ORGANIC LETTERS

2006
Vol. 8, No. 13
2795−2798

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

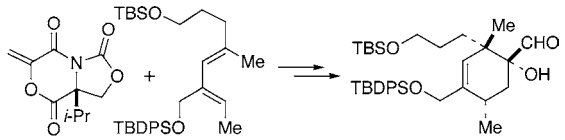
Jun Qi[†] and William R. Roush*[,‡]

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, and Department of Chemistry, Scripps-Florida, Jupiter, Florida 33458

roush@scripps.edu

Received April 15, 2006

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), the influenza virus, and the human immunodeficiency virus (HIV).[2,3] Oki and co-workers 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. On the basis of published ^{1}H NMR data,[1] supporting synthetic studies in our group,[4] and consideration of possible biosynthetic precursors, we proposed [5] the relative stereochemistry of quartromicins A_3 and D_3 depicted in Figure 1. We refer to the two spirotetronate fragments as endo (i.e., that bearing the galactose residue in quartromicin A_3) 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]

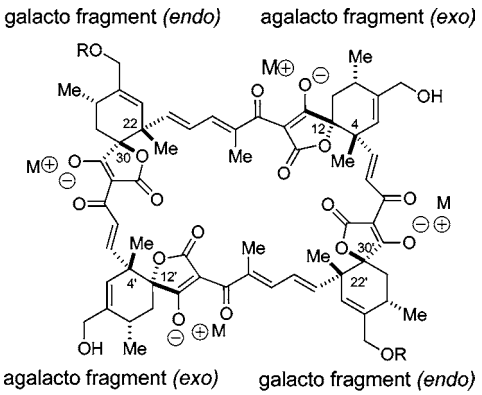


Figure 1. Structures of quartromicins A_3 and D_3.

[†] University of Michigan.
[‡] Scripps-Florida.

(1) Kusumi, T.; Ichikawa, A.; Kakisawa, H.; Tsunakawa, M.; Konishi, M.; Oki, T. *J. Am. Chem. Soc.* **1991**, *113*, 8947.
(2) Tsunakawa, M.; Tenmyo, O.; Tomita, K.; Naruse, N.; Kotake, C.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 180.
(3) Tanabe-Tochikura, A.; Nakashima, H.; Murakami, T.; Tenmyo, O.; Oki, T.; Yamamoto, N. *Antiviral Chem. Chemother.* **1992**, *3*, 345.
(4) Roush, W. R.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1539.
(5) Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002**, *58*, 6433.

10.1021/ol0609208 CCC: $33.50
Published on Web 05/23/2006

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 the synthesis of *exo*-**5**, proved to be quite difficult and has been accomplished only via multistep sequences.[5,7] We therefore were interested in developing a more straightforward strategy that would allow the hydroxyl group of *exo*-**5** to be installed in many fewer steps, ideally during an exo-selective Diels−Alder reaction.

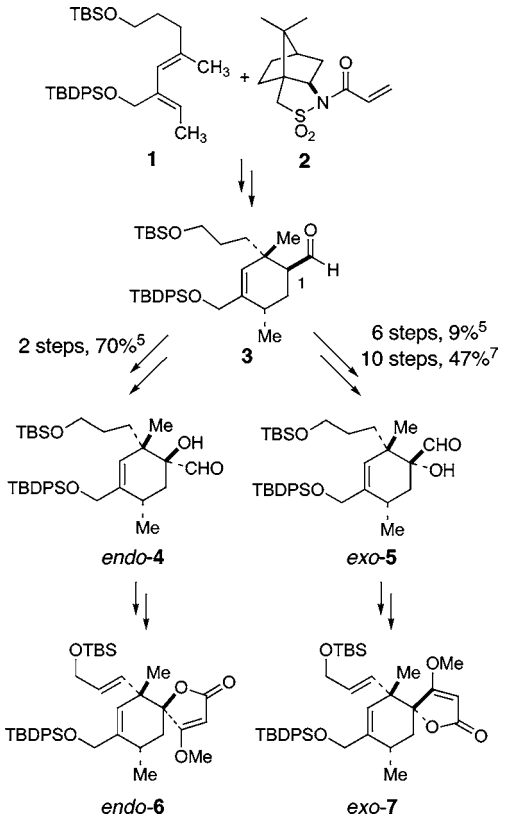


Figure 2. Previous syntheses of *endo*-**6** and *exo*-**7**.

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]

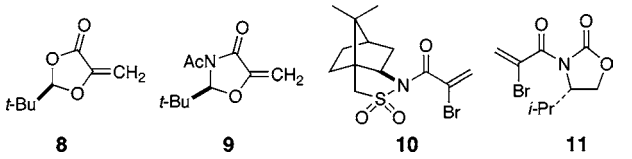


Figure 3. Exo-selective Diels−Alder dienophiles.

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] Although 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] as well as with 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.

On the basis of 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.

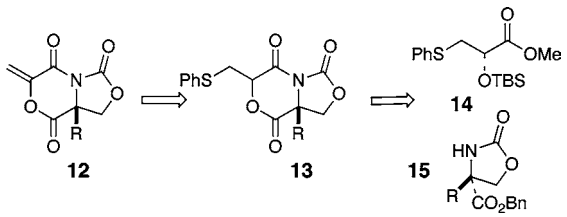
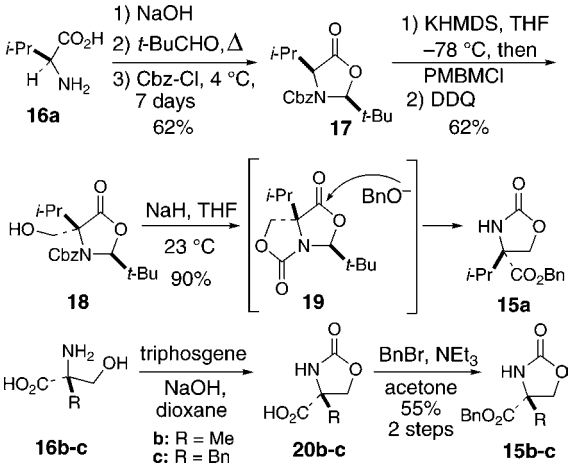


Figure 4. Retrosynthetic analysis of dienophile **12**.

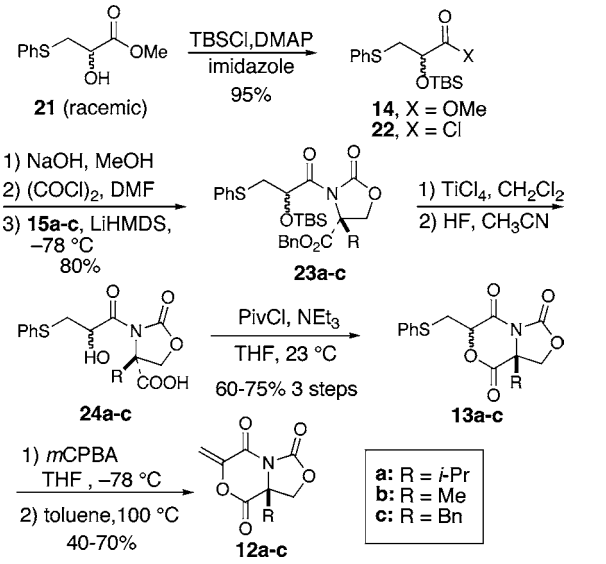
Syntheses of oxazolidinones **15a**−**c** are outlined in Scheme 1. Conversion of L-valine (**16a**) to 5-oxazolidinone **17** as a

(6) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543.
(7) Trullinger, T. K.; Qi, J.; Roush, W. R. *J. Org. Chem.* **2006**, *71*, to be submitted.
(8) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.
(9) (a) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305. (b) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708. (c) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.
(10) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402.
(11) Treatment of the exo cycloadduct deriving from Diels−Alder reaction of **1** and **9** with a variety of nucleophilic reagents led to rapid cleavage of the *N*-acetyl group, giving a very hindered lactam that could not be further manipulated.
(12) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.
(13) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Boeckman, R. K.; Liu, Y. *J. Org. Chem.* **1996**, *61*, 6984.

Scheme 1. Synthesis of Oxazolidinones **15a**−**c**



Scheme 2. Synthesis of Bicyclic Dienophiles **12a**−**c**



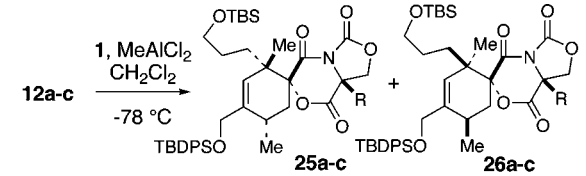
single diastereomer proceeded via a three-step sequence.[14] Alkylation of **17** with *p*-methoxybenzyloxymethyl chloride (PMBMCl) followed by DDQ oxidative deprotection of the PMB group provided primary alcohol **18**.[15] Treatment of **18** with sodium hydride induced a ring-closing event that provided **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** using Evans' procedure[18] 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 afforded the targeted dienophiles **12a**−**c** in 40−70% yield.

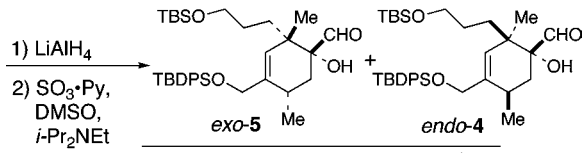
Results of Diels−Alder reactions of dienophiles **12a**−**c** with (*Z*)-diene **1** are summarized in Scheme 3. The best results were obtained using $MeAlCl_2$ among the range of Lewis acids tested.[10] Treatment of **1** and dienophile **12a** (R = *i*-Pr) with $MeAlCl_2$ at −78 °C for 5 days provided a 5:1 mixture of 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 procedure[20] provided *exo*-hydroxy aldehyde **5** and the endo diastereomer **4** in 60% combined yield. The spectroscopic data for **4** and **5** matched those 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** (R = 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** (R = CH_2Ph) exhibited good solubility, it displayed low reactivity and also was significantly less exo selective in the Diels−Alder reaction with **1**. Thus, a

Scheme 3. Diels−Alder Reactions of Dienophiles **12a**−**c** and Diene **1**



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



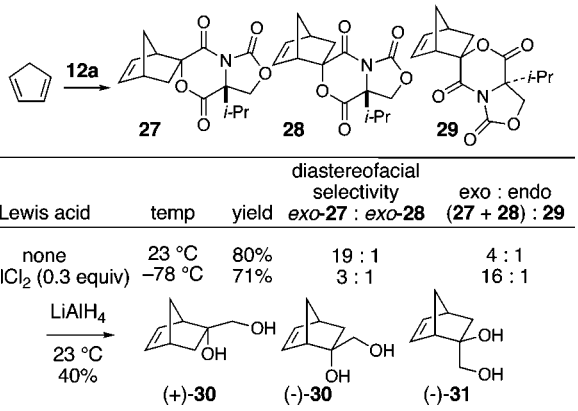
	yield	*exo*-**5** : *endo*-**4**
a, R = *i*-Pr	60%	5 : 1
b, R = Me	54%	4 : 1
c, R = Bn	45%	2 : 1

(14) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243.
(15) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; Deshong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. *J. Org. Chem.* **1999**, *64*, 3171.
(16) Avenoza, A.; Cativiela, C.; Corzama, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195.
(17) (a) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194. (b) Xi, N.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595.
(18) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(19) (a) Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1979**, *20*, 2793. (b) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981.
(20) Parikh, J. R.; von Doering, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

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 quartromicin 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).

Scheme 4. Diels−Alder Reactions of **12a** with Cyclopentadiene

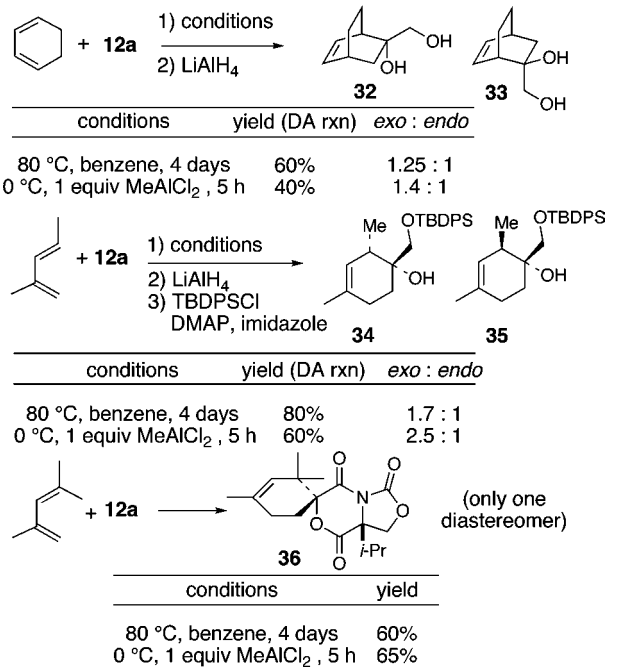


Lewis acid	temp	yield	diastereofacial selectivity *exo*-**27** : *exo*-**28**	exo : endo (**27** + **28**) : **29**
none	23 °C	80%	19 : 1	4 : 1
$MeAlCl_2$ (0.3 equiv)	−78 °C	71%	3 : 1	16 : 1

$LiAlH_4$ 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 $MeAlCl_2$ at −78 °C), the exo/endo selectivity increased to 19:1 (entry 2). However, the exo diastereofacial selectivity was significantly reduced (**27**/**28** = 3:1). We do not understand the erosion of the 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 those 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

Scheme 5. Diels−Alder Reactions of **12a** with Other Dienes



conditions	yield (DA rxn)	*exo* : *endo*
80 °C, benzene, 4 days	60%	1.25 : 1
0 °C, 1 equiv $MeAlCl_2$, 5 h	40%	1.4 : 1

conditions	yield (DA rxn)	*exo* : *endo*
80 °C, benzene, 4 days	80%	1.7 : 1
0 °C, 1 equiv $MeAlCl_2$, 5 h	60%	2.5 : 1

conditions	yield
80 °C, benzene, 4 days	60%
0 °C, 1 equiv $MeAlCl_2$, 5 h	65%

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 stepwise 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 A_3 and D_3 are underway and will be reported in due course.

Acknowledgment. Financial support from the National Institute of Health (GM 26782) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0609208