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Diastereoselective Synthesis of the *endo*- and *exo*-Spirotetronate Subunits of the Quartromicins. The First Enantioselective Diels–Alder Reaction of an Acyclic (*Z*)-1,3-Diene

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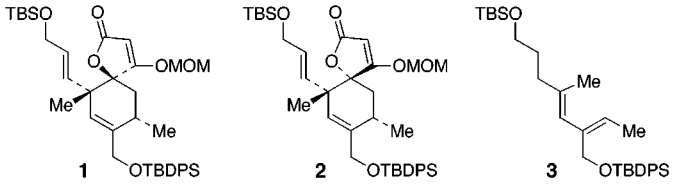
ABSTRACT



Diastereoselective syntheses of the *endo*- and *exo*-spirotetronates 1 and 2, corresponding to the galacto and agalacto fragments of quartromicins A_3 and D_3, are described. The key step of these syntheses are highly enantio- and diastereoselective Lewis acid catalyzed Diels–Alder reactions of the 1,1,3,4-tetrasubstituted diene 3.

Quartromicins A_3 and D_3 are members of a structurally complex group of C_2 symmetric, macrocyclic natural products that possess significant activity against a number of human viral targets, including HIV.[2−4] We were attracted to these compounds, although their stereochemistry had not been addressed in the isolation papers,[3,2] in view of our experience with the synthesis of other spirotetronate natural products.[5−7] We recognized that the four sets of adjacent quaternary centers (C4/C4′ and C12/C12′ in the agalacto fragments; C22/C22′ and C30/C30′ in the galacto fragments, respectively) would provide a demanding test of strategy and synthetic methodology.[8,9] In fact, these issues stimulated our efforts on the development of Lewis acid catalyzed Diels−Alder reactions of acyclic (*Z*)-dienes.[10]

In the preceding Letter we proposed the stereochemistry of quartromicins A_3 and D_3, as depicted in Figure 1, by comparison of published ^{1}H NMR data for the natural products with NMR data for a number of structurally related spirotetronates that we have synthesized[8,9] or that have been described in the literature.[11] On the basis of this analysis, we concluded that the two galacto subunits of quartromicins A_3 and D_3 are in the same stereochemical series as the *endo*-spirotetronate **1**, whereas the two agalacto subunits, which occupy alternating corners of the rectangular-shaped macrocyclic structure, are in the same stereochemical series as the *exo*-spirotetronate **2**.[12] While we have previously reported syntheses of **1** and **2**,[8,9] the routes employed in the first and second generation syntheses are lengthy, suffer from poor

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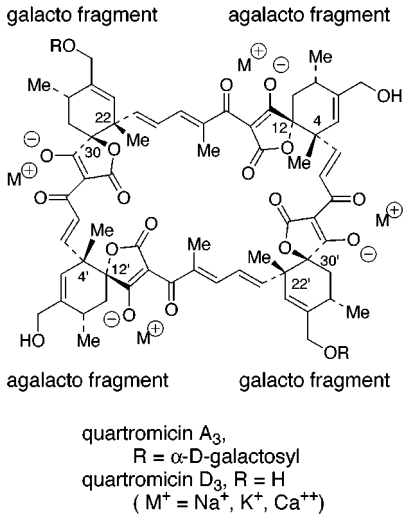


Figure 1.

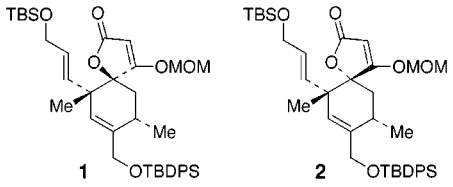


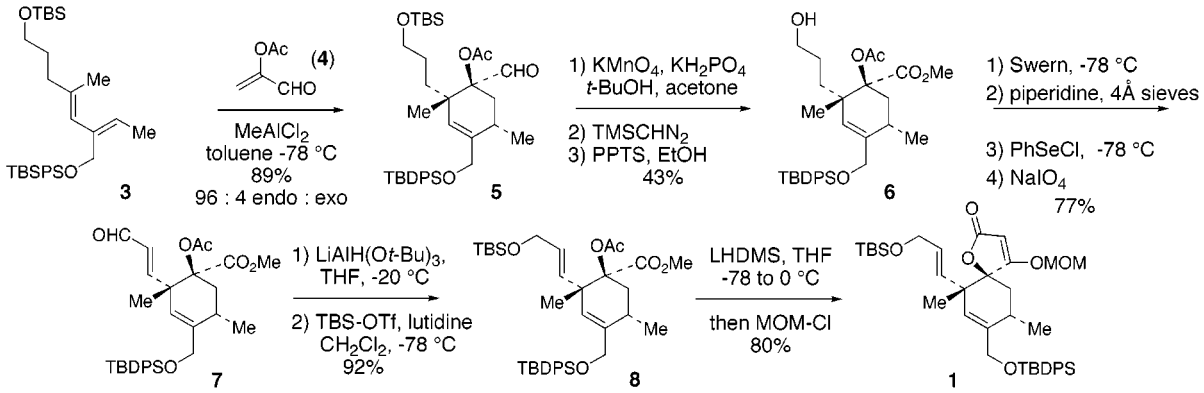
Figure 2.

diastereoselectivity, and are not easily modified to permit the synthesis of other diastereomers of **1** and **2** (which are of interest for the synthesis of analogues). Accordingly, we describe herein third-generation syntheses of **1** and **2** by routes involving highly diastereoselective Diels−Alder reactions of the acyclic 1,1,3,4-tetrasubstituted diene **3**.[10] We also report the first enantioselective Diels−Alder reactions of **3**.

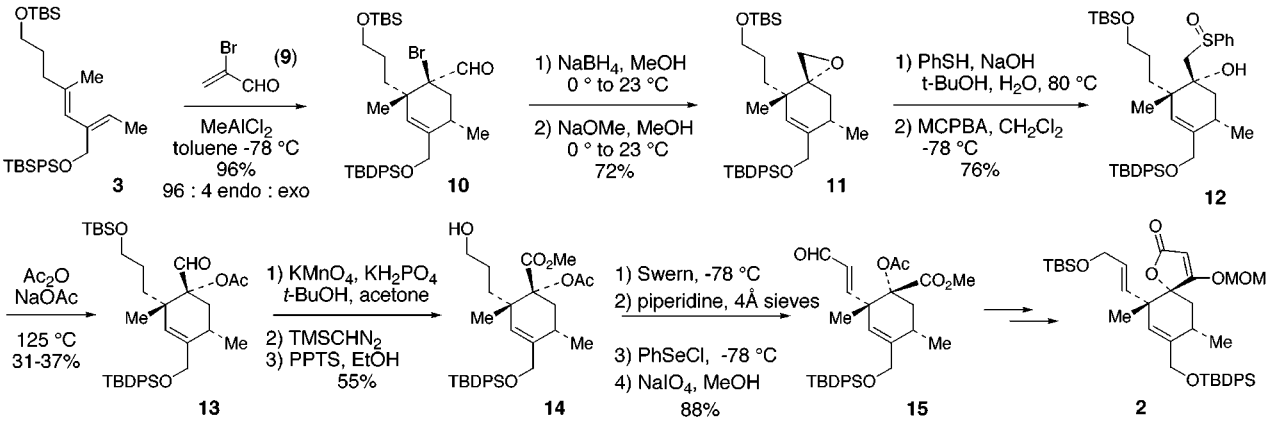
Because we have been unsuccessful in attempts to perform Diels−Alder reactions of diene **3** with acrylate dienophiles, the synthesis of racemic **1** (Scheme 1) commenced with the $MeAlCl_2$-promoted Diels−Alder reaction of **3** and α-acetoxyacrolein (**4**). This reaction provided *endo*-cycloadduct **5** in 89% yield and 96:4 *endo*−*exo* selectivity.[10] Oxidation of the exceptionally hindered aldehyde unit was accomplished by treatment of **5** with $KMnO_4$ in a 3:1 mixture of *t*-BuOH and acetone in the presence of KH_2PO_4.[13] Treatment of the crude carboxylic acid with $TMSCHN_2$ gave the corresponding methyl ester. Deprotection of the side chain TBS ether (PPTs, MeOH) then provided **6** in 43% yield for the three steps. Elaboration of **6** to the *endo*-spirotetronate **1** proceeded smoothly via intermediates **7** and **8** by using minor modification of the sequence previously disclosed for the synthesis of a diastereomer.[9]

Synthesis of the *exo*-spirotetronate **2** proved to be quite challenging (Scheme 2). Because we have not yet devised a direct Diels−Alder route to the *exo*-Diels−Alder adduct **13**, we elected to use the readily available product **10**[10] of the *endo*-Diels−Alder reaction of **3** and α-bromoacrolein (**9**) as the starting material for this synthesis.[14] Inversion of the extremely hindered α-bromo aldehyde stereocenter was readily accomplished by reduction of **10** with $NaBH_4$ in MeOH, followed by treatment of the resulting bromohydrin with NaOMe in MeOH to provide epoxide **11** in 72% yield. However, the epoxide unit of **11** proved to be extraordinarily unreactive, as it survived treatment with a variety of oxygen nucleophiles under forcing reaction conditions. Fortunately, treatment of **11** with PhSH and NaOH in aqueous *t*-BuOH at 80 °C effected the desired ring opening. Oxidation of the resulting sulfide to the sulfoxide by treatment with MCPBA in CH_2Cl_2 at −78 °C then provided a diastereomeric mixture of sulfoxides **12** in 76% overall yield. Pummerer reaction of **12** with Ac_2O and NaOAc at 125 °C provided the targeted *exo*-α-acetoxy aldehyde **13**, but in only 31−37% yield.[15] Numerous attempts to improve the efficiency of this reaction were unsuccessful. We suspect that the poor yield of **13** is due to competing Pummerer rearrangement of the intermediate α-hydroxysulfenium ion intermediate. Oxidation of aldehyde **13** to the carboxylic ester by using the conditions described for the oxidation of **5**, followed by deprotection of the TBS ether, provided the racemic *exo*-α-acetoxy ester **14** in 55% yield. Finally, oxidation of **14** under standard

Scheme 1. Diastereoselective Synthesis of *endo*-Spirotetronate **1**



Scheme 2. Diastereoselective Synthesis of *exo*-Spirotetronate **2**

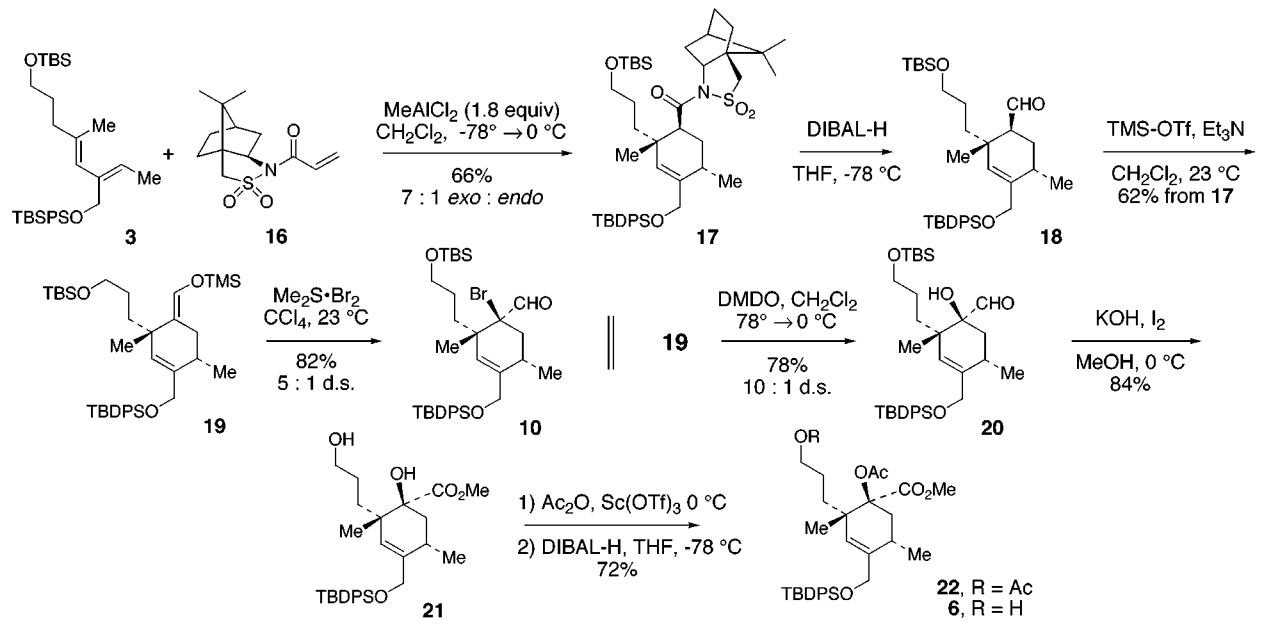


Swern conditions (DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C) and conversion of the aldehyde to the α,β-unsaturated aldehyde by using Williams' procedure[16] then provided enal **15** in 88% overall yield. Enal **15** is a known precusor to the *exo*-spirotetronate **2**.[8]

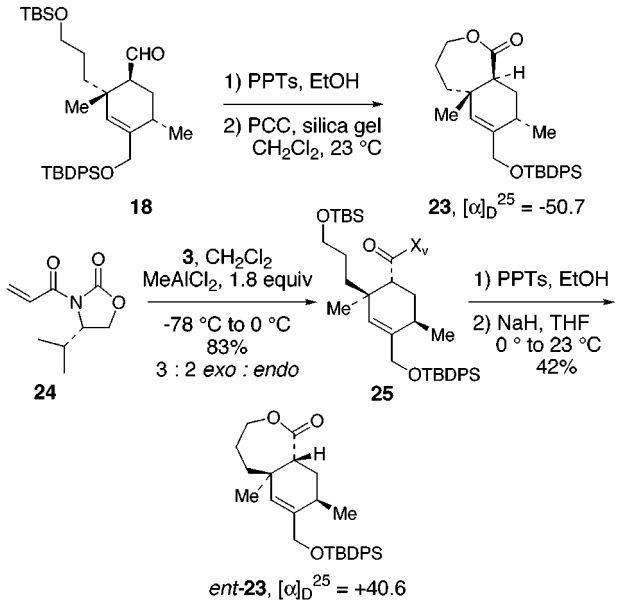
While these sequences established that the targeted *endo*- and *exo*-spirotetronates **1** and **2** can be synthesized with excellent diastereoselectivity, it is also necessary for these fragments to be prepared enantioselectively to avoid production of diastereomers in the coupling sequence leading to the quartromicins. We were very pleased to discover, therefore, that the $MeAlCl_2$-promoted Diels−Alder reaction of **3** and *N*-acryloyl sultam **16** provided the *exo*-cycloadduct **17** with 7:1 diastereoselectivity (Scheme 3).[17] This constitutes an expansion of the scope of Lewis acid mediated Diels−Alder reactions of acyclic (*Z*)-dienes[10] and also represents the first example of an enantioselective Diels−Alder reaction of an acyclic (*Z*)-diene.

The stereochemistry of **17** was assigned as shown in Scheme 4 following reductive conversion to *exo*-aldehyde **18**. Deprotection of the TBS ether provided a hemiacetal that was oxidized to give lactone (+)-**23** by using PCC on silica gel. The enantiomeric lactone *ent*-(−)-**23** was prepared by a sequence involving the $MeAlCl_2$-promoted Diels−Alder reaction of **3** and *N*-acryloyl oxazolidinone **24**.[18] This provided a 3:2 mixture of *exo*- and *endo*-diastereomers, among which the *exo*-isomer **25** predominated. Deprotection of the TBS ether and treatment of the resulting alcohol with NaH gave *ent*-(−)-**23** in 42% yield. This correlation establishes that the two *exo*-Diels−Alder adducts **17** and **25** are heterochirally related. In both cases, the assigned stereostructures are fully consistent with the well-established diastereofacial selectivity preferences of *N*-acryloyl sultam and *N*-acryloyl oxazolidinone dienophiles.[18,19] The *exo*-stereochemistry of **17**, **18**, and **23** was verified by NOE studies (see Supporting Information).

Scheme 3. Enantioselective Synthesis of Spirotetronate Precursors **6** and **10**



Scheme 4. Stereochemical Correlations



All attempts to hydroxylate enolates generated from **17** or the derived methyl ester have been unsuccessful. Consequently, utilization of **17** as a precursor to the spirotetronates **1** and **2** required that the enolate functionalization be performed at the stage of the derived aldehyde **18**.[20] Treatment of **18** with TMS−OTf and Et_3N in CH_2Cl_2 at 23 °C provided the enol silane **19** as a 3:1 isomeric mixture (62% yield from **17**). Bromination of **19** with bromodimethylsulfonium bromide[21] gave a separable 5:1 mixture of the *endo*-bromide **10** and its *exo*-diastereomer in 82% yield, thereby establishing an enantioselective route to the *exo*-spirotetronate **2** (Scheme 2). Alternatively, treatment of enol silane **19** with dimethyldioxirane provided the *endo*-alcohol **20** in 78% yield with 10:1 diastereoselectivity.[22] Oxidation of the α-hydroxy aldehyde to the α-hydroxy ester **21** was best accomplished (84% yield) by using I_2 and KOH in MeOH.[23] Unfortunately, the primary TBS ether was also cleaved under these conditions. Acylation of **21** using $Sc(OTf)_3$ in Ac_2O (as solvent) gave the diacetate **22** in good yield.[24] Finally, selective DIBAL reduction of the primary acetate then provided **6** (72% yield from **21**). This sequence thus provides formal enantioselective access to the *endo*-spirotetronate **1**.

In summary, we have developed highly diastereo- and enantioselective sequences to the *endo*- (**1**) and *exo*- (**2**) spirotetronate subunits of quartromicins A_3 and D_3 by routes involving Lewis acid catalyzed Diels−Alder reactions of diene **3**. Nevertheless, it is clear that problems remain to be solved in the establishment of the adjacent quaternary centers in nonracemic intermediates **6** and **14**. Studies addressing these problems along with further progress toward the total synthesis of quartromicins A_3 and D_3 will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health to W.R.R. (GM 26782) and a U.S. Department of Education GAANN Fellowship (P200A980233-00) to R.K.K. is gratefully acknowledged.

Supporting Information Available: ^1H NMR spectra for new compounds and stereochemical assignments of **17**, **18**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We use the terms "*endo*" and "*exo*" to describe the stereochemistry of the spirotetronate substructures in recognition of the fact that **1** and **2**, at least formally, can be synthesized from the products of *endo*- or *exo*-Diels−Alder reactions of diene **3** and an α-acetoxyacrylate dienophile, respectively.

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