Preparation of cis-Fused Tetrahydropyranyl Lactones via Palladium-Catalysed Cyclocarbonylation of Enediols

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Abstract The stereoselective palladium-catalysed cyclocarbonylation of hex-5-ene-1,4-diols affords cis-fused bicyclic lactones only. Ring-opening with N,O-dimethylhydroxylamine hydrochloride gives the corresponding Weinreb amides, and their subsequent recyclisation provides advanced synthons for the prospective synthesis of decarestric-tine L. The relative configurations of all the prepared tetrahydropyrans are determined by NOESY. The attempted transformations of lactones into methyl ketones leads to an unexpected furan, the formation of which is discussed.

Key words stereoselectivity, palladium, carbonylation, tetrahydropyrans, lactones

Fused tetrahydropyranyl lactones are frequently present as substructures of many bioactive natural products including macrocyclic polyethers, with halichondrines,1a schindlactones,1b and rubriflorines1c being typical examples. Moreover, the title compounds also represent very useful building blocks2 for the total synthesis of a number of complex target molecules, e.g., pyranicin,3a dysiherbaine,3b pseudomonic acid,3c and aspergillide.3d

Thus, there is a significant interest in the stereoselective preparation of tetrahydropyranyl lactones.4 One of the efficient and straightforward methods relies on the Pd-catalysed intramolecular oxycarbonylation of alkene diols producing the corresponding 2,3-fused lactones.5 However, the carbonylation cyclisation of pent-4-ene-1,3-diols providing exclusively cis-fused6 tetrahydrofuranyl lactones is already well established,7 the cyclocarbonylation of homologous hex-5-ene-1,4-diols is much less elaborated.8 However, while the carbonylation cyclisation of pent-4-ene-1,3-diols providing exclusively cis-fused6 tetrahydrofuranyl lactones is already well established,7 the cyclocarbonylation of homologous hex-5-ene-1,4-diols is much less elaborated.8 Moreover, a diastereoselectivity issue arises in the case of the latter substrates furnishing the more flexible bicyclic [4.3.0] skeleton of cis-/trans-fused tetrahydropyranyl lactones9 (Scheme 1).

Preparation of Enediols

The preparation of enediols 1 features lactol 6 as the key intermediate that is accessible either from commercially available (R)-γ-valerolactone (7) or the much cheaper (R)-propylene oxide (8). For preliminary studies, we first chose racemic (±)-γ-valerolactone rac-7 as a model substrate. Thus, lactone rac-7 was directly transformed into an epi-
meric mixture (1:4:1) of known (±)-γ-valerolactol rac-6 by low-temperature reduction12 with DIBAL-H and was obtained in 87% yield after short-path vacuum distillation (Kugelrohr, 108–115 °C, 23 Torr). Next, we screened the C=O additions of various vinylic nucleophiles (Table 1) to pure racemic lactol13 rac-6 in order to establish the optimum reaction conditions regarding both the diastereoselectivity and yield of (±)-(syn/anti)-enediols rac-1 (Scheme 3).

![Scheme 3](image)

Scheme 3 Reagents and conditions: (a) ref. 12; (b) vinylic nucleophile (2–3 equiv), THF or Et2O or hexane, −78 °C to r.t. or 0 °C to r.t., 16–36 h, 0–86% (syn/anti = 1:1) (see Table 1 and the Supporting Information).

The challenging 1,4-asymmetric induction in lactol rac-6 was tested under chelating conditions using Mg-, Zn-, Ce-, Sn- and Ti-derived reagents. While the employment of magnesium,14a zinc and cerium nucleophiles,14b furnished racemic enediols rac-1 in high yields (Table 1, entries 1–3), the use of vinylic tin14c and/or titanium14d,e compounds did not yield the desired adducts (Table 1, entries 4–6). Moreover, only equimolar mixtures of flash liquid chromatography (FLC)-inseparable15 syn-/anti-diols rac-1 were obtained in successful cases (Table 1, entries 1–3).

![Table 1](image)

Table 1 Screening of Vinylic Carbonyl Additions to rac-6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile (equiv)</th>
<th>Reaction conditions</th>
<th>FLC yield of rac-1 (syn/anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>vinylMgBr (3)</td>
<td>THF, 0 °C to r.t.</td>
<td>86% (1:1:1)</td>
</tr>
<tr>
<td>2</td>
<td>vinylZn (2)</td>
<td>THF, 0 °C to r.t.</td>
<td>85% (1:2:1)</td>
</tr>
<tr>
<td>3</td>
<td>vinylCeCl2 (3)</td>
<td>THF, 0 °C to r.t.</td>
<td>81% (1:1:1)</td>
</tr>
<tr>
<td>4‡</td>
<td>vinylSn (2)</td>
<td>THF, 0 °C to r.t.</td>
<td>–</td>
</tr>
<tr>
<td>5‡</td>
<td>vinylTiCl3 (2)</td>
<td>Et2O, −78 °C to r.t.</td>
<td>–</td>
</tr>
<tr>
<td>6‡</td>
<td>vinylTi(Oi-Pr) (2)</td>
<td>hexane, −78 °C to r.t.</td>
<td>–</td>
</tr>
</tbody>
</table>

* See Scheme 3.

* Zero conversion of substrate rac-6.

‡ Incomplete conversion of rac-6 and generation of a complex reaction mixture with no formation of rac-1.

Building on these preliminary results, we have prepared non-racemic enediols 1. For this purpose, however, we chose commercially available (R)-(+)-propylene oxide (8) as a more affordable substrate for their bulk preparation. Thus, the epoxide 8 first underwent regioselective Cu-catalysed ring opening16 with an allylic Grignard nucleophile to furnish known alkenol 917 in 90% yield after short-path vacuum distillation (Kugelrohr, 100–125 °C, 144 mbar). Subsequently, pure alkenol 9 was ozonolysed to give hydroxaldehyde 6 that was immediately subjected to the Grignard addition of excess vinylmagnesium chloride (4 equiv). This one-pot, two-step sequence18 furnished an FLC-inseparable mixture of the desired enediols 1 (syn/anti = 1:1) in an overall combined yield of 54% over three steps starting from 8. Interestingly, when a larger excess of vinylmagnesium chloride (6 equiv) and/or the addition of more nucleophilic vinylmagnesium bromide (2 equiv) was employed, the unexpected divinyldiol 10 was isolated as the major product along with an equimolar mixture of enediols 1 after FLC of the crude reaction mixture (Scheme 4). The former was probably generated via a precededent Meerwein–Ponndorf–Verley (MPV)-type redox mechanism with double C=O addition.19

![Scheme 4](image)

Scheme 4 Reagents and conditions: (a) ref. 16; (b) O2, NMO (3 equiv), CH2Cl2, 0 °C, 1 h; (c) vinylMgCl (4 equiv), THF, 0 °C to r.t., 48 h, FLC, 1 (60% over 2 steps, syn/anti = 1:1); (d) vinylMgCl (6 equiv) and/or vinylMgBr (2 equiv), THF, 0–39 °C, 8 d, FLC, 10 (27%), 1 (19%, syn/anti = 1:1).

Cyclocarbonylation of Eneediols

With a pure mixture of the desired enediols syn-/anti-1 (~ 1:1) in hand, we performed a screening of their Pd-catalysed intramolecular oxycarbonylation under different reaction conditions (Scheme 5, Table 2). We varied the nature of the palladium salt [PdCl2, Pd(OAc)2, PdCl2(MeCN)2], the reoxidant [CuCl2, 1,4-benzoquinone (BQ), Cu(OAc)2], the base (AcONa, ACONH2), the additive [LiCl, N,N,N,N-tetramethyliourea (TMTU), propylene oxide (PO)], the carbon monoxide source [gaseous CO, liquid Fe(CO)5], and the solvent (AcOH, THF, DCE).

![Scheme 5](image)

Scheme 5 Pd-catalysed cyclocarbonylation of an equimolar mixture of enediols 1

Surprisingly, all but one (Table 2, entry 1) of the tested sets of conditions failed to provide any of the expected bicyclic lactones. The only useful catalytic system operated under the ‘classical’ oxycarbonylation7a–c conditions (CO, cat. PdCl2, excess CuCl2 and AcONa in AcOH) and provided an equimolar mixture of FLC-inseparable cis-fused tetrahydropyrylan lactones 2 and 3 in 67% combined yield. The
A 1:1 ratio of obtained cis-lactones clearly indicates a high degree of stereoselectivity during the cyclocarbonylation of the equimolar mixture of enediols 1. Apparently, the configuration at the allylic carbon of 1 dictates the stereochemistry of the newly formed chiral centre in 2 and 3 (syn-1→3, anti-1→2). While the use of 1,4-benzoquinone \(^b\) instead of CuCl\(_2\) as the reoxidant (Table 2, entry 2) or the employment\(^c\) of Pd(OAc)\(_2\) instead of PdCl\(_2\) as the catalyst (Table 2, entry 3) led to complex reaction mixtures; the addition of tetramethylthiourea\(^d\) as the ligand completely inhibited the cyclocarbonylation of 1 (Table 2, entry 4). Finally, the employment of iron pentacarbonyl \(^e\) as an alternative CO source led to the incomplete conversion of substrate 1 (Table 2, entry 5). The relative configurations of the obtained 2,3-cis-fused tetrahydropyranyl lactones 2 and 3 were determined by NOESY experiments (vide infra).

The working carbonylative conditions (Table 2, entry 1) were also applied to the Pd-catalysed cyclisation of pure divinylidiol 10. In this case, we isolated bicyclic lactone 17 as a single diastereoisomer in modest yield. Its relative 2,3-cis-configuration was determined by NOESY experiments (Scheme 6). To the best of our knowledge, besides our case, there is only one known\(^d\) example of the generation of a quaternary stereogenic centre in a fused tetrahydropyranyl lactone via intramolecular oxycarbonylation of an enediol.

In order to obtain pure separate diastereomers of lactones 2 and 3, we first converted them into the corresponding Weinreb amides 11 and 12 via a known one-pot procedure.\(^2\) Thus, an equimolar mixture of 2 and 3 (~1:1) was exposed to an excess of the complex generated in situ from DIBAL-H and \(\text{N},\text{O}\)-dimethylhydroxylamine hydrochloride to furnish FLC-separable tetrahydropyranols 11 and 12 in 83% combined yield and in a ratio (~1:1) reflecting the composition of the starting mixture of the substrates 2 and 3 (Scheme 7).

The relative 2,3-cis-configurations of both Weinreb amides 11 and 12 were determined by 1D NOESY experiments (Figure 1). This result retrospectively indicated that the parent lactones 2 and 3 obtained by cyclocarbonylation of 1 should possess 2,3-cis-fusion.

Definitive proof was obtained after the unexpected observation that an attempted O-protection\(^3\) of both tetrahydropyranols 11 and 12 resulted in mixtures of silyl ethers.

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**Transformations of Lactones**

**Table 2 Cyclocarbonylation Screening of Enediols 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd salt (0.1 equiv)</th>
<th>Reagents (equiv)</th>
<th>Solvent, conditions</th>
<th>FLC yield (%) of 2 and 3 (1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>PdCl(_2)</td>
<td>CuCl(_2) (3), AcONa (3)</td>
<td>AcOH, 40 °C, 21 h</td>
<td>67%</td>
</tr>
<tr>
<td>2(^b,c)</td>
<td>PdCl(_2)</td>
<td>BQ (1), LiCl (2), AcONa (2)</td>
<td>THF, 60 °C, 48 h</td>
<td>crmf</td>
</tr>
<tr>
<td>3(^b)</td>
<td>Pd(OAc)(_2)</td>
<td>CuCl(_2) (3), 4 Å MS, AcONa (3)</td>
<td>DCE, r.t., 5 h</td>
<td>crmf</td>
</tr>
<tr>
<td>4(^b,d)</td>
<td>Pd(OAc)(_2)</td>
<td>CuCl(_2) (2.5), TMTU (0.1), AcONH(_2) (2), PO (5)</td>
<td>THF, 70 °C, 72 h</td>
<td>–</td>
</tr>
<tr>
<td>5(^b,e)</td>
<td>PdCl(_2)(MeCN)(_2)</td>
<td>Cu(OAc)(_2) (4), LiCl (4)</td>
<td>AcOH, 60 °C, 72 h</td>
<td>–</td>
</tr>
</tbody>
</table>

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\(^a\) See Scheme 5.

\(^b\) CO balloon (1 atm).

\(^c\) Incomplete conversion of substrate 1.

\(^d\) Zero conversion of substrate 1.

\(^e\) Fe(CO)\(_5\) (0.25 equiv) was used as the carbon monoxide source.

\(^f\) A complex reaction mixture (crm) was obtained after the full conversion of substrate 1.

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**Scheme 6** Reagents and conditions: (a) CO (balloon), PdCl\(_2\) (0.1 equiv), CuCl\(_2\) (3 equiv), AcONa (3 equiv), glacial AcOH, 40 °C, 2.5 d, FLC, 28%.

**Scheme 7** Reagents and conditions: (a) HNMeOMe·HCl (3 equiv), Dibal-H (3 equiv), glacial AcOH, 40 °C, 2.5 d, FLC, 31%.

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**Figure 1** Key NOESY interactions of Weinreb amides 11 and 12.
13–15 and bicyclic lactones 2 and 3. Apparently, Weinreb amides 11 and 12 spontaneously cyclised under silylating conditions back to their parent lactones 2 and 3 (Scheme 8).

Thus, the relative 2,3-cis-configuration of the fortuitously obtained pure separate lactones 2 and 3 was finally determined by 1D NOESY experiments (Figure 2).

With pure separated cis-fused bicyclic lactones 2 and 3 in hand, we have attempted their direct conversion into methyl ketones 4 and 5 via a one-pot transformation. However, treatment of either lactone with N,O-dimethyldroxylamine and excess MeMgBr led to the formation of a mixture of Weinreb amides 11 or 12 and furanol 16 as an unexpected side product (Scheme 9).

The latter was probably formed via initial base-promoted THP ring opening involving a retro-Michael reaction that was followed by direct addition of MeMgBr to the Z-configured α,β-unsaturated Weinreb amide. The resulting methyl ketone underwent cyclisative addition to give an intermediate 3,4-dihydrofuran that finally aromatised into the furanol 16. Meanwhile, the E-configured acyclic α,β-unsaturated Weinreb amide undergoes ring closure to give the isolable tetrahydropyran 11 (Scheme 10).

In conclusion, the intramolecular Pd-catalysed oxycarbonylation of enediols 1 has served as a key step in the preparation of enantio- and diastereomerically pure cis-fused bicyclic lactones 2 and 3. The attempted transformation of the lactones into methyl ketones yielded mixtures of Weinreb amides 11 and 12 and unexpected furanol 16. The proposed formation of 16 involves a (retro) Michael reaction followed by Grignard addition and a final aromatisation.

All chemicals and reagents were purchased from commercial sources (Alfa Aesar, Sigma-Aldrich) and were used without further purification, unless otherwise noted. All solvents were distilled prior to use. Anhydrous solvents were prepared either by filtration through a column of activated alumina or by standing over activated 4 Å molecular sieves and stored under an argon atmosphere. Hexanes refer to a mixture of C-6 alkanes (bp 60–80 °C). Yields refer to chromatographically and spectrscopically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on aluminium sheets precoated with silica gel 60 F254 (Merck) or aluminium oxide 60 F254 (neutral, Merck). Visualisation was performed using shortwave UV light followed by dipping the TLC plates in either a basic solution of KMnO4, an acidic solution of vanillin or an acidic solution of ceric ammonium nitrate followed by heating with a heat gun. Flash column chromatography (FLC) was performed using Fluka Silica Gel 60 (particle size 0.040–0.063 mm). Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of 10–1 deg·cm2·g−1. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron), equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000–400 cm−1). NMR spectra were recorded in CDCl3 on Varian Mercury Plus (300 MHz for 1H, 75 MHz for 13C) or Varian Unity Inova 600 (600 MHz for 1H, 151 MHz for 13C) spectrometers and were calibrated using residual non-deuterated solvent or tetramethylsilane as an internal reference (CDCl3: 7.26 ppm 1H NMR, 77.16 ppm 13C NMR, TMS: 0.00 ppm).
(2R,5R,2R,5S)-Hept-6-ene-2,5-diol (syn-anti-1) and (R)-5-Vinyl-hept-6-ene-2,5-diol (10)

Oxygen gas (1 atm) was bubbled through a chilled (0 °C) solution of alkenol 9 (1.0 g, 10 mmol) and N-methylmorpholine-N-oxide (NMO) (3.7 g, 31 mmol, 3.1 equiv) in anhydrous CH2Cl2 (125 mL) over 5 min, followed by stream of ozone (3% O3 in O2) for 1 h until the complete conversion of the substrate (TLC monitoring), Next, a solution of vinylmagnesium chloride (35.3 mL, 1.6 M in THF, 49.4 mmol, 6 equiv) and/or vinylmagnesium bromide (18.8 mL, 1.0 equiv) was added to furnish a deep red oil (320 mg) that was purified by FLC (15 g SiO2, gradient elution: hexanes–EtOAc, 8:1 → 3:1) yielding a pure mixture (~1:1) of the diastereomeric syn-anti-diols 1 (804 mg, 60%) as a colourless oil. Their ratio was determined approximately by integration of the partially overlapping doublets of the H-1 protons (1.17 vs 1.19 ppm).

Diols syn-anti-1

RI = 0.28 (EtOAc–hexanes, 2:1).

IR (ATR): 3313 (OH), 1641, 1419, 1371, 1121, 1077, 990 (CH=CH 2), 4.07–4.19 (m, 2 × 1 H, 2 × H-5), 4.77 (br s, 4 × 1 H, 4 × OH, D 2O exch), 5.08 (ddt, J = 10.4, 2.8, 1.3 Hz, 2 × 1 H, 2 × H-7), 5.21 (dt, J = 17.2, 1.4 Hz, 2 × 1 H, 2 × H-7), 5.77–5.96 (m, 2 × 1 H, 2 × H-6).


When a larger excess of vinylmagnesium chloride (35.3 mL, 1.6 M in THF, 49.4 mmol, 6 equiv) was added to furnish a deep red oil (320 mg), this was purified by FLC (15 g SiO2, gradient elution: hexanes–EtOAc, 8:1 → 3:1) to afford the major divinyldiol 10 (393 mg, 27%) as a yellow oil along with an equimolar mixture of 1 (231 mg, 19%) as a colourless oil.

Divinylidiol 10

Rf = 0.51 (EtOAc–hexanes, 4:1).

1H NMR (300 MHz, CDCl3): δ = 1.18 (dd, J = 6.2, 0.6 Hz, 3 H, H-1), 1.47–1.57 (m, 2 H, H-3–H-4), 1.67–1.75 (m, 2 H, H-3–H-4), 3.80 (dq, J = 12.6, 6.3 Hz, 1 H, H-2), 5.08–5.16 (m, 2 × 1 H, 1 H, H-7, H-9), 5.22–5.31 (m, 2 × 1 H, H-7, H-9), 5.91 (ddd, J = 17.3, 10.7, 4.4, 0.7 Hz, 2 × 1 H, H-6, H-8).

13C NMR (75 MHz, CDCl3): δ = 32.3 (q, C-1), 68.6 (d, C-2), 75.9 (s, C-5), 113.1 (t, C-7=C-9), 113.3 (t, C-7=C-9), 143.0 (d, C-6=C-8), 143.1 (d, C-6=C-8).

LC–MS (APCI): tR = 0.15 min; m/z (%) = 89.2 (100), 137.2 [M + H]+ (66), 139.2 [M – OH]+ (41).

(1R,3R,6R)-3-Methyl-2,7-dioxabicyclo[4.3.0]nona-8-one (2) and (1S,3R,6S)-3-Methyl-2,7-dioxabicyclo[4.3.0]nona-8-one (3)

A flask containing a blue suspension of anhydrous CuCl2 (0.909 g, 6.84 mmol, 3 equiv) and an equimolar mixture of enediols 1 (300 mg, 2.28 mmol) in glacial AcOH (4.5 mL) was fitted with a CO balloon (1 atm) and the suspension was vigorously stirred at r.t. for 30 min while its colour changed from brown to green. Next, anhydrous PdCl2 (40.4 mg, 0.228 mmol, 0.1 equiv) was added and the mixture was stirred at 40 °C until the complete conversion of the substrate (TLC monitoring). The ochre suspension was diluted with Et2O (5 mL), filtered through Celite and washed with Et2O (20 mL). The filtrate was evaporated in vacuo to furnish a deep red oil (320 mg) that was purified by FLC (15 g SiO2, gradient elution: hexanes–EtOAc, 8:1 → 3:1) yielding a pure mixture (~1:1) of diastereomeric syn-anti-diols 1 (804 mg, 60%) as a colourless oil. Their ratio was determined approximately by integration of the partially overlapping doublets of the H-3 signals (2.40–4.10 ppm vs 3.39–3.50 ppm) in the 1H NMR spectrum.

Lactone 2

[α]D 25 +50.73 (c 3.25, CHCl3); RI = 0.34 (EtOAc– hexanes, 2:1).

IR (ATR): 2931, 1773 (C=O), 1446, 1373, 1298, 1259, 1187, 1138, 1057, 1032, 987, 970, 918, 903, 872, 843, 787, 756, 706, 623 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.12 (dq, J = 6.7 Hz, 3 H, Me), 1.28–1.34 (m, 1 H, H-4), 1.91–2.09 (m, 3 H, H-4, H-5, H-5′), 2.51 (dd, J = 174.9, 1 Hz, H-5, H-5′), 2.67 (dd, J = 17.4, 4.8 Hz, 1 H, H-9′), 4.00–4.10 (m, 1 H, H-3), 4.36–4.44 (m, 2 × 1 H, H-6, H-6′).

13C NMR (75 MHz, CDCl3): δ = 17.3 (q, Me), 20.9 (t, C-5), 24.0 (t, C-5), 37.7 (t, C-9), 67.2 (d, C-1=C-6), 67.8 (d, C-3), 77.1 (d, C-1=C-6), 176.2 (s, C=O).


Lactone 3

[α]D 25 −72.15 (c 2.25, CHCl3); RI = 0.34 (EtOAc–hexanes, 2:1).

IR (ATR): 2976, 2958, 2910, 2848, 1797 (C=O), 1448, 1400, 1361, 1297, 1214, 1197, 1149, 1098, 1053, 1025, 974, 933, 898, 883, 850, 822, 708, 696 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.15 (dq, J = 6.2 Hz, 3 H, Me), 1.41–1.50 (m, 2 H, H-4, H-4′), 1.73–1.87 (m, 1 H, H-5, H-5′), 2.25–2.35 (m, 1 H, H-5, H-5′), 2.52 (dd, J = 17.2 Hz, 1 H, H-9′), 2.67 (dd, J = 17.2, 4.2 Hz, 1 H, H-9′), 3.39–3.50 (m, 1 H, H-3), 4.21–4.25 (m, 1 H, H-1), 4.30 (dt, J = 3.8, 3.2 Hz, 1 H, H-6).

13C NMR (75 MHz, CDCl3): δ = 21.9 (q, Me), 25.5 (t, C-5), 26.5 (t, C-4), 39.4 (t, C-9), 71.9 (d, C-3), 73.4 (d, C-1), 76.5 (d, C-6), 176.6 (s, C=O).
To a cooled (0 °C) solution of N,O-dimethylhydroxylamine hydrochloride (213 mg, 2.19 mmol, 3 equiv) in anhydrous THF (2.2 mL) was added a soln of DiBAL-H (2.2 mL, 1 M in hexane, 2.19 mmol, 3 equiv) dropwise and the mixture was stirred at r.t. for 2.5 h. This mixture was then added dropwise to a cooled (0 °C) soln of an equimolar mix-
merric lactones 2 and 3 (114 mg, 0.73 mmol) in anhydrous THF (1.5 mL). After stirring for 1.5 h at r.t. (full conversion by TLC monitoring), the reaction was quenched by the addition of H2O (2.2 mL) and aq KHSO4 (6 mL, 1 M soln) in anhydrous THF (1.5 mL). After stirring for 1.5 h at r.t. (full conversion by TLC monitoring), the reaction was quenched by the addition of H2O (5 mL). The separated aq layer was extracted with CH2Cl2 (5 × 4 mL) and Et2O (2 × 5 mL), and the combined organic extracts were dried over anhydrous Na2SO4. Evaporation in vacuo furnished a yellow oil (177 mg) that was purified by FLC (8.9 g SiO2, 2 × 7 cm, gradient elution: hexanes–EtOAc, 4:1→1:1) affording pure Weinreb amides 11 (49 mg, 31%) and 12 (45 mg, 29%) along with a combined fraction of both dia-
esteroers (37 mg, 23%) as pale yellow oils.

**Weinreb Amide 11**

Rf = 0.51 (CHCl3–MeOH, 8:1).

1H NMR (300 MHz, CDCl3): δ = 1.18 (d, J = 6.4 Hz, 3 H, C-6), 1.24–1.33 (m, 1 H, H-5), 1.60–1.69 (m, 1 H, H-4), 1.72–1.83 (m, 2 H, H-4, H-5), 2.73–2.85 (m, 2 H, H-7, H-7′), 3.17 (s, 3 H, N-Me), 3.69 (s, 3 H, O-
Me), 3.78–3.82 (m, 1 H, H-3), 3.83–3.88 (m, 1 H, H-6), 4.33 (dd, J = 9.9, 6.4 Hz, 1 H, H-2).

13C NMR (75 MHz, CDCl3): δ = 19.5 (q, C-Me), 26.7 (t, C-4), 27.7 (t, C-5), 32.5 (q, N-Me), 32.5 (t, C-7), 61.7 (s, O-Me), 67.3 (d, C-3), 67.8 (d, C-6), 70.5 (d, C-2), 175.8 (s, C-8).

**Weinreb Amide 12**

[a]D 25 = −7.52 (c 0.2, CH2Cl2): Rf = 0.54 (CHCl3–MeOH, 8:1).

1H NMR (300 MHz, CDCl3): δ = 1.15 (d, J = 6.2 Hz, 3 H, C-6), 1.38–1.59 (m, 2 H, H-5, H-5′), 1.65–1.79 (m, 1 H, H-4), 1.82–1.93 (m, 2 H, H-4, H-4′), 2.56–2.86 (m, 2 H, H-7, H-7′), 3.16 (s, 3 H, N-Me), 3.46–3.60 (m, 1 H, H-3), 3.65 (s, 3 H, O-
Me), 3.89 (dt, J = 6.7, 1.0 Hz, 1 H, H-2).

13C NMR (75 MHz, CDCl3): δ = 22.1 (q, C-Me), 27.5 (t, C-5), 30.8 (t, C-
4), 32.3 (q, N-Me), 34.7 (t, C-7), 61.6 (q, O-Me), 67.0 (d, C-3), 74.6 (d, C-6), 76.6 (d, C-2), 172.2 (s, C-8).


**HRMS (ESI): m/z [M + H]+ calcd for C30H39NO4Na: 521.2781; found: 521.2789.**

(R)-4-(5-Methylfuran-2-yl)butan-2-ol (16)

To a cooled (0 °C) soln of lactone 2 (20 mg, 0.13 mmol) in anhydrous THF (0.26 mL) was added N,O-dimethylhydroxylamine hydrochloride (15 mg, 0.15 mmol, 1.2 equiv) and a soln of MeMgBr (0.34 mL, 3 M in Et2O, 0.62 mmol, 8 equiv). Full conversion of 2 was observed after stirring for 40 min (TLC monitoring), and then another portion of MeMgBr soln (0.09 mL, 3 M in Et2O, 0.26 mmol, 2 equiv) was added. After stirring the mixture for an additional 2 h at 0 °C and for 3 h at r.t., the reaction was quenched by the addition of sat. aq NH4Cl (6 mL) and the mixture was diluted with EtO (5 mL). The separated aq layer was extracted with EtOAc (5 × 5 mL) and the combined organic extracts were dried over anhydrous Na2SO4. Evaporation in vacuo furnished a yellow oil (27 mg) that was purified by FLC (1.4 g SiO2, 1 × 4 cm, gradient elution: hexanes–EtOAc, 3:1→1:2) affording Weinreb amide 11 (4.5 mg, 16%) and furanol 16 (6 mg, 30%) as pale yellow oils.

Rf = 0.28 (hexanes–EtOAc, 1:2).

1H NMR (300 MHz, CDCl3): δ = 1.22 (dd, J = 6.2 Hz, 3 H, H-1), 1.65 (br s, 1 H, OH), 1.72–1.81 (m, 2 H, H-3), 2.25 (s, 3 H, Me), 2.58–2.78 (m, 2 H, H-
4), 2.39–3.00 (m, 1 H, H-2), 5.82–5.86 (m, 2 × 1 H, 2 × CH3O).

13C NMR (75 MHz, CDCl3): δ = 13.8 (q, Me), 23.8 (q, C-1), 24.7 (t, C-4), 37.8 (t, C-3), 67.8 (d, C-2), 105.8, 106.1 (2 × d, 2 × CH3O), 150.7, 154.2 (2 × s, 2 × C6).
A blue suspension of anhydrous PdCl$_2$ (36 mg, 0.21 mmol, 0.1 equiv), anhydrous CuCl$_2$ (833 mg, 6.19 mmol, 3 equiv), and anhydrous AcONa (508 mg, 6.19 mmol, 3 equiv) in glacial AcOH (6 mL) was vigorously stirred under a CO atmosphere (balloon) at r.t. for 90 min during which time the colour changed to green. Next, a soln of divinylidol 10 (322 mg, 2.06 mmol) in glacial AcOH (14.5 mL) was added and the mixture was stirred under CO at 40 °C for 2.5 d until the complete conversion of the substrate (TLC monitoring). The grey-green suspension was filtered through Celite and washed with Et$_2$O (100 mL). The filtrate was evaporated in vacuo furnishing a brown oil (231 mg) that was purified by FLC (9.2 g SiO$_2$, hexanes–EtOAc, 3:1) yielding diastereomically pure cis-fused lactone 17 (104 mg, 28%) as a yellow oil.

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**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588326.

**References**


(13) (a) Tomooka, K.; Oinakina, T.; Suzuki, K.; Tsuchihashi, G. Tetrahe-


(15) Neither acetylation nor benzoylation of an equimolar mixture of rac-6 allowed the FLC separation of the respective syn/anti-diastereomers of their acylated derivatives.


(20) The ratio of 2/3 was determined by integration of the H-3 signals (2.40–4.10 ppm vs 3.39–3.50 ppm) in the 1H NMR spectra of the FLC-purified mixtures.


(23) The Weinreb amide 11 is relatively unstable and spontaneously cyclises to give lactone 2 even on standing in CDC13 solution at r.t. or as a neat oil in a freezer (−18 °C) for 30 days.


(26) Racemic (±)-16 is known, see: (a) Francke, W.; Reith, W. Tetrahe-

(27) The acid-catalysed cyclodehydration of hydroxylated E/Z-