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Concise and Stereoselective Synthesis of the N_7–C_{25} Fragment of Psymberin

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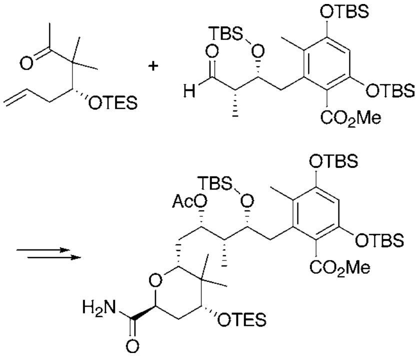
ABSTRACT



The N_7–C_{25} fragment of the potent and selective cytotoxic agent psymberin has been prepared through a short (12 linear steps, 15 total steps) and stereoselective sequence. Highlights of this route include a very rapid construction of the pentasubstituted arene, a substrate-controlled diastereoselective fragment coupling using a Mukaiyama aldol reaction, and an efficient entry into a key tetrahydropyranyl cyanide.

The family of compounds that contains pederin,[1] the mycalamides,[2] the theopederins,[3] and the onnamides[4] has attracted a considerable amount of attention[5] from practitioners of organic synthesis due to their unique structures and potent biological activity. Synthetically challenging structural motifs include the stable acylaminal linkage, the high density of stereocenters, and the unstable β,γ-unsaturated acetal. From a biological perspective, these compounds demonstrate potent cytotoxic[6] and immunosuppressive[7] activities and moderate antiviral activity.[2] Studies from Burres and Clement[8] have shown that these compounds inhibit protein synthesis. Recently, Fusetani and co-workers demonstrated[9] that pederin and theopederin A (Figure 1) are high-affinity ribosome-binding agents.

While the biological activities of these compounds are mechanistically intriguing, the lack of cell line specific toxicity casts doubts upon their viability as clinical agents. In 2004, Pettit[10] and Crews[11] independently reported the

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(1) (a) Pavan, M.; Bo, G. *Physiol. Comp. Oecol.* **1953**, *3*, 307. (b) Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Quilico, A. *Tetrahedron Lett.* **1965**, 2537. (c) Matsumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett.* **1968**, 6297.

(2) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.

(3) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1992**, *57*, 3828.

(4) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851.

(5) Representative total and formal syntheses: (a) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290. (b) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48. (c) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. (d) Roush, W. R.; Pfeifer, L. A. *Org.* Lett. **2000**, *2*, 859. (e) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159. (f) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9694. (g) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (h) Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. *Tetrahedron* **1990**, *46*, 1767. (i) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1988**, *44*, 7063.

(6) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull.* **1991**, *39*, 2152.

(7) Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immunol.* **1993**, *23*, 283.

(8) Burres, N. S.; Clement, J. J. *Cancer Res.* **1989**, *49*, 2935.

(9) Nishimura, S.; Matsunaga, S.; Yoshida, M.; Hirota, H.; Yokoyama, S.; Fusetani, N. *Bioorg. Med. Chem.* **2005**, *13*, 449.

(10) Pettit, G. R.; Xu, J.; Chapuis, J.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

10.1021/ol0520267 CCC: $30.25

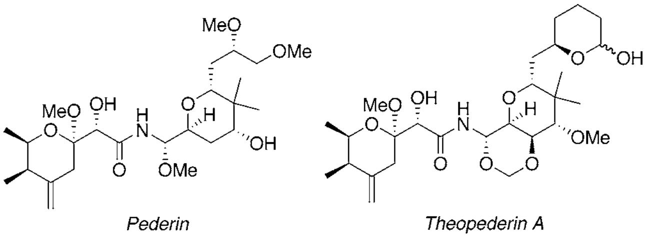

Figure 1. Representative acylaminal-containing cytotoxic agents.

isolation and structure of compound **1** from South Pacific sponges *Ircinia ramosa* and *Psammocinia* sp. The Pettit group named the structure irciniastatin A and the Crews group named it psymberin on the basis of its proposed[12] biogenesis from symbiotic bacteria. Psymberin is structurally related to pederin through the acylaminal group and the dimethyl tetrahydropyran ring but is unique in this family because of the acyclic acyl group and the presence of the dihydroisocoumarin (Figure 2). Of particular importance is that psymberin shows exceptional cell line specific cytotoxicity, with LC_{50} values for even some closely related cell lines varying by more than 4 orders of magnitude.[11] The structural basis for this selectivity apparently resides in either the dihydroisocoumarin, the acyclic acyl group, or both. Synthesis is a uniquely powerful tool for addressing this issue. We have had a long-term interest in this class of molecules[13] and were drawn to the potential for identifying the structural origin of psymberin's selectivity through rational analogue design. Prompted by De Brabander's elegant completion of psymberin's total synthesis,[14] we report our studies on the preparation of the $N_7{-}C_{25}$ subunit.[15] Notable features include the use of cycloaddition chemistry to access the pentasubstituted arene, the application of a Mukaiyama aldol reaction to a diastereoselective fragment coupling and an efficient construction of an amide group that is suitable for elaboration into the natural product and its analogues.

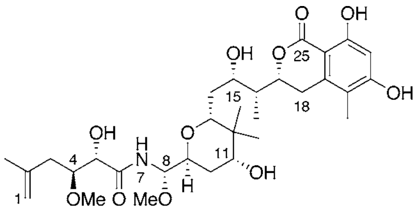

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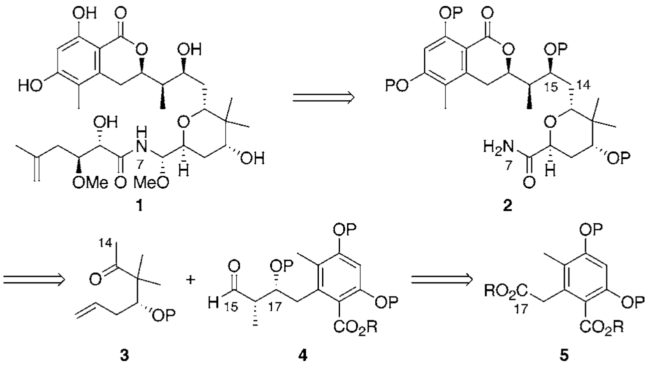
Figure 2. Structure of psymberin.

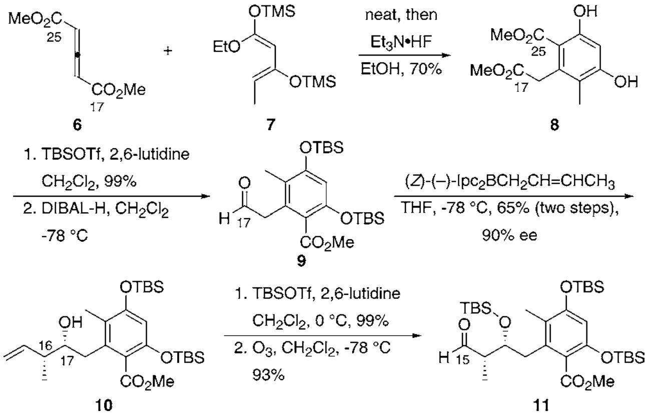
Scheme 1. Retrosynthetic Analysis



We envisioned **1** to be accessible (Scheme 1) through the classic coupling strategy that was developed for pederin syntheses in which the acylaminal arises from a reductive coupling between a left-hand acid chloride and a right-hand methyl imidate. Therefore, amide **2**, or a suitable structural variant, was selected as our initial target. The carbon framework of **2** was seen to be accessbile through the addition of ketone **3** into aldehyde **4**. Pentasubstituted arene **5** was selected as a logical precursor of **4**.

Due to the importance of accessing bulk quantities of **5**, we needed a pentasubstituted arene synthesis that is not excessively lengthy and is amenable to large-scale reactions. Thus, we chose to approach this problem through de novo arene synthesis (Scheme 2) rather than through arene manipulation. Cycloaddition[16] of allene dicarboxylate **6**, available in one step from commercially available dimethyl 1,3-acetonedicarboxylate,[17] with silylketene acetal **7**[18] at

Scheme 2. Arene Synthesis and Elaboration



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

(12) Piel, J.; Butzke, D.; Fusetani, N.; Hui, D. Q.; Platzer, M.; Wen, G. P.; Matsunaga, S. *J. Nat. Prod.* **2005**, *68*, 472.

(13) Rech, J. C.: Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495.

(14) Jiang, X.; García-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254.

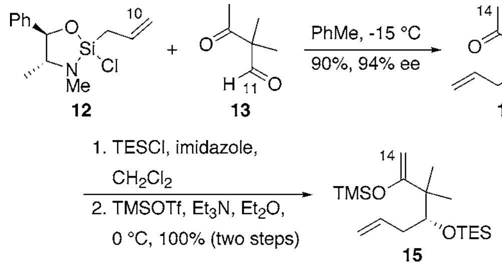
(15) For studies on the acyl fragment, see: (a) Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2907. (b) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 4117.

(16) Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545.

ambient temperature and in the absence of solvent provided, after treatment with ethanolic $Et_3N{\cdot}HF$,[19] arene **8** in 70% yield. Protection of the phenolic groups proceeded in essentially quantitative yield with TBSOTf and lutidine. *This rapid arene construction can be scaled to provide multigram quantities without loss of efficiency*. Selective monoreduction of the aliphatic ester with a single equivalent of DIBAL-H at −78 °C yielded aldehyde **9** in sufficient purity to obviate the need for further purification. The stereocenters at C_{16} and C_{17} were established through a Brown crotylation reaction[20] which provided **10** as a single diastereomer in 90% ee as determined through HPLC (Chiralcel OD-H column). Protection of the C_{17} hydroxyl group followed by ozonolysis resulted in the uneventful formation of aldehyde **11** in excellent yield.

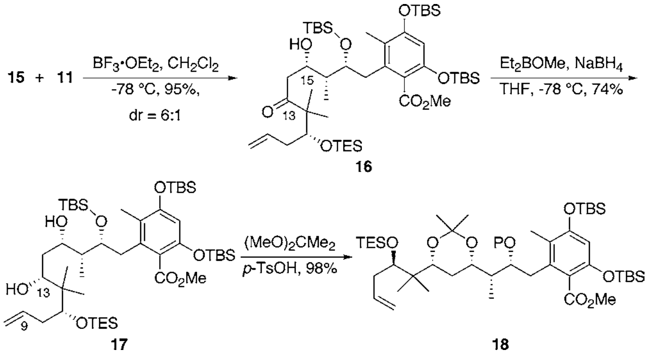
The preparation of the nucleophilic component of the aldol coupling (Scheme 3) commenced with the addition of Leighton's allylsilane **12**[21] to keto aldehyde **13**.[22] This reaction proceeded efficiently and in 94% ee as determined by GC (Chiraldex G-TA column) to form **14**. No ketone addition was observed. Protection of the resulting alcohol and enolsilane formation proceeded in quantitative yield to provide **15**.

Scheme 3. Enolsilane Preparation



The Lewis acid-mediated coupling of **15** with **11** (Scheme 4) proceeds with antagonistic stereodirection from the substituents at C_{16} and C_{17}. A Felkin−Anh approach[23] (α-direction) of the nucleophile is expected to provide the *syn,syn*-stereotriad, while direction from the β-silyloxy group is expected to yield the *anti,syn*-triad.[24] Congruent with Evans' observations[25] that α-direction overrides β-direction when bulky nucleophiles are employed, the Mukaiyama aldol reaction between **11** and **15** in the presence of $BF_3{\cdot}OEt_2$ proceeded with good preference (6:1) for the formation of **16**. Evidence for the presence of the *syn,syn*-stereoisomer was tentatively provided by analyzing the NMR chemical shifts and coupling constants of the C_{14} hydrogens, in accord with the model reported by the Roush group,[26] and was verified in subsequent intermediates. Chelation-controlled reduction of the resulting β-hydroxy ketone with Et_2BOMe and $NaBH_4$[27] provided diol **17** with excellent stereocontrol. While **16** and its *anti,syn*-isomer were inseparable, the diols that formed from the reduction were readily purified as single stereoisomers. The *syn*-relationship in the major product was confirmed through a ^{13}C chemical shift analysis[28] of acetonide **18**.

Scheme 4. Fragment Coupling



With the carbon framework intact we turned our attention to the formation of the tetrahydropyran ring (Scheme 5). Toward this goal the terminal alkene of **17** was subjected to ozonolytic cleavage. The resulting lactol was acetylated at C_9 and C_{15} under standard conditions to yield **19**. Selective ionization of the anomeric acetoxy group and trapping the intermediate oxocarbenium ion with TMSCN provided nitrile **20** as a single stereoisomer in excellent yield.[29] Hydrating the cyano group under classical conditions resulted in extensive and nonselective protecting group cleavage. To circumvent this problem, we employed the remarkably selective Parkin catalyst (**21**)[30] to produce amide **22** in nearly quantitative yield, thereby completing the synthesis of the N_7−C_{25} fragment of psymberin.

While optimzing workup conditions for **20** we isolated varying amounts of monodesilylated product **23**. Since the structure of **1** was determined solely by NMR, we felt that

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[17] Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. *Tetrahedron Lett.* **1998**, *39*, 6331.

[18] Barker, D.; Brimble, M.; Do, P.; Turner, P. *Tetrahedron* **2003**, *59*, 2441.

[19] Other sources of fluoride led to the formation of significant quantities of the C_{23} ethyl ether.

[20] Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

[21] Kinnaird, J. W. A.; Ng, P. Y., Kubota, K.; Wang, X.; Leighton, J. A. *J. Am.* Chem. Soc. **2002**, *124*, 7920.

[22] Prepared from the condensation of the enamine of isobutyraldehyde with acetyl chloride. See: Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404.

[23] (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

[24] Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537.

[25] (a) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem.* Soc. **2001**, *123*, 10840. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

[26] Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwenhze, M. S.; Gustin, D. J.; Dilley, G. J.; Scheidt, K. A.; Smith, W. J. *J. Org. Chem.* **2002**, *67*, 4284.

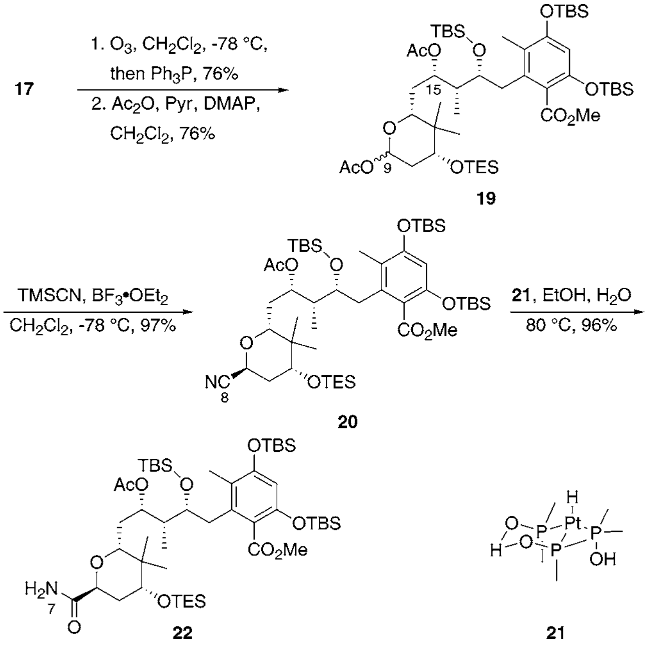
[27] Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

[28] (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

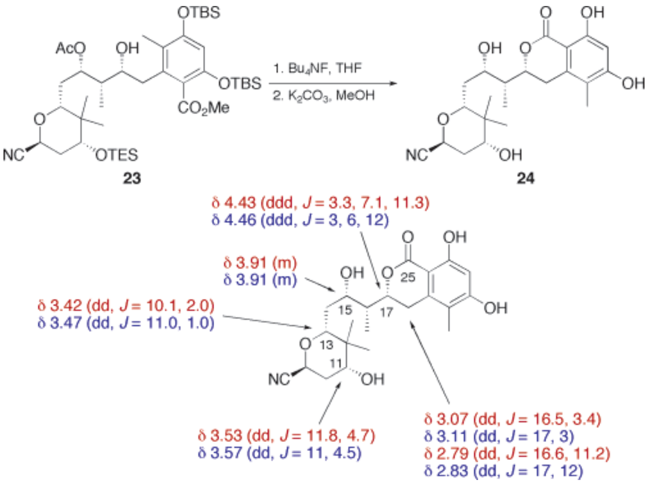
[29] For a related strategy, see: Hoffmann, R. W.; Schlapbach, A. *Tetrahedron Lett.* **1993**, *34*, 7903.

[30] (a) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249. (b) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett*. **1995**, *36*, 8657.

Scheme 5. Completion of the N_7-C_{25} Fragment



Scheme 6. Dihydroisocoumarin Formation and NMR Analysis[a]



[a] ^1H NMR signals in CD_3OD. Values for 24 are in red, and reported[11] values for the corresponding hydrogens in psymberin are in blue.

a correlation study would be beneficial. Therefore, we subjected **23** to TBAF to cleave all remaining silyl ethers and close the dihydroisocoumarin and then to K_2CO_3 in MeOH to form **24** (Scheme 6). The ^1H NMR of **24** in the $C_{11}-C_{25}$ region matched that of psymberin remarkably well, providing strong indication that Crews' structural assignment is indeed valid.

We have completed the synthesis of the N_7-C_{25} fragment of psymberin through an efficient and stereoselective route. The longest linear sequence is 12 steps from known materials and proceeds in 15% overall yield (13 steps from commercially available reagents), with a total step count of 15 steps from known materials (17 steps from commercially available reagents). Significant transformations include a rapid de novo pentasubstituted arene construction, a diastereoselective fragment coupling through a Mukaiyama aldol reaction, and a chemoselective nitrile hydration reaction. This approach is well-suited for completing the total synthesis and, more importantly, for preparing analogues that can be used to study the structural basis for psymberin's uniquely selective cytotoxicity.

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Supporting Information Available: Experimental procedures and characterization for all reactions and procedures for enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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