Convenient Synthesis of (3*S*,5*S*)-5-Hydroxy- and (3*R*,5*S*)-5-Chloropiperazic Acids of a Peptide Antibiotic, Monamycin G_3

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Convenient synthesis of (3*S*,5*S*)-5-hydroxy- and (3*R*,5*S*)-5-chloropiperazic acids, which are the important constituting moieties of an antibiotic monamycin G_3, and their possible stereoisomers constructing of similar antibiotics was achieved from D- and L-glutamic acids in short steps.

An antibiotic monamycin G_3 (**1**),[1] isolated from the culture of *Streptomyces jamaicensis*, has a unique cyclic depsihexapeptide structure containing two kinds of (3*S*,5*S*)-5-hydroxy (**2b**)- and (3*R*,5*S*)-5-chloropiperazic acid (**3c**) residues, as shown in Figure 1.

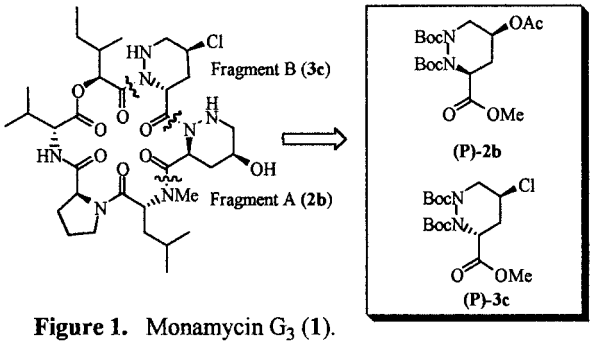
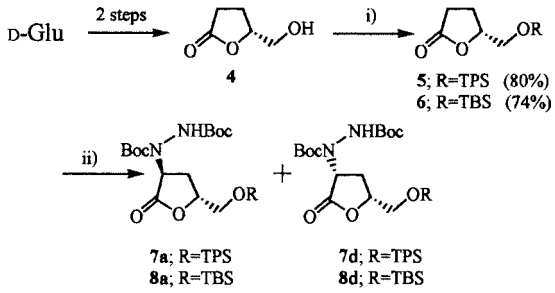


Figure 1. Monamycin G_3 (**1**).

So far, various synthetic methods for the protected 5-hydroxypiperazic acid [protected Fragment A: (**P**)-**2b**], except for the 5-chloro derivative [protected Fragment B: (**P**)-**3c**], have been already reported. However, the methods have required not only many steps but also the Evans chiral auxiliary group in the diastereoselective substitution of an appropriate substrate, derived from D-mannitol, D-glutamic acid (Glu) or 5-bromovaleryl chloride, with di-*tert*-butyl azodicarboxylate (DBAD).[2–4] Similarly to the above case, we (C. S.) have also reported the synthesis of (3*S*)- and (3*R*)-tetrahydropyridazic acid derivative by the reaction of dimethoxybutanoic acid with DBAD by the Evans method.[5]

In connection with the total synthesis of **1**, an efficient synthetic method for the important two constructing moeties, **2b** and **3c**, was investigated. Herein, we would like to report a convenient synthesis of the protected **2b** [(**P**)-**2b**], **3c** [(**P**)-**3c**], and their possible stereoisomers, (3*S*,5*R*)-**2a**, (3*R*,5*S*)-**2c**, (3*R*,5*R*)-**2d**, and (3*R*,5*R*)-**3d** derivatives from D- and L-Glu in short steps without using the Evans auxiliary group.

First of all, (*S*)-(–)-γ-hydroxymethyl-γ-butyrolactone (**4**)[6] as the starting material was prepared from D-Glu. Subsequent protection of the hydroxy group of **4** with *t*-butyldiphenylsilyl chloride (TPS–Cl) in the presence of imidazole gave the corresponding 5-(*O*-TPS)methyl derivative **5**. To introduce a 1,2-bis(*N*-Boc)hydrazino group (Boc = *t*-butoxycarbonyl) to the 2-position of **5**, usual lithiation with lithium diisopropylamide (LDA) in THF was followed by substitution with DBAD in CH_2Cl_2 at –78 °C. As a result, the expected (2*S*)-[1,2-bis(*N*-Boc)hydrazino]-(4*R*)-(*O*-TPS)methyl-γ-butyrolactone [(2*S*,4*R*)-**7a**][7] and a small amount of **7d** were obtained in 77% yield in a 93:7 ratio. The obtained (2*S*,4*R*)-**7a** could be completely purified on a silica-gel column using a mixture of hexane and EtOAc (4:1 v/v). On the other hand, in the case of smaller *O*-*t*-butyldimethylsiloxy(TBS) hydroxymethyl derivative **6**, the difference in the formation ratio between the obtained (2*S*,4*R*)-**8a** and (2*R*,4*R*)-**8d** appreciably decreased to 66:34. Accordingly, the diastereoselective substitution could be conformed to take place apparently by the effect of the steric hindrance of the bulky protecting group of the (*S*)-4-hydroxymethyl group, as shown in Scheme 1.

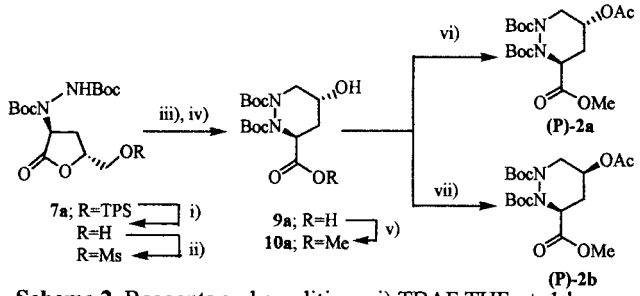


Scheme 1. Reagents and conditions: i) TPSCl or TBSCl, imidazole, $CHCl_3$, 0 °C, 30 min, rt, 6 h; ii) a) LDA , THF, –78 °C, 20 min, b) DBAD, CH_2Cl_2, –78 °C, 40 min.

Furthermore, deprotection of the TPS group of (2*S*,4*R*)-**7a** (R = TPS) with *t*-butylammonium fluoride (TBAF), followed by successive mesylation with methanesulfonyl chloride (MsCl), treatment with NaH and then hydrolysis with 1 M LiOH gave 1,2-bis(*N*-Boc)-(3*S*,5*R*)-5-hydroxypiperazic acid (**9a**). Subsequent esterification of **9a** with MeI in the presence of $KHCO_3$ gave the corresponding methyl ester (**10a**), the hydroxy group of which was then acetylated with acetic anhydride to give the corresponding (3*S*,5*R*)-5-*O*-acetyl derivative (**P**)-**2a**.[8] On the other hand, the inversion and acetylation of the 5-hydroxy group of **10a** with trifluoromethanesulfonic anhydride (Tf_2O) and 4-(dimethylamino)pyridine (DMAP) and then with CH_3COOCs in the presence of 18-crown-6-ether was performed to give the expected (3*S*,5*S*)-5-acetoxy derivative (**P**)-**2b**,[9] as shown in Scheme 2.

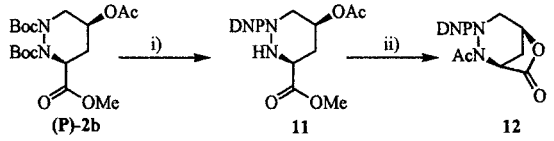
Quite similarly to the above case, the protected methyl (3*R*,5*S*)-5-hydroxypiperazinoate (**10c**) and its 5-acetoxy derivatives of two stereoisomers **(P)-2c** and **(P)-2d** were also readily synthesized from L-Glu.

To examine and determine the configurational structure of the synthesized **(P)-2b**, comparison was made with the (3*S*,5*S*)-2-acetyl-1-(2,4-dinitrophenyl)-5-hydroxypiperazic acid lactone **12**,[4] derived by reaction of the naturally occurring **2b** with 2,4-



Scheme 2. Reagents and conditions: i) TBAF,THF, rt, 1 h (80%); ii) MsCl, Et_3N, $CHCl_3$, 0 °C, 30 min, rt, 30 min (84%); iii) NaH, DMF, 0 °C, 30 min, rt, 1 h; iv) 1M LiOH, dioxane-H_2O, 0 °C, 10 min, rt, 20 min; v) MeI, $KHCO_3$, DMF, 0 °C, 30 min, rt, 6 h (3 steps 68%); vi) Ac_2O, pyridine, rt, 6 h (92%); vii) a)Tf_2O, DMAP, pyridine, 0 °C, 30 min, rt, 6 h, b) CH_3COOCs, 18-crown-6-ether , DMF, 0 °C, 30 min, rt, 8 h (68%).

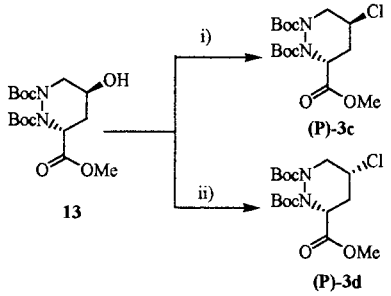
dinitrophenyl fluoride (DNP-F). That is, deprotection of the Boc group of (**P**)-**2b** with trifluoroacetic acid (TFA) and then *N*-arylation with DNP-F in the presence of Et_3N gave the corresponding 1-(*N*-DNP) piperazine derivative **11**. Subsequent lactone ring formation by the hydrolyses of both the methyl ester and acetoxy group of **11** with 1 M LiOH and then again acetylation with Ac_2O gave the expected **12**,[10] as shown in Scheme 3.



Scheme 3. Reagents and conditions: i) a) TFA, $CHCl_3$, rt, 30 min, b) DNPF, Et_3N, $CHCl_3$; ii) a) 1M LiOH, MeOH, b) Ac_2O.

As a result, the spectral data (IR and ^{1}H NMR) and the specific rotation of the synthesized **12** {$[\alpha]_D$ +380° (*c* 0.09, dioxane)} were completely identical with those {$[\alpha]_D$ +380° (*c* 0.06, dioxane)} derived from the natural product **2b**.[1c]

Furthermore, another important constructing component, (3*R*,5*S*)-5-chloropiperazic acid (**P**)-**3c**,[11] was also readily synthesized by substitution of the hydroxy group of **13**, which was derived from **10c**, with *N*-chlorosuccinimide (NCS) and Ph_3P in CH_2Cl_2.[12] On the other hand, (3*R*,5*R*)-5-chloro derivative (**P**)-**3d**[13] was also obtained by S_N2 reaction of **13** with Ph_3P in a mixture of CCl_4 and MeCN, by the method reported by Hale,[2] as shown in Scheme 4.



Scheme 4. Reagents and condition: i)Ph_3P, NCS, CH_2Cl_2, 0 °C, 30 min, rt, 6 h (55 %); ii) Ph_3P, CCl_4, MeCN, 0 °C, 30 min, rt, 6 h (79%).

In conclusion, it is noteworthy that a convenient synthesis of the possible stereoisomers of 5-hydroxy- and 5-chloropiperazic acids was achieved in short steps by the new method and this synthetic method is applicable to the synthesis of various similar 5-substituted derivatives.

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References and Notes

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7 **(3*S*,5*R*)-7a**: Colorless crystals. Mp 58.0–59.5 °C. $[\alpha]_D^{26}$ –25.6° (*c* 1.00, MeOH). IR(KBr) 3403, 2976, 2933, 2361, 1785, 1716 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 1.07(s, 9H, TPS's *t*-Bu), 1.46 and 1.47(each s, 18H, Boc × 2), 2.45–2.62 (m, 2H, H-4), 3.65 and 3.87 (each dd, 2H, H-6, *J* = 3.0, 11.5 Hz), 4.58 (d, 1H, H-5, *J* = 8.5 Hz), 5.14 (br s, 1H, H-3), 6.50 (br s, 1H, NH), 7.34–7.44 and 7.59–7.70 (each m, 10H, TPS's Ph × 2).

8 **(P)-2a**: Colorless needles. Mp 100.0–103.0 °C. $[\alpha]_D^{26}$ +11.4° (*c* 1.06, MeOH). IR(KBr) 3445, 2977, 2930, 1692 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 1.52 (s, 18H, Boc × 2), 1.99 (s, 3H, Ac) , 2.03–2.14 (m, 1H, H-4 ax), 2.40 (dd, 1H, H-4 eq, *J* = 1.4, 14.6 Hz), 3.08–3.10 (m, 1H, H-6 ax), 3.76 (s, 3H, Me), 4.19 (br d, 1H, H-6 eq, *J* = 13.8 Hz), 4.89 (br s, 1H, H-5), 4.96 (d, 1H, H-3, *J* = 6.8 Hz).

9 **(P)-2b**: Colorless needles. Mp 96.0–98.5 °C. $[\alpha]_D^{26}$ –5.9° (*c* 1.08, MeOH). IR(KBr) 3444, 2981, 2360, 1739, 1713, 1648, 1539 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 1.32 and 1.39 (each s, 18H, Boc × 2), 1.81 (s, 3H, Ac), 1.99 (ddd, 1H, H-4 eq, *J* = 3.0, 6.5, 14.8 Hz), 2.26 (br d,1H, H-4 ax, *J* = 14.5 Hz), 2.91 and 3.05 (each d, 1H, H-6 ax, *J* = each 14.5 Hz), 3.60 (s, 3H, OMe), 3.97–4.05 (m, 1H, H-6 eq), 4.67–4.85 (m, 2H, H-3 and H-5).

10 **12**: Yellow syrup. $[\alpha]_D^{20}$ +380° (*c* 0.09, dioxane). ^{1}H NMR δ = 2.14 (s, 3H, Ac), 2.26 (d, 1H, H-4 ax, *J* = 12.4 Hz), 2.46–2.54 (m, 1H, H-4 eq), 3.16 (dd, 1H, H-6 eq, *J* = 3.2, 13.5 Hz), 3.83 (d, 1H, H-6 eq, *J* = 13.2 Hz), 5.00 (t, 1H, H-5, *J* = 4.3 Hz), 5.20 (d, 1H, H-3, *J* = 3.5 Hz), 7.55 (d, 1H, DNP's Ph-6, *J* = 9.7 Hz), 8.34 (dd, 1H, DNP's Ph-5, *J* = 2.7, 9.7 Hz), 8.77 (d, 1H, DNP's Ph-4, *J* = 2.7 Hz).

11 **(P)-3c**: Colorless syrup. $[\alpha]_D^{26}$–29.3° (*c* 0.14, MeOH). IR(KBr) 2979, 2932, 2361, 1738, 1709 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 1.40 and 1.45 (each s, 18H, Boc × 2), 1.89 (ddd, 1H, H-4 ax, *J* = 5.9, 10.7, 13.8 Hz), 2.44 (br s, 1H, H-4 eq), 2.88 (dd, 1H, H-6 ax, *J* = 9.9, 12.6 Hz), 3.68 (s, 3H, OMe), 4.31 (ddd, 1H, H-6 eq, *J* = 3.5, 5.7, 10.3 Hz), 4.41 (dt, 1H, H-5, *J* = 5.7, 10.3 Hz), 5.00 (dd, 1H, H-3, *J* = 2.7, 5.9 Hz).

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13 **(P)-3d**: Colorless syrup. $[\alpha]_D^{26}$ –47.0° (*c* 0.99, MeOH). IR(KBr) 2979, 2932, 2361, 1738, 1709 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 1.39 and 1.44 (each s, 18H, Boc × 2), 1.88 (ddd, 1H, H-4 ax, *J* = 6.0, 11.0, 13.5 Hz), 2.44 (br d, 1H, H-4 eq, *J* = 13. 5Hz), 2.87 (t, 1H, H-6 ax, *J* = 11.0 Hz), 3.67 (s, 3H, OMe), 4.30 (dd, 1H, H-6 eq, *J* = 4.5, 12.8 Hz), 4.40 (ddd, 1H, H-5, *J* = 4.5, 11.0, 15.4 Hz), 4.99 (d, 1H, H-3, *J* = 3.5 Hz).