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Enzymatic Kinetic Resolution of 5-Hydroxy-4-oxa-endo-tricyclo[5.2.1.0^2,6]dec-8-en-3-ones: A Useful Approach to D-Ring Synthons for Strigol Analogues with Remarkable Stereoselectivity

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Racemic 5-hydroxy-4-oxa-endo-tricyclo[5.2.1.0^2,6]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(6H)-furanone.

[(+)-Strigol (1) and some structurally related sesquiterpene lactones sorgolactone (2) and alectrol (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 menthylation with l-menthol to give a 1:1 mixture of diastermesic methyl ethers, separation of the diastereomers, followed by acidic hydrolysis to give the enantiopure 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.


an acyl donor R'C(OO)R², catalyzed by a lipase. The charm of this methodology lies in the facts 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 cinnamoyl 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-acetoxy-2(5H)furanones rac-6 with 1-butanol resulting in ee's ranging from 68—98% (eq 1) with hitherto unknown stereochemistry.¹⁹

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{O} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O}
\end{align*}
\]

(1)

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 when 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 'H-NMR analysis. The acetate 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.

![Scheme 2](image_url)

**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>product distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>30.8</td>
<td>30.2 (&gt;90) 69.2 (41) 0.6</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>48.0</td>
<td>46.7 (87) 52.0 (79) 2.3</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>56.2</td>
<td>51.6 (87) 43.8 (85) 4.6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>entry</th>
<th>time, h</th>
<th>conversion (%)</th>
<th>product distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>39.0</td>
<td>39.0 (&gt;90) 61.0 (56) 0</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>53.5</td>
<td>50.0 (&gt;90) 46.5 (&gt;90) 3.5</td>
</tr>
<tr>
<td>3</td>
<td>17 days</td>
<td>60.8</td>
<td>45.2 (&gt;90) 39.2 (&gt;90) 15.6</td>
</tr>
</tbody>
</table>

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 AcOOp-TsOH, gave exclusively the exo-acetates 8. In order to gain information about the existence of the exo/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.

![Scheme 3](image_url)

**References**


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 or 8a,b was observed even after 17 days. This implies that the formation ofexo-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 AcO5b and 8b. Without further purification this mixture was subjected to a cyclization 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 stereodifferentiation 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-methanol to give the corresponding l-methoxy lactones 10a and 10b as a mixture of diastereomers with known absolute stereochemistry.13,21 The ee’s could thus be determined by comparison of the relative intensities of the acetal H5 proton signals in the 1H-NMR spectrum. As there is no stereochemical preference in the methylation reaction,13 this derivatization allows the determination of the ee’s of the hydroxy lactones 5. Moreover, this derivatization to methyl 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 acetals 10a,b and ent-10a,b. These methylation 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 10b24 was calculated on the basis of a 0.03 ppm difference of chemical shift of the acetyl proton H5 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 5R(2).

**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 synths for the preparation of homochiral strigolactones.13 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 for ee (vide infra).

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

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l-methyl ethers. 12,13 Alternatively, 5a and 5b were converted to the corresponding exo-methoxy lactones 10a, 10b and subsequently analyzed by 400 MHz 1H-NMR (CDCl3) in the presence of ca. 1.5 equiv of Eu(hfc)3 (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.

(5R)-Acetoxy-4-oxa-endo-tricyclo[5.2.1.02,6]dec-8-en-3-one (5a).

Analytical samples of 5a and 5b were in complete agreement with those reported previously. 11,12 Yield 39.0 mg, 98% of pure rac-5a. A solution containing 50 mg, 0.28 mmol) was treated with methanol (2 mL) and subsequently analyzed by 400 MHz 1H-NMR and mass data were the same as for compound 5b.

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for rac-11. Addition of Eu(hfc)₃ (0.4 equiv) gave a separation of CH₃ 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 × 10⁻² mbar] starting from a 1:1 mixture of diastereomeric acetates 7b and 8b (110 mg, 0.53 mmol). Yield 64.9 mg, 86% as a colorless oil. [α]D −34.2° (c 0.5, CH₂Cl₂), ee 94%.

Acknowledgment. We thank Amano Enzyme Europe Ltd. for a generous gift of lipase PS and several other lipases. We thank H. Amatdjais, P. v Galen, and A. Swolfs for conducting elemental analysis, mass, and 400 MHz ¹H-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 ¹H NMR spectra of rac-8a, rac-8b, 7a, 7b (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.