PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher’s version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/28335

Please be advised that this information was generated on 2017-10-16 and may be subject to change.
Enzymatic Kinetic Resolution of 5-Hydroxy-4-oxa-endo-tricyclo[5.2.1.02\(^2\)6\(^8\)]dec-8-en-3-ones: A Useful Approach to D-Ring Synthons for Strigol Analogues with Remarkable Stereoselectivity

Jan Willem J. F. Thurin, Gerard H. L. Nefkens, Margreth A. Wegman, Antonius J. H. Klunder, and Binne Zwanenburg

NSR-Center for Molecular Structure, Design and Synthesis, Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Received May 31, 1996

Enzymatic kinetic resolution of 5-hydroxy-4-oxa-endo-tricyclo[5.2.1.02\(^2\)6\(^8\)]dec-8-en-3-one and its 2-methyl analogue were resolved employing a lipase-catalyzed acetylation reaction. The latter compound thus gave access to a homochiral D-ring synthon for strigolactones. The enzymatic acetylation reaction occurred with a remarkable inversion of configuration at C-5, through which it is possible to achieve a highly efficient asymmetric synthesis of 5-acetoxy-2(6R)-furanone.

(+)-Strigol (1) and some structurally related sesquiterpene lactones sorgolactone (2) and electrol (3) are members of the "strigolactone" family, which induce germination of seeds of the parasitic weeds Striga and Orobanche. These weeds cause severe damage to graminaceous and leguminous crops in tropical and semitropical areas in the eastern hemisphere. As part of our interest in the (asymmetric) synthesis of the strigolactones and their synthetic analogues, we recently devised an asymmetric synthesis of the tricyclic exo-chloro lactone 4a (Scheme 1), which can be regarded as a homochiral D-ring synthon. This D-ring is a common structural feature of the strigolactones and is of prime importance for full biological activity. Even the absolute stereochemistry at C-2' is essential for optimal stimulation of germination.

The key step in the synthesis of 4a involves menthlylation with l-menthol to give a 1:1 mixture of diasteroomeric methyl ethers, separation of the diastereomers, followed by acidic hydrolysis to give the enantiopure hydroxy lactone 5a. This method provides access to both enantiomers of 5a by choosing the appropriate enantiomer of menthol. However, the resolution is quite laborious since it requires two steps and a careful selective recrystallization. Moreover, 1 equiv of the chiral auxiliary is required. In order to circumvent these problems, a study was undertaken to improve the resolution, using an enzymatic approach.

Enzymes currently find widespread use in synthetic organic chemistry. A prominent example of an enzymatic asymmetric transformation is the kinetic resolution of a racemic alcohol R*OH in the presence of


S0022-3263(96)01022-5 CCC: $12.00 © 1996 American Chemical Society
an acyl donor RCO(OR)², catalyzed by a lipase. The charm of this methodology lies in the fact that organic solvents can be used, workup is extremely simple, and a large variety of substrates is tolerated in this transformation. The application of enol esters as irreversible acyl donors¹⁶ makes this type of resolution even more attractive. In the present paper we describe the kinetic resolution of racemic endo-tricyclic hydroxy lactones 5 employing vinyl acetate as irreversible acyl donor, catalyzed by lipase PS.

Results and Discussion

Starting endo-tricyclic exo-hydroxy lactones 5 were obtained by standard literature procedures. Hydroxy lactone 5a was prepared by a Diels–Alder reaction of citraconic anhydride and cyclopentadiene, followed by partial reduction according to the procedure of Canonne.¹⁷ Hydroxy lactone 5b was obtained by photooxidation of furfural¹⁸ and subsequent Diels–Alder reaction with cyclopentadiene.

Kinetic Resolution. In a recent paper Kellogg et al. described the lipase-mediated transesterification of 5-acyloxy-2(5H)furanones rac-6 with 1-butanol resulting in ee’s ranging from 68–98% (eq 1) with hitherto unknown stereochemistry.¹⁹

\[
\text{lipase PS} + \text{vinyl acetate} \rightarrow \text{lipase PS} + \text{AcO} - \text{H} + \text{reaction products}
\]

We have studied the irreversible acetylation of endo-tricyclic exo-hydroxy lactones 5 in the presence of vinyl acetate in dichloromethane catalyzed by lipase PS (Scheme 2). The results are collected in Tables 1 and 2.

As can be deduced from the data shown in Tables 1 and 2, the lipase PS-mediated acetylation of hydroxy lactones 5 is accomplished in good to excellent ee’s. It should be emphasized that this conversion does not take place with other lipases were employed (lipase A, lipase R). Along with the endo-acetates 7a and 7b, exo-acetates 8a and 8b were formed in minor amounts (Tables 1 and 2). A striking observation is the fact that this reaction takes place with epimerization at C-5. The formation of the endo-acetates 7a and 7b could readily be deduced from ¹H-NMR analysis. The acetyl proton H₂ of the endo-isomers 7a and 7b exhibited a doublet (J = 7 Hz for 7a and 6 Hz for 7b) at ca. 0.6 ppm lower field as compared to the corresponding exo-isomers (J = 1 Hz), which is in agreement with previous observations.¹³ These results suggest that the reaction takes place via the thermodynamically unfavorable endo-hydroxy epimers 9, which can be formed from the corresponding exo-isomers by mutarotation (eq 2). During NMR experiments in CDCl₃, we never observed the presence of the endo-epimers in the solution.

It should be noted that it is not possible to obtain the endo-acetates by any other means. Acetylation reactions under conventional conditions, such as Ac₂O/pyridine or Ac₂O/p-TsOH, gave exclusively the exo-acetates 8. In order to gain information about the existence of the exol endo equilibrium (eq 2), we subjected the endo-acetate 7b to a transesterification reaction. However, employing MeOH as a solvent in the presence of K₂CO₃ the expected exo-hydroxy lactone ent-5b was not obtained, but exomethoxy lactone ent-10b was isolated as the main product (eq 3). Therefore, we switched to the enzymatic approach. Lipase PS-catalyzed transesterification in the presence of 10 equiv of n-BuOH in CH₂Cl₂ led to the exclusive formation of exo-hydroxy lactone ent-5b (eq 3). Again, no trace of endo-hydroxy lactone could be detected.

The results obtained with lipase PS-catalyzed acetylation of racemic hydroxy lactones 5 (Scheme 2) fit into a model in which only one enantiomer of the thermodynamically unfavorable endo-hydroxy lactones 9 is withdrawn from the exol endo equilibrium (eq 2) to undergo a relatively fast enzymatic acetylation reaction. This sequence is an example of the Curtin–Hammett principle.²⁰ This remarkably large kinetic difference between

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time, h</th>
<th>Conversion (%)</th>
<th>7a (%) ee</th>
<th>5a (%) ee</th>
<th>8a (%) ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>30.8</td>
<td>30.2 (90)</td>
<td>69.2 (41)</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>48.0</td>
<td>46.7 (87)</td>
<td>52.0 (79)</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>56.2</td>
<td>51.6 (87)</td>
<td>43.8 (85)</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Table 1. Lipase PS-Catalyzed Transesterification of endo-Tricyclic Hydroxy Lactone rac-5a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time, h</th>
<th>Conversion (%)</th>
<th>7b (%) ee</th>
<th>5b (%) ee</th>
<th>8b (%) ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>39.0</td>
<td>39.0 (90)</td>
<td>61.0 (56)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>53.5</td>
<td>50.0 (90)</td>
<td>46.5 (90)</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>17 days</td>
<td>60.8</td>
<td>45.2 (90)</td>
<td>39.2 (90)</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Table 2. Lipase PS-Catalyzed Transesterification of endo-Tricyclic Hydroxy Lactone rac-5b

the endo- and exo-hydroxy lactones results in an excellent selectivity of product formation. It should be noted that in the absence of the lipase no conversion into 7a,b or 8a,b was observed even after 17 days. This implies that the formation of exo-acetates 8a,b (e.g. Table 2, entry 3) is also catalyzed by the lipase, albeit in a much lower rate. The formation of the exo-acetates 8a and 8b, which are diastereomeric to the initially formed products 7a,b, takes place via the exo-epimers 5a and 5b, respectively. This formation of diastereomers 7 and 8, which is the ultimate result of the exo/endo equilibrium as depicted in eq 2, is quite unusual in kinetic resolutions.

The interesting finding shown in Scheme 2 can be advantageously utilized to achieve a sequence with full chiral economy (Scheme 3) in the following manner.

The crude mixture of 7b and 5b, obtained by kinetic resolution of rac-5b is acetylated under standard conditions to give the diastereomeric products 7b and 8b. Without further purification this mixture was subjected to a clycloreversion reaction, employing the technique of flash vacuum pyrolysis (FVT). This reaction led to the formation of one single isomer of 5-acetoxy-2(5H)-furanone 11. This remarkable result can be rationalized by taking into account that a double stereo differentiation has taken place. These results demonstrate the successful application of an enzymatic kinetic resolution of a racemic mixture, providing one single enantiomer without purification of any intermediate.

**Determination of Enantiomeric Excess and Absolute Configuration.** The ee’s of the tricyclic hydroxy lactones 5a and 5b were established after methylation with l-menthol to give the corresponding l-menthonyxylactones 12a and 12b as a mixture of diastereomers with known absolute stereochemistry. The de’s could thus be determined by comparison of the relative intensities of the acetate H3 proton signals in the 1H-NMR spectrum. As there is no stereochemical preference in the menthylation reaction, this derivatization allows the determination of the ee’s of the hydroxylactones 5. Moreover, this derivatization to menthyl acetals 12 with known stereochemistry enables the unambiguous assignment of the absolute stereochemistry as is shown (Scheme 2).

Although effective, a more convenient procedure to determine the respective ee’s involves the conversion of hydroxy lactones 5 and endo-acetoxy lactones 7 into the corresponding methyl acetics 10a,b and ent-10a,b. These methylations occurred with complete exo selectivity in almost quantitative yields.

The ee’s then were determined employing 400 MHz 1H-NMR analysis in the presence of the chiral shift reagent Eu(hfc)3 (1.5 equiv). In the case of methoxy lactones 10a and ent-10a a difference of 0.03 ppm was observed for the α-methyl protons. On the other hand, the ee of methoxy lactone 10b was calculated on the basis of a 0.03 ppm difference of chemical shift of the acetal proton H2 as compared to its enantiomer ent-10b. The determination of ee of acetoxy-2(5H)-furanone 11 was accomplished by comparison of the relative intensities of the CH3 signals in the 1H-NMR spectrum using 0.4 equiv of Eu(hfc)3, which resulted in a downfield shift of approximately 0.8 ppm and a difference of 0.16 ppm for both enantiomers. On the basis of the above assignment of the absolute stereochemistry the levorotatory 5-acetoxy-2(5H)-furanone 11, obtained by Kellogg et al. according to eq 1,19 can be assigned as 5(R).

**Conclusion**

Lipase PS-mediated acetylation proved to be a simple, highly efficient method for the kinetic resolution of racemic tricyclic hydroxy lactones 5. Employing this methodology it is possible to synthesize both enantiomers of exo-chloro lactones 4a. These optically active latent butenolides are useful synthons for the preparation of homochiral strigolactones. The kinetic resolution was accompanied with a remarkable epimerization, which could be used to demonstrate the synthesis of enantiopure 5-acetoxy-2(5H)-furanone 11 with optimal "chiral economy".

**Experimental Section**

**General.** For general methods and instrumentation, see ref 13. GC-MS spectra were run on a Varian Saturn 2 GC-MS ion-trap system. Separation was carried out on a fused-silica capillary column (DB-5, 30 m x 0.25 mm). Helium was used as carrier gas, and electron impact (EI) was used as ionization mode. Lipase PS was obtained from Amano as a gift.

**General Procedure for the Enzymatic Kinetic Resolution of the Tricyclic Hydroxy Lactones rac-5a and rac-5b.** To a solution containing exo-hydroxy tricyclic lactone rac-5a17 (500 mg, 2.79 mmol) and vinyl acetate (2.57 mL, 27.9 mmol) in CH2Cl2 (25 mL) were added lipase PS (1.0 g) and powdered 4A molecular sieves (0.5 g). The suspension was stirred vigorously at room temperature. At given intervals (Tables 1 and 2) samples were taken (3 mL) and filtered over hyflo. The hyflo was washed with CH2Cl2, and the crude mixture was analyzed by 100 MHz 1H-NMR (CDCl3) for conversion. Purification by chromatography (SiO2, hexane/ethyl acetate 3:1) afforded exo-acetate 7a as a white solid and exo-alcohol 5a as a white solid, which were analyzed for ee (vide infra).

**Enantiomeric Excess Determination.** The hydroxy lactones 5a and 5b were transformed into the corresponding

---


l-methyl ethers. Alternatively, 5a and 5b were converted into the corresponding exo-methoxy lactones 10a, 10b and subsequently analyzed by 400 MHz 1H-NMR (CDCl3) in the presence of 1.5 equiv of Eu(hfc)2 (vide infra). Similarly, endo-acetates 7a and 7b were methylated to give ent-10a and ent-10b, respectively (vide infra), which were analyzed for ee in the same manner.

5(R)-Acetoxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (7a) and 5(R)-hydroxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (5a). These compounds were synthesized according to the general procedure starting from rac-6a (3.0 g, 16.7 mmol). The reaction was stopped after 73 h. Purification by chromatography (SiO2, hexane/ethyl acetate 3:1) gave 7a (1.25 g, 34%) as a white solid and 5a (1.18 g, 39%) as a white solid. Analytical samples of 5a and 7a were obtained by recrystallization from hexane/ethyl acetate.

7a: mp 98.5-101.5 °C; [α]D = -88.4° (c 0.4, CH2Cl2); 1H-NMR (CDCl3, 100 MHz): δ 1.54 (s, 3H), 1.69 (m, 2H), 2.15 (s, 3H), 2.85 (m, 1H), 2.87 (dd, J = 3.9, 7.0 Hz, 1H), 3.04 (m, 1H), 6.26 (m, 2H), 6.50 (d, J = 7.0 Hz, 1H); GC-MS (EI, m/z, rel int (%)): 166 (M+ - OAc, 40.4), 157 (17), 152 (23.4), 97 (13.6), 91 (16.0), 66 (100). Anal. Calcd for C16H16O4: C, 62.98; H, 6.31. Found: C, 62.88; H, 6.31.

5a: All analytical data (Mp, [α]D, 1H-NMR, and mass data) were in complete agreement with those reported previously.18

5(R)-Acetoxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (7b) and 5(R)-hydroxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (5b). These compounds were synthesized according to the general procedure starting from rac-5b (3.0 g, 18.1 mmol). The reaction was stopped after 46 h. Purification by chromatography (SiO2, hexane/ethyl acetate 3:1) gave 7b (1.56 g, 44%) as a white solid and 5b (1.41 g, 47%) as a white solid. Analytical samples of 5b and 7b were obtained by recrystallization from hexane/ethyl acetate.

7b: mp 116.5-118 °C; [α]D = -126.0° (c 1.0, CH2Cl2); 1H-NMR (CDCl3, 100 MHz): δ 1.47 (dt, J = 1.0 Hz, 9.0, 1H), 1.65 (dt, J = 1.0 Hz, 9.0, 1H), 1.21 (2.5 s, 3H), 1.56 (m, 2H), 2.58 (d, J = 6.0 Hz, 1H); GC-MS (EI, m/z, rel int (%)): 166 (M+ - OAc, 49.2), 137 (12.2), 91 (42.3), 83 (91), 66 (100). Anal. Calcd for C16H16O4: C, 62.45; H, 5.81. Found: C, 62.85; H, 5.79.

5b: mp 134-136.5 °C; [α]D = +53.2° (c 0.2, CH2Cl2); 1H-NMR (CDCl3, 100 MHz): δ 1.37 (dt, J = 1.0 Hz, 8.5, 1H), 1.56 (dt, J = 1.0 Hz, 8.5, 1H), 2.86 (m, 1H), 3.13 (m, 1H), 3.36 (m, 3H), 3.62 (m, 2H), 4.68 (4H), 4.91 (m, 2H); GC-MS (EI, m/z, rel int (%)): 166 (M+ - OAc, 149.0), 137 (12.2), 91 (42.3), 83 (91), 66 (100). Anal. Calcd for C16H16O4: C, 62.45; H, 5.81. Found: C, 64.97; H, 6.00.

5(S)-Hydroxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (6a). A solution containing 7b (50 mg, 0.24 mmol) and n-BuOH (0.22 mL, 24 mmol) in CH2Cl2 (3 mL) was treated with lipase PS (100 mg) and powdered 4A molecular sieves (50 mg). The suspension was stirred vigorously at room temperature. After 24 h the suspension was filtered over hyflo and washed with CH2Cl2 and the filtrate was concentrated in vacuo to a small volume. Yield 47.2 mg (84%) as a white solid. Anal. Calcd for C16H16O4: C, 62.98; H, 6.31. Found: C, 62.88; H, 6.31.

5(S)-Methoxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (6b). This compound was prepared by hydrolysis of 6a (105 mg, 0.56 mmol) in the same way as described for the synthesis of rac-8a. Yield 121.8 mg, 98% of pure rac-8a as a colourless oil: 1H-NMR (CDCl3, 100 MHz): δ 1.39 (dt, J = 1.0 Hz, 8.7, 1H), 1.60 (dt, J = 1.0 Hz, 8.7, 1H), 2.03 (3s, 3H), 2.96 (m, 1H), 3.25 (m, 3H), 5.86 (d, J = 1.2 Hz, 1H), 6.19 (m, 2H); GC-MS (EI, m/z, rel int (%)): 163 (M+ - OAc, 36.3), 157 (30.0), 97 (18.2), 91 (15.1), 66 (100). Anal. Calcd for C16H16O4: C, 63.44; H, 6.00; Found: C, 63.40; H, 6.00.

5(R)-Acetoxy-2(R)-methyl-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (8a). This compound was prepared from 5a (100 mg, 0.56 mmol) in the same way as described for the synthesis of rac-8a. Yield 123.1 mg, 99% of 8a as a colourless oil: [α]D = -79.3° (c 0.4, CH2Cl2). 1H-NMR and mass data were the same as for compound 8b.

5(R)-Acetoxy-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (8b). This compound was prepared from 5b (100 mg, 0.60 mmol) in the same way as described for the synthesis of rac-8b. Yield 119.5 mg, 87% of 8b as a white solid. Analytically pure sample was obtained by recrystallization from hexane/ethyl acetate: mp 84-85.5 °C; [α]D = -27.2° (c 0.4, CH2Cl2). 1H-NMR and mass data were the same as for compound 8a.

5(R)-Acetoxy-2(S)-methyl-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (9a). This compound was prepared from 5a (100 mg, 0.56 mmol) in the same way as described for the synthesis of rac-8a. Yield 123.1 mg, 99% of 9a as a colourless oil: [α]D = +79.3° (c 0.4, CH2Cl2). 1H-NMR and mass data were the same as for compound 9a.

5(R)-Acetoxy-2(S)-methyl-4-oxa-endo-tricyclo[5.2.1.02,8]dec-8-ene-3-one (9b). This compound was prepared from 5b (100 mg, 0.60 mmol) in the same way as described for the synthesis of rac-8b. Yield 119.5 mg, 87% of 9b as a white solid. Analytically pure sample was obtained by recrystallization from hexane/ethyl acetate: mp 84-85.5 °C; [α]D = -27.2° (c 0.4, CH2Cl2). 1H-NMR and mass data were the same as for compound 9a.
for rac-11.\textsuperscript{23} Addition of Eu(hfc)\textsubscript{3} (0.4 equiv) gave a separation of CH\textsubscript{3} signals amounting 0.16 ppm for the corresponding enantiomers (0.8 ppm downfield shift), ee 94%.

The same compound 11 was obtained by FVT [sample temp: 120 °C; oven temp: 500 °C; cold trap temp: −78 °C; pressure: 5 × 10\textsuperscript{−2} mbar] starting from a 1:1 mixture of diastereomeric acetates 7\textsubscript{b} and 8\textsubscript{b} (110 mg, 0.53 mmol). Yield 64.9 mg, 86% as a colorless oil. [α]\textsubscript{D} \textbf{−34.2° (c 0.5, CH\textsubscript{2}Cl\textsubscript{2}), ee 94%}.

**Acknowledgment.** We thank Amano Enzyme Europe Ltd. for a generous gift of lipase PS and several other lipases. We thank H. Amatdjaïs, P. v Galen, and A. Swolfs for conducting elemental analysis, mass, and 400 MHz \textsuperscript{1}H-NMR measurements, respectively. These investigations were supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Research (NWO).

**Supporting Information Available:** Copies of \textsuperscript{1}H NMR spectra of rac-8\textsubscript{a}, rac-8\textsubscript{b}, 7\textsubscript{a}, 7\textsubscript{b} (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.