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Assignment of the C5' Relative Stereochemistry in (+)-Lepadin F and (+)-Lepadin G and Absolute Configuration of (+)-Lepadin G

Gang Li and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, WI 53705

Abstract

Concise assignments of the C5' stereochemistry in (+)-lepadin F and (+)-lepadin G, and the absolute configuration of (+)-lepadin G via the first total syntheses of (+)-5'-*epi*-lepadin F, (+)-lepadin G, and (+)-5'-*epi*-lepadin G are described. This work represents an illustrative example in which a diastereomeric pair can possess sufficient spectroscopic difference for clear assignment despite differing only at a highly insulated acyclic stereocenter.

We recently completed a total synthesis of (+)-lepadin F¹⁻³ featuring an *aza*-[3 + 3] annulation^{4,5} of vinylogous amide **1** and iminium ion **2**. [Scheme 1].⁶ Close spectroscopic comparisons with those reported by Davis-Carroll-Quinn^{1,7} for the isolated sample and Blechert⁸ for synthetic (+)-lepadin F allowed us to claim a completed total synthesis. However, the C5' stereocenter was never defined in the isolation reports.^{1,2} Despite our close spectroscopic comparisons, the margin of error to ascertain the C5' stereochemistry remains high especially in the absence of an authentic sample of (+)-5'-*epi*-lepadin F because the C5' stereocenter is both acyclic and highly insulated on the lepadin side chain. We report here assignments of the C5' stereochemistry in (+)-lepadin F and (+)-lepadin G, and absolute configuration of (+)-lepadin G via concise enantioselective total syntheses of (+)-5'-*epi*-lepadin F, (+)-lepadin G, and (+)-5'-*epi*-lepadin G.

Total synthesis of (+)-5'-*epi*-lepadin F commenced with an advanced intermediate aldehyde **6** that was used in (+)-lepadin F synthesis [Scheme 2]. Homologation of the side chain in **6** was achieved in 90% yield through Kocienski modified Julia olefination⁹ employing sulfone (*R*)-**7**.^{10,11} Subsequent hydrogenation of the resulting C2'-3' olefin in **8** followed by desilylation led to alcohol **9**, which could be converted to (+)-5'-*epi*-lepadin F in two steps featuring esterification under Yamaguchi conditions.

With (+)-5'-*epi*-lepadin F in hand, we were able to attain comprehensive comparisons of respective spectral data. As shown in Figure 1, both proton and carbon NMR chemical shift

rhsung@wisc.edu.

Supporting Information Available: Experimental procedures as well as NMR spectra and characterizations are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

differences in C_6D_6 between Carroll's natural (+)-lepadin F¹ and our synthetic (+)-lepadin F⁶ and (+)-5'-*epi*-lepadin F were tabulated, and all non-zero $\Delta\delta$ values are displayed as bar graphs along the axis indicating their respective proton and carbon numberings: $\Delta\delta$ values for (+)-lepadin F are in blue with $\Delta\delta$ for (+)-5'-*epi*-lepadin F in red. We note here that Carroll's 1H spectra data were collected on a 600-MHz spectrometer [150 MHz for ^{13}C NMR], whereas ours were collected on a 500 MHz spectrometer [125 MHz for ^{13}C]. These two sets of spectroscopic comparisons distinctly reveal that the synthetic (+)-lepadin F is better matched with Carroll's natural (+)-lepadin F than (+)-5'-*epi*-lepadin F, thereby confirming that the relative stereochemistry at C5' in (+)-lepadin F should be *S*.

In addition, careful spectroscopic comparisons between synthetic (+)-lepadin F and (+)-5'-*epi*-lepadin F were carried out with ^{13}C NMR differences being tabulated in the bar graph shown in Figure 2. Intriguingly, despite differing only at C5', which is an acyclic and stereochemically insulated stereocenter, (+)-lepadin F and (+)-5'-*epi*-lepadin F are quite distinct spectroscopically. Their difference was further manifested with the 1.93-1.75 ppm region of 1H NMR where the resonances are assigned to H4'' and H4 β [Figure 3]. In comparison with Carroll's spectra [black], our synthetic (+)-lepadin F [red] matches the natural sample precisely, whereas (+)-5'-*epi*-lepadin F [blue] does not.

The fact that two complex structures differing only at a remote acyclic and highly insulated stereocenter can still be differentiated spectroscopically provoked us to synthesize (+)-lepadin G and (+)-5'-*epi*-lepadin G in an attempt to concisely assign C5' stereochemistry in (+)-lepadin G. Consequently, total syntheses of both (+)-lepadin G and (+)-5'-*epi*-lepadin G were carried out as summarized in Scheme 3.

With both synthetic (+)-5'-lepadin G and (+)-5'-*epi*-lepadin G in hand, we were able to tabulate $\Delta\delta$ values for both proton and carbon NMR chemical shift differences in C_6D_6 between Carroll's natural (+)-lepadin G¹ and our synthetic (+)-lepadin G and (+)-5'-*epi*-lepadin G [Figure 4]. Although ^{13}C -NMR comparison is less unambiguous than 1H -NMR, the synthetic (+)-lepadin G appears to match the natural (+)-lepadin G better than (+)-5'-*epi*-lepadin G. The specific difference in 1H -NMR for (+)-lepadin G and (+)-5'-*epi*-lepadin G can be again revealed in the 1.90-1.72 ppm region of 1H -NMR spectra for which the resonances are assigned to H4 β and H6'' [Figure 5]. Our synthetic (+)-lepadin G [red] would again match more closely with Carroll's spectra [black] relative to (+)-5'-*epi*-lepadin G [blue], thereby suggesting that the relative stereochemistry at C5' should be *R* for (+)-lepadin G.

Finally, the absolute configuration for (+)-lepadin G could also be assessed in an unambiguous manner. Blechert's synthesis of (-)-lepadin G led to an $[\alpha]_D^{23}$ value of -14.5° [*c* 0.26, CH_2Cl_2], the $[\alpha]_D^{23}$ value of our synthetic (+)-lepadin G is $+10.2^\circ$ [*c* 0.26, CH_2Cl_2] with Carroll's natural sample being $[\alpha]_D^{23} = +12.5^\circ$ [*c* 0.31, CH_2Cl_2]. On the other hand, both antipodes of lepadin F were reported with Wright² documenting (-)-F and Carroll¹ reporting (+)-F. Thus, assigning the absolute configuration of lepadin F is not as critical especially since the reported values ($[\alpha]_D^{22} = -1.5^\circ$ [*c* 0.1, $CHCl_3$] and $[\alpha]_D^{23} = +5.55^\circ$ [*c* 0.12, CH_2Cl_2], respectively from Wright and Carroll) are too small to make meaningful comparisons. Nevertheless, based on the current information, it implies that stereochemically (+)-lepadin F and (+)-lepadin G are essentially enantiomeric at the 1-*aza*-decalinic core and the alkyl side chain, while differing only in the degree of unsaturation for the ester side chain.

We were intrigued by the fact that these two diastereomeric pairs possessed sufficient spectroscopic difference for clear assignment despite being differed only at a highly insulated acyclic stereogenic center. Consequently, we carried out calculations to analyze lowest-energy equilibrium conformers for (+)-lepadin F and (+)-5'-*epi*-lepadin F as well as (+)-lepadin G and (+)-5'-*epi*-lepadin G. SpartanTM Molecular Mechanics/MMFF was employed for identifying

the lowest-energy conformer with Hartree-Fock/6-31G* being adopted for the equilibrium geometry optimization. The overlapping conformers of (+)-lepadin F [gold] and (+)-5'-*epi*-(+)-lepadin F [grey] as well as (+)-lepadin G [gold] and (+)-5'-*epi*-lepadin G [grey] are shown in Figure 6.

While a great ideal of overlap can be seen with the *cis* 1-*aza*-decalinic core being virtually identical, they are different particularly in all the respective side chains. Although these are not calculations in C₆D₆ nor do they represent an average conformation, we believe these readily observable conformational differences on the side chains can contribute to the observed spectroscopic differences.

In addition, these calculations suggest the presence of the H-bonding between the C5'-OH and C1''-C=O in the two respective pairs of conformers: (+)-lepadin F [red dotted line] *versus* (+)-5'-*epi*-(+)-lepadin F [blue dotted line], and (+)-lepadin G [red dotted line] *versus* (+)-5'-*epi*-lepadin G [blue dotted line]. The clear difference in the H-bonding distance in these two pairs of conformers can contribute prominently to their respective conformational difference, thereby providing a rationale for two complex structures to be spectroscopically distinct despite differing only at a highly insulated acyclic stereocenter.

We have described here concise assignments of the C5' relative stereochemistry in both (+)-lepadin F and (+)-lepadin G as well as the absolute configurations of (+)-lepadin G through enantioselective total syntheses of (+)-5'-*epi*-lepadin F, (+)-lepadin G, and (+)-5'-*epi*-lepadin G. This work documents the possibility of a diastereomeric pair possessing sufficient spectroscopic difference for clear differentiation even when both isomers differ only at a highly insulated acyclic stereogenic center. These efforts support that total synthesis remains a useful tool in stereochemical assignments of natural products.

Supplementary Material

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Acknowledgments

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11. See Supporting Information.

Figure 1. NMR Comparisons of Synthetic (+)-Lepadine F and (+)-5'-Epi-Lepadine F with Carroll's Natural (+)-Lepadine F.

Figure 2.
¹³C NMR Differences Between (+)-Lepadine F and (+)-5'-Epi-Lepadine F.

Figure 3.
 ^1H NMR Spectra of Carroll's Natural (+)-Lepadin F Versus Synthetic (+)-Lepadin F and (+)-5'-*Epi*-Lepadin F.

Figure 4.
NMR Comparison of Synthetic (+)-Lepadin G and (+)-5'-Epi-Lepadin G with Carroll's Natural (+)-Lepadin G.

Figure 5.
 ^1H NMR Spectra of Carroll's Natural (+)-Lepadin G Versus Synthetic (+)-Lepadin G and (+)-5'-Epi-Lepadin G.

Figure 6.
Models of (+)-Lepadins and (+)-5'-Epi-Lepadins.

Scheme 1.
C5' Stereochemistry of (+)-Lepadins F and G.

Scheme 2.
Synthesis of (+)-5'-*Epi*-Lepadine F.

Scheme 3.

Total Syntheses of (+)-Lepadine G and (+)-5'-Epi-Lepadine G.

a. Pd(OH)₂/C, 60 *psi* H₂, 4.0 equiv (BOC)₂O, MeOH, 24 h. **b.** K₂CO₃, MeOH, 50 °C. **c.** Dess-Martin periodinane [DMP] reagent, NaHCO₃, CH₂Cl₂. **d.** NaBH₄, MeOH, -41 °C. **e.** 10.0 equiv TBDPSCl, imidazole, CH₂Cl₂, 40 °C, 12. **f.** DIBAL-H, -40 °C. **g.** DMP oxidation. **h.** NaHMDS, THF, -78 °C, (*R*)-**7** or (*S*)-**7**. **i.** Pd/C, 20 *psi* H₂, MeOH, rt. **j.** TBAF, THF, 50 °C.