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Partial Stereochemical Assignment of Quartromicins A_3 and D_3

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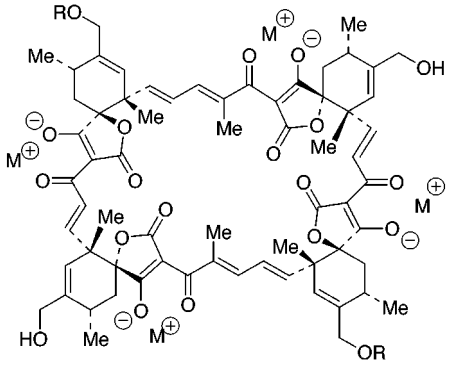
ABSTRACT



A partial stereochemical assignment of quartromicins A_3 (R = α-D-galactosyl) and D_3 (R = H, M^+ = Na^+, K^+, Ca^+) is presented.

The quartromicins[1−3] are a structurally unique group of metabolites from actinomycetes species with a wide array of biological properties, including activity against several important viral targets including herpes simplex virus (HSV) type 1,[2] influenza,[2] and human immunodeficiency virus (HIV).[3] Members of the quartromicin family are also known to inhibit phospholipase A_2 (PLA_2).[4] PLA_2 is a human enzyme that catalyzes the hydrolysis of membrane phospholipids in the synthesis of eicosanoids, an important step in the inflammatory response associated with arthritis, psoriasis, asthma, and atherosclerosis.[5,6]

The quartromicins are characterized by a novel 32-membered carbocyclic structure consisting of four spirotetronic acid units connected by enone linkers in a head-to-tail fashion. Quartromicins A_3 and D_3 are C_2 symmetric and therefore contain two distinct spirotetronate subunits,[1] which we have designated as the galacto and agalacto fragments, respectively. However, no information on the relative or absolute stereochemistry of the quartromicins has been reported. In connection with our studies on the synthesis of the quartromicins[7,8] we have developed a partial stereochemical assignment of quartromicins A_3 and D_3, the details of which are described herein.

We anticipated at the outset that it would be possible to assign the stereochemistry of quartromicins A_3 and D_3 by comparison of the published ^1H NMR data[1] for the natural products with that of spirotetronates **1**−**4**,[7,8] which represent all four of the possible stereoisomers of the galacto and agalacto subunits. Spirotetronates **2** and **3** were synthesized from precursors whose stereochemistry was assigned by X-ray analysis.[7] Spirotetronate **1** has been synthesized by three different routes, including one involving an enantioselective Diels−Alder reaction of an acyclic (*Z*)-1,3-diene.[9,10]

(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) Eli Lilly and Co., European Patent Application 92307089, 1993; *Chem Abstr.* **1993**, *118*, 190102k.
(5) Farooqui, A. A.; Litsky, M. L.; Farooqui, T.; Horrocks, L. A. *Brain Res. Bull.* **1999**, *49*, 139.
(6) Balsinde, J.; Balboa, M. A.; Insel, P. A.; Dennis, E. A. *Annu. Rev. Pharmacol. Toxicol.* **1999**, *39*, 175.
(7) Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781.
(8) Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8785.

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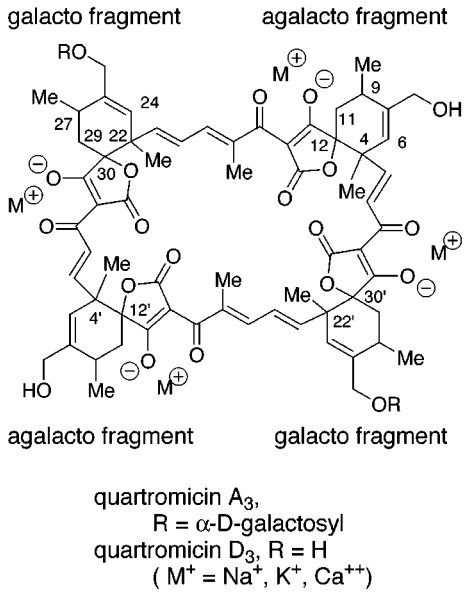


Figure 1.

Unfortunately, as we have noted previously,[8] spirotetronate model systems **2** and **4** preferentially adopt conformations with C(13) of the tetronic acid units in axial positions with respect to the cyclohexenyl ring, completely opposite to the conformational preferences of **1** and **3** and also opposite to the preferred conformations of the galacto and agalacto fragments of the natural quartromicins (vide infra). The conformational preferences of **1**−**4** are easily assigned by inspection of the large ^{1}H−^{1}H coupling constant between H_{11a} and H_9 (e.g., $J_{11a,9}$), which defines the C(9)-methyl group as equatorial in each of these four structures (Figure 2). The shielded nature of the quaternary methyl group (C(4)-Me; δ 1.05−1.07) in **1** and **2**, compared to the deshielded chemical shifts for C(4)-Me in diastereomers **3** and **4** (δ 1.27 and 1.19, respectively), allows us to assign the C(4)-Me group as equatorial in the former and as axial in the latter, vide infra.

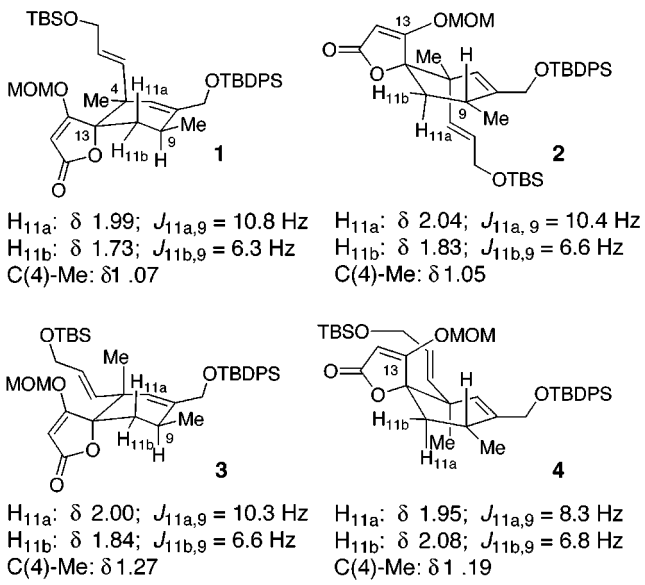


Figure 2. Conformational analysis of spirotetronates **1**−**4** (^{1}H NMR data obtained in $CDCl_3$).

Comparative ^{1}H NMR data for the galacto and agalacto fragment of quartromicin D_3 are presented in Figure 3.[11]

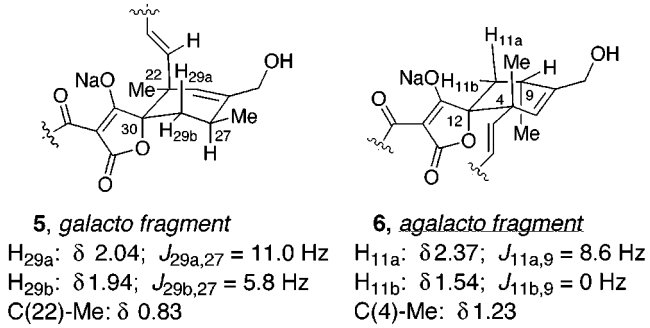


Figure 3. Selected ^{1}H NMR data for the galacto and agalacto fragments of quartromicin D_3 (^{1}H NMR data obtained in D_2O)[11].

Inspection of these data makes it possible to assign the secondary C(27)-Me group as equatorial in the galacto fragment **5** ($J_{29a,27}$ = 11.0 Hz; $J_{29b,27}$ = 5.8 Hz), and C(9)-Me as axial in the agalacto fragment **6** ($J_{11a,9}$ = 8.6 Hz; $J_{11b,9}$ = 0 Hz), given the strikingly different $J_{11b,9}$ and $J_{29b,27}$ values for the two substructures. Moreover, we assign C(22)-Me as equatorial in the galacto fragment **5**, owing to the highly shielded chemical shift (δ 0.83) of this unit, compared to the considerably more deshielded C(9)-Me in the agalacto fragment **6** (δ 1.23), which must be in an axial position in order to avoid anisotropic shielding by the spirotetronate unit. The latter assignment is supported by the strikingly similar chemical shift of the axial C(4)-Me of spirotetronate **3** (δ 1.27), which has the same local stereochemical environment as **6**. *Therefore, on the basis of this analysis we conclude that the galacto and agalacto fragments have the two methyl groups in trans relationships and that the two spirotetronate units of the quartromicins must be epimeric at the C(30) and C(12) stereocenters, respectively.*[12]

Additional support for the assignment of *trans*-diaxial methyl groups in the agalacto fragment **6** can be gleaned

(9) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402.

(10) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543.

(11) The ^{1}H NMR data summarized in Figure 3 are literature values taken from the Supporting Information to ref 1.

(12) We have also considered the possibility that all four of the spirotetronate units of the quartromicins have identical stereochemistry, such that the natural product exists with the two galacto fragments in a dimethyl equatorial conformation (i.e., analogous to the conformations depicted for **1** and **5**) and with the two agalacto fragments in "inverted" conformations as depicted in structure **2**. However, extensive molecular modeling studies have failed to identify a sufficiently stable quartromicin stereoisomer that would satisfy these criteria. Accordingly, we regard this possibility as highly unlikely at this time. We thank Dr. Marty Pagel (Indiana University) for assisting with the molecular modeling studies.

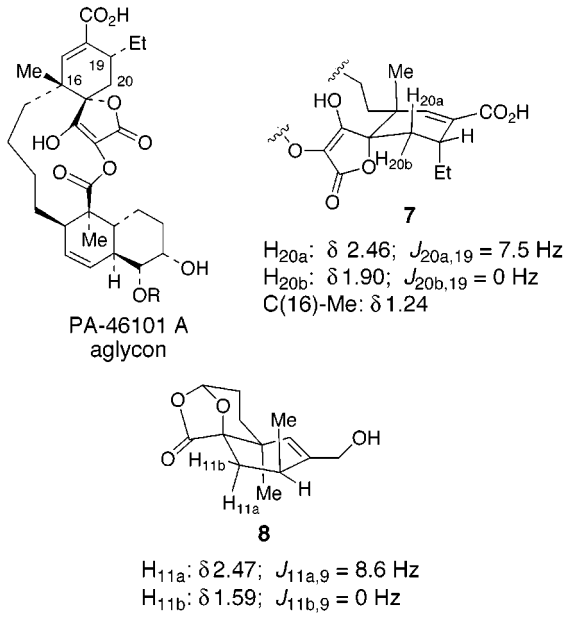


Figure 4. Selected ^{1}H NMR data for **7** and **8** (in $CDCl_3$).

from the data summarized in Figure 4. PA-46101A is a spirotetronate-containing natural product whose structure and stereochemistry are known on the basis of an X-ray crystal structure analysis.[13] The data summarized in Figure 4 for the PA-46101A spirotetronate **7** ($J_{20a,19}$ = 7.5 Hz; $J_{20b,19}$ = 0 Hz; δ 1.24 for C(16)-Me) are strikingly similar to the data reported in Figure 3 for the agalacto fragment **6**. The coupling constant data reported for spiroacetal **8** ($J_{11a,9}$ = 8.6 Hz; $J_{11b,9}$ = 0 Hz), the stereochemistry of which also was assigned by X-ray methods,[7] support the conclusion that if the C(9)-Me group is axial, then $J_{11b,9}$ will be very small, as is the case in the agalacto fragment **6**.

Our assignment of the stereochemistry of C(9)- and C(22)-Me groups in quartromicin fragments **5** and **6** is based on the strikingly different chemical shifts of the quaternary methyl groups in the two isomers, which we have attributed to anisotropic shielding by the tetronic acid fragment when C(9)-Me and C(22)-Me are equatorial. Support for this conclusion is provided by the data in Figure 5, deriving from synthetic studies on kijanolide.[14,15] The important information here is the substantially shielded chemical shift of H(20) (δ 3.17) in the *endo* spirotetronate **9**,[14] compared to the considerably more deshielded H(20) (d 3.45) in the *exo* spirotetronate **10**.[15] The ^{1}H NMR data summarized for **9** and **10** once again illustrate the characteristic coupling constants that enable the secondary methyl group (e.g., C(27)-Me in **5** and C(9)-Me in **6**) to be defined as equatorial or axial on the cyclohexenyl ring system.

While it can be concluded from the data presented here that the galacto (**5**) and agalacto (**6**) fragments of quartromicin D_3 must have the stereochemistry and conformations depicted in Figure 3,[12] the absolute stereochemical relationships between the two fragments has not been assigned. Consideration of possible biosynthetic sequences for construction of **5** and **6** leads us to speculate that a Prins-type cyclization might be involved, as illustrated in Figure 6. This

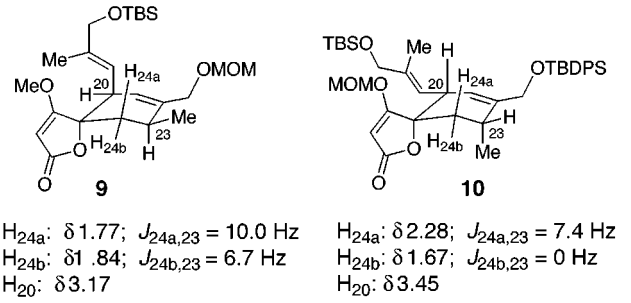


Figure 5. Selected ^{1}H NMR data for **9** and **10** (in $CDCl_3$).

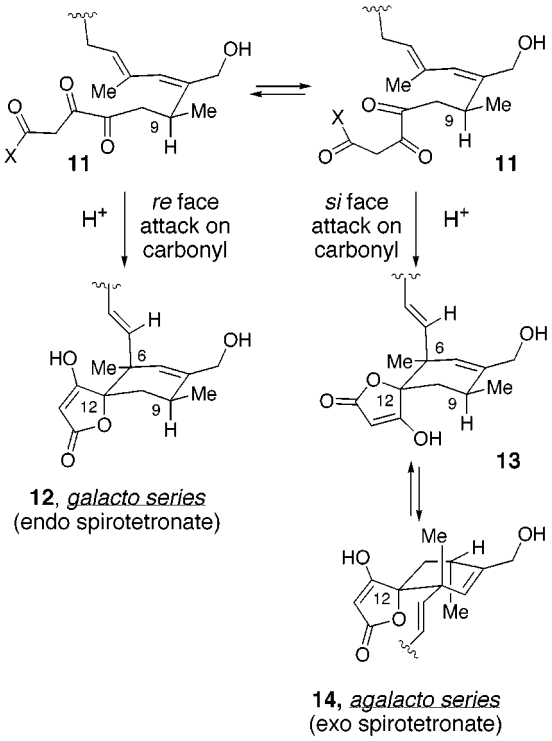
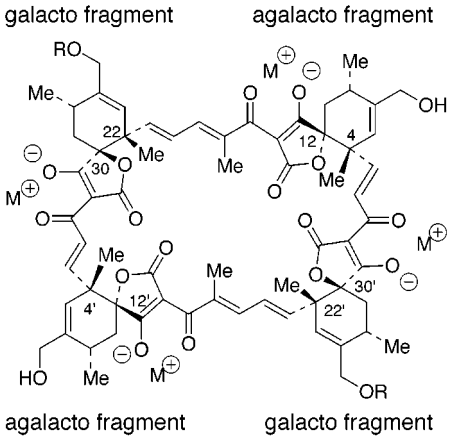


Figure 6. Possible biosynthesis of fragments **5** and **6**.

postulate would permit both spirotetronate series to be derived from a common biosynthetic intermediate such as **11**, in which the stereochemistry of the C(9)-methyl group has already been set in earlier biosynthetic steps. Accordingly, the two spirotetronates **12** (corresponding to the galacto fragment **5**) and **14** (corresponding to the agalacto fragment **6**) would be produced with identical absolute stereochemistries at C(9) and C(6) and with the absolute configuration

(13) Matsumoto, M.; Kawamura, Y.; Yoshimura, Y.; Terui, Y.; Nakai, H.; Yoshida, T.; Shoji, J. *J. Antibiot.* **1990**, *43*, 739.
(14) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135.
(15) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.

of the C(12) spirotetronate center being opposite in the two structures. This is the stereochemical relationship depicted in Figure 3 for fragments **5** and **6** and in the proposed stereostructure of quartromicins A_3 and D_3 in Figure 7.



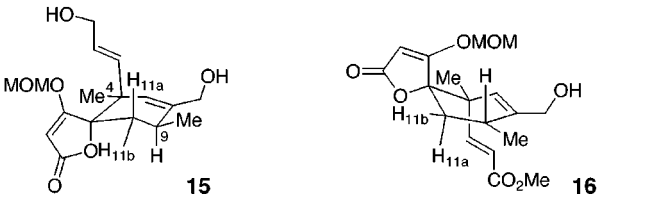
quartromicin A_3,
R = α-D-galactosyl
quartromicin D_3, R = H
($M^+ = Na^+, K^+, Ca^{++}$)

Figure 7. Proposed structures of quartromicins A_3 and D_3.

According to the stereochemical assignment presented above, the quartromicin galacto fragment **5** and the agalacto fragment **6** are in the same stereochemical series as the *endo* and *exo* spirotetronates **1** and **2**, respectively. The *endo*−*exo* nomenclature that we use in describing the stereochemical features of **1** and **2** derives from the recognition that these compounds may be synthesized from products of (formal) *endo*- or *exo*-Diels−Alder reactions of an α-acetoxy acrylate dienophile and a 1,1,3,4-tetrasubstituted diene.[7,9,10]

An interesting issue concerns the very different conformational preferences of the synthetic *exo*-spirotetronate **2** and the agalacto unit **6** of the natural product. We speculate that this may be due to constraints present in the macrocyclic natural product that do not influence the conformation of **2** when free in solution. Conformational analysis of the *endo*- and *exo*-spirotetronates **15** and **16** (related to **1** and **2**, respectively) in D_2O, the NMR solvent used in the analysis of the natural quartromicins, reveals that they have the same conformational preferences as do **1** and **2** in $CDCl_3$. Therefore, we think it unlikely that the differences in the conformational preferences of **2** and **6** are due to solvent effects alone.

In conclusion, we have developed a partial stereochemical assignment of quartromicins A_3 and D_3 by comparison of published ^{1}H NMR data for the natural products with NMR data for a number of structurally related spirotetronates. Consideration of a possible biosynthetic origin of the spirotetronate systems presented in Figure 6 leads us to suggest that the two spirotetronate substructures have identical stereochemistry at C(6) and C(9) and are epimeric at the spirotetronate center C(5).[12] The resulting quartromicin stereostructure presented in Figure 7 currently serves as our primary target for total synthesis.[10] This exercise will permit the absolute stereochemistry of the galacto and agalacto subunits **5** and **6** to be assigned unequivocally.



H_{11a}: δ 1.92; $J_{11a,9}$ = 10.6 Hz
H_{11b}: δ 1.78; $J_{11b,9}$ = 6.6 Hz
C(4)-Me: δ 0.92

H_{11a}: δ 1.80; $J_{11a,9}$ = 10.0 Hz
H_{11b}: δ 1.92; $J_{11b,9}$ = 6.7 Hz
C(4)-Me: δ 0.98

Figure 8. Conformational analysis of *endo*- and *exo*-spirotetronates **15** and **16** in D_2O.

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Supporting Information Available: ^{1}H NMR data for **1**−**4**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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