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Configuration of the Psymberin Amide Side Chain

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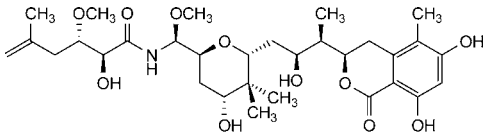
ABSTRACT

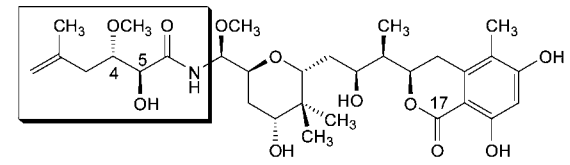


Psymberin

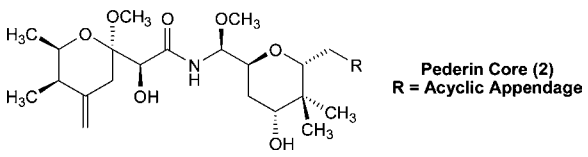
The structure of the amide side chain of psymberin, a potent and selective cytotoxin, is proposed. *Syn* and *anti* models of the amide side chain were prepared, and the structural assignment was confirmed by X-ray crystallographic analysis of the *anti* isomer. Comparison of ^{1}H and ^{13}C NMR data establishes homology between the natural product and the synthetic model compound of *anti* configuration and not the corresponding *syn* isomer.

Psymberin[1,2] (**1**), a new member of the pederin family of natural products, was isolated from the *Psammocinia* sp. sponge in the waters of Papua, New Guinea. Although only preliminarily assessed, this substance displays potent and selective activity against a panel of solid tumor cell lines. Characteristically, the pederin family contains two pyran rings conjoined by an amide wherein the pyran of the amine segment contains an acyclic appendage (designated as R in **2**, Figure 1).[3] Structurally, psymberin differs from other members of the pederin class in that it contains a pendant dihydroisocoumarin moiety and lacks a ring system in the carboxyl segment. These differences coupled with the resultant antitumor activity suggest a rich and underappreciated structure-based activity for this class of natural products. Since we were drawn to the synthesis of **1** and its analogues in particular, our initial interests focused on the structure of psymberin.

The psymberin structural assignment relied primarily on the use of multidimensional ^{1}H and ^{13}C NMR.[1] Absolute and relative configuration was based in part on homology to other pederins, including similar NMR signatures, optical rotation, probable biogenetic origin,[4] and a positive Cotton effect attributable to a chiral dihydroisocoumarin of *R* configuration (C17). The structural inferences notwithstanding, the configuration of the amide side chain was not assigned. The 5*S*



Psymberin (1)



Pederin Core (2)
R = Acyclic Appendage

Figure 1. Psymberin and the pederin core.

(1) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951−1954.

(2) Irciniastatins A and B, isolated from *Ircinia* sp. near Samporna, Borneo, were reported along with limited structure determination. See: Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schimdt, J. M. *J. Med. Chem.* **2004**, *47*, 1149−1152. Irciniastatin A and psymberin are thought to be identical; see ref 1.

(3) A full list of the members of this class of natural products is listed, with relevant literature citations, in the Supporting Information of ref 1.

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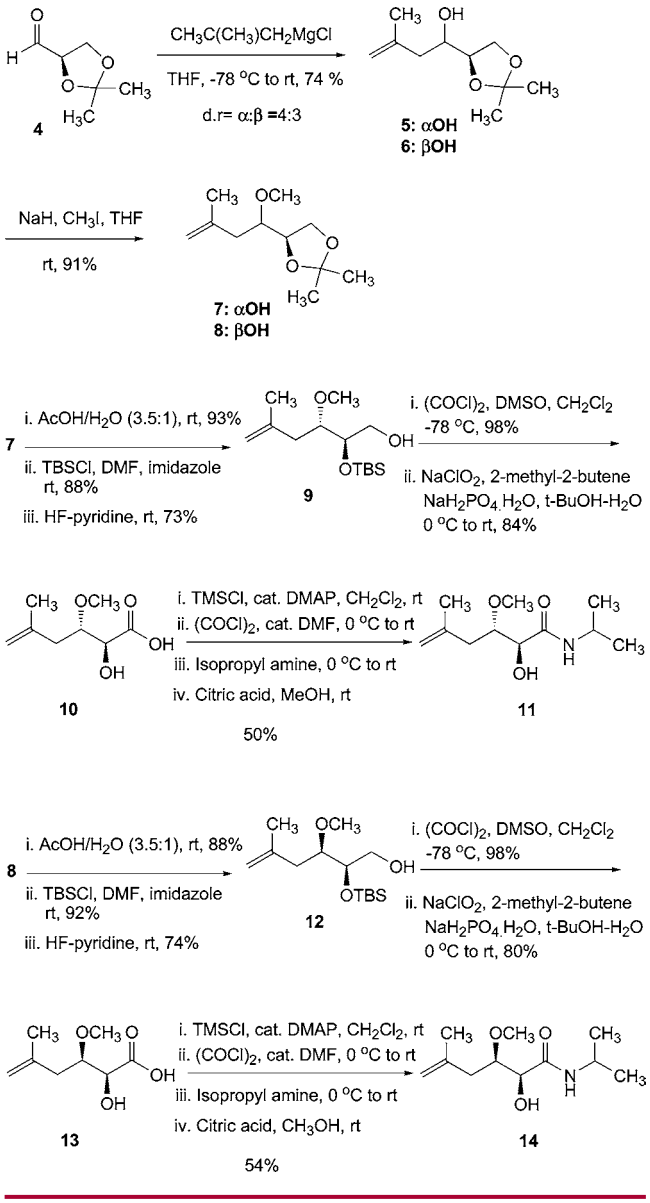
configuration was proposed on the basis of analogy to other pederins, whereas the spectral data relating to C4 proved inconclusive. We propose that the relative assignment of the psymberin amide side chain is *anti* (4*S*,5*S*), as shown in **1**, on the basis of NMR homology studies of the model compounds discussed below.

Our approach was to prepare model compounds of *anti* and *syn* configuration and to compare their NMR data with the reported spectral data for the amide side chain of **1**. It has been hypothesized and demonstrated that the ^{1}H and ^{13}C NMR signatures of stereoclusters are inherent to the specific arrangement of the stereogenic carbons and are otherwise virtually context independent.[5] Hence by application of the logic of a universal NMR database, the structure of a segment of a molecule, such as a complex natural product, can be assigned by comparison of NMR spectra of isostructural model compounds. There are limitations to this strategy;[6] nevertheless, several classes of polyols and several highly complex natural products have been assigned in this way.[7]

Scheme 1 summarizes the preparation of the model compounds. Treatment of mannitol-derived **4**[8] with methallylmagnesium chloride[9] gave a 4:3 mixture of alcohols **5** and **6** as an inseparable mixture. Upon methylation[10] the resultant ethers were conveniently separated by silica gel chromatography. The pure ethers were then subjected to the following sequences to arrive at *anti* amide **11** and *syn* amide **14**. Exposure of **7** or **8** to acid effected hydrolysis of the acetonide.[11] Diol protection as silyl ethers, removal of the primary silyl protecting group, oxidation of the resultant alcohol first to the aldehyde and then to the carboxylic acid gave the hydroxy acid.[12] Direct amidation of the unprotected acid[13] led to the desired *anti* and *syn* models as shown.

Scheme 1. Synthesis of Amide Side-Chain Models



Structural assignment of the *syn* and *anti* series was established as follows. Nucleophilic addition of Grignard reagents to **4** favors the formation of *anti* over *syn* products.[14] Asymmetric methallylation[15] using *R*-binol is also expected to favor *anti* addition. Methallylation of **4** under Keck

(4) See: Piel, J.; Hui, D.; Wen, G.; Butzke, D.; Platzer, M.; Fusetani, N.; Matsunaga, S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16222−16227. Piel, J.; Butzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S. *J. Nat. Prod.* **2005**, *68*, 472−479.

(5) (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Angew. Chem., Int. Ed*. **2000**, *39*, 4279−4281. (b) Tan, C.-H.; Kobayashi, Y. Kishi, Y. *Angew. Chem., Int. Ed*. **2000**, *39*, 4282−4284. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc*. **2001**, *123*, 2076−2078. (d) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379−14393. (e) Higashibayashi, S.; Kishi, Y. *Tetrahedron* **2004**, *60*, 11977−11982.

(6) The references listed in ref 5 above discuss the difficulties and limitations of the NMR database approach. Reference 5e focuses on vicinal diols. See also: (a) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem*. **1999**, *64*, 866−876. (b) Bifulco, G.; Bassarello, C.; Riccio, R.; Gomez-Paloma, L. *Org. Lett*. **2004**, *6*, 1025−1028. (c) Dambruoso, P.; Bassarello, C.; Bifulco, G.; Appendino, G. Battaglia, A.; Fontana, G.; Gomez-Paloma, L. *Org. Lett*. **2005**, *7*, 983−986. (d) Dambruoso, P.; Bassarello, C.; Bifulco, G.; Appendino, G. Battaglia, A.; Guerrini, A.; Fontana, G.; Gomez-Paloma, L. *Tetrahedron Lett*. **2005**, *46*, 3411−3415.

(7) See, for example: (a) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y, *Org. Lett*. **1999**, *1*, 2177−2180. (b) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett*. **1999**, *1*, 2181−2184. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562−2571. (d) Fidanze, S.; Song, F.; Szlosek-Pinaud, M.; Small, P. L.; Kishi, Y. *J. Am. Chem. Soc*. **2001**, *123*, 10117−10118. (e) Benowitz, A. B.; Fidanze, S.; Small, P. L.; Kishi, Y. *J. Am. Chem. Soc*. **2001**, *123*, 5128−5129. (f) Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett*. **2001**, *3*, 2245−2248. (g) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett*. **2001**, *3*, 2249−2252. (h) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett*. **2001**, *3*, 2253−2255. (i) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett*. **2002**, *4*, 411−414. (j) Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett*. **2003**, *5*, 93−96. (k) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Tetrahedron Lett*. **2003**, *44*, 7489−7491. (l) Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc*. **1994**, *116*, 4995−4996. See also ref 5 and references therein.

(8) Schmid, C. R.; Bryant, J. D.; Dowalatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056−4058.

(9) Masilamani, D.; Manahan, E. H.; Vitrone, J.; Rogic, M. M. *J. Org. Chem.* **1983**, *48*, 4918−4931.

(10) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423.

(11) Taber, D. F.; Xu, M.; Hartnett, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 13121−13126.

(12) For a sequence that effects preparation of a closely related aldehyde, see: (a) Nazare, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363−3376. (b) Enders, D.; Lenzen, A.; Muller, M. *Synthesis* **2004**, *9*, 1486−1496. For a related aldehyde-to-carboxylic acid oxidation, see: (c) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616−2617. (d) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397−2400.

(13) Kelly, S. E.; Lacour, T. G. *Synth. Commun.* **1992**, *22*, 859−869.

conditions gave a single product, albeit in poor yield (30%), which matched the spectral data of the major alcohol **5**. Methylation of this alcohol produced a substance that proved identical to the corresponding methyl ether **7**. Single-crystal X-ray diffraction studies on amide **11** reveal three closely related conformers (see Figure 2) and unambiguously establish the series as *anti*.

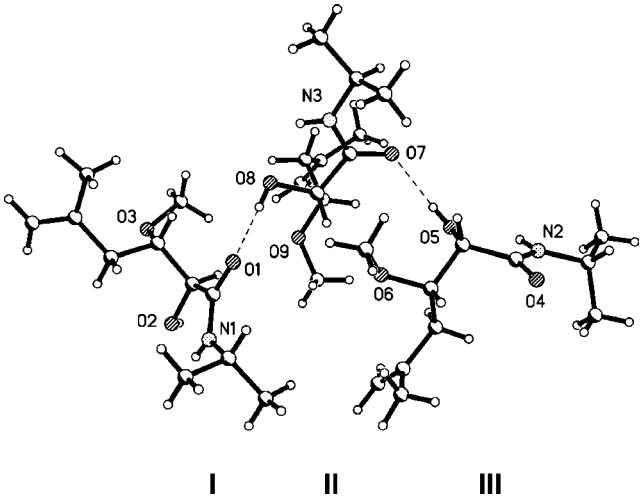


Figure 2. Crystal structure: three conformers of **11**.

Shown in Figure 3 are histograms of the differences in the ^{1}H and ^{13}C chemical shifts ($\Delta\delta$) between the model compounds and the corresponding reported signals of the natural product. The ^{1}H signals for **11**, especially the key signals[16] of H3a, H3b, H4, and H5, match the signals of the natural product, whereas the corresponding signals of the *syn* amide (**14**) do not. Similarly, the ^{13}C signals of **11** match the corresponding signals of psymberin, whereas **14** does not.

Structure assignment by comparison of spectral data with simple models has been successfully applied to such complex targets as tetrafibricin,[7j] desertomycin, and oasomycin.[5a−c,17] Each of these studies demonstrate that the proton and carbon chemical shifts of an isolated stereocluster depend on the relative stereochemistry. Thus, diastereoisomers have distinctly different NMR signatures. The difference between chemical shifts of a short model polyol and the mean chemical shift of the set of polyols appears to be ~0.10 ppm for ^{1}H signals and ~1.0 ppm for ^{13}C signals and these differences are significant.[5,6,18] Chemical shift differences of

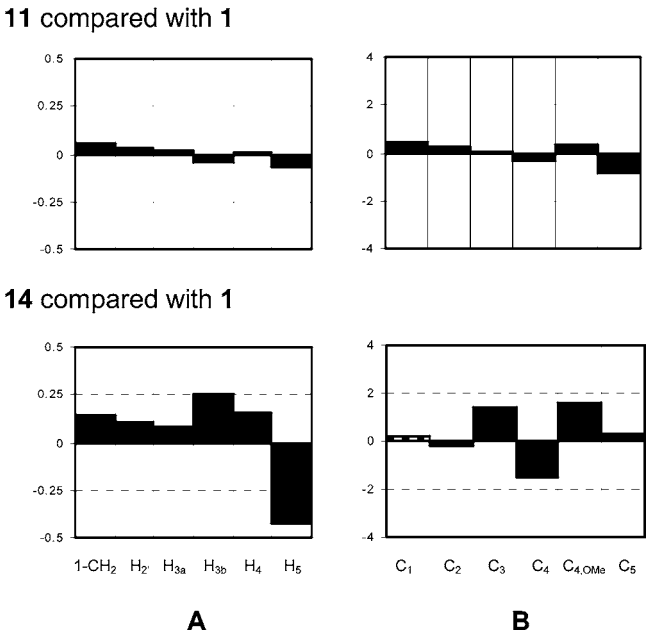


Figure 3. $\Delta\delta$ of **1** and the *anti* (**11**) and *syn* (**14**) models. (A) Difference between ^{1}H-δ of **1** and the *anti* and *syn* model. (B) Difference between ^{13}C-δ of **1** and the *anti* and *syn* model. The *x*-axis identifies the signal (^{1}H or ^{13}C) and the *y*-axis corresponds to $\Delta\delta = \delta(\mathbf{1}) - \delta(anti \text{ or } syn)$. Data collected at 300 MHz for ^{1}H and 75 MHz for ^{13}C in CD_3OD. The chemical shift data for **1** was taken from ref 1.

magnitude <0.05 for ^{1}H and <0.50 for ^{13}C between a model and a natural product indicate good structure correlation and appear insignificant. Dependability of the NMR database structure assignment, therefore, relies on two criteria: $\Delta\delta$ of significant magnitude between the mismatched diastereomeric model and the stereochemically undetermined structure, and insignificant differences between the matched diastereomeric model and the undetermined structure.

The data presented satisfy both of the above criteria and favor the *anti* assignment for the natural product. The success of the approach was not guaranteed, since determination of the relative stereochemistry of vicinal diols is usually complicated by small $\Delta\delta$.[19] For example, unfunctionalized 1,2-diol models exhibit an average difference of <0.4 ppm for ^{13}C and <0.04 ppm for ^{1}H signals when compared to the mean signals of both isomers.[5e] Hence, it may be difficult to confidently assert that a model diol is isostructural with an otherwise undetermined structure. However, these difficulties have been documented for isolated secondary 1,2-diols. The present case is more densely functionalized.[20] Comparison of **11** and **1** reveal a $\Delta\delta$ of <0.05 for ^{1}H and <0.5 for ^{13}C, whereas the *syn* isomer (**14**) varies >0.25 ppm for ^{1}H and >1.0 ppm for ^{13}C on average for the

(14) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, 24, 2843−2846. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422−424. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.

(15) Keck, G. E.; Tarbet, H. K.; Geraci, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543−6544.

(16) See Figure 4 for atom numbering.

(17) See also studies on caylobolide: MacMillan, J. B.; Molinski, M. F. *Org. Lett.* 2002, *4*, 1535−1539.

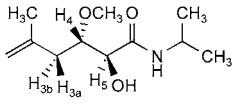
(18) This is in reference to the absolute value of $\Delta\delta$.

(19) Chiral solvent has proven an effective alternative in the event that the unknown compound is available for such analysis; see ref 5e.

(20) A densely functionalized mixed secondary/tertiary system; however, was not amenable to the NMR database logic. See ref 6c. In the present system, correction factors as applied in ref 6c were not necessary.

relevant and proximal signals. These differences are significant and are attributable to the context of the secondary diol system.

Examination of the coupling constants for the vicinal protons and the adjacent methylene also indicates homology between the natural product and **11** and offers conformational insight. For the *syn* isomer, the H5−H4 coupling appears as a doublet (J = 1.8 Hz) and the H4−H3a and H4−H3b couplings appear as multiplets (data not shown). In contrast, the *anti* isomer exhibits the same pattern and magnitude of coupling as the natural product (Figure 4). Moreover, conformers **I**, **II**, and **III**, identified in the crystal structure of **11**, are all very similar and would be expected to exhibit the same approximate coupling as that found for **11** and **1** in solution. We conclude the conformers observed in the crystal serve as realistic models of the side chain of the natural product in solution.[21]



Average Dihedral Angles for I, II, III		H-H Coupling Constants (Hz)		
		Estimated Average for I, II, III	11	1
H^5CCH^4	-66	1-3	3.0	2.5
H^4CCH^{3a}	-66	1-3	3.0	3.5
H^4CCH^{3b}	177	9-10	9.3	9.5

Figure 4. Vicinal coupling for **1** and **11** in solution and the conformers of **11** in the solid state. Average dihedral angles extracted from the crystal structure of **11**. Estimated coupling constants based on the Karplus relation. Spectral data for **11** and **1** (ref 1) collected in CD_3OD at 300 MHz.

Based on these results, we propose that the amide side chain of the natural product is *anti* and that the full stereostructure of psymberin is as shown in **1**. This report emphasizes that assignment of vicinal secondary alcohols by the NMR database approach may be most problematic for alcohols isolated from other functionality by multiple methylene units. The context of proximal carbonyl and methallyl functionality and methylation of one of the two alcohols appears to render this diol system amenable to structural assignment. Additionally, the crystal structure of **11** serves as a model for the ground state conformation of the psymberin amide side chain. Further synthetic and structural studies will be reported in due course.

Acknowledgment. Financial support by Merck & Co., Johnson & Johnson Innovative Research Award, ACS-PRF, and Rutgers, The State University of New Jersey, is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) These results are consistent with conformation-dependent coupling discussed in ref 6 and: Duin, M. v.; Baas, J. M. A.; Graaf, B. v. d. *J. Org. Chem.* **1986**, *51*, 1298−1302.