Enantioselective syntheses of 3,4,5-trisubstituted γ-lactones: formal synthesis of (−)-blastmycinolactol

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Abstract—A kinetic resolution process of Rh-catalyzed intramolecular Alder-ene reaction is described along with the studies of the substrate scope and stereochemistry of this remarkably efficient process. 3,4,5-Trisubstituted γ-lactones were synthesized in high enantioselectivity (>99% ee) and efficiency. The formal asymmetric syntheses of (−)-blastmycinolactol and (+)-blastmycinone, degradation products of the macrocyclic dilactone (+)-antimycin, were reported to address the applications of this methodology.

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The development of new methodologies for the synthesis of butyrolactone natural products has received considerable attention from organic chemists.¹ This can be attributed to the wide and potent biological activities exhibited by many classes of compounds containing the butyrolactone frameworks such as alkaloids, macrocyclic antibiotics, lignans, pheromones, antileukemics, and flavor component.² The effort to develop efficient, practical, environment friendly, and low cost approaches relies on the design of effective synthetic methodologies. Several important polyketide metabolites, which are shown in Figure 1, have polysubstituted γ-lactones as the structure motif.

3,4,5-Trisubstituted γ-lactones have posed a significant challenge for synthetic chemists because of the contiguous chiral centers in the five-membered ring, and there are very limited asymmetric methods known for their synthesis. Control of the relative as well as absolute stereochemistry of this type of compounds in a general way would be desirable for the efficient synthesis. Some of the strategies include transformation of natural products,³ enzymatic resolution,⁴ Sharpless dihydroxylation,⁵ ring-open aldol reaction,⁶ intramolecular lactonization,⁷ and oxidative heterocyclization.⁸ Recent example of paraconic acids synthesis by Reiser and co-workers gives a nice example of enantioselective synthesis of trisubstituted γ-lactones.⁹ Addition of highly stabilized ester to 1,2-dioxines can also afford γ-lactones with good yields and high diastereoselectivity.¹⁰

Kinetic resolution has been considered as a useful strategy for syntheses of enantiomerically pure compounds and has been studied extensively in the past few decades.¹¹ We previously reported a novel procedure by using [RhCODCl₂/BINAP/AgSbF₆] as the catalyst in a Rh-catalyzed kinetic resolution reaction to synthesize 4-alkylidine-2,3-disubstituted tetrahydrofurans, and the kinetic resolution process was analyzed in great detail therein.¹² In this communication, we described a kinetic resolution process of Rh-catalyzed intramolecular Alder-ene reaction to synthesize enantiomeric form of...
3,4,5-trisubstituted γ-lactones as well as the enantio-meric pure of enyne esters.

Compared to the asymmetric synthesis of polysubstituted tetrahydrofurans, enantiomeric pure polysubstituted γ-lactones have more synthetic values. So far there are very few general methods available for realizing this task. Encouraged by the previous kinetic resolution results, the asymmetric Rh-catalyzed Alder-ene reactions were carried out in the presence of [Rh(COD)Cl]_2, (R)- or (S)-BINAP, and AgSbF_6 at room temperature, which is similar to previous catalyst system. Extraordinarily high enantioselectivity (>99% ee) and high yields for both products 2a-h that contained two adjacent stereogenic centers and unreacted starting materials 1a-h were observed. The excellent results via kinetic resolution process can be obtained with a wide range of substituents (Table 1). More stabilized alkynic ester (R^1 = Ph) are tend to slow down this transformation and could take 20–30 min to achieve high conversion (entries 6, 7, and 8). However, bulky groups at allylic position (R^2 = i-Pr or Ph) will inhibit the cycloisomerizations and substrates with those groups show no conversion at current catalytic condition. It is worth to note that the corresponding chiral products and enynes are all separable by flash column chromatography.

The substrates with hydroxyl group at the terminal allylic position were reported previously for Alder-ene reactions and kinetic resolution.13 As we expected, polyfunctionalized lactones with methyl ketone side chain, such as 6a, b, can be formed in a similar manner with excellent enantioselectivities. LiOH can hydrolyze the remaining enyne esters 3a-c and 5a,b in THF–H_2O (1:1) solution to produce chiral allylic alcohols, which are very useful building blocks for organic synthesis.14

As we reported before, kinetic resolution gives 2,3-trans-tetrahydrofurans as the only products.12 The configuration was elucidated by interpret NOSEY spectra. Similar stereochemistry pattern has been observed in the kinetic resolution of enyne esters. After Rh coordinated with enyne substrate, H^+ and H^0 are in trans-position will derive a favored intermediate, in which the 2-methyl group is oriented away from metal center (Fig. 2). If cis-double bond is coordinated in a pseudo twist-boat con-

Table 1. Rh-catalyzed kinetic resolution of enyne esters^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Substrate</th>
<th>2 Ee % (yield)</th>
<th>1 Ee % (yield)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>OMe</td>
<td>1a</td>
<td>&gt;99 (47)</td>
<td>&gt;99 (47)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>C_3H_7</td>
<td>1b</td>
<td>&gt;99 (39)</td>
<td>&gt;99 (42)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>C_3H_11</td>
<td>H</td>
<td>1c</td>
<td>&gt;99 (48)</td>
<td>&gt;99 (46)</td>
</tr>
<tr>
<td>4</td>
<td>C_3H_11</td>
<td>Me</td>
<td>C_3H_7</td>
<td>1d</td>
<td>&gt;99 (45)</td>
<td>&gt;99 (48)</td>
</tr>
<tr>
<td>5</td>
<td>C_3H_11</td>
<td>Me</td>
<td>OMe</td>
<td>1e</td>
<td>&gt;99 (43)</td>
<td>&gt;99 (48)</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Me</td>
<td>C_3H_7</td>
<td>1f</td>
<td>&gt;99 (41)</td>
<td>&gt;99 (49)</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Me</td>
<td>OMe</td>
<td>1g^c</td>
<td>&gt;99 (45)</td>
<td>&gt;99 (48)</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>C_3H_11</td>
<td>H</td>
<td>1h</td>
<td>&gt;99 (49)</td>
<td>&gt;99 (50)</td>
</tr>
</tbody>
</table>

^a The reaction was carried out with 5 mol% catalyst loading and 2–10 min is the typical reaction time.

^b Enantiomeric excesses (ee) were determined by chiral HPLC and GC. The yield reported here is all isolated yield.

^c For 1a and 1g, ee were determined by its derivatives. See supplementary data for more details.
formation, the 2-methyl group is oriented toward Rh center and will generate a disfavored intermediate, which gives cis-product. The Cache\textsuperscript{a} modeling by using MM2 calculation of Rh–substrate complex also agrees with our hypothesis. In this model, enyne substrate coordinates with Rh–BINAP complex in such a manner that the allylic methyl group should keep away from the chiral pocket and lower the energy of this complex intermediate. Indeed, this intermediate should generate trans-product and compliance with our observation.

(+)-Blastmycinone is a degradation product of the macrocyclic dilactone (+)-antimycin, an antifungal-antibiotic isolated from a family of Streptomyces species.\textsuperscript{15} Recently, blastmycinone has attracted remarkable attention in part because it is a potential precursor to synthetically isolated as a challenge. The key intermediate methyl ketone \textsuperscript{11} was synthesized with 80\% yield by PdCl\textsubscript{2} and CuCl\textsubscript{2} catalyzed oxidation reaction in DMF:H\textsubscript{2}O (9:1) at ambient temperature.\textsuperscript{16} Further transformation to (+)-blastmycinolactol can be conducted by employing bis(trimethylsilyl) peroxide [(TMSO)\textsubscript{2}].\textsuperscript{17} Consequently, (+)-blastmycinone can be synthesized via a simple esterification from (+)-blastmycinolactol.

In summary, a highly stereoselective kinetic resolution process of enyne esters as well as Rh-catalyzed intramolecular cycloisomerization reaction was developed.\textsuperscript{18} Polyfunctionalized \(\gamma\)-lactones with two or three adjacent stereogenic centers and enantiomeric pure enyne esters were obtained in this process. Formal syntheses of (-)-blastmycinolactol and (+)-blastmycinone were performed with high enantioselectivity. Syntheses of more complex molecules and polysubstituted \(N\)-heterocyclic compounds are currently under investigation in our laboratory and the results will be published in due course.

Acknowledgements

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Supplementary data

Experimental details, spectroscopic data, and analyses for all compounds prepared in Table 1 and Schemes 1 and 2 are given. The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at 10.1016/j.tetlet.2005.01.112.

References and notes


18. Typical experimental procedure (9): In a dried Schlenk tube, the [Rh(COD)Cl]$_2$ (12.5 mg, 0.025 mmol), BINAP (34.5 mg, 0.054 mmol) were dissolved in 6 mL 1,2-dichloroethane (in Sure/Seal™ bottles without further purify), then freshly prepared hex-2-ynoic acid 1-methyl-but-2-enyl ester 8 (180 mg, 1.0 mmol) was added into the solution at room temperature under nitrogen atmosphere. After stirring for 1 min, AgSbF$_6$ (0.1 mmol, 0.05 M solution in 1,2-dichloroethane) was added into the mixture. The reaction was run at room temperature for 10 min, and the reaction mixture was directly subjected to column chromatography to provide colorless oil (84 mg, 47% yield). The chiral starting material was isolated in 48% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.99 (dt, $J = 2.7$, 7.8 Hz, 1H), 5.61–5.50 (m, 1H), 5.23 (dd, $J = 1.4$, 10.1 Hz, 1H), 5.17 (d, $J = 17.0$, 1H), 4.17–4.13 (m, 1H), 3.17–3.03 (m, 1H), 2.69–2.61 (m, 2H), 1.45–1.36 (m, 2H), 1.37 (d, $J = 6.2$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.31, 144.76, 134.99, 128.50, 119.71, 78.20, 54.02, 29.32, 22.22, 19.37, 13.64; MS (APCI) mlz: [M$^+$ + 1], 181.1; HRMS (APCI), Calcd for C$_{11}$H$_{17}$O$_2$ [M$^+$ + 1]: 181.1229, found: 181.1228; $[\alpha]_{D}^{20}$ +44.57 (c 1.0, CHCl$_3$) from $(S)$-BINAP. GC: Supelco* gamma-DEX 225, 100 °C, 2 mL/min, $t_1 = 98.14$, $t_2 = 117.51$ min.