JOC*Note*

pubs.acs.org/joc

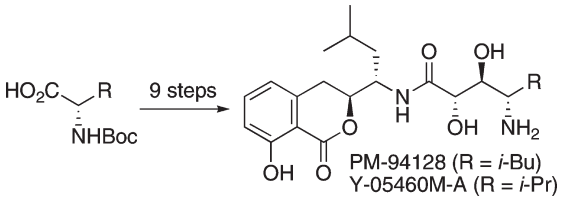
Concise Synthesis of PM-94128 and Y-05460M-A

Masaru Enomoto and Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

skuwahar@biochem.tohoku.ac.jp

Received July 13, 2009



The enantioselective total synthesis of PM-94128, a potent cytotoxin of microbial origin, was accomplished by a concise nine-step sequence of reactions in 14% overall yield from *N*-Boc-L-leucine. The synthesis of Y-05460M-A, a one-carbon lower homologue of PM-94128, was also achieved from *N*-Boc-L-valine by the same approach, which enabled its stereochemical determination.

A small family of natural products characterized by a dihydroisocoumarin ring system linked to an unusual dihydroxyamino acid through an amide bond, as exemplified by amicoumacin A and AI-77-B (Figure 1),[1] have been reported to possess various intriguing biological properties such as antibacterial,[1−5] anti-inflammatory,[1,3,4] antiulcer,[1,3,4] herbicidal,[6] and cytotoxic activities.[2,7] PM-94128 (**1**) and its one-carbon lower homologue Y-05460M-A (**2**) isolated from the culture broths of *Bacillus* sp. PhM-PHD-090 and *Bacillus* sp. Y-05460M, respectively, are also among this type of natural products. PM-94128 (**1**) was shown to exhibit potent cytotoxicity against several tumor cell lines (P-388, A-549, HT-29, MEL-28) with an IC_{50} value of 50 nM,[8] while Y-05460-A (**2**) was found to be highly toxic to L1210 and P388 cancer cell lines with IC_{50} values of 130 and 45 nM, respectively.[9] The structure of **1** was originally proposed as its planar structure on the basis of spectroscopic analyses, and its absolute configuration was unambiguously determined by Py and co-workers through their synthetic study,[10] in which they assumed that the stereochemistry of **1** would probably be the same as that of AI-77-B from biogenetic considerations. As part of our continuing efforts for the synthesis of isocoumarin−unusual amino acid conjugate-type natural products,[11] we planned to assign the unknown stereochemistry of the analogous compound **2** by synthetic means as well as to develop a concise general approach to this type of compounds. We describe herein the expeditious enantioselective total synthesis of **1** and a stereoisomer of **2**, which led to the determination of the absolute configuration of Y-05460M-A (**2**).

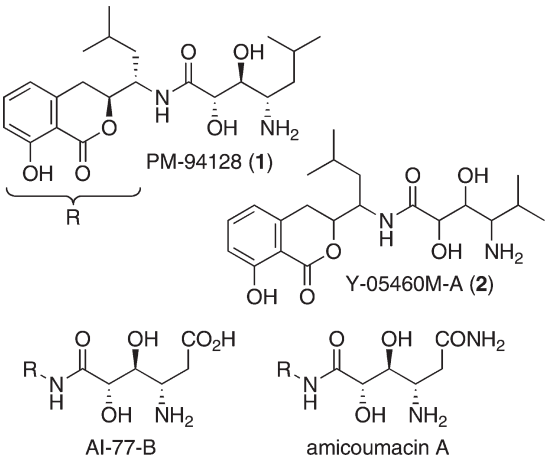


FIGURE 1. Structures of PM-94128, Y-05460M-A, and related natural products.

Our retrosynthetic analysis of **1** is shown in Scheme 1. Compound **1** should be obtainable via condensation of amine segment **3** and acid segment **4**, the latter of which would be derived from hydrolysis of *N*-protected lactam **5**. The dihydroxy lactam **5** was considered to be readily accessible by stereoselective dihydroxylation of unsaturated lactam **6**, which would be traced back to *N*-Boc-protected L-leucine **7**.

Based on the synthetic plan described above, our synthesis of PM-94128 (**1**) began with the conversion of **7** into known

(1) (a) Itoh, J.; Omoto, S.; Shomura, T.; Nishizawa, N.; Miyado, S.; Yuda, Y.; Shibata, U.; Inouye, S. *J. Antibiot*. **1981**, *34*, 611–613. (b) Itoh, J.; Shomura, T.; Omoto, S.; Miyado, S.; Yuda, Y.; Shibata, U.; Inouye, S. *Agric. Biol. Chem*. **1982**, *46*, 1255–1259. (c) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Agric. Biol. Chem*. **1982**, *46*, 1823–1829. (d) Shimojima, Y.; Shirai, T.; Baba, T.; Hayashi, H. *J. Med. Chem*. **1985**, *28*, 3–9.

(2) Okazaki, H.; Kishi, T.; Beppu, T.; Arima, K. *J. Antibiot*. **1975**, *28*, 717–719.

(3) McInerney, B. V.; Taylor, W. C.; Lacey, M. J.; Akhurst, R. J.; Gregson, R. P. *J. Nat. Prod*. **1991**, *54*, 785–795.

(4) Pinchuk, I. V.; Bressollier, P.; Sorokulova, I. B.; Verneuil, B.; Urdaci, M. C. *Res. Microbiol*. **2002**, *153*, 269–276.

(5) Pinchuk, I. V.; Bressollier, P.; Verneuil, B.; Fenet, B.; Sorokulova, I. B.; Mégraud, F.; Urdaci, M. *Antimicrob. Agents Chemother*. **2001**, *45*, 3156–3161.

(6) (a) Gebhardt, K.; Schimana, J.; Müller, J.; Fiedler, H.-P.; Kallenborn, H. G.; Holzenkämpfer, M.; Krastel, P.; Zeeck, A.; Vater, J.; Höltzel, A.; Schmid, D. G.; Rheinheimer, J; Dettner, K. *FEMS Microbiol. Lett*. **2002**, *217*, 199–205. (b) Azumi, M.; Ogawa, K.; Fujita, T.; Takeshita, M.; Yoshida, R.; Furumai, T.; Igarashi, Y. *Tetrahedron* **2008**, *64*, 6420–6425.

(7) Huang, Y.-F.; Li, L.-H.; Tian, L.; Qiao, L.; Hua, H.-M.; Pei, Y.-H. *J. Antibiot*. **2006**, *59*, 355–357.

(8) Cañedo, L. M.; Fernández Puentes, J. L.; Baz, J. P. *J. Antibiot*. **1997**, *50*, 175–176.

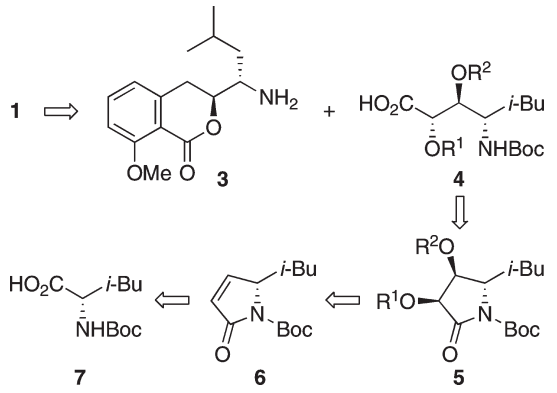
(9) Sato, T.; Nagai, K.; Suzuki, K.; Morioka, M.; Saito, T.; Nohara, C.; Susaki, K.; Takebayashi, Y. *J. Antibiot*. **1992**, *45*, 1949–1952.

(10) Patel, S. K.; Murat, K.; Py, S.; Vallée, Y. *Org. Lett*. **2003**, *5*, 4081–4084.

(11) For syntheses of AI-77-B and related natural products, see: Enomoto, M.; Kuwahara, S. *Angew. Chem., Int. Ed*. **2009**, *48*, 1144–1148. and references cited therein.

Published on Web 09/01/2009 DOI: 10.1021/jo9014968

SCHEME 1. Retrosynthetic Analysis of 1

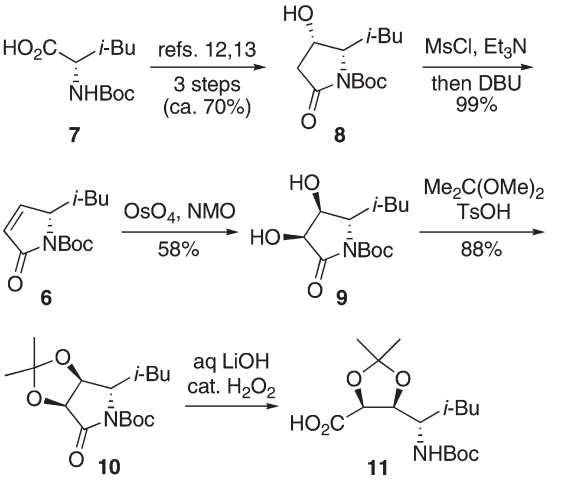


β-hydroxy lactam **8** in ca. 70% yield by a convenient three-step sequence involving the acylation of Meldrum's acid with **7**, which was originally developed by Jouin and Castro and later modified by Ma and co-workers.[12,13] Subjection of **8** to a one-pot mesylation/elimination protocol quantitatively provided dehydration product **6**, which was then exposed to dihydroxylation conditions to give **9** as a single diastereomer, albeit in a moderate isolated yield of 58%.[14,15] After protection of the diol **9** as its acetonide **10**, the product was hydrolyzed with aq LiOH in the presence of a catalytic amount of H_2O_2 to furnish the acid segment **11** (Scheme 2).

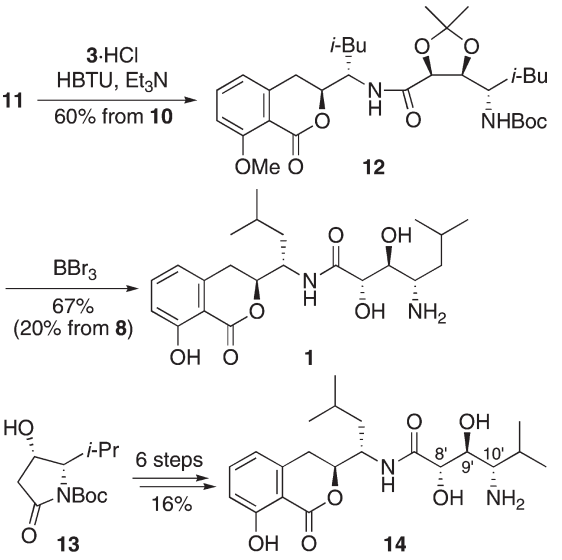
With the acid segment **11** in hand, we proceeded to the final stage of the synthesis of PM-94128 (**1**). The carboxylic acid **11** was condensed with the known amine segment **3**, prepared by our epoxide ring-opening approach,[11] to give amide **12**. Exposure of **12** to BBr_3 in CH_2Cl_2 brought about deprotection of all of its three protecting groups to afford **1** in an acceptable yield of 67%. The ^1H and ^{13}C NMR spectra of **1** were identical with those reported previously,[8,10] and the specific rotation of **1** ($[\alpha]^{22}_D$ −94.1 (*c* 0.195, $CHCl_3$)) showed good agreement with literature values (lit.[8] $[\alpha]^{25}_D$ −88.9 (*c* 2.0, $CHCl_3$), lit.[10] $[\alpha]^{20}_D$ −90.1 (*c* 2.00, $CHCl_3$)).

Having completed the enantioselective synthesis of PM-94128 (**1**), we next turned our attention to the determination of the absolute stereochemistry of Y-05460M-A (**2**) through synthesis. From structural similarity between **1** and **2** as well as the fact that both **1** and **2** were produced by bacteria of the same genus, it seemed appropriate to postulate that Y-05460M-A has the same stereochemical arrangement as PM-94128 (**1**). Based on these considerations, we decided to synthesize stereoisomer **14** as the most probable structure for Y-05460M-A (Scheme 3). By precisely following the synthetic sequence used for **1**, compound **14** was obtained uneventfully in 16% overall yield from L-valine-derived hydroxy lactam **13**.[12,13,16] The ^1H and ^{13}C NMR of **14** were,

SCHEME 2



SCHEME 3



as a matter of course, very analogous to those of **1** except for the signals due to the terminal isopropyl region in its acid segment part, indicating our synthetic compound to be undoubtedly **14**. Unexpectedly, however, the spectral data of **14** were considerably different from those reported for natural Y-05460M-A, especially in the ^1H NMR chemical shifts of the 8′-H, 9′-H, and 10′-H (δ 4.04, 3.31, 2.81 ppm for **14**, respectively; 4.53, 4.26, and 3.21 ppm for natural Y-05460M-A, respectively).[17] Faced with this disagreement, we suspected that the substantial downfield chemical shifts for natural Y-05460M-A might be due to its protonation at the 10′-amino group. Thus, we prepared the hydrochloride of **14** and measured the ^1H and ^{13}C NMR spectra of the salt. Just as we thought, the NMR spectra of **14**·HCl were virtually identical with those of natural Y-05460M-A; the signals for 8′-H, 9′-H, and 10′-H were, for example, observed at δ 4.52, 4.25, and 3.20, respectively, in good accordance with the values for natural Y-05460M-A noted above (see the Supporting Information for more details). Unfortunately,

(12) Jouin, P.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177–1182.
(13) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2365–2370.
(14) (a) Muramatsu, T.; Yamashita, S.; Nakamura, Y.; Suzuki, M.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2007**, *48*, 8956–8959. (b) Ward, R. A.; Procter, G. *Tetrahedron* **1995**, *51*, 12301–12318.
(15) Monitoring of the reaction by TLC, together with the ^1H NMR spectrum of the crude reaction product, indicated that the dihydroxylation proceeded cleanly without formation of any noticeable byproduct, giving **9** as a single stereoisomer. The moderated isolated yield (58%) is, therefore, considered to be ascribable to the difficulty in the isolation of **9** because of its high water solubility.
(16) Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S. *Synthesis* **1993**, 216–220.
(17) The numbering of **14** follows that of this type of natural products (see refs 8 and 9).

we could not verify that the NMR spectra of the natural product had actually been recorded as its ammonium salt because the natural sample of Y-05460M-A was no longer available. However, the virtually complete agreement of **14**·HCl with Y-05460M-A in ^{1}H and ^{13}C NMR, coupled with the stereochemical uniformity of this class of natural products,[1d,4,6b,7,10] would be enough for concluding the structure of Y-05460M-A to be **14**.

In conclusion, the enantioselective total synthesis of PM-94128 (**1**) was accomplished in 14% overall yield from *N*-Boc-L-leucine (**7**) by the concise nine-step sequence of reactions. The synthesis of its one-carbon lower homologue **14** was also achieved by the same approach from *N*-Boc-L-valine in 11% overall yield, which, through NMR spectral comparison, enabled us to assign the stereochemistry of Y-05460M-A as depicted in **14**. Our efficient approach to PM-94128 (**1**) and Y-05460M-A (**14**) would readily be applicable to the synthesis other members of this type of natural products simply by changing the starting amino acid.

Experimental Section

***tert*-Butyl (*S*)-2,5-Dihydro-2-isobutyl-5-oxo-1*H*-pyrrole-1-carboxylate (6).** To a stirred solution of **8** (140 mg, 0.546 mmol) in CH_2Cl_2 (4.5 mL) were added MsCl (72 μL, 0.928 mmol) and Et_3N (228 μL, 1.637 mmol) at 0 °C under N_2, and the mixture was stirred for 1 h at rt. DBU (122 μL, 0.818 mmol) was then added, and the resulting mixture was stirred for 40 min. The mixture was poured into saturated aq NH_4Cl at 0 °C and extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 129 mg (99%) of **6** as a colorless oil: $[\alpha]^{22}_D$ +140.3 (*c* 2.89, $CHCl_3$); IR ν_{max} 2959 (m), 1774 (s), 1737 (s), 1713 (s), 1314 (s); ^{1}H NMR δ 0.96 (3H, d, J = 6.5 Hz), 1.00 (3H, d, J = 6.5 Hz), 1.43 (1H, ddd, J = 13.5, 10.3, 4.5 Hz), 1.64−1.75 (1H, m), 1.99 (1H, ddd, J = 13.5, 9.5, 3.0 Hz), 4.61 (1H, dt, J = 10.3, 1.5 Hz), 6.10 (1H, dd, J = 6.3, 1.5 Hz), 7.23 (1H, dd, J = 6.3, 1.5 Hz); ^{13}C NMR δ 22.0, 23.8, 25.0, 28.0, 41.0, 61.3, 82.7, 126.1, 149.1, 150.6, 169.3; HRMS (EI) m/z calcd for $C_{13}H_{21}O_3N$ (M^+) 239.1521, found 239.1528.

***tert*-Butyl (2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-isobutyl-5-oxo-1-pyrrolidinecarboxylate (9).** To a stirred solution of **6** (150 mg, 0.627 mmol) in water/acetone/acetonitrile (1:1:1, 4.5 mL) were added NMO (147 mg, 1.25 mmol) and a catalytic amount of OsO_4 at rt, and the mixture was stirred for 32 h at rt. Saturated aq $Na_2S_2O_3$ was then added, and the resulting mixture was extracted with $CHCl_3$. The extract was successively washed with saturated aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 2:1−1:4) to give 99.7 mg (58%) of **9** as a white crystalline soild: mp 65−66 °C; $[\alpha]^{22}_D$ +18.0 (*c* 0.52, MeOH); IR ν_{max} 3430 (br s), 2957 (s), 1782 (s), 1719 (s); ^{1}H NMR δ 0.98 (3H, d, J = 6.5 Hz), 1.02 (3H, d, J = 6.5 Hz), 1.35 (1H, ddd, J = 13.5, 11.0, 4.5 Hz), 1.50−1.58 (1H, m), 1.54 (3H, s), 1.69−1.80 (1H, m), 2.77 (1H, br s), 3.11 (1H, br s), 4.11 (1H, dd, J = 11.5, 3.5 Hz), 4.21 (1H, d, J = 4.5 Hz), 4.39 (1H, d, J = 4.5 Hz); ^{13}C NMR δ 21.7, 23.5, 25.6, 28.0, 40.0, 61.6, 69.1, 71.0, 83.7, 149.4, 173.5; HRMS (EI) m/z calcd for $C_{13}H_{23}O_5N$ (M^+) 273.1576, found 273.1581.

***tert*-Butyl (3a*S*,6*S*,6a*S*)-Tetrahydro-6-isobutyl-2,2-dimethyl-4-oxo-5*H*-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylate (10).** To a stirred solution of **9** (64.3 mg, 0.235 mmol) in 2,2-dimethoxypropane (2.0 mL) was added TsOH·H_2O (4.5 mg, 0.024 mmol) at rt under N_2. After 50 min, the mixture was poured into saturated aq $NaHCO_3$ at 0 °C and extracted with Et_2O. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 1:0−4:1) to give 56.7 mg (88%) of **10** as a white crystalline solid: mp 57−58 °C; $[\alpha]^{22}_D$ +72.39 (*c* 1.42, $CHCl_3$); IR ν_{max} 2959 (s), 1788 (s), 1759 (s), 1719 (s) 1151 (s); ^{1}H NMR δ 0.99 (3H, d, J = 6.5 Hz), 1.03 (3H, d, J = 6.5 Hz), 1.26 (1H, ddd, J = 16.0, 9.5, 4.0 Hz), 1.38 (3H, s), 1.46 (3H, s), 1.55 (9H, s), 1.62 (1H, ddd, J = 13.5, 9.5, 2.8 Hz) 1.71−1.81 (1H, m), 4.18 (1H, dd, J = 11.0, 2.8 Hz) 4.38 (1H, d, J = 5.5 Hz), 4.66 (1H, d, J = 5.0 Hz); ^{13}C NMR δ 21.5, 23.5, 25.0, 25.7, 27.0, 27.9, 41.6, 58.8, 75.8, 83.5, 112.6, 149.4, 170.9; HRMS (FAB) m/z calcd for $C_{16}H_{28}O_5N$ ([M + H]$^+$) 314.1964, found 314.1967.

(4*S*,5*S*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-3-methylbutyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylic Acid (11). To a stirred solution of **10** (35.7 mg, 0.123 mmol) in THF/water (4:1, 2.5 mL) were added LiOH·H_2O (14.4 mg, 0.342 mmol) and a drop of 30% aq H_2O_2 at 0 °C. After 40 min, the mixture was quenched with 5% aq acetic acid and then extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **11** (37.7 mg), which was employed directly in the next step without further purification.

Amide 12. To a stirred solution of HBTU (43.2 mg, 0.114 mmol) and Et_3N (40 μL, 0.285 mmol) in CH_2Cl_2/DMF (10:3, 2.6 mL) were added a solution of **3**·HCl (ca. 0.095 mmol, see the Supporting Information) in CH_2Cl_2/DMF (2.5:1, 1.05 mL) and a solution of crude **11** (37.7 mg) in CH_2Cl_2/DMF (1.05 mL, 2.5:1) at −15 °C under Ar. After 5.5 h, the mixture was quenched with water and extracted with Et_2O. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 2:1) to give 32.7 mg (60%) of **12** as a white powder: mp 85−86 °C; $[\alpha]^{22}_D$ −72.6 (*c* 0.88, MeOH); IR ν_{max} 3360 (m), 2955 (m), 1702 (br s); ^{1}H NMR (acetone-d_6) δ 0.90 (3H, d, J = 6.5 Hz), 0.92 (3H, d, J = 7.0 Hz), 0.98 (6H, d, J = 7.0 Hz), 1.15−1.24 (1H, m), 1.35 (3H, s), 1.40 (9H, s), 1.52 (3H, s), 1.60 (1H, ddd, J = 13.5, 7.5, 5.5 Hz), 1.65−1.82 (4H, m), 2.85 (1H, dd, J = 16.0, 2.5 Hz), 2.97 (1H, dd, J = 16.0, 12.3 Hz), 3.88 (3H, s), 4.01−4.09 (1H, m), 4.29−4.37 (1H, m), 4.51 (1H, dd, J = 7.5, 4.0 Hz), 4.55 (1H, dd, J = 12.3, 2.0 Hz), 4.66 (1H, d, J = 7.5 Hz), 5.76 (1H, br s), 6.91 (1H, d, J = 7.5 Hz), 7.04 (1H, d, J = 8.5 Hz), 7.14 (1H, d, J = 10.0 Hz), 7.51 (1H, t, J = 8.0 Hz); ^{13}C NMR δ 23.1, 24.2, 24.7, 25.5, 26.2, 26.7, 26.8, 28.3, 30.0, 33.6, 40.5, 42.5, 50.9, 57.6, 78.2, 79.9, 80.7, 82.3, 111.1, 113.2, 115.9, 121.7, 136.6, 144.6, 162.7, 163.3, 171.8; HRMS (FAB) m/z calcd for $C_{31}H_{47}O_8N_2$ ([M − H]$^-$) 575.3332, found 575.3336.

PM-94128 (1). To a stirred solution of **12** (11.8 mg, 0.0205 mmol) in CH_2Cl_2 (2.0 mL) was added a solution of BBr_3 in CH_2Cl_2 (1.0 M, 307 μL, 0.307 mmol) at −78 °C under Ar. The mixture was gradually warmed to rt over 4 h. The reaction was quenched with saturated aq $NaHCO_3$ at 0 °C and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 ($CHCl_3$/MeOH, 40:1) to give 5.8 mg (67%) of **1** as a white powder: mp 160−161 °C; $[\alpha]^{22}_D$ −94.1 (*c* 0.195, $CHCl_3$); IR ν_{max} 3380 (br s), 2956 (s), 1672 (s); ^{1}H NMR δ 0.91 (3H, d, J = 6.0 Hz), 0.95 (3H, d, J = 6.5 Hz), 0.98 (6H, t, J = 7.0 Hz), 1.16 (1H, ddd, J = 14.0, 11.0, 4.0 Hz), 1.49 (1H, ddd, J = 13.5, 9.0, 5.0 Hz), 1.58−1.69 (1H, m), 1.70−1.80 (1H, m), 1.82−1.90 (2H, m), 2.83 (1H, dd, J = 16.3, 2.5 Hz), 2.94 (1H, ddd, J = 11.0, 8.5, 2.5 Hz), 3.09 (1H, dd, J = 16.3, 12.8 Hz), 3.25 (1H, t, J = 8.5 Hz), 4.08 (1H, d, J = 8.0 Hz), 4.36 (1H, ddd, J = 10.0, 9.5 4.5 Hz), 4.62 (1H, d, J = 12.8 Hz), 6.70 (1H, d, J = 7.0 Hz), 6.88 (1H, d, J = 9.0 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.43 (1H, d, J = 9.5 Hz); ^{13}C NMR δ 21.0, 21.9, 23.1, 23.5, 24.0, 24.8, 30.3, 40.5, 44.2, 48.6, 55.1, 73.6, 74.8, 81.0, 108.1, 116.2, 118.2, 136.5, 139.4, 162.1, 169.5, 175.3; HRMS (FAB) m/z calcd for $C_{22}H_{35}O_6N_2$ ([M + H]$^+$) 423.2495, found 423.2497.

Y-05460M-A (14):. white powder; mp 55−56 °C; $[\alpha]^{22}_{D}$ −63.5 (*c* 0.055, $CHCl_3$); IR ν_{max} 3385 (br s), 1677 (br s), 1462 (s); ^{1}H NMR δ 0.84 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 6.5 Hz), 0.98 (3H, d, J = 7.0 Hz), 1.42−1.74 (2H, m), 1.85 (1H, dd, J = 14.0, 10.5, 6.0 Hz), 2.32−2.41 (1H, m), 2.81 (1H, dd, J = 9.0, 2.8 Hz), 2.83 (1H, dd, J = 16.0, 2.5 Hz), 3.08 (1H, dd, J = 16.0, 13.5 Hz), 3.31 (1H, t, J = 9.0 Hz), 4.04 (1H, d, J = 8.5 Hz), 4.31−4.39 (1H, m), 4.63 (1H, d, J = 12.5 Hz), 6.70 (1H, d, J = 7.5 Hz), 6.84 (1H, d, J = 8.5 Hz), 7.41 (1H, d, J = 8.0 Hz), 10.84 (1H, br s); ^{13}C NMR δ 13.5, 19.3, 21.9, 23.0, 24.8, 27.0, 30.3, 40.4, 48.5, 61.3, 70.7, 74.8, 80.9, 108.1, 116.2, 118.2, 136.5, 139.4, 162.2, 169.5, 175.6; HRMS (EI) m/z calcd for $C_{21}H_{32}O_6N_2$ (M^+) 408.2260, found 408.2259.

Acknowledgment. We are grateful to Astellas Pharma, Inc., for providing the ^{1}H NMR spectrum of Y-05460M-A. This work was financially supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 19380065).

Supporting Information Available: Characterization data and NMR spectra for Y-05460M-A synthetic intermediates, experimental procedure for **3·HCl**, and comparison of NMR data among **14**, **14·HCl**, and natural Y-05460M-A. This material is available free of charge via the Internet at http://pubs.acs.org.