Stereoselective Heck–Matsuda Arylations of Chiral Dihydrofurans with Arenediazonium Tetrafluoroborates; An Efficient Enantioselective Total Synthesis of (−)-Isoaltholactone

Paulo Roberto Rodrigues Meira, Angélica Venturini Moro, Carlos Roque Duarte Correia*
Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP 13084-971, Campinas, São Paulo, Brazil
Fax +55(19)35213086; E-mail: roque@iqm.unicamp.br
Received 1 March 2007
Dedicated to Professor Paul A. Wender on the occasion of his 60th birthday for his outstanding contributions to organic chemistry

Abstract: The Heck–Matsuda arylation of chiral 2-(S)-hydroxy-methyl dihydrofurans (endocyclic enolethers) and its derivatives, employing arenediazonium tetrafluoroborates, was developed into a highly efficient, practical and diastereoselective synthetic process. This methodology was applied to the total synthesis of the styrylactone (−)-isoaltholactone in seven steps with an overall yield of ~25%, from the readily available chiral 2-hydroxymethyl dihydrofuran. The strategy permits the synthesis of several other aromatic analogues of isoaltholactone.

Key words: Heck reaction, palladium, diazonium compounds, catalysis, stereoselectivity

The styrylactones are a diverse group of secondary metabolites displaying an outstanding range of biological activities. Several of its members have been indicated as possessing cytotoxic activity against cancer cells, anti-inflammatory and antibiotic activity, action as immunosuppressors, trypanocidal and antifertility agents. The styrylactone family encompasses many basic frameworks ranging from the simple pyranones (goniothalamins) and furanones to the more complex bicyclic pyrano-pyranones, furano-pyranone, and furano-furanones (Figure 1).1

In view of such structural diversity associated with the potential therapeutic applications of these compounds, it is no surprise they have been attracting a lot of attention from the scientific community. Much work has been done and the syntheses of the natural and unnatural analogues for biological screening have been one of the major objectives of these studies.1,2 Synthetic efficiency, allied to route flexibility are desirable features of a modern synthetic strategy in order to permit the synthesis of analogues.3

Attracted by the fact that many of these important compounds bear an aromatic ring next to a heteroatom in a furan substructure, we felt that the Heck arylation of dihydrofurans employing arendediazonium salts could be an excellent alternative to the construction of the natural compounds and an entry to the synthesis of new analogues.4 The phosphine-free Heck arylation of electron-rich olefins using arenediazonium tetrafluoroborates offers several advantages over the traditional Heck methodology using aryl halides and aryl triflates; they are usually milder, easier to carry out, much faster and more economical.5

An overview of the general strategy for the synthesis of styrylactones of several types is illustrated in Figure 2. The designed strategy also has the advantage of adding synthetic flexibility by simple changes in the nature of the arendediazonium. Stereocontrol of the Heck process can also open the possibility of addressing the synthesis of other styrylactones and closely related compounds.

Our expectations at the onset of these studies were centered on the delicate stereocontrol of the Heck arylation reaction of a chiral dihydrofuran, based on previous results derived from the Heck arylation of endocyclic enecarbamates.5a,6 Excellent trans selectivity can be achieved in the preparation of substituted 3-pyrrolines 9 as indicated in Table 1.5 Since the trans Heck adduct was expected to be the major adduct, we directed the synthetic application of these Heck studies to the total synthesis of isoaltholactone 4. Isoaltholactone 4,7 a furano-pyranone

SYNTHESIS 2007, No. 15, pp 2279–2286
Advanced online publication: 12.07.2007
DOI: 10.1055/s-2007-983781; Art ID: C01007SS
© Georg Thieme Verlag Stuttgart · New York
natural product belonging to the styryllactone family, was isolated from several species of the malaysian tree Goniothalamus (G. malayanus, G. montanus and G. tapis). For strategic and economical reasons we targeted the synthesis of the enantiomer of the natural product, the \((-\))-isoaltholactone (\(\text{ent}\)-4). As for many other styrylactones, isoaltholactone also displays important biological activities, including antitumor, antifungal and antibacterial properties.\(^1\) For strategic and economical reasons we targeted the synthesis of the enantiomer of the natural product, the \((-\))-isoaltholactone (\(\text{ent}\)-4). As for many other styrylactones, isoaltholactone also displays important biological activities, including antitumor, antifungal and antibacterial properties.\(^1\) With the enantiomerically enriched dihydrofuran \(12\) in hand, we then initiated our study of the Heck arylation using a few representative arenediazonium tetrafluoroborates. The Heck arylation was probed with borates bearing an electron-rich substituent and with non-substituted benzenediazonium tetrafluoroborate in order to find optimum conditions for the arylation process (Table 2). As the benzenediazonium tetrafluoroborate is a rather unstable compound when in solution, especially when exposed to light or warmed above 40 °C (generation of an aryl cation), optimizing the arylating conditions for this salt was important since it would be needed for the synthesis of most of the natural styrylactones.

Employing the same reaction conditions applied previously for the arylation of endocyclic enecarbamates,\(^6\) provided only moderate to good yields of the desired Heck adducts (Table 2). As expected, the trans stereoisomer was observed as the major adduct in almost all cases, except for entries 7 and 8. The efficiency of the Heck arylation seems to parallel the stability of the arenediazonium salt in solution. Hence, higher yields were obtained with arenediazonium salts bearing electron-donating substituents. An intriguing feature of these Heck arylations is the sharp change in the stereoselectivity observed with the unprotected dihydrofuran \(13\) when reacting with \(p\)-methoxybenzenediazonium tetrafluoroborate (Table 2, entries 7 and 8). The trans:cis ratio of the diastereomeric Heck adduct seems to depend very subtly on the amount of water content in the reaction solvent in a relationship that is still unclear. Also intriguing is the fact that no changes in the stereoselectivity were observed with the other two diazonium salts tested. Changing the reaction solvent from acetonitrile to other polar solvents, such dimethyl sulfoxide (DMSO) and acetone did not improve yields or change the stereoselectivity of these Heck reactions.

With the aim of improving the synthetic potential of the Heck–Matsuda arylation of the chiral dihydrofuran \(12\), some changes in the reaction conditions were evaluated. Changes in the catalyst, the catalyst loading, influence of

---

Table 1  Heck–Matsuda Arylation of Endocyclic Enecarbamates

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>trans: cis ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBDPS</td>
<td>92</td>
<td>92:08</td>
</tr>
<tr>
<td>Tr</td>
<td>96</td>
<td>90:10</td>
</tr>
<tr>
<td>H</td>
<td>95</td>
<td>48:52</td>
</tr>
</tbody>
</table>

* Reaction conditions: Pd\(_2\)(dba)\(_3\) (1 mol%), NaOAc, MeCN, r.t., 15–30 min.

These previous studies have demonstrated the critical role played by steric hindrance in controlling the facial selectivity of the olefin during the Heck arylation. The function played by the free alcohol, however, is still not clear. We hypothesize that it could, to some extent, direct the Heck arylation by interacting with the incoming cationic arylpalladium complex. The Heck arylation of dihydrofurans (endocyclic enolethers) offers another opportunity to evaluate the influence of these structural elements on the stereochemical outcome of the Heck–Matsuda reaction.

We started our studies by preparing chiral tert-butyldimethylsiloxyethyl-4,5-dihydrofuran (\(12\)) in multigram quantities from L-glutamic acid, following the procedure described by Silverstein and Kocienski in five steps with an overall yield of 55%.\(^8\) The synthesis of the chiral dihydrofuran occurred uneventfully, but one should be careful with the volatility of the compounds obtained after diborane reduction of the carboxylic acid \(11\) (Scheme 1).\(^9\)
additives to improve the performance of the catalyst, temperature of the reaction, and the ratio of olefin to arenediazonium salts were evaluated. These studies were initially carried out with the most stable $p$-methoxybenzenediazonium tetrafluoroborate. It is worth noting that, on a few occasions, we found it advantageous to generate the active palladium(0) catalyst just before the Heck arylation by in situ reduction of palladium(II) acetate using equimolecular amounts of dihydrofuran in acetonitrile. 10 This procedure generates a finely suspended palladium(0) that is made somewhat more stable by the addition of anisole as an additive. Anisole seems to considerably slow down the formation of the inactive palladium black, which precipitates with time. When the olefin was added just after formation of the pre-catalysts, followed by the addition of the arenediazonium salt, a considerable increase in yields for the Heck arylation was observed (Table 3). Using only 2 mol% of palladium(II) acetate at 50 °C, the Heck adduct 14 was obtained in 85% yield as a 94:6 diastereomeric mixture favoring the trans adduct (Table 3, entry 6).

A further effort was carried out to improve yields of the Heck–Matsuda arylation when using benzenediazonium tetrafluoroborate, since the trans adduct 15a from this arylation reaction should constitute the starting material for the synthesis of the (−)-isoaltholactone 4 (Table 4). As shown in Table 4, the desired 2-phenyl-3,4-dihydrofurans 15 could be prepared in good to excellent yields as a mixture of diastereomers, favoring the trans adduct, by using an excess of the starting olefin 12. Best conditions were achieved with 4 mol% of Pd$_2$(dba)$_3$, employing 1.2 equivalents of the chiral endocyclic enolether 12 (Table 4, entry 9), affording the phenyldihydrofurans 15a and 15b in 90% yield as a 94:06 diastereomeric mixture. Though the two diastereomers formed a mixture that was inseparable by column chromatography, luckily, the desilylated Heck adducts (use of TBAF, in THF as indicated in

### Table 2 Heck Arylation of Dihydrofuran 12 and 13 with Arenediazonium Tetrafluoroborates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>G</th>
<th>Solvent</th>
<th>Ratio $\text{trans/cis}^b$</th>
<th>Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>TBS</td>
<td>4-OMe</td>
<td>MeCN</td>
<td>92:08</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>TBS</td>
<td>4-OMe</td>
<td>MeCN–H$_2$O (10:1)</td>
<td>92:08</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>TBS</td>
<td>H</td>
<td>MeCN</td>
<td>92:08</td>
<td>55</td>
</tr>
<tr>
<td>4$^d$</td>
<td>15</td>
<td>TBS</td>
<td>H</td>
<td>MeCN</td>
<td>92:08</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>MeCN</td>
<td>93:07</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>MeCN–H$_2$O (1:1)</td>
<td>91:09</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>MeCN–H$_2$O (10:1)</td>
<td>50:50</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>MeCN–H$_2$O (10:0.5)</td>
<td>60:40</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>DMSO</td>
<td>92:08</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>H</td>
<td>4-OMe</td>
<td>MeCN–DMSO (1:1)</td>
<td>93:07</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>H</td>
<td>H</td>
<td>MeCN</td>
<td>92:08</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>H</td>
<td>H</td>
<td>MeCN–H$_2$O (10:1)</td>
<td>93:07</td>
<td>55</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>H</td>
<td>H</td>
<td>acetone</td>
<td>93:07</td>
<td>55</td>
</tr>
<tr>
<td>14</td>
<td>18</td>
<td>H</td>
<td>NHCO$_2$Me</td>
<td>MeCN</td>
<td>92:08</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>H</td>
<td>NHCO$_2$Me</td>
<td>MeCN–H$_2$O (10:1)</td>
<td>93:07</td>
<td>72</td>
</tr>
</tbody>
</table>

$^a$ Reactions carried out using 2 mol% of the catalyst.

$^b$ Determined by GC.

$^c$ Yields for isolated compounds as diastereomeric mixtures.

$^d$ Reaction carried out using 4 mol% of the catalyst.
Table 3  Optimization of the Heck Arylation of 12 with p-Methoxybenzenediazonium Tetrafluoroborate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading (mol%)</th>
<th>Additive b</th>
<th>Ratio trans/cis c</th>
<th>Yield (%) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PhCN)₂Cl₂</td>
<td>2</td>
<td>–</td>
<td>90:10</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>2</td>
<td>anisole (15:1)</td>
<td>95:05</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>2</td>
<td>anisole (4:1)</td>
<td>95:05</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>8</td>
<td>anisole (4:1)</td>
<td>94:06</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>4</td>
<td>anisole (4:1)</td>
<td>95:05</td>
<td>86</td>
</tr>
<tr>
<td>6 e</td>
<td>Pd(OAc)₂</td>
<td>2</td>
<td>anisole (4:1)</td>
<td>94:06</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>10</td>
<td>phenanthroline f</td>
<td>––</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Pd₂(dba)₃</td>
<td>2</td>
<td>–</td>
<td>92:08</td>
<td>65</td>
</tr>
</tbody>
</table>

a Pd(OAc)₂ and Pd(PhCN)₂Cl₂ were reduced in situ with an equimolar amount of dihydrofuran prior to the addition of the substrate and the arenediazonium salt.
b Additive added to the reaction mixture to help stabilize the Pd species. The parenthesis indicate the ratio of additive to Pd.
c Determined by GC.
d Yields for isolated compounds as diastereomeric mixtures (homogeneous material by TLC).
e Reaction carried out at 50 °C.
f No reaction observed when using phenanthroline as additive.

Table 4  Optimization of the Heck Arylation of 12 with Benzenediazonium Tetrafluoroborate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Olefin (equiv)</th>
<th>Ratio trans/cis c</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1.0</td>
<td>92:08</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1.2</td>
<td>93:07</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.3</td>
<td>92:08</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1.5</td>
<td>94:06</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1.7</td>
<td>93:07</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>1.0</td>
<td>92:08</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>1.0</td>
<td>91:09</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1.1</td>
<td>93:07</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>1.2</td>
<td>94:06</td>
<td>90</td>
</tr>
</tbody>
</table>

a Determined by GC
b Yields for isolated compounds as diastereomeric mixtures (homogeneous material by TLC).
Scheme 2) could be easily separated by flash chromatography.

With the optimal conditions for the synthesis of aryl dihydrofuran 15a attained, we proceeded with the synthesis of (−)-isooltholactone (ent-4), as indicated in Scheme 2. Removal of the silyl protecting group, followed by treatment with potassium osmate and N-methylmorpholine N-oxide (NMO) afforded the triol 19 which, without further purification, was treated with 2,2-dimethoxypropane and p-toluenesulfonic acid to provide acetonide 20 in good overall yields over the three steps (Scheme 2).

The dihydroxylation was carried out in high yield (90%), with excellent stereocontrol, to furnish only one detectable diastereomeric triol, which was converted into the corresponding 2,3,4-cis acetonide 20 using two different protocols. Surprisingly, acetonide formation was a rather capricious transformation. Treatment of triol 19 with 2,2-dimethoxypropane in acetone led to the corresponding acetonide in an inconsistent 60–80% yield, together with the generation of several side products. Changing the reaction solvent to dichloromethane led to the corresponding acetonide in an inconsistent 60–80% yield, together with the generation of several side products.

We believe that dihydroxylation is controlled by steric hindrance of the larger phenyl group, combined with a directing effect from the primary alcohol, as an example of a substrate-directable reaction (Equation 1).11 A similar transformation was performed by us during the total synthesis of codonopsinine.6

As previously reported, treatment of cis-enolate 21 with catalytic p-toluenesulfonic acid in methanol, followed by sonication, provided (−)-isooltholactone (ent-4) in 70% yield (2 steps).7b A slightly better protocol for acetonide deprotection and the final closure of the intermediate hydroxy ester to the desired lactone was the use of 50% aqueous trifluoroacetic acid (Equation 2). Thus, treatment of cis-enolate 21 with an aqueous solution of trifluoroacetic acid for 48 hours at room temperature furnished (−)-isooltholactone ([α]23 24.5 ± 0.5 (c 0.20, EtOH)) in 80% yield. The spectroscopic and spectrometric data obtained for the (−)-isooltholactone obtained in this work was in excellent agreement with those reported in the literature.7a

According to the work of Valverde and co-workers,12 this cis stereochemistry seems to be characteristic of α-alkoxy aldehydes. In an attempt to improve yields at this stage, an alternative olefination procedure was also pursued in order to generate the cis-enolate 21 starting from the acetonide 20. Thus, after Swern oxidation of 20, the aldehyde intermediate was reacted with ethyl [bis(3-methylphenyl)phosphoryl]acetate [(o-cresol)_2P(O)(OCH_2COOEt)] to generate the cis-enolate 21 in a moderate 64% yield (over 2 steps). Although specific for the construction of cis-α,β-unsaturated esters, the protocol developed by Ando was not advantageous in the present case.13

From this point on, the synthesis of isooltholactone was rather straightforward and followed, in part, the approach proposed by Yadav and co-workers (Scheme 3).7a,b Thus, oxidation of the primary alcohol functionality present in 20, using Swern conditions, gave an unstable aldehyde which was immediately subjected to a Wittig olefination with ethoxycarbonylmethylene phosphorane in methanol to furnish the cis-enolate 21 in 75% yield (over 2 steps). According to the work of Valverde and co-workers,12 this

Scheme 3 Completing the synthesis of (−)-isooltholactone 4 using Yadav’s strategy

Enantioselective Total Synthesis of (−)-Isooltholactone

In conclusion, the total synthesis of \( \text{(--)-isothalactone} \) was achieved in seven steps with an overall yield of \(~25\%\) from the readily available chiral dihydrofurran 12. The key steps in the synthetic route featured a highly stereoselective and efficient Heck–Matsuda arylation of a chiral endocyclic enolether (an electron-rich olefin) using arene-diazonium tetrafluoroborates, a substrate-directed dihydroxylation to set the correct configuration of four adjacent stereocenters, and a straightforward acetonide deprotection-lactonization promoted by trifluoroacetic acid. The strategy contains enough flexibility to permit the synthesis of the natural product \((+)-isoaltholactone\) \(m\)-analogues of these styrylactones for pharmacological assays. Results along these lines will be reported in due course.

All reagents were of the highest available purity from commercial sources and were used as supplied, unless stated otherwise in the experimental procedures. Solvents were purified by standard methods.\(^{15}\) \(^1\)H NMR and \(^{13}\)C NMR data were recorded on a Varian (250 MHz, 300 MHz, CDCl\(_3\); 75 MHz, CDCl\(_3\)). ESI-MS spectra were recorded on a Thermo-Nicolet IR-200 spectrometer and absorptions were obtained on a Jasco F720 Spectro polarimeter. Infrared spectra (IR) were obtained with a Perkin–Elmer 341 polarimeter or on a Hewlett–Packard HP-1100/HP-3395. Optical rotations were measured with a Perkin–Elmer 341 polarimeter or on a Jasco F720 Spectro polarimeter.

**Heck Arylation: General Procedure**

To a stirred solution of the endocyclic enolether 12 \((0.079 \text{ g}, 0.36 \text{ mmol})\) in MeCN \((2 \text{ mL})\), was added NaOAc \((0.097 \text{ g}, 1.08 \text{ mmol})\), to a stirred solution of the endocyclic enolether \((0.058 \text{ g}, 0.3 \text{ mmol})\). The reaction mixture was stirred for ~15 min, until nitrogen evolution was no longer noticeable. The crude reaction mixture was then filtered through SiO\(_2\) and the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (hexane–EtOAc, 7:3) to provide the corresponding trans primary alcohol 17a (homogeneous material on TLC).

**Equation 2** Alternative protocol for the synthesis of \( \text{(--)-isothalactone} \)

\[ \text{Equation 2} \]

\[ \text{[1H NMR (300 MHz, CDCl}_3; \delta = 0.07 (s, 3 \text{ H}), 0.08 (s, 3 \text{ H}), 0.91 (s, 9 \text{ H}), 3.65 (dd, } J = 10.2, 6.8 \text{ Hz, 1 H}), 3.77 (dd, } J = 10.2, 4.6 \text{ Hz, 1 H}), 3.79 (s, 3 \text{ H}), 5.77 (dt, } J = 5.8, 1.8 \text{ Hz, 1 H}), 5.91 (dt, } J = 4.4, 1.8 \text{ Hz, 1 H}), 6.00 (dt, } J = 5.5, 1.8 \text{ Hz, 1 H}), 6.87 (d, } J = 8.4 \text{ Hz, 2 H}), 7.22 (d, } J = 8.4 \text{ Hz, 2 H}) \]

**HRMS (ESI):** \(m/z[\text{M + 1}]^+\) calcd for C\(_{17}\)H\(_{26}\)O\(_2\)Si: 291.1886; found: 291.1915.

**Methyl 4-[(2S,5S)-5-(Hydroxymethyl)-2,5-dihydrofuran-2-yl]phenylcarbamate** \((18a)\)

To a stirred solution of Heck adduct 15 \((0.29 \text{ g}, 1 \text{ mmol})\) in THF \((1 \text{ mL})\), was added TBAF \((1.0 \text{ M, 1.2 mL, 1.2 mmol})\). The reaction mixture was stirred for ~1 h then quenched by addition of H\(_2\)O \((2 \text{ mL})\) and extracted into EtOAc \((3 \times 5 \text{ mL})\). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (hexane–EtOAc, 7:3) to provide the corresponding trans primary alcohol 17a (homogeneous material on TLC).

Yield: 0.158 g (90%); yellowish oil; \( [\alpha]_D^{20} = 385 \text{ (c 0.4, CHCl}_3) \).

**HRMS (ESI):** \(m/z[\text{M + 1}]^+\) calcd for C\(_{11}\)H\(_{12}\)O\(_2\): 177.0916; found: 177.0878.

**[(2S,5R)-5-(4-Methoxyphenyl)-2,5-dihydrofuran-2-yl]methanol** \((16a)\)

\[ [\alpha]_D^{20} = 301 \text{ (c 0.32, CHCl}_3) \)

**HRMS (ESI):** \(m/z[\text{M + 1}]^+\) calcd for C\(_{12}\)H\(_{14}\)O\(_3\): 207.1021; found: 207.1063.
To a stirred solution of the crude intermediate aldehyde, was used in the next step without further purification.

Wittig Olefination; General Procedure 2
To a stirred suspension of NaNH (0.006 g, 0.70 mmol, 60% dispersion in mineral oil) in anhyd THF (0.3 mL), under argon, at 0 °C, was added (o-cresol)PO(CH2)2COEt (0.052 g, 0.70 mmol) dissolved in anhyd THF (0.3 mL). The reaction mixture was stirred at 0 °C for 10 min then cooled to –78 °C. To this mixture was then added the crude aldehyde prepared above (0.035 g, 0.14 mmol) dissolved in anhyd THF (0.3 mL) and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched by the addition of sat. NH4Cl (3 mL) and extracted into Et2O (3 × 5 mL). The combined organic layers were dried over Na2SO4, filtered and the solvent evaporated in vacuo. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to furnish the corresponding cis-enoate 21.

Yield: 0.025 g (64% yield over two steps); [α]D20 = −82.0 (c 1.43, CHCl3). [Lit.3c [α]D20 = −97.3 (c 1.50, CHCl3)].

1H NMR (300 MHz, CDCl3): δ = 1.29 (t, J = 7.4 Hz, 3 H), 1.34 (s, 3 H), 1.55 (s, 3 H), 4.15 (q, J = 7.4 Hz, 2 H), 4.93−5.03 (m, 2 H), 5.21 (s, 1 H), 5.34−5.42 (m, 1 H), 5.95 (dd, J = 11.8, 1.4 Hz, 1 H), 6.42 (dd, J = 11.8, 6.7 Hz, 1 H), 7.21−7.36 (m, 5 H).

13C NMR (75 MHz, CDCl3): δ = 14.1, 24.9, 26.3, 60.3, 78.2, 83.0, 85.0, 87.3, 112.7, 120.9, 125.5, 127.4, 128.6, 138.5, 145.6, 165.6, 171.1.


Enantioselective Total Synthesis of (–)-Isoaltholactone

(2S,4S,5S,3R)-2-Hydroxymethyl-5-phenyltetrahydro-3,4-furandiol (19) (0.019 g, 80% yield) as homogeneous mate-
rial. The reaction mixture was stirred at r.t. for 4 h then the solvent was evaporated in vacuo to furnish a white solid. This crude solid was dissolved in benzene (1 mL) and placed in an ordinary laboratory ultrasonic bath at r.t. for 6 h. The solvent was then evaporated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 2:8) to give a colorless oil (0.008 g, 70% yield over two steps) corresponding to (–)-isoaltholactone (ent-4) (homogeneous material on TLC).

Alternative procedure: To a stirred solution of the cis-enoate 21 (0.016 g, 0.05 mmol) in anhyd MeOH (0.25 mL) was added PTSA (0.04 mg, 0.005 mmol) to give a slightly cloudy solution. The reaction mixture was stirred at r.t. for 4 h then the solvent was evaporated in vacuo to furnish a white solid. This crude solid was dissolved in benzene (1 mL) and placed in an ordinary laboratory ultrasonic bath at r.t. for 6 h. The solvent was then evaporated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 2:8) to give a colorless oil (0.008 g, 70% yield over two steps) corresponding to (–)-isoaltholactone (ent-4) (homogeneous material on TLC).

[α]D20 = −24.5 (c 0.2, EtOH). [Lit.3c [α]D20 = −32.2 (c 0.3, EtOH).

IR (film): 3452, 2985, 2936, 1373, 1209, 1069, 1047 cm⁻1.

Yield: 0.1 g (54% over two steps).

IR (film): 3452, 2985, 2936, 1373, 1209, 1069, 1047 cm⁻1.

To a stirred solution of the crude intermediate aldehyde 21 (0.035 g, 0.14 mmol) in anhyd CH2Cl2 (9 mL), under argon, was added dropwise and the reaction mixture was stirred at –78 °C for 15 min. A solution of acetonide in anhyd CH2Cl2 (0.14 mL) was added dropwise and the reaction was stirred at –78 °C for 2 h. Freshly distilled Et3N (0.1 mL, 0.69 mmol) was added and the reaction was stirred at –78 °C for a further 15 min then the cooling bath was then removed and the temperature was allowed to come to r.t. After stirring for 20 min, the reaction medium was then diluted with Et2O (0.7 mL) and quenched with H2O (5 mL). After extraction into Et2O (3 × 5 mL), the combined organic layers were washed with sat. NaCl (3 mL), dried over anhyd MgSO4, and concentrated in vacuo. The crude material, corresponding to the intermediate aldehyde, was used in the next step without further purification.

Wittig Olefination; General Procedure 1
To a stirred solution of the crude intermediate aldehyde 21 (0.035 g, 0.14 mmol) in anhyd CH2Cl2 (0.25 mL), under argon, was added the ylide ethoxycarbonylmethylene phosphorane (0.039 g, 0.17 mmol) and the reaction mixture stirred at 25 °C for 14 h. The reaction mixture was concentrated in vacuo and n-pentane (5 mL) was added to the resulting residue to cause the precipitation of triphosphine oxide that was removed by filtration. Further n-pentane (5 mL) was added to the filtrate and the mixture was placed in an ice bath at 0 °C to promote the precipitation of the remaining triphosphine oxide. After a second filtration, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 9:1) to furnish the corresponding cis-enoate 21 (0.029 g, 75% yield over two steps).

1H NMR (300 MHz, CDCl3): δ = 1.36 (s, 3 H), 1.58 (s, 3 H), 2.55 (br s, 1 H), 3.93−4.03 (m, 2 H), 4.05−4.12 (m, 1 H), 4.78 (dd, J = 5.9, 4.0 Hz, 1 H), 4.95 (dd, J = 6.2, 1.5 Hz, 1 H), 5.22 (s, 1 H), 7.21−7.36 (m, 5 H).

13C NMR (75 MHz, CDCl3): δ = 24.7, 26.2, 61.4, 80.4, 81.6, 84.5, 87.5, 113.1, 125.5, 127.5, 128.6, 138.5, 251.1283; found: 251.1273.

Ethyl (Z)-3-[(4S,6S,6aS,3aR)-2,2-Dimethyl-6-phenylhydrofuro[3,4-d][1,3]dioxol-4-yl]-2-propenoate (21)

To a stirred solution of anhyd DMSO (0.02 mL, 0.28 mmol) in anhyd CH2Cl2 (0.05 mL), at –78 °C, under argon, was added acetonide in anhyd CH2Cl2 (0.14 mL) was added dropwise and the reaction mixture was stirred at r.t. for 4 h then the solvent was evaporated in vacuo to furnish a white solid. The crude solid was dissolved in benzene (1 mL) and placed in an ordinary laboratory ultrasonic bath at r.t. for 6 h. The solvent was then evaporated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 2:8) to give a colorless oil (0.008 g, 70% yield over two steps) corresponding to (–)-isoaltholactone (ent-4) (homogeneous material on TLC).

[α]D20 = −24.5 (c 0.2, EtOH). [Lit.3c [α]D20 = −32.2 (c 0.3, EtOH).

IR (film): 3500, 3030, 1730, 1645 cm⁻1.

Synthesis 2007, No. 15, 2279–2286 © Thieme Stuttgart · New York
Acknowledgment

This work was supported by a grant from the Research Supporting Foundation of the State of São Paulo (FAPESP, 05/00721-3). We also thank CNPq and FAPESP for fellowships and Professor Fábio Gozzo (Chemistry Institute, Unicamp) for the ESI-MS analyses.

References


