Structure Reassignment of Laurefurenynes A and B by Computation and Total Synthesis

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In 2010, the structures of six new cyclic ethers isolated from Laurencia spp. were reported and named the laurefurenynes.[1] Laurefurenynes A and B were assigned the 2,2'-bifuranyl structures 1 on the basis of extensive 1D and 2D NMR experiments with the relative configuration being assigned on the basis of 1H NMR NOESY experiments in conjunction with molecular modelling (Figure 1a). Laurefurenynes A and B are structurally related to a number of other 2,2'-bifuranyl natural products from Laurencia spp. including notoryne 2,[2] (Z)-[3,4] and (E)-elatenyne 3,[5] and laurendecumenyne 4.[4] The structure of elatenyne was originally assigned as a pyrano[3,2-b]pyran.[3] We have previously reassigned the originally proposed structure of elatenyne on the basis of DFT calculations of NMR chemical shifts,[6] biophysical postulates and total synthesis.[7-10] Herein, we report the reassignment of the stereostructures of laurefurenynes A and B as 5 on the basis of a 13C NMR chemical shift/relative configuration correlation coupled with DP4 analysis (Figure 1b).[11,12] Additionally, confirmation of the reassigned stereostructure of laurefurenyne B 5b is reported on the basis of total synthesis both by us and by the Britton research group.[13] The reassigned structures of laurefurenynes A and B fit with our recently proposed biogenesis of elatenyne.[8,10] This work further demonstrates the power of this combined computational/synthetic approach for the structure determination of natural products and small highly flexible organic molecules.

Our synthetic and computational interest in 2,2'-bifuranyl natural products coupled with their embedded C2 symmetry made laurefurenynes A and B (1) attractive targets for total synthesis. As part of our structure determination research program, we had synthesized the 2,2'-bifuranyl 15 with the same relative configuration as the originally proposed structures for laurefurenynes A and B (1), along with two further related 2,2'-bifuranyl anones 16 and 18 (Scheme 1). The synthesis of the 2,2'-bifuranyls 15, 16 and 18 followed a similar course to our recently reported synthesis of elatenyne 3a.[9] Self-metathesis of the known epoxy alkene 6[14] by using Grubbs’ second generation catalyst 19 in the presence of acetic acid to minimize isomerization of the starting material,[13] followed by an oxidative workup to remove ruthenium residues[16] gave a 3:1 mixture of partially separable E/Z geometric isomers 7 and 8 in 67% yield. Diastereoselective Sharpless dihydroxylation[17] of the pure (E)-alkene 7 with the hydroquinine 1,4-phthalaldehydine diether (DHO2PHAL) ligand gave a 3.5:1 mixture of the diols 9 and 10 along with a small amount of the corresponding cyclized material in 97% overall yield. Separation of the individual diols 9 and 10 was not possible, because silica gel caused further cyclisation to give the highly polar 2,2'-bifuranyl anones 11 and 12. Cyclisation was further promoted by the use of Amberlyst acidic resin to give a mixture of 2,2'-bifuranyl anones which were immediately converted into the separable dimesylates 13 and 14. The major dimesylate 13 could be readily converted into the model 2,2'-bifuranyl 15 by reduction with Superhydride followed by hydrolysis of the benzyl protecting groups. We also prepared two related 2,2'-...
Scheme 1. Synthesis of model 2,2'-bifuranyls. a) Catalyst 19 (1 mol%), CH₂CO₂H (10 mol%), CH₃Cl₂, reflux, 3:1 partially separable mixture of 7/8 (67%); b) (DHQD)₂PHAL, K₂FeCN₆, K₂OsO₄, CH₂SO₂NH₂, tBuOH, water, 0°C, 3.5:1 mixture of 9/10 with cyclized 11 and 12 (97%); c) (DHQD)₂PHAL, K₂FeCN₆, K₂OsO₄, CH₂SO₂NH₂, tBuOH, water, 0°C; 1:7 mixture of 9/10, with cyclized 11 and 12 (quant.); d) Amberlyst-15, CDCl₃, RT; e) MsCl, Et₃N, CH₂Cl₂, 0°C→RT; f) (CH₂CH₃)₂BHLLi, THF, 0°C→RT; g) H₂, Pd/C, EtOH, RT, 97%. Bn = benzyl, Ms = methanesulfonyl.

bifuranyls 16 and 18 by Sharpless dihydroxylation[17] of the alkene 7 using the (DHQD)₂PHAL ligand (1:7 mixture 9:10, and some cyclized material), and from the (Z)-alkene 8 according to the routes shown in Scheme 1. Comparison of the ¹³C NMR spectra of the three model 2,2'-bifuranyls with those of the natural product led us to question the assigned stereostructure of laurefenynes A and B (1). In particular, we noted that with the asymmetric 2,2'-bifuranyl 18 derived from the (Z)-alkene 8, the ¹³C NMR chemical shifts of the ring methylene carbons were more in keeping with those of the natural products than for the C₃-symmetric derivatives 15 and 16.[18] As part of our work on the structure determination of elatenyne 3a, we had also synthesized several 2,2'-bifuranyls with hydroxyl groups at C-7 and C-12 (laurefenyne numbering);[9] close structural analogues of laurefenynes A and B (1). Examination of the ¹³C NMR chemical shifts of seven synthetic 2,2'-bifuranyls indicated that when the hydroxyl group and the adjacent side chain are cis-related, C-ØH resonates at δ≈71 ppm; however, when the hydroxyl group and the adjacent side chain are trans-related, C-ØH resonates at δ≈75–76 ppm (Figure 2).[19]

This is clearly a small sample; however, comparison with the reported ¹³C NMR chemical shifts of laurefenynes A and B was informative. The relevant ¹³C NMR chemical shifts in laurefenynes A and B occur at δ≈75 ppm (C-7, CCl₃ or [D₆]DMSO) and δ≈71 ppm (C-12, CDCl₃ or [D₆]DMSO), respectively. On the basis of these data, we propose that laurefenynes A and B (1) are not pseudo-C₂ symmetric, and specifically that the C-6/C-7 substituents are trans-disposed (rather than cis-disposed) with the C-12/C-13 substituents being cis-disposed.

In tandem with our synthetic studies, we also turned to quantum-chemical calculations to compare the predicted ¹H and ¹³C NMR data of the reported structures for laurefenynes A and B against the experimental values obtained for the natural products.[20] The relative accuracy and affordability of ¹H and ¹³C NMR chemical shifts obtained from DFT data means that such calculations are increasingly used to probe and validate structural hypotheses for small to medium-sized organic molecules.[21,22] To benchmark our calculations, we computed GIAO ¹³C NMR chemical shifts for 113 rigid small molecules containing only C, H, N, O and F[23] at the mPW1PW91/6-311G(d,p)/wB97XD/6-31G(d) level, which (following linear scaling)[21] gave a small mean unsigned error (MUE) of 1.6 ppm and standard deviation of 1.5 ppm with respect to experiment demonstrating the accuracy of the technique. Nevertheless, laurefenynes A and B pose a considerable challenge for computation, in large part due to the flexibility of the two rings and freely rotatable single bonds, which give rise to large numbers of thermally accessible conformers that must be taken into consideration.

Rotation about the central inter-ring torsion also makes the determination of relative stereochemistry of the two THF rings difficult. Given these computationally challenging molecules prompted us to examine whether the sensitivity of DFT-computed chemical shifts is sufficient to discriminate between correct and incorrect structures by using various metrics. In fact, as is described below, our computations cast doubt over the previous assignment and accurately predicted the correct stereostructure 5b for laurefenyne B.
For each of the 32 possible diastereomers of laurefurenyne B, we carried out a Monte Carlo multiple minimum (MCM) conformational search with MMFF and subsequently reoptimized all low energy conformers (within 10 kJ mol⁻¹) at the dispersion-corrected DFT, wB97XD/6-31G(d) level in CHCl₃. This choice was motivated by the observation that the potential energy hypersurface is characterized by intramolecular hydrogen bonding and medium and long-range non-bonding interactions. The number of conformers for each diastereomer ranges from 10 to 167, for which ¹³C NMR and 'H NMR GIAO-mPW1PW91/6-311G(d,p) chemical shifts were calculated in CHCl₃. For comparison against experimental values, the average isotropic shielding tensors for the conformational ensemble was computed using Boltzmann factors from the electronic energies at 298 K; conversion into chemical shifts was performed following a linear regression against the experimental data.

Chemical shifts for pairs of diastereotopic protons were automatically assigned so as to minimize the computational errors.

Compared against the natural product data, the average isotropic shielding tensors for the conformational ensemble was computed using Boltzmann factors from the electronic energies at 298 K; conversion into chemical shifts was performed following a linear regression against the experimental data. Linear regression against the experimental data.

Across all diastereomers, the MUEs span the range of δ = 0.9–3.1 ppm (¹³C) and 0.15–0.36 ppm ('H). Linear regression gives R² values all close to unity (see the Supporting Information).

The previous stereocchemical assignment of laurefurenyne B, which corresponds to diastereomer #1, has an MUE of 1.5 and 0.23 ppm for ¹³C and 'H NMR shifts, respectively. In contrast to the MUE, the DP4 metric rules out structures from consideration that have one or more significant errors in predicted 'H and/or ¹³C NMR chemical shifts; under this metric diastereomer #1 is highly unlikely to be correct (Figure 3b). Computationally, structure 5b (diastereomer #6 in the computational studies) has the smallest errors for ¹³C and 'H chemical shifts and correspondingly the highest DP4 probability (Figure 3a and b). In accord with our experimental observations, the C₆-C₇ cis-stereochemistry in 1b leads to a computed ¹³C NMR chemical shift value at C-7 that is >3 ppm below that of C-7 of the natural product. This relationship between relative configuration and chemical shift is true across all 32 computed diastereomers. All of our synthetic and computational data gave us confidence that the actual stereostructures of laurefurenynes A and B are as represented by 5.

We had previously prepared the protected 2,2'-bifuranyl 20 as an intermediate en route to elatenyne. Converting this bis-benzyl ether into the reassigned structure of laurefurenyne B required inversion of configuration at both C-12 and C-7. Deprotection of both the 4-methoxybenzyl (PMB) and the 4-bromobenzyl (PBB) groups in 20 was readily achieved by using boron trichloride and the resultant diol 21 was inverted at C-7 and C-12 (laurefurenyne numbering) by using a Mitsunobu reaction giving 22 (Scheme 2). Conversion of the alkene 22 into a terminal E-enyne was readily achieved by using Kim’s method by cross metathesis with crotonaldehyde followed by Colvin–Ohira homologation. The 'H and ¹³C NMR spectra of synthetic 5b were in excellent agreement with the corresponding reported data for natural laurefurenyne B. This work defines the stereostructures of laurefurenynes A and B as 5. Moreover, the optical rotation of synthetic 5b ([α]₀₂₀ ≈ −20 (c = 0.1 in MeOH)) was in agreement with that of natural laurefurenyne B ([α]₀₂₀ ≈ −13 (c = 0.1 in MeOH)), indicating that the likely absolute configurations of laurefurenynes A and B are represented by 5 (Figure 1).

We recently proposed a biosynthesis of (E) and (Z)-elatenyne 3 and laurendecumenyne 4 closely paralleling previous work on the biogenesis of C₅₆ halogenated marine natural products from Laurencia spp. Close inspection of the stereostructures of laurefurenynes A and B indicates that...
they may be biosynthesized similarly from \((E)\)\(^{31,32}\) or \((Z)\)-bromofucin \(24\)^{33,34} which may be biosynthesized from \((3E)\ Z,6S,7S,12E\)-laurefurenynes \(23\) (Scheme 3)\(^{35,36}\). Transannular expulsion of bromide leads to the tricyclic oxonium ion \(25\) that may be opened by bromide, to give elatene \(3\) or by chloride to give laurefurenynes \(A\) and \(B\). In terms of natural products, the missing links on the proposed biosynthetic pathway towards the laurefurenynes are the bromoalcohols \(26\), which we postulate as yet-to-be-isolated natural products. This biosynthesis places laurefurenynes \(A\) and \(B\) in the same absolute stereochemical series as that proposed for \((Z)\)-elatene.\(^{37}\)

In summary, reassignment of the stereostructure of laurefurenynes \(A\) and \(B\) was achieved on the basis of close analysis of NMR data in model compounds and DFT calculations of NMR chemical shifts. Total synthesis of the proposed structure of laurefurenynes \(B\) confirmed the reassigned structures, which places laurefurenynes on the same biosynthetic pathway, as was recently proposed for elatene. This work further highlights the difficulty of unambiguously assigning relative configuration in highly flexible organic molecules by using NMR methods, and the power of a combined computational/synthetic approach for structure determination. Further application of this approach to the structure determination of small molecules along with a full discussion of the computational aspects of this work will be reported in due course.

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figuration of the laurefurenynes was found to be different to that of model 2,2'-bifuranlyls; however, 13C NMR analysis of 15, 16 and 18 led us to question the original structural assignment of laurefurenynes A and B.

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