KINETIC RESOLUTION OF 2-FURYLCARBINOLS USING THE SHARPLESS OXIDATION AND ITS APPLICATION TO THE SYNTHESIS OF (5R,6S)-6-ACETOXY-5-HEXADECANOLIDE

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Abstract — Kinetic resolution of 2-furylcarbinols employing 10 mol % of Ti(0'-Pr)₄ in the presence of molecular sieves 3Å under the Sharpless oxidation condition generally affords corresponding optically active 2-furylcarbinols in a range of 80-98% ee. Application of the optically active 1f to the synthesis of (5R,6S)-6-acetoxy-5-hexadecanolate (8), the major component of the oviposition attractant pheromone of the mosquito Culex pipens fatigans, has also been achieved.

Recently we have developed the stereoselective syntheses of physiologically active steroids, where the oxidation of 2-furylcarbinol has been employed as a key reaction.¹ As our continuing work on the utilization of this strategy in the synthesis of natural products, we have investigated kinetic resolution² of 2-furylcarbinols employing the Sharpless reagent³ to prepare optically active 1.⁴ Here we report successful results for the catalytic asymmetric kinetic resolution of racemic 1 affording optically active 1 and its application to the synthesis of (5R,6S)-6-acetoxy-5-hexadecanolate as an oviposition attractant pheromone of the mosquito Culex pipens fatigans.⁵

Our results for catalytic asymmetric kinetic resolution⁶ of racemic 1 which were carried out in the presence of 3Å molecular sieves using TBP (0.7 eq), Ti(0'-Pr)₄ (10% mol), and tartrate (15% mol) are summarized in Table I. The reactions proceed rapidly to produce the optically active 2-furylcarbinols of high enantiomeric purity except for 1a and 1d, whose reaction conditions might not be
optimized. It is noteworthy that reaction of 2-furylpropenylcarbinol 1d afforded the kinetically resolved 1d and its corresponding lactol 2d. This result suggests that the rate for oxidation of 2-furylcarbinol is faster than that for epoxidation of allylic alcohol. The absolute configurations of 1 were deduced by the comparison with the specific rotations of the corresponding products, and confirmed unambiguously by transformation of the optically active 1f into (5R,6S)-6-acetoxy-5-hexadecanolide (8).

As outlined in Scheme 1, treatment of 1f (>98% optical purity) with N-bromosuccinimide in aqueous tetrahydrofuran afforded the corresponding lactol 2f, whose catalytic hydrogenation followed by dithioacetalization gave the \( \alpha \)-hydroxy ketone 3, \([\alpha]_D^{25} = 32.3^\circ\) (c 1.56, CHCl\(_3\)), in 77% overall yield. Reduction of 3 with zinc borohydride in ether furnished an inseparable mixture of the diols, which was acetonized to give a chromatographically separable (1:4.6) mixture of acetonides 4, \([\alpha]_D^{25} = 22.0^\circ\) (c 0.64, CHCl\(_3\)), and 5, \([\alpha]_D^{25} = 11.1^\circ\) (c 1.3, CHCl\(_3\)) in 87% yield. Hydrolysis of the dithioacetal 5 with red mercuric oxide and boron trifluoride in aqueous tetrahydrofuran afforded the corresponding aldehyde, whose reaction with 2-lithio-2-trimethylsilyl-1,3-dithiane gave the ketene thioacetal 6, \([\alpha]_D^{25} = 7.1^\circ\) (c 0.5, CHCl\(_3\)), in 61% yield. Finally, treatment of 6 with mercuric chloride in methanol and water followed by lactonization of the crude product furnished (5R,6S)-6-hydroxy-5-hexadecanolide 7, mp 68-69 °C (from n-hexane), \([\alpha]_D^{22} = 12.5^\circ\) (c 0.2, CHCl\(_3\)) [lit.\(^5b\) mp 67-68 °C (n-hexane), \([\alpha]_D^{20} = 12.5^\circ\) (c 0.54, CHCl\(_3\))], in 50% overall yield. Since acetylation of 7 was already accomplished by several groups,\(^5\) this constitutes a synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide (8).

Thus, we have developed a simple and efficient method for preparation of the optically active 2-furylcarbinols employing catalytic asymmetric kinetic resolution of the racemic 2-furylcarbinols. The absolute configurations of the resolved 2-furylcarbinols could be predictable by regarding the tartrate employed.\(^3\) As an application of the optically active 2-furylcarbinols to natural products synthesis, we demonstrated an efficient synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide (8) starting from (S)-(2-furyl)-undecanol 1d in 9 steps. The optically active 2-furylcarbinols thus resolved serve as highly versatile intermediates for the synthesis of a variety of natural products.
Table I. Kinetic Resolution of 2-Furylcarbinols

<table>
<thead>
<tr>
<th>R</th>
<th>temp.</th>
<th>time</th>
<th>yield %</th>
<th>ee</th>
<th>[α]_D^25 (C, CHCl₃)</th>
<th>abs. yield %</th>
<th>Config.</th>
</tr>
</thead>
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<tr>
<td>methyl</td>
<td>-20</td>
<td>5</td>
<td>36</td>
<td>80</td>
<td>+17.4° (1.78)</td>
<td>38</td>
<td>R</td>
</tr>
<tr>
<td>ethyl</td>
<td>-20</td>
<td>3.5</td>
<td>32</td>
<td>95</td>
<td>+12.6° (2.09)</td>
<td>42</td>
<td>R</td>
</tr>
<tr>
<td>butyl</td>
<td>-35</td>
<td>6</td>
<td>43</td>
<td>94</td>
<td>+9.2° (1.07)</td>
<td>46</td>
<td>R</td>
</tr>
<tr>
<td>propenyl</td>
<td>-30</td>
<td>7</td>
<td>32</td>
<td>82f</td>
<td>-40.4° (1.95)</td>
<td>52</td>
<td>R</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>-25</td>
<td>7</td>
<td>44</td>
<td>&gt;98e</td>
<td>+20.0° (1.19)</td>
<td>52</td>
<td>R</td>
</tr>
<tr>
<td>decyl</td>
<td>-25</td>
<td>4</td>
<td>44</td>
<td>&gt;98</td>
<td>-9.6° (2.49)</td>
<td>51</td>
<td>S^g</td>
</tr>
</tbody>
</table>

a All reactions were carried out with 10% Ti(OiPr)_4, 15% L-(+)-DIPT, and 0.7 equiv. of THF / isooctane in the presence of 3A molecular sieves, except as noted. b All recovered 2-furylcarbinols had the depicted (R) stereochemistry, except if. c Isolated yields. d Determined by 400 MHz ^1H nmr analysis of the corresponding MTPA ester. e >98% ee indicates that the other enantiomer was not detectible by nmr. f Determined by 400 MHz ^1H nmr analysis of the MTPA ester of 2-furylpropylcarbinol after hydrogenation of the optically active 1d because of the instability of the product on reaction with MTPA chloride. g D-(−)-DIPT was employed.

Scheme I

(a) NBS, THF-H₂O; (b) H₂, 10% Pd-C, AcOEt; (c) HS(CH₂)₂SH, BF₃·OEt₂, CH₂Cl₂; (d) Zn(BH₄)₂, Et₂O, -25°C; (e) acetone, p-TsOH; (f) HgO, BF₃·OEt₂, THF-H₂O; (g) Li[SMe₃]₂, THF; (h) HgCl₂, MeOH-H₂O, 100°C; (i) p-TsOH, benzene, 80°C.
REFERENCES


2. During this work, the similar work has been published in J. Org. Chem., 1988, 53, 1586 by Prof. F. Sato independently, and this prompted us to report our own results.


Received, 22nd June, 1988