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Synthesis of Precursors of the Agalacto (*Exo*) Fragment of the Quartromicins via an Auxiliary-Controlled *Exo*-Selective Diels-Alder Reaction

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Abstract

A direct synthesis of the α -hydroxyaldehyde *exo*-5, a precursor of the *exo*-spirotetronate subunit of the quartromicins, was achieved through an *exo*-selective Lewis acid-catalyzed Diels-Alder reaction of dienophile 12a and diene 1.

The quartromicins are a structurally unique group of spirotetronate natural products isolated in 1991 by Oki and co-workers.¹ They display antiviral activity against herpes simplex virus type 1 (HSV-1), influenza virus, and human immunodeficiency virus (HIV).^{2,3} Oki and coworkers demonstrated that the quartromicins possess a unique 32-membered carbocyclic ring system containing two different spirotetronic acid units connected in an alternating head to tail manner. Based on published ¹H NMR data,¹ supporting synthetic studies in our group,⁴ and consideration of possible biosynthetic precursors we proposed⁵ the relative stereochemistry of quartromicins A₃ and D₃ depicted in Figure 1. We refer to the two spirotetronate fragments as *endo* (i.e., that bearing the galactose residue in quartromicin A₃) and *exo* (also referred to as the agalacto unit) by virtue of the Diels-Alder chemistry that has been targeted for their synthesis.^{5,6}

We have previously reported syntheses of the enantiomerically pure monomeric *endo* (**6**) and *exo* (**7**) spirotetronate units of the quartromicins via the Diels-Alder reaction of (*Z*)-substituted diene **1** and the *N*-acryloyl sultam dienophile **2** (Figure 2).^{5,6} The major (*exo*) product of this Diels-Alder reaction was converted to aldehyde *exo*-3, which was further elaborated to *endo*- α -hydroxy aldehyde **4** via a stereoselective two-step installation of the C-1 β -face hydroxyl group.⁵ However, installation of the hydroxyl group on the hindered α -face of C-1, required for synthesis of *exo*-5, proved to be quite difficult and has been accomplished only via multi-step sequences.^{5,7} We therefore were interested in developing a more straightforward strategy that would allow hydroxyl group of *exo*-5 to be installed in many fewer steps, ideally during an *exo*-selective Diels-Alder reaction.

Conformationally restricted (*S*)-*cis* enone and (*S*)-*cis* enoate dienophiles exhibit a striking preference for *exo*-Diels-Alder cycloaddition.⁸ In previous studies, we have demonstrated that chiral dienophiles **8** and **9** (Figure 3) give excellent *exo*- and diastereofacial selectivity in thermal Diels-Alder reactions with a range of (*E,E*)-dienes.^{8,9} However, dienophile **8** is not stable to the Lewis acidic reaction conditions required for the Diels-Alder coupling to the relatively unreactive (*Z*)-substituted diene **1**.¹⁰ While the chiral imide dienophile **9** underwent

a MeAlCl_2 -catalyzed Diels-Alder reaction with **1** (data not shown), attempted manipulation of the major Diels-Alder product proved unproductive.¹¹ In addition, attempts to effect Lewis-acid mediated Diels-Alder reactions of **1** with α -substituted dienophiles **10** and **11** were unsuccessful.⁵ The latter studies are consistent with literature reports that methacryloyl sultams adopt ground state conformations with the dienophilic double bond out of conjugation with the methacrylate carbonyl unit,¹² well as knowledge that the α -methyl group of methacryloyl imide dienophiles destabilizes the ground state *s-cis* conformation,¹³ which causes these dienophiles to display poor Diels-Alder reactivity.

Based on these observations, we designed the conformationally constrained dienophile **12** which we envisaged would undergo an *exo*-selective Lewis-acid mediated Diels-Alder reaction with (*Z*)-diene **1** (Figure 4). It was anticipated that the R group in **12** would play a critical role in inducing synthetically useful levels of diastereofacial selectivity in the Diels-Alder reactions.

Syntheses of oxazolidinones **15a–c** are outlined in Scheme 1. Conversion of L-valine (**16a**) to 5-oxazolidinone **17** as a single diastereomer proceeded via a three-step sequence.¹⁴ Alkylation of **17** with *p*-methoxybenzyloxymethyl chloride (PMBMCl) followed by DDQ oxidative deprotection of the PMB group provided primary alcohol **18**.¹⁵ Treatment of **18** with sodium hydride induced a ring-closing event that provided **15a** in 90% yield.¹⁶ Oxazolidinones **15b–c** were readily synthesized in two steps from α -substituted serine derivatives **16b–c**.¹⁷

Synthesis of dienophiles **12a–c** was initiated by protection of racemic **21**⁸ as the TBS ether **14** (Scheme 2). The corresponding acid chloride **22** was coupled with oxazolidinones **15a–c** by using Evans' procedure¹⁸ which provided N-acyl oxazolidinones **23a–c** in 80% yield. Deprotection of the benzyl ester with titanium tetrachloride followed by deprotection of the TBS group using HF produced hydroxy acids **24a–c**.¹⁹ Treatment of the hydroxy acids with pivaloyl chloride provided lactones **13a–c** in 60–75% yield. The sulfide units of **13a–c** were then oxidized to the corresponding sulfoxides, subsequent thermal elimination of which then afforded the targeted dienophiles **12a–c** in 40–70% yield.

Results of Diels-Alder reactions of dienophiles **12a–c** with (*Z*)-diene **1** are summarized in Scheme 3. Best results were obtained using MeAlCl_2 among the range of Lewis acids tested.¹⁰ Treatment of **1** and dienophile **12a** ($\text{R} = i\text{-Pr}$) with MeAlCl_2 at -78°C for 5 d provided a 5 : 1 mixture cycloadducts **25a** and **26a** in 70% yield. Reduction of this mixture with LiAlH_4 and then oxidation of the resulting diols using the Parikh-Doering procedure²⁰ provided *exo*-hydroxy aldehyde **5** and the *endo*- diastereomer **4** in 60% combined yield. The spectroscopic data for **4** and **5** matched that for samples obtained from previous synthetic studies.^{5,7}

These data demonstrate that dienophile **12a** displays excellent diastereofacial selectivity and synthetically useful *exo*-selectivity in the Diels-Alder reaction with (*Z*)-substituted diene **1**. Comparable selectivity was obtained when dienophile **12b** ($\text{R} = \text{Me}$) was used, but the Diels-Alder reaction was considerably less efficient in this case owing to the poor solubility of **12b** at -78°C . Although dienophile **12c** ($\text{R} = \text{CH}_2\text{Ph}$) exhibited good solubility, it displayed low reactivity, and also was significantly less *exo*-selective in the Diels-Alder reaction with **1**. Thus, a preparatively useful three-step synthesis of α -hydroxy aldehyde *exo*-**5** has been achieved by the *exo*-selective, MeAlCl_2 -mediated Diels-Alder reaction of **12a**. This synthesis is considerably shorter than any of the previous routes to this important quartromycin intermediate that we have examined to date.^{5,7}

The Diels-Alder reactions of **12a** with several other dienes were examined. The thermal Diels-Alder reaction of **12a** with cyclopentadiene at 23°C provided a mixture of three diastereomeric cycloadducts in 80% yield (Scheme 4). LiAlH_4 reduction of this mixture provided a 4 : 1 ratio of **30** (*exo*) and **31** (*endo*). This result indicated that the cycloadducts were formed with an *exo/endo* ratio of 4 : 1. Dienophile **1a** also exhibited excellent diastereofacial selectivity at

this reaction condition (**27** : **28** = 19 : 1). Under Lewis acid catalyzed conditions (0.3 equiv of MeAlCl₂ at -78 °C), the *exo/endo* selectivity increased to 19 : 1 (entries 2). However, the *exo* diastereofacial selectivity was significantly reduced (**27** : **28** = 3 : 1). We do not understand the erosion of diastereofacial selectivity under these reaction conditions.

The Diels-Alder reactions of dienophile **12a** with less reactive dienes such as 1,3-cyclohexadiene and *trans*-2-methyl-1,3-pentadiene required higher reaction temperatures than with cyclopentadiene (Scheme 5). These reactions gave two diastereomers under both thermal and Lewis acid catalyzed reaction conditions, with the *exo*-cycloadduct predominating under all conditions; stereochemical assignments were made by ¹H nOe analysis after reduction of the cycloadducts to the diol derivatives **32–35**. In contrast, the Diels-Alder reaction of **12a** and 2,4-dimethyl-1,3-pentadiene gave only one diastereomeric product **36**. In all of the reactions summarized in Scheme 5, near perfect diastereofacial selectivity was observed with respect to the dienophile **12a**.

In summary, the new conformationally constrained chiral dienophile **12a** undergoes a preparatively useful Lewis acid-catalyzed and *exo*-selective Diels-Alder reaction with (*Z*)-trisubstituted diene **1**, thereby paving the way for the development of a direct and step-wise efficient synthesis of α -hydroxy aldehyde *exo*-**5** and the derived *exo*-spirotetronate fragment of the quartromicins. Utilization of these intermediates in ongoing efforts to complete total syntheses of quartromicins A₃ and D3 are underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of quartromicins A₃ and D₃

Figure 2.
Previous syntheses of *endo*-6 and *exo*-7

Figure 3.
Exo-selective Diels-Alder dienophiles.

Figure 4.
Retrosynthetic analysis of dienophile **12**

Scheme 1.
Synthesis of oxazolidinones **15a-c**.

Scheme 2.
 Synthesis of bicyclic dienophiles **12a-c**.

dienophile		yield	25 : 26
12a	R = <i>i</i> -Pr	70%	5 : 1
12b	R = Me	50%	4 : 1
12c	R = Bn	40%	2 : 1

	yield	exo-5 : endo-4
a , R = <i>i</i> -Pr	60%	5 : 1
b , R = Me	54%	4 : 1
c , R = Bn	45%	2 : 1

Scheme 3.

Diels-Alder reactions of dienophiles **12a-c** and diene **1**.

Scheme 4.
Diels-Alder reactions of **12a** with cyclopentadiene.

Scheme 5.
Diels-Alder reactions of **12a** with other dienes.