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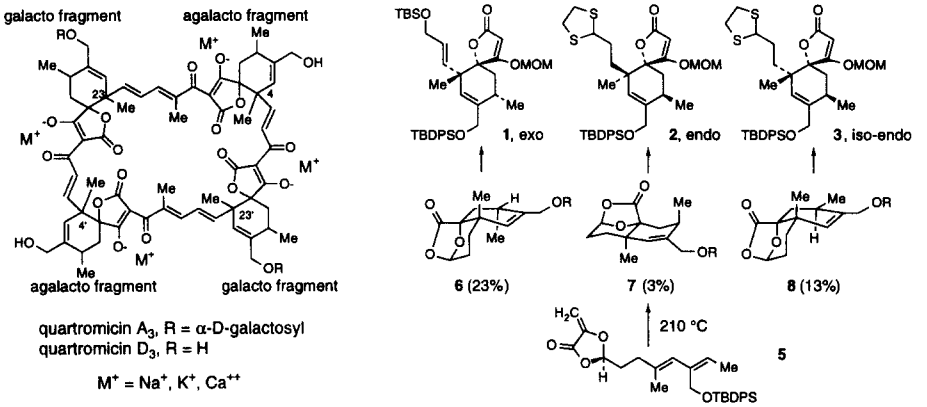
Second Generation Synthesis of the Quartromicin Spirotetronic Acid Subunits Via a Claisen Rearrangement-Intramolecular Aldol Sequence

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

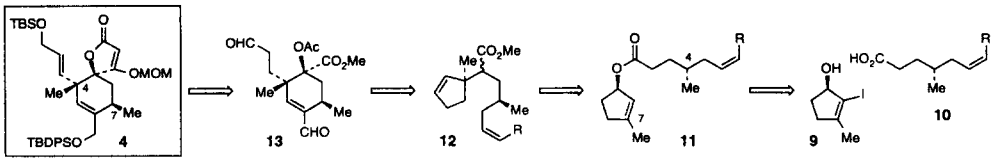
Department of Chemistry, Indiana University, Bloomington, IN 47405

*Abstract: Spirotetronate **4** needed for the assignment of stereochemistry to the quartromicins has been synthesized from **9** and **10** by a route featuring a Claisen rearrangement and intramolecular aldol reaction to establish the stereochemistry of the carbon framework.*. © 1997 Elsevier Science Ltd.

In the preceding communication[2] we described syntheses of three of the four diastereomeric spirotetronate substructures (**1-3**) needed for stereochemical assignment of the quartromicins.[3,4] The key step of this synthesis was the intramolecular Diels-Alder reaction of **5** which provided three cycloadducts **6**, **7** and **8** in 23%, 3% and 13% yields, respectively.[5] While cycloadducts **6-8** were elaborated to spirotetronates **1-3**, it was clear that this route was too inefficient--both in terms of chemical yield and stereoselectivity--for use ultimately in a total synthesis of the quartromicins. In addition, this route did not provide access to the fourth diastereomeric spirotetronate, **4**, and the quantity of **7** was not sufficient to permit us to introduce the 2',3'-allylic ether unit (present in **1** and **3**) into the derived spirotetronate **2**. Accordingly, we developed and report herein a second-generation synthesis that addresses these problems.

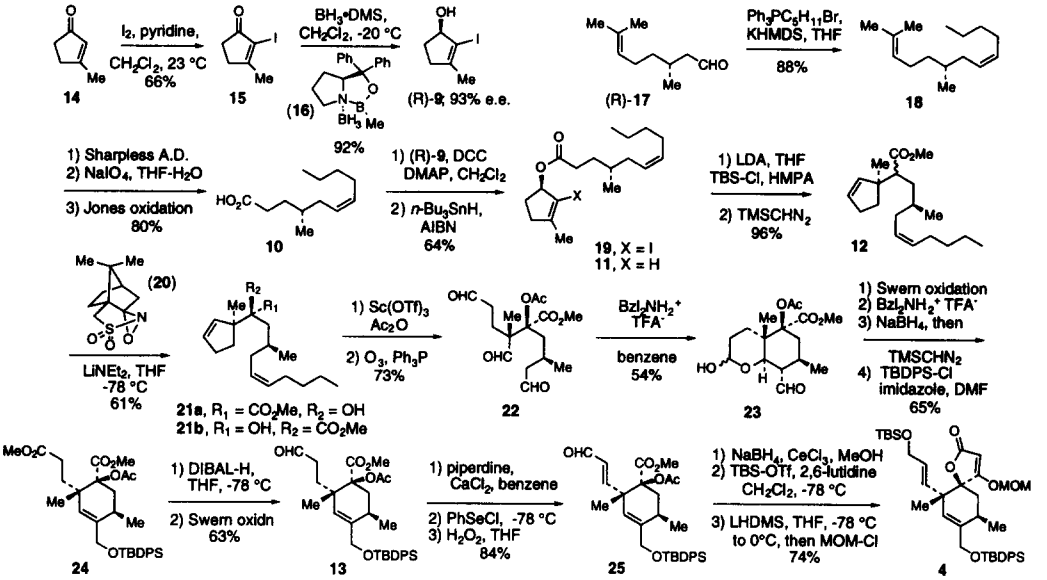


The plan that evolved, illustrated here for the fourth spirotetronate stereoisomer, **4**, focused on the independent control of the C(4) and C(7) stereocenters via a sequence involving the enolate Claisen rearrangement of **11**.[6] Further, we anticipated that the C(5)-α-acetoxy ester stereocenter in **13** could be introduced stereoselectively by an enantioselective hydroxylation of the ester enolate,[7] and that the cyclohexene nucleus of **13** would be elaborated from **12** via an ozonolysis-intramolecular aldol sequence. Accordingly, since all three stereocenters of **4** would be introduced via totally independent methods, each of the spirotetronate



diastereoemers could be accessed simply by using the appropriately paired, enantiomerically enriched precursors **9** and **10**.

2-Iodo-3-methyl-2-cyclopentenol (**9**) was prepared by iodination of 3-methylcyclopentenone (**14**) using Johnson's procedure,[8] followed by enantioselective reduction[9,10] of the resulting α-iodo enone **15** by using 10 mol % of **16**[11] and 0.7 equiv. of BH_3-SMe_2 in CH_2Cl_2 at 0 °C. The enantiomeric purity of **9** was determined to be 93% e.e. via the Mosher ester technique.[12] The α-iodo substituent of **15** effectively served as a steric directing group in this step, as the enantioselectivity of the analogous reduction of **14** was only 35% e.e.

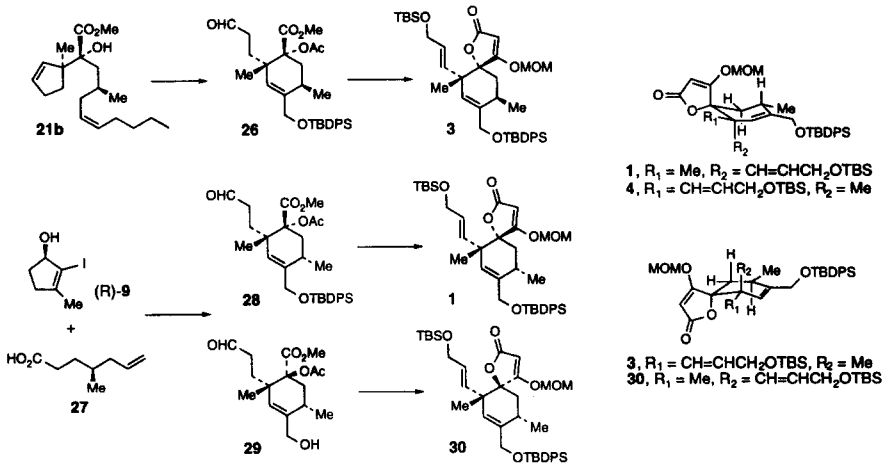


Carboxylic acid **10** was prepared starting from (R)-citronellal (**17**). Thus, (*Z*)-selective Wittig reaction[13,14] of **17** with *n*-pentyltriphenylphosphonium bromide and KHDMS in THF provided **18** (88%) with excellent stereocontrol. Selective oxidative cleavage of the trisubstituted olefin was accomplished by Sharpless asymmetric dihydroxylation[15,16] followed by periodate cleavage of the diol and Jones oxidation of the resulting aldehyde, which provided **10** in 80% overall yield. It proved necessary to use the enantioselective dihydroxylation protocol in order to achieve maximum selectivity for oxidation of the trisubstituted olefin.[16]

Alcohol **9** and acid **10** were coupled by using DCC and DMAP,[17] and the α-iodo subsitutent of **19** was removed by reduction with *n*-Bu_3SnH and AIBN.[18] The resulting ester **11** was then subjected to standard conditions of the Ireland enolate Claisen rearrangement[6,19,20] (LDA, THF, -78 °C, 1 h, then TBS-Cl, HMPA, 20 h, 80 °C), giving a ca. 1 : 1 mixture of diastereomeric methyl esters **12** in 96% yield following esterification of the crude carboxylic acids with $TMSCHN_2$.[21] The unseparated mixture of diastereomers was directly metallated by treatment with $LiNEt_2$ in THF at -78 °C, and the resulting enolate was then oxidized by using Davis' chiral oxaziridine **20**.[22] This reaction provided a ca. 1 : 1 mixture of diastereomeric α-hydroxy esters, from which the desired isomer **21a** was isolated chromatographically. Unfortunately, extensive studies performed with a related substrate generated during studies directed towards the synthesis of **1** and **2** revealed that this oxidation was virtually non-stereoselective when either enantiomer of **20** or (-)-(8,8-dichlorocamphorsulfonyl)oxaziridine was used. Nevertheless, we have continued to use (camphorsulfonyl)oxaziridine (**20**) in these reactions, since the reaction efficiency is best with this reagent.

Acylation of the extremely hindered 3° hydroxyl group of **21a** was accomplished in excellent yield (97%) by using catalytic $Sc(OTf)_3$ in Ac_2O at -20 °C.[23] Trialdehyde **22** was then obtained in 73% yield overall yield following a standard ozonolysis sequence. This set the stage for closure of the cyclohexene via an intramolecular aldol reaction. Best results were obtained when **22** was treated with $Bzl_2NH_2^+$ $CF_3CO_2^-$ in benzene at 50 °C,[24] which provided hemiacetal **23** in 54% yield. However, dehydration of **23** proved difficult owing to the equatorial placement of the β-alkoxy group in the *trans*-oxadecalin nucleus. Accordingly, it proved necessary to oxidize the hemiacetal to the corresponding lactone (DMSO, $(COCl)_2$, Et_3N, -78 °C)[25] before the β-elimination was performed by treatment with $Bzl_2NH_2^+$ $CF_3CO_2^-$. Finally, reduction of the α,β-unsaturated aldehyde, esterification of the carboxylic acid and protection of the alcohol as a TBDPS ether provided **24** in 65% yield for the four step sequence. Selective reduction of the less hindered, side chain carbomethoxyl group with 5.0 equiv. of DIBAL (THF, -78 °C) gave a mixture of **13** and the corresponding primary alcohol, which was reoxidized via the standard Swern protocol[25] thereby giving **13** in 63% overall yield. This set the stage for introduction of the α,β-unsaturation in the side chain by using Williams' procedure.[26] Thus, treatment of **13** with piperdine and $CaCl_2$ gave the corresponding enamine, which smoothly reacted with PhSeCl in THF at -78 °C. Finally, selenoxide elimination provided enal **25** in 84% overall yield. Reduction of the enal under Luche conditions,[27] protection of the resulting allylic alcohol as a TBS ether and then Dieckmann closure[28,29] and protection of the spirotetronate by sequential treatment with LHDMS in THF-HMPA at -78 °C with warming to 0 °C followed by addition of MOM-Cl completed the synthesis of the targeted spirotetronate, **4** (74% yield from **25**).

Although our original goal of developing a totally stereocontrolled synthesis of the spirotetronate substructures of the quartromicins was not completely successful, the sequence described herein has proven to be superior to the first generation IMDA-based route described in the accompanying communication,[2] in that it enabled us to prepare all four of the quartromicin spirotetronate diastereomers or their immediate precursors. Cyclopentene **21b** was elaborated into **26** (an intermediate in the synthesis of **3**)[2] by the sequence described above. By choosing (*R*)-**9** and carboxylic acid **27** (deriving from (*S*)-citronellal) as starting materials, **28** and **29** were prepared which are intermediates in the synthesis of spirotetronates **1**[2] and **30**,[30] respectively. Interestingly, spirotetronates **3** and **30** adopt conformations with the tetronate ring oxygen in an axial position with respect to the cyclohexene, whereas **1** and **4** preferentially adopt the opposite conformations in which the



tetronate ring oxygen is in an equatorial position on the cyclohexenyl system. Needless to say, this has complicated the stereochemical analysis of the quartromicins. Accordingly, details of the conformational analyses of **1**, **3**, **4** and **30** will be reported in a subsequent publication from our laboratory, along with molecular modelling studies which have permitted us to propose stereostructures for quartromicins A_3 and D_3.

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(1) Address correspondence to this author at the Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055.
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(30) Intermediate **29** is more easily prepared via a sequence involving the Lewis acid catalyzed Diels-Alder reaction of a (*Z*)-diene (related to **5**) and α-acetoxy acrolein (Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402) followed by oxidation of the aldehyde to the methyl ester. Elaboration of **29** to **30** was performed following the sequence described for the conversion of **13** to **4.**

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