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On the stereochemistry of palmerolide A

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Abstract—Degradative studies of the anticancer macrolide palmerolide A have resulted in re-assignment of the C-7, C-10, and C-11 stereocenters.

As part of our program to investigate the chemical diversity of cold-water marine organisms,[1] we recently reported the structure of palmerolide A (**1**).[2] An enamide-bearing macrolide isolated from the Antarctic tunicate *Synoicum adareanum*, palmerolide A is a potent inhibitor (2 nM) of vacuolar-ATPase (V-ATPase). In the National Cancer Institute's 60 cell line panel, palmerolide A displays potent and selective cytotoxicity toward melanoma and cytostatic activity toward leukemia, CNS, renal and breast cancer cell lines, as well as melanoma, with GI_{50}'s <10 nM (the lowest concentration tested). Palmerolide A was active in the NCI hollow-fiber assay[3] and is currently being evaluated in xenograft assays.

The planar structure of palmerolide A was established on the basis of extensive 2D NMR experimentation while the stereochemical assignment required a combination of spectroscopic and derivatization techniques.[2] The two secondary alcohols, C-7 and C-10, were amenable to stereochemical analysis by Mosher's method.[4] The remaining stereocenters were determined relative to C-10 using through-space NMR techniques such as ROESY along with $^{n}J_{CH}$-based analysis.[5]

In follow up to these spectroscopic techniques, we have subjected palmerolide A to degradative studies to confirm the stereochemical assignments (Fig. 1). Reductive ozonolysis of palmerolide A produced, among other fragments, triol **2**, which we expected was the *R* isomer of 1,2,6-trihydroxyhexane. However, degradation fragment **2** displayed an optical rotation of −9.0, a result

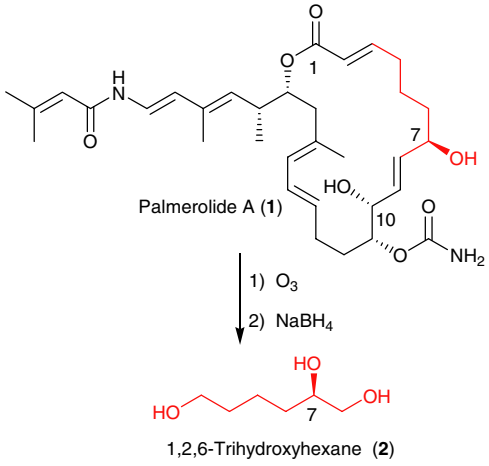

Figure 1. Reductive ozonolysis of the proposed[2] palmerolide A structure.

at odds with the value published in the literature (+3.4),[6] both in magnitude as well as sign. We therefore prepared (*R*)-1,2,6-hexanetriol, based on a chiral pool synthesis, for direct comparison.

We initially attempted preparation of (*R*)-1,2,6-trihydroxyhexane (*R*-**2**) from the (*R*)-acetonide of glycerol (**3**) (Fig. 2). In the course of this preparation the Wittig product **4** was reductively ozonized back to **3** to confirm the stereochemical integrity of the Wittig reaction. Recovered **3**, however, was found to have significantly epimerized (ee 56% of original).

We subsequently found that a homologue of **3**, the acetonide of (*R*)-1,2,4-trihydroxybutane (*R*-**5**) could be subjected to Wittig olefination to *R*-**6** while retaining its

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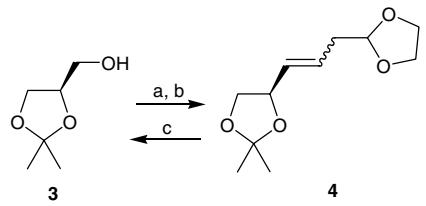

Figure 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, TEA, DCM, −60 °C–rt, 63%; (b) $Ph_3P(CH_2)_2CH(OCH_2)_2Br$, BuLi, THF, −78 °C, 60–80%; (c) O_3, −78 °C, then $NaBH_4$, 44% yield, 56% ee.

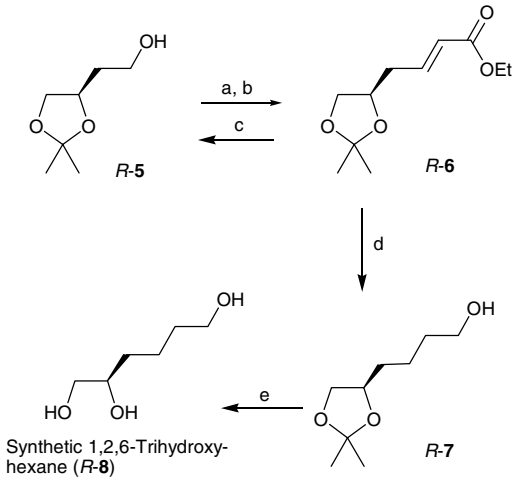

Figure 3. Reagents and conditions: (a) Dess–Martin periodinane, pyridine, DCM, rt, 2 h, 74–82%; (b) $Ph_3PCH_2CO_2EtBr$, Et_3N, rt, 15–17 h, 45–52%; (c) O_3, −78 °C, then $NaBH_4$ in MeOH, 55–60%; (d) $LiAlH_4$, THF, rt, 2 h, 37–45%; (e) 50% AcOH, rt, 30 min, 89–93%.

optical purity, based on a similar reductive ozonolysis back to *R*-**5** (Fig. 3). Degradation of product **2** could then be obtained in two additional steps from **6**. 1,4-reduction of the conjugated ester with LAH produced the terminal alcohol **7**, which was hydrolyzed to triol *R*-**8** under mild acid conditions. Spectral and chromatographic data (^{1}H NMR, ^{13}C NMR, GC/MS, and ESIMS) of (*R*)-1,2,6-trihydroxyhexane matched that of commercially available (±)-1,2,6-trihydroxyhexane.

With (*R*)-1,2,6-hexatriene in hand, we compared the optical rotation of synthetic product (*R*-**8**, +11.1) to degradation product (**2**, −9.0). We were satisfied to find the magnitude of the optical rotation from the synthetic product more closely matched the degradation product, but the sign of the rotation was opposite that of the degradation product.

Final verification of the C-7 stereochemistry was therefore achieved by preparation of (*S*)-1,2,6-trihydroxyhexane (*S*-**8**), starting from the acetonide of (*S*)-1,2,4-trihydroxybutane (*S*-**5**). The optical rotation of the *S*-triol (*S*-**8**, −11.6) matched the degradation product (**2**, −9.0) obtained from ozonolysis of palmerolide, establishing the configuration of palmerolide A's C-7 stereocenter as bearing the *S* configuration, rather than the originally published 7*R*.

This stereochemical revision took us back to the data from our Mosher's analysis to establish whether our procedures were in error or the method made the wrong prediction. Our notebooks indicated the correct conversion of the acid chloride stereochemistry to the corresponding ester stereochemistry ((*R*)-acid chloride results in the (*S*)-ester) was made, ruling out a not-uncommon mistake.[7] We therefore repeated the esterification of palmerolide A with (*R*)-methoxytrifluoromethylphenylacetoyl chloride, which we found to bear ^{1}H NMR shifts that matched the data originally assigned to the (*R*)-MTPA ester instead of the (*S*)-MTPA ester, suggesting they had been transposed.[8]

Palmerolide A's C-10 configurational assignment was made from the same MTPA products, necessitating that we re-evaluate the C-7/C-10 MTPA diester. We found that C-10 had been subject to the same sample or data transposition. Because the C-11 configuration is based on $^2J_{CH}$ and $^3J_{CH}$ conformational analysis of the C-10/C-11 spin system, both C-10 and C-11 must be revised to the *S* configuration. Thus, palmerolide stereocenters at positions 7, 10, and 11 must be revised from *R* to *S*.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.053.

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