039, wR2 = 0.121. Flack parameter 0.03(3), max. residual electron density 0.49 (−0.63) e Å⁻³, two almost identical molecules in the asymmetric unit, hydrogens calculated and refined as riding atoms.

rac-(3R,3aSR,8aRS)- and rac-(3R,3aSR,8aRS)-3-(4-Bromophenyl)-3a-methyloctahydrocycloheptafuran-1-one [rac-8e(i) and rac-8e(i)]

According to GP2, rac-6fi (179 mg, 0.40 mmol) was cyclized with Hg(OAc)₂ (6.4 mg, 0.02 mmol) and MeSO₃H (58 mg, 0.60 mmol). The crude mixture of 7e was oxidized according to GP3 with mCPBA (515 mg, 2.09 mmol, content ca. 60%) and BF₃·OEt₂ (400 µL, 3.10 mmol). Purification by flash chromatography (petroleum ether–EtOAc, 20:1) yielded the cis-isomer rac-8e(i) (58 mg, 44%); Rf 0.25 (petroleum ether–EtOAc); NOE between 3a-CH₃ and 8a-H.

rac-8e(i)

IR (film): 1767 (C=O) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.21 (s, 3 H), 0.69–1.58 (m, 9 H), 2.00–2.14 (m, 2 H), 4.24 (s, 1 H), 6.73 (m, 2 H), 7.23 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 14.1 (CH₃), 22.3 (CH₂), 25.2 (CH₂), 26.2 (CH₃), 26.6 (CH₂), 38.0 (CH₂), 48.1 (C₂), 49.1 (CH), 87.3 (CH), 122.2 (C₂), 128.2 (CH), 131.5 (CH), 134.8 (C₆), 176.5 (C=O).

HRMS: m/z calculated for C₁₇H₁₉BrO₂ (323.22): 322.05685; found [for C₁₇H₁₉BrO₂] = 322.05641.

rac-8e(i)

IR (KBr): 1767 (C=O) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.21 (s, 3 H), 0.69–1.58 (m, 9 H), 2.00–2.14 (m, 2 H), 4.24 (s, 1 H), 6.73 (m, 2 H), 7.23 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 14.1 (CH₃), 22.3 (CH₂), 25.2 (CH₂), 26.2 (CH₃), 26.6 (CH₂), 38.0 (CH₂), 48.1 (C₂), 49.1 (CH), 87.3 (CH), 122.2 (C₂), 128.2 (CH), 131.5 (CH), 134.8 (C₆), 176.5 (C=O).

HRMS: calculated C₁₇H₁₉BrO₂ (322.05685); found [for C₁₇H₁₉BrO₂] = 322.05645.

rac-(3R,3aSR,9aRS)- and rac-(3R,3aSR,9aRS)-3-(4-Bromophenyl)-3a-methyloctahydrocyclohepta[furan-1-one [rac-8f(i) and rac-8f(i)]

According to GP2, rac-6fi (233 mg, 0.48 mmol) was cyclized with Hg(OAc)₂ (7.6 mg, 0.024 mmol) and MeSO₃H (69 mg, 0.72 mmol). According to GP3 the crude diastereometric rac-7fi was oxidized with mCPBA (515 mg, 2.09 mmol, content ca. 60%) and BF₃·OEt₂ (400 µL, 3.10 mmol). Purification by flash chromatography (petroleum ether–EtOAc, 20:1) yielded an inseparable mixture of diastereomers rac-8f(i) and rac-8f(i) (103 mg, 62%); Rf 0.12 (petroleum ether–EtOAc, 20:1); ratio 25:75, as a colourless solid; chemical shift of minor diastereomer in parenthesis.

1H NMR (400 MHz, CDCl₃): δ = 0.25 [0.31] (s, 3 H), 0.59–2.24 (m, 13 H), 4.31 [4.46] (s, 1 H), 6.70–7.79 (m, 2 H), 7.19–7.72 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 16.0 [19.7] (CH₃), 22.7 (CH₂), 24.3 (CH₂), 24.5 (CH₂), 24.6 (CH₂), 25.3 (CH₂), 26.2 (CH₂), 26.9 (CH₂), 27.0 (CH₂), 27.8 (CH₂), 30.5 (CH₂), 31.8 (CH₂), 36.3 (CH₂), 46.3 [45.2] (C₁), 54.4 [48.0] (CH), 85.5 [86.6] (CH), 122.5 [122.4] (C₁), 129.0 [128.8] (CH), 131.4 [131.3] (CH), 134.2 [134.4] (C₂), 177.1 [179.4] (C=O).

ESI–MS: m/z calcd for C₁₇H₁₉BrO₂ (323.25): 359, 361 (M + Na)⁺.

rac-(3RS,3aSR,6aSR)-3-Methyl-6a-(2-naphthylmethyl)hexahydro-cyclopenta[a]fur'an-1-one (rac-12a)

According to GP4, 1,1,1,3,3,3-hexamethyldisilazane (163 mg, 1.01 mmol) was deprotonated with n-BuLi (0.60 mL, 0.96 mmol). Compound rac-8aa (90 mg, 0.64 mmol) was added and the enolate was quenched with 2-bromomethyl-naphthalene (170 mg, 0.77 mmol). After purification by flash chromatography (petroleum ether–EtOAc, 5:1) rac-12a (80 mg, 45%) was obtained as a colourless solid; Rf 0.56 (petroleum ether–EtOAc, 5:1); mp 93 °C (petroleum ether–EtOAc).

IR (KBr): 1755 (C=O) cm–1.

1H NMR (300 MHz, CDCl3); δ = 0.67 (d, J = 6.4 Hz, 3 H), 1.44–2.32 (2 x m, 6 H), 2.36 (dd, J = 4.6, 6.7 Hz, 1 H), 2.79 (d, J = 13.6 Hz, 1 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.95 (qd, J = 4.6, 6.4 Hz, 1 H), 7.32 (dd, J = 1.7, 8.2 Hz, 1 H), 7.43 (m, 2 H), 7.64 (br s, 1 H), 7.74–7.81 (m, 3 H).

13C NMR (75 MHz, CDCl3); δ = 21.2 (CH), 25.2 (CH), 33.7 (CH3), 39.9 (CH3), 42.7 (CH2), 48.9 (CH), 58.8 (Cq), 81.8 (CH), 125.7 (CH), 126.1 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 132.4 (Cq), 133.4 (Cq), 135.4 (Cq), 182.0 (C=O).


rac-(3RS,3aSR,6aSR)-3-Iso-propyl-6a-(2-naphthylmethyl)hexahydro-cyclopenta[a]fur'an-1-one (rac-12b)

According to GP4, 1,1,1,3,3,3-hexamethyldisilazane (204 mg, 1.26 mmol) was deprotonated with n-BuLi (0.75 mL, 1.20 mmol). Compound rac-8ad (286 mg, 1.20 mmol) was added and the enolate was quenched with 2-bromomethyl-naphthalene (292 mg, 1.32 mmol). After purification by flash chromatography (petroleum ether–EtOAc, 10:1) rac-12d (218 mg, 48%) was obtained as a colourless solid; Rf 0.27 (petroleum ether–EtOAc, 10:1); mp 71 °C (petroleum ether–EtOAc).

IR (KBr): 1749 (C=O) cm–1.

1H NMR (300 MHz, CDCl3); δ = 0.58–2.31 (3 x m, 20 H), 0.86 (t, J = 7.0 Hz, 3 H), 2.38 (dd, J = 4.4, 7.2 Hz, 1 H), 2.76 (d, J = 13.5 Hz, 1 H), 3.49 (d, J = 13.5 Hz, 1 H), 3.76 (dd, J = 4.4, 6.3, 7.3 Hz, 1 H), 7.31 (dd, J = 1.9, 8.6 Hz, 1 H), 7.42 (m, 2 H), 7.62 (br s, 1 H), 7.70–7.82 (m, 3 H).

13C NMR (75 MHz, CDCl3); δ = 14.0 (CH), 22.6 (CH), 24.7 (CH), 25.2 (CH), 29.0 (CH), 31.7 (CH), 34.1 (CH), 35.3 (CH), 39.7 (CH3), 42.7 (CH), 47.1 (CH), 58.4 (Cq), 85.7 (CH), 125.7 (CH), 126.0 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 132.4 (Cq), 133.4 (Cq), 135.4 (Cq), 182.0 (C=O).


rac-(3RS,3aSR,6aSR)-6a-(2-Naphthylmethyl)-3-propylyhexahydro-cyclopenta[a]fur'an-1-one (rac-12e)

According to GP4, 1,1,1,3,3,3-hexamethyldisilazane (163 mg, 1.01 mmol) was deprotonated with n-BuLi (0.60 mL, 0.96 mmol). Compound rac-8ae (127 mg, 0.63 mmol) was added and the enolate was quenched with 2-bromomethyl-naphthalene (170 mg, 0.77 mmol). Purification by flash chromatography (petroleum ether–EtOAc, 1:4) yielded rac-12e (160 mg, 46%) as a colourless solid; Rf 0.35 (petroleum ether–EtOAc, 5:1); mp 123 °C (petroleum ether–EtOAc).

IR (KBr): 1754 (C=O) cm–1.

1H NMR (300 MHz, CDCl3); δ = 1.53–2.92 (2 x m, 6 H), 2.65–2.87 (m, 2 H), 3.49 (d, J = 13.4 Hz, 1 H), 4.77 (d, J = 5.3 Hz, 1 H), 6.36–7.87 (6 x m, 12 H).

13C NMR (75MHz,CDCl3); δ = 25.0 (CH3), 33.3 (CH3), 39.4 (CH3), 42.6 (CH3), 51.0 (CH3), 58.5 (Cq), 85.6 (CH3), 124.7 (CH3), 125.6 (CH3), 126.0 (CH3), 127.4 (CH3), 127.6 (CH3), 128.1 (CH3), 128.2 (CH3), 128.4 (CH3), 128.9 (CH3), 132.5 (Cq), 133.4 (Cq), 134.3 (Cq), 140.1 (Cq), 181.8 (C=O).

HRMS: m/z calcd for C19H19O2: 308.17764; found: 308.17760.

rac-(3S,3aSR,6aSR)-6a-(2-Naphthylmethyl)-3-propylyhexhydro-cyclopenta[e]fur'an-1-one (rac-12f)

According to GP4, 1,1,1,3,3,3-hexamethyldisilazane (202 mg, 1.26 mmol) was deprotonated with n-BuLi (0.60 mL, 0.96 mmol). Compound rac-8af (218 mg, 0.83 mmol) was added and the enolate was quenched with 2-bromomethyl-naphthalene (275 mg, 1.25 mmol). After purification by flash chromatography (petroleum ether–
EtOAc, 20:1) rac-12e was yielded (145 mg, 52%) as a colourless solid; Rf 0.24 (petroleum ether–EtOAc, 20:1); mp 129 °C (petroleum ether–EtOAc).

IR (KBr): 1759 (C=O) cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 0.89–1.12 (m, 6 H), 1.16–1.80 (m, 12 H), 2.81 (d, J = 14.2 Hz, 1 H), 3.20 (d, J = 14.2 Hz, 1 H), 4.53 (dd, J = 9.7, 1.8 Hz, 1 H), 7.32–7.95 (2 J, 7 H).

¹³C NMR (75 MHz, CDCl₃): 36.2 (CH₂), 44.5 (Cq), 49.5 (Cq), 81.7 (CH), 125.4 (CH), 125.4 (CH₂), 20.8 (CH₂), 21.2 (CH₂), 27.0 (CH₂), 30.5 (CH₂), 31.5 (CH₂), 36.2 (CH₃), 44.5 (Cₚ), 49.5 (Cₚ), 81.7 (CH), 125.4 (CH), 125.4 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 129.7 (CH), 132.3 (Cₚ), 133.3 (Cₚ), 135.0 (Cₚ), 180.5 (C=O).


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References

(1) Responsible for X-Ray crystal structure data.
(7) In related cases, we recently observed an oxidative dimer of I. We suspect that a one-electron transfer from titanium to the allylic anion is the cause. The use of CITI(NEt₃)₂ as exchange reagent is recommended. ³d
(12) Data sets were collected with an Enraf-Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf-Nonius B.V., 1990), structure solution SHELXS-97 (Sheldrick, G. M. Acta Cryst. 1990, A46, 467), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997), graphics MOPICT 3.2 (M. Brüggemann, Universität Münster, 2001). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 182787 and 182786. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk].
(15) Determined via the lactone derivative.