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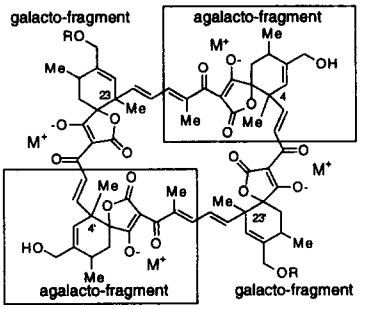
An Intramolecular Diels-Alder Approach to the Spirotetronic Acid Subunits of the Quartromicins

William R. Roush[1]* and David A. Barda

Department of Chemistry, Indiana University, Bloomington, IN 47405

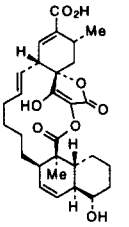
*Abstract: Three of the four diastereomeric spirotetronates (**2**, **19** and **24**) corresponding to the quartromicins were synthesized by a sequence featuring the intramolecular Diels-Alder reaction of **3**. An olefin isomerization pathway accounts for formation of the second most abundant cycloadduct, **16**.*

The quartromicins are a family of structurally complex antibiotics that possess excellent antiviral activity against herpes simplex virus type 1, influenza virus type A, and human immunodeficiency virus.[2-4] As a consequence of our studies on the synthesis of the spirotetronate-containing natural products chlorothricolide, kijanolide and tetronolide,[5-8] we were attracted to the quartromicins as synthetic targets. In contemplating an approach to the total synthesis of these novel compounds, two major issues needed to be addressed. First and foremost is the fact that the stereochemistry of the quartromicins has not yet been assigned. It is known that quartromicins A_3 and D_3 possess symmetrical, dimeric structures, which requires that the spirotetronic acid subunits at opposite corners of the "rectangular" structures are identical; we refer to these as the *galacto* and *agalacto* fragments. Correlation of published[2] ^1H NMR data for quartromicin D_3 with that of several spirotetronates[6,9] generated during our work on the top halves of chlorothricolide and kijanolide led us to propose that the quartromicin *galacto* fragment is an endo-spirotetronate, and that the *agalacto* fragment is an exo-spirotetronate (e.g., stereochemistry analogous to the top half fragment of chlorothricolide).[10] Several other recently isolated natural products with spirotetronic acid units resembling those of the quartromicins are antibiotics PA-46101 A[11] (with an exo-spirotetronate) and pyrrolosprorin A,[12] A88696 C and F[13] (which have endo-spirotetronate substructures). Accordingly, we anticipated that we would be able to make unambiguous stereochemical assignments in the quartromicin series following the synthesis of all four diastereomeric spirotetronate subunits.

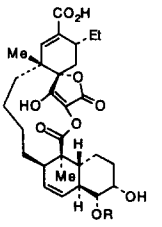


quartromicin A_3, R = α-D-galactosyl
quartromicin D_3, R = H

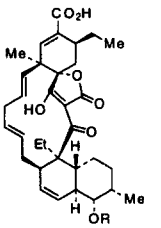
$M^+ = Na^+, K^+, Ca^{++}$



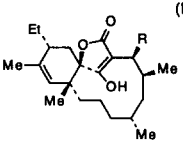
chlorothricolide



PA-46101 A
(R = disaccharide)



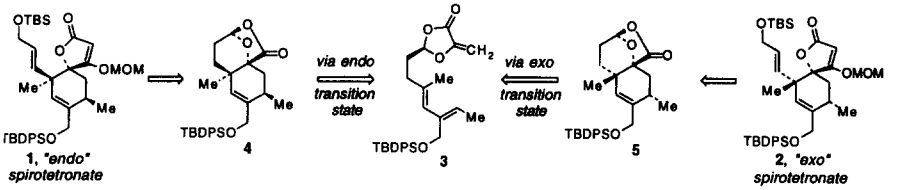
pyrrolosporin A
(R = disaccharide)



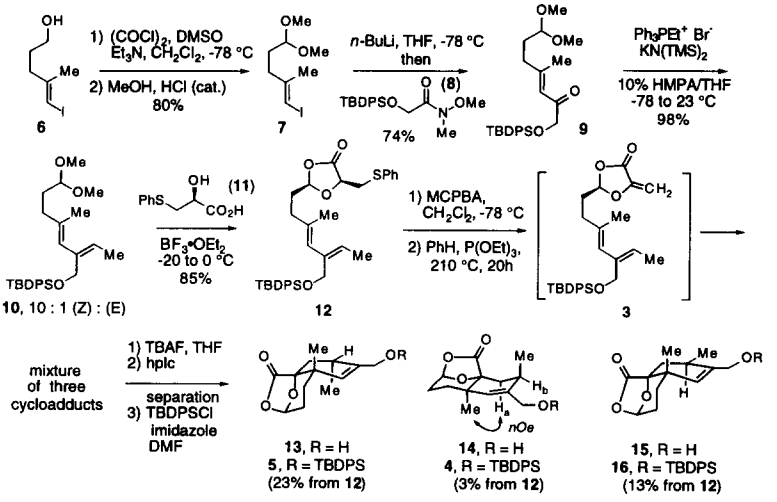
A88696C R=H
A88696F R=OH

The second problem concerns the development of a suitable strategy for introducing the quaternary methyl group at C(4) and C(23) of the quartromicin *agalacto* and *galacto* fragments. At the outset, it seemed

highly probable that this extra methyl group would prevent us from applying the bimolecular Diels-Alder strategy developed for the synthesis of the chlorothricolide-kijanolide spirotetronates,[5-8] since this would require use of an acyclic 1,1,3,4-tetrasubstituted diene--an acyclic (Z)-diene--which are notoriously poor substrates for Diels-Alder reactions.[14,15] In contrast, (Z)-dienes have been successfully employed in intramolecular Diels-Alder reactions,[16-20] especially in the taxane series.[21-25] We therefore decided to pursue the synthesis of the endo- and exo-spirotetronates **1** and **2** via the intramolecular Diels-Alder reaction of **3**. Based on prior studies,[26] we anticipated that this reaction would provide mixtures of the endo-and exo-cycloadducts **4** and **5**, respectively, thereby leading to two of the four diastereomeric spirotetronates needed for the stereochemical assignment of the natural product.

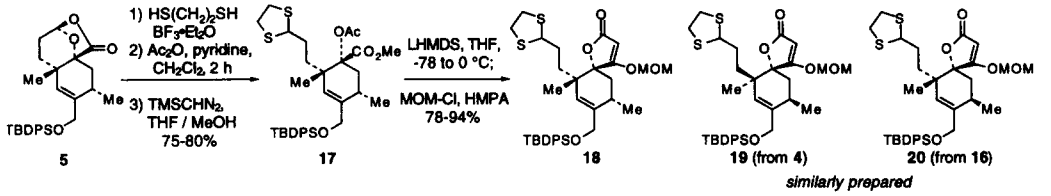


Swern oxidation[27] of **6**[28] followed by protection of the aldehyde as a dimethyl acetal provided **7** in 80% yield. Conversion of **7** to the corresponding vinyllithium followed by addition of the Weinreb's amide **8** smoothly provided enone **9** (74%). Olefination of **9** by using $Ph_3PEt^+ Br^-$ and $KN(TMS)_2$ in 9 : 1 THF-HMPA provided the (*Z,E*)-diene **10** with at least 10 : 1 selectivity (98% yield).[29] Condensation of **10** with hydroxy acid **11** in the presence of $BF_3{\bullet}Et_2O$ provided the *cis*-dioxalanone **12** as the only observed diastereomer.[30] Oxidation of **12** with 1.2 equiv. of MCPBA at -78 °C provided the corresponding sulfoxide, which was heated at 210 °C in benzene (sealed tube; external bath temperature) in the presence of triethyl phosphite (2 equiv.). The in situ generated triene **3** underwent IMDA cyclization to provide an inseparable mixture of three cycloadducts (**4**, **5**, and **16**). This mixture was separated by HPLC following temporary removal of the TBDPS ethers. The resulting alcohols **13**, **14** and **15** were reprotected by treatment with TBDPS-Cl and imidazole in DMF, thereby providing **5**, **4**, and **16** in 23%, 3% and 13% overall yields. The stereostructures of **13**, m.p. 86-87 °C, and **15**, m.p. 81-84 °C, were determined by single crystal X-ray analysis,[31] while the stereostructure of **4** was assigned

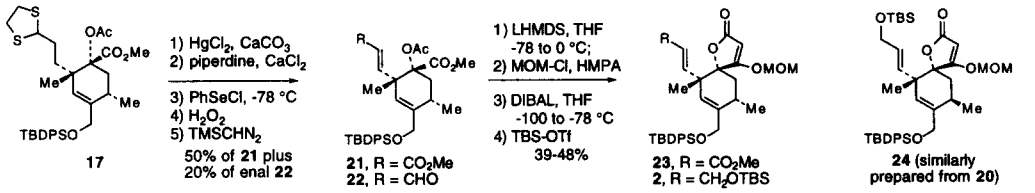


on the basis of nOe's observed between the angular methyl group and both H_a and H_b. While **4** and **5** derive from triene **3** via endo and exo transition states, respectively, it is clear that **16** must arise by a pathway involving diene isomerization prior to IMDA cyclization. Competitive isomerization of (*Z*)-dienes during IMDA reactions has been noted previously.[17]

Diels-Alder adducts **5**, **4** and **16** were elaborated to spirotetronates **18**, **19**, and **20** as illustrated by the conversion of **5** to **18**. Treatment of **5** with ethanedithiol and BF_3•Et_2O provided the thioacetal α-hydroxy acid. Acylation of the very hindered 3° hydroxyl group was accomplished by treatment with Ac_2O and pyridine in CH_2Cl_2,[32] and then the carboxylic acid was esterified by treatment with $TMSCHN_2$, thereby providing **17** in 75-80% yield. Finally, treatment of **17** with LHDMS in THF at -78 °C with subsequent warming of the enolate to 0 °C and then addition of MOM-Cl and HMPA provided the exo-spirotetronate **18** (75-80% yield).[5,6,33]



We have also demonstrated that it is possible to introduce the unsaturated side chain in **2** and **23** starting from **17**. Deprotection of the dithioacetal by treatment with $HgCl_2$ and $CaCO_3$ in aqueous CH_3CN (reflux, 24 h) gave the corresponding aldehyde. This intermediate was converted to the piperidine enamine, which was treated with PhSeCl at -78 °C.[34] After an acidic workup, the crude α-selenophenyl aldehyde was oxidized with 50% H_2O_2 (excess), providing the α,β-unsaturated ester **21** in 50% yield from **17** (following treatment with Me_3SiCHN_2), along with 20% of enal **22**. Dieckmann cyclization of **21** using the procedure described for the conversion of **17** to **18** provided the exo-spirotetronate **23** in 74-88% yield. Subsequent controlled reduction of the enoate (DIBAL, THF, -100 to -78 °C) and protection of the resulting allylic alcohol provided **2** (54%).[35] Spirotetronate **24**, the "iso-endo" spirotetronate diastereomer, was similarly prepared from thioacetal **20**.[36]



In summary, the intramolecular Diels-Alder reaction of **3** proved to be less selective than anticipated at the outset, owing to a competitive olefin isomerization pathway that led to cycloadduct **16** as the second most abundant product. Nevertheless, this sequence led to the synthesis of three of the four spirotetronate substructures needed for the stereochemical assignment of the quartromicins, and two of these were also elaborated to include the unsaturated side chain in the quatromicins. Further efforts along these lines are reported in the accompanying communication.

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(32) It is likely that the carboxylic acid is first converted to the mixed anhydride, and that acylation of the very hindered 3° alcohol occurs by intramolecular acyl transfer. In support of this hypothesis, we note that attempted acylation of the methyl ester was completely unsuccessful under these conditions.
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(36) The selenide oxidation in the synthesis of **24** was performed under carefully controlled conditions to prevent over-oxidation of the enal to the carboxylic acid, as occurred in the conversion of **17** to **22**. Elaboration of the enal intermediate to **24** was performed as summarized in ref. 35 for **22**. The yield of **24** was 20% yield for the 10 step sequence from **16**.

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