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Asymmetric Total Synthesis and Stereochemical Elucidation of the Antitumor Agent PM-94128

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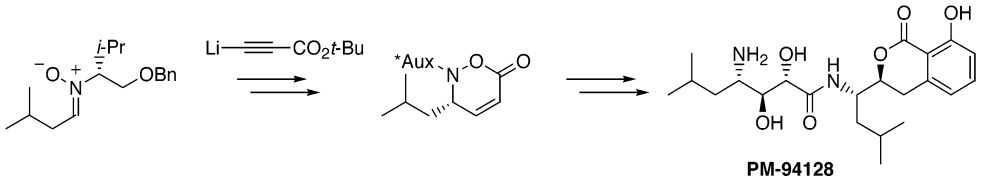
ABSTRACT



PM-94128

PM-94128, a novel depsipeptide antitumor agent, has been synthesized for the first time through a highly stereocontrolled route. The key steps for the synthesis of the dihydroxyamino acid moiety involve a diastereoselective addition of *tert*-butyl lithiopropiolate to a chiral nitrone and a 2,3-dihydro[1,2]oxazin-6-one dihydroxylation. The synthesis serves to define the relative as well as the absolute configuration of the natural product (bearing five stereogenic centers).

In the course of a screening program for new antitumor compounds, PM-94128 (**1**) was isolated in 1997 from the culture broth of *Bacillus* sp. PhM-PHD-090, a bacterium growing in marine sediment.[1] This natural product, for which neither the absolute nor the relative configuration was elucidated, was shown to exhibit cytotoxic activity against several tumor cell lines and to be an inhibitor of protein and DNA synthesis.

As part of an ongoing program in our laboratories aimed at designing stereocontrolled access to propargylic and allylic amine derivatives,[2] we became interested in synthesizing the amino diol fragment **2** of PM-94128 from the propargylic *N*-hydroxylamine **4** and coupling it with the aminodihydroisocoumarin **3** in order to prepare the natural product and determine its relative, as well as its absolute, configuration (Scheme 1).

Aminodihydroisocoumarins have been reported to exhibit a variety of biological activities.[3] Among the most studied of these natural products stands AI-77-B (**5**), a potent gastroprotective agent for which several syntheses have been described.[4,5] As AI-77-B was also isolated from a bacterium

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(2) (a) Pandya, S. U.; Garçon, C.; Chavant, P. Y.; Py, S.; Vallée, Y. *Chem. Commun.* **2001**, *18*, 1806−1807. (b) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallée, Y. *Org. Lett.* **2002**, *4*, 1463−1466. (c) Patel, S. K.; Py, S.; Pandya, S. U.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 525−528. (d) Pandya, S. U.; Pinet, S.; Chavant, P. Y.; Vallée, Y. *Eur. J. Org. Chem.* **2003**, in press.

(3) See, for example: (a) Baciphelacin: Okazaki, H.; Kiski, T.; Beppu, T.; Arima, K *J. Antibiot.* **1975**, *28*, 717−719. (b) Aminocoumacin: Itoh, J.; Omoto, S.; Shomura, T.; Nishizawa, N.; Miyado, S.; Yuda, Y.; Shibata, U.; Inouye, S. *J. Antibiot.* **1981**, *34*, 611−613. Itoh, J.; Omoto, S.; Shomura, T.; Nishizawa, N.; Miyado, S.; Yuda, Y.; Shibata, U.; Inouye, S. *Agric. Biol. Chem.* **1982**, *46*, 1255−1259. (c) Xenocoumacins: McInerney, B. V.; Taylor, W. C.; Lacey, M. J.; Akhurst, R. J.; Gregson, R. P. *J. Nat. Prod.* **1991**, *54*, 785−795. (d) Y-05460M−A: Sato, T.; Nagai, K.; Suzuki, K.; Morioka, M.; Saito, T.; Nohara, C.; Susaki, K.; Takebayashi, Y. *J. Antibiot.* **1992**, *45*, 1949−1952. (e) AI-77B: Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Tetrahedron Lett.* **1982**, *23*, 5535−5538. Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Tetrahedron* **1984**, *40*, 2519−2527.

(4) For total syntheses of AI-77-B, see: (a) Hamada, Y.; Kawai, A.; Kohno, Y.; Hara, O.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 1524−1525. (b) Broady, S. D.; Rexhausen, J. E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1991**, 708−710. (c) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635−8652. (d) Ward, R. A.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3359−3362. (e) Durgnat, J. M.; Vogel, P. *Helv. Chim. Acta* **1993**, *76*, 222−240. (f) Ward, R. A.; Procter, G. *Tetrahedron* **1995**, *51*, 12301−12318. (g) Broady, S. D.; Rexhausen, J. E.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1083−1094. (h) Kotsuki, H.; Tomohiro, A.; Miyazaki, A.; Datta, P. K. *Org. Lett.* **1999**, *1*, 499−502. (i) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Org. Lett.* **2001**, *3*, 2677−2680. (j) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, 821−832.

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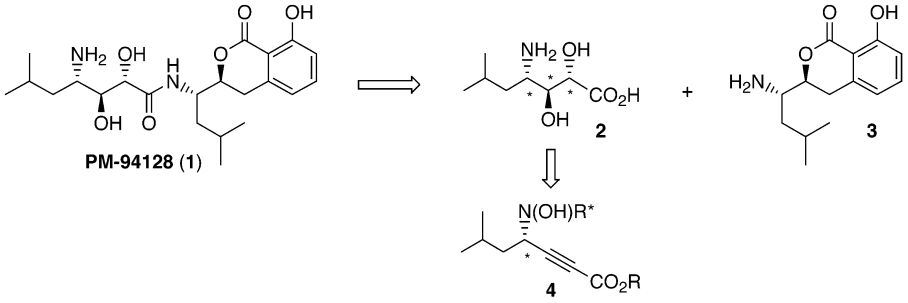
Scheme 1. Retrosynthesis of PM-94128



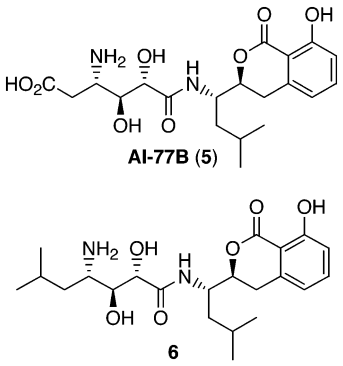


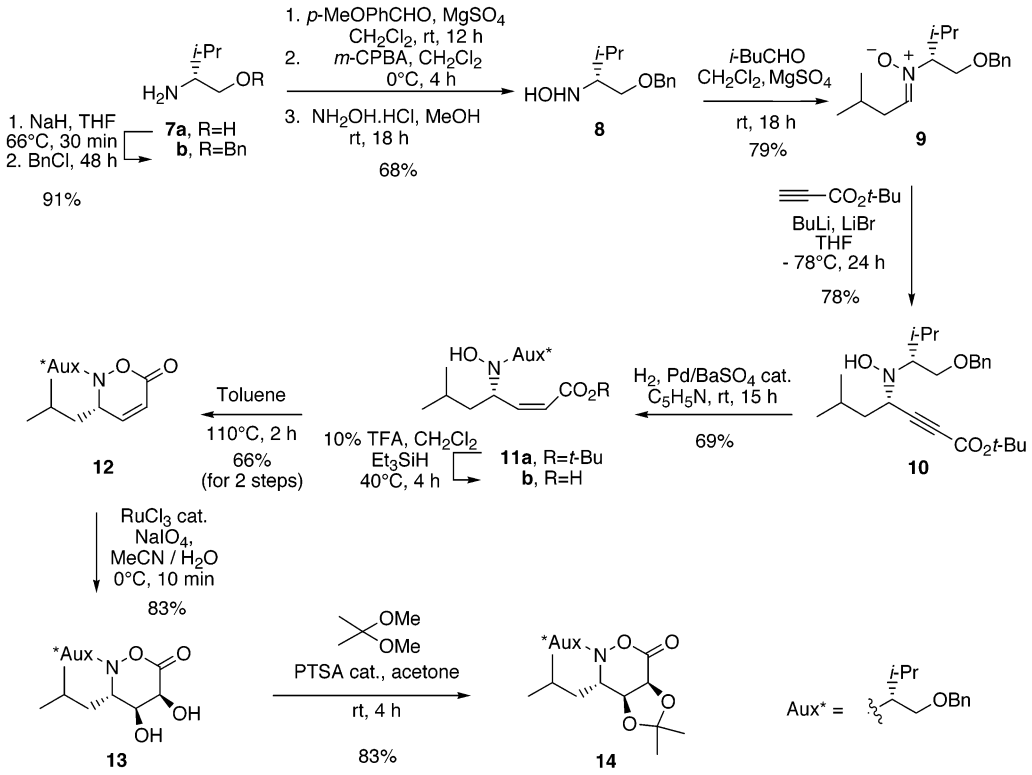
Figure 1. Stereochemistry proposed for PM-94128.

of the *Bacillus* genus, we hypothesized that PM-94128 could arise from a biogenetic process related to that for AI-77-B and, hence, might likewise display "*all (S)*" configurations at its stereogenic centers (Figure 1).

The synthesis of the proposed γ-amino-α,β-dihydroxy acid fragment of PM-94128 was planned to involve direct asymmetric addition of a 3C-synthon, such as a metallopropiolate, to a C=N bond, followed by transformation of the adduct into a diol derivative. The synthesis of nitrone **9**, bearing a valinol-derived chiral auxiliary, started with selective *O*-benzylation of valinol to give amine **7b** (Scheme 2), which was oxidized to the corresponding hydroxylamine **8**. This, in turn, condensed readily with isovaleraldehyde to provide nitrone **9** in 49% overall yield (from (*R*)-valinol).

Although the addition of a variety of alkynes to chiral nitrones had previously been successful using catalytic

Scheme 2



amounts of diethylzinc, the addition of propiolic esters to nitrone **9** in this way failed.[2c] In searching for an effective method to prepare the required γ-*N*-hydroxyamino-ynoate with high diastereoselectivity, it was found that *tert*-butyl lithiopropiolate smoothly added to nitrone **9** in THF at low temperature (−78 °C) with excellent selectivity.[6] Indeed, only one diastereomer (**10**), displaying the desired 4*S*,2′*R* configurations, was produced in this addition.

Controlled reduction of the triple bond to the corresponding *Z* double bond was next necessary to set the stage for dihydroxylation at C-2 and C-3. Selective hydrogenation of the triple bond was performed using Pd/$BaSO_4$ as the catalyst, to yield exclusively the hydroxylamine **11a**.[7]

Hydroxylamines are known to be highly sensitive to the oxidants; thus, to avoid nitrone formation during the dihydroxylation step, protection was necessary.

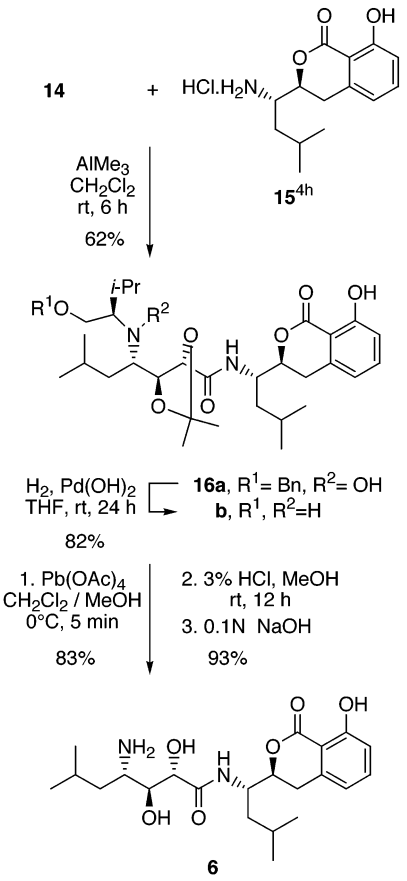
Cyclic protection could be conveniently realized in a two-step sequence that involved acidic cleavage of the *tert*-butyl ester,[8] followed by dehydration−cyclization by refluxing the resultant acid **11b** in toluene.

Although dihydroxylation of 1,2-oxazines had previously been described,[5j,9] no examples were found involving the 2,3-dihydro[1,2]oxazin-6-one system.[10] To our delight, it was found that Shing's "flash dihydroxylation" conditions, using a catalytic amount of ruthenium trichloride in the presence of stoichiometric sodium metaperiodate, gave highly satisfactory results in terms of both yield and diastereoselectivity.[11]

A single diol, **13**, was obtained under these conditions in 83% yield. The configuration of the three new stereogenic centers could be assigned from the X-ray analysis of the protected diol **14**.[12] Starting from (*R*)-valinol, the obtained oxazinone **14** was found to have the desired 2*S*, 3*S*, and 4*S* stereocenters. The stereoselectivity of the dihydroxylation is consistent with that previously reported with 1,2-oxazines and results from reagent approach opposite to the isobutyl group.[8,5j]

The protected oxazinone **14** was next coupled with the (3*S*,5′*S*)-aminodihydroisocoumarin hydrochloride salt **15** (Scheme 3), which was synthesized according to Kotsuki's

Scheme 3



method.[4h] The coupling was performed in the presence of Me_3Al with 3.5 equiv of the salt **15**, in 62% yield.[13] Attempts to open oxazinone **14** with only 1.5 equiv of **15** in the presence of sodium 2-ethylhexanoate[14] gave only very poor yields of the desired product.

Removal of the chiral auxiliary involved concomitant hydrogenolysis of the *O*-benzyl and the N−O bonds, followed by oxidative amino alcohol cleavage using $Pb(OAc)_4$, which provided the free amine.[15]

(5) For synthetic approaches to AI-77-B, see: (a) Kawai, A.; Hara, O.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6331−6334. (b) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1989**, *30*, 6503−6506. (c) Hamada, Y.; Kawai, A.; Matsui, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823−4846. (d) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Chem. Lett.* **1992**, 1255−1258. (e) Kotsuki, H.; Iwasaki, M.; Ochi, M. *Heterocycles* **1994**, *38*, 17−20. (f) Shinozaki, K.; Mizuno, K.; Masaki, Y. *Heterocycles* **1996**, *43*, 11−14. (g) Superchi, S.; Minutolo, F.; Pini, D.; Salvadori, P. *J. Org. Chem.* **1996**, *61*, 3183−3186. (h) Mukai, C.; Miyakawa, M.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 913−917. (i) Ghosh, A. K.; Cappiello, J. *Tetrahedron Lett.* **1998**, *39*, 8803−8806. (j) Davies, G.; Russell, A. T. *Tetrahedron Lett.* **2002**, *43*, 8519−8522.

(6) A full account on the asymmetric addition of metallopropiolates to chiral nitrones will be published separately.

(7) Reduction of **10** was initially performed in the presence of Zn (MeOH/AcOH, 9:1, 60 °C, see: Dagoneau, C.; Denis, J. N.; Vallée, Y. *Synlett* **1999**, *5*, 602−604) to yield the corresponding *Z*-γ-amino enoate. However, no dihydroxylation of the latter could be achieved using OsO_4, or AD-Mix, or $KMnO_4$. Carbamoylation to reduce the coordinating ability of the nitrogen (which was thought to be hampering the dihydroxylation) was attempted but was unsuccessful.

(8) The use of Et_3SiH in the *tert*-butyl ester acidolysis proved necessary; complex mixtures were obtained in the absence of this hydride source. See: Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441−5444.

(9) (a) McClure, K. F.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 850−853. (b) Defoin, A.; Pires, J.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 1653−1670. (c) Defoin, A.; Pires, J.; Tissot, I.; Tschambert, T.; Bur, D.; Zehnder, M.; Streith, J. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1209−1221. (d) Behr, J.-B.; Defoin, A.; Mahmood, N.; Streith, J. *Helv. Chim. Acta* **1995**, *78*, 1166−1177. (e) Bach, P.; Bols, M. *Tetrahedron Lett.* **1999**, *40*, 3461−3464. (f) Davies, G.; Russell, A. T.; Sanderson, A. J.; Simpson, S. J. *Tetrahedron Lett.* **1999**, *40*, 4391−4394. (g) Zimmer, R.; Homann, K.; Angerrmann, J.; Reissig, H.-U. *Synthesis* **1999**, 1223−1235. (h) Arribas, C.; Carreno, M. C.; Garcia-Ruano, J. L.; Rodriguez, J. F.; Santos, M.; Sanz-Tejedor, M. A. *Org. Lett.* **2000**, *2*, 3165−3168.

(10) Model studies on dihydroxylation with *N*-benzyl-2,3-dihydro-3-isobutyl[1,2]oxazin-6-one showed that typical conditions (cat. OsO_4, NMO, acetone/H_2O, or $KMnO_4$, 18-cr-6, CH_2Cl_2) gave unsatisfactory results.

(11) (a) Shing, T. K. M.; Tai, V. W. F.; Tam, E. K. W. *Ang. Chem. Int. Ed.* **1994**, *33*, 2312−2313. (b) Shing, T. K. M.; Tam, E. K. W. *Tetrahedron Lett.* **1999**, *40*, 2179−2180.

(12) See the Supporting Information.

(13) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995−3000.

(14) Liu, W.; Xu, D. D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439−2441.

Deprotection of the vicinal hydroxyl groups was then accomplished in 3% methanolic HCl to afford cleanly compound **6** (mp 170−171 °C; $[\alpha]^{20}_D$ −90.1, *c* 2.00, $CHCl_3$), which provided ^1H and ^{13}C spectra identical with those of the naturally derived product (mp 172−173 °C; $[\alpha]^{25}_D$ −88.9, *c* 2.00, $CHCl_3$).[1]

In conclusion, an efficient and totally stereocontrolled synthesis of PM-94128, the first of this natural product, has allowed assignment of its stereochemistry. The method used to prepare the dihydroxyamino acid part of PM-94128 can also be applied for the synthesis of other γ-amino-α,β-dihydroxy acid derivatives, such as AI-77-B or the calyculins,[16] which are potent phosphatase inhibitors that exhibit antitumor activity.

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Supporting Information Available: Experimental procedures and full characterization for compounds **6**−**16**, ^1H NMR and ^{13}C NMR spectra for compounds **6**−**16** and for the naturally derived sample of PM-94128, and crystallographic data for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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