Convenient Synthesis of a Central 2,3,6-Trisubstituted Pyridine Skeleton of a Macrobicyclic Antibiotic, Cyclothiazomycin

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The first convenient synthesis of the main central 2,3,6-trisubstituted pyridine skeleton [protected Fragment A-B] of a macrobicyclic antibiotic, cyclothiazomycin, was achieved.

Cyclothiazomycin (**1**),[1] isolated from the culture of *Streptomyces NR0516*, is a macrobicyclic antibiotic and features a unique structure. The main pyridine skeleton [Fragment A-B: **2**] is composed of a central 2,3,6-trisubstituted pyridine skeleton [Fragment B: **4**] and a bithiazolylthiazoline segment [Fragment A: **3**], as shown in Figure 1. Recently, we have reported a novel synthesis of an *N*-protected 2-[2-(1-aminoethenyl)bithiazolyl]thiazoline-4-carboxylate derivative [protected Fragment A: (**P**)-**3**].[2,3]

In connection with the total synthesis of **1**, herein we wish to report a convenient synthesis of the main central pyridine skeleton [protected Fragment A-B: (**P**)-**2**].

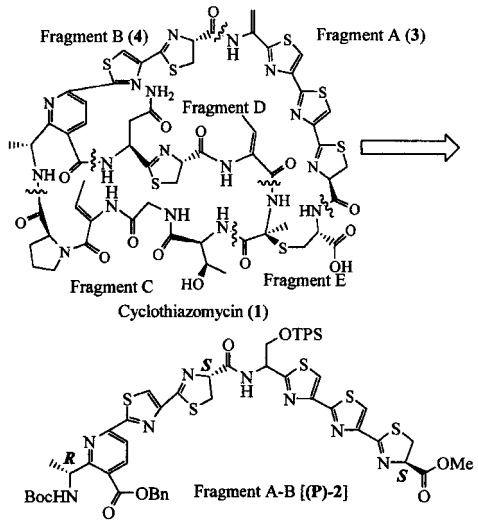
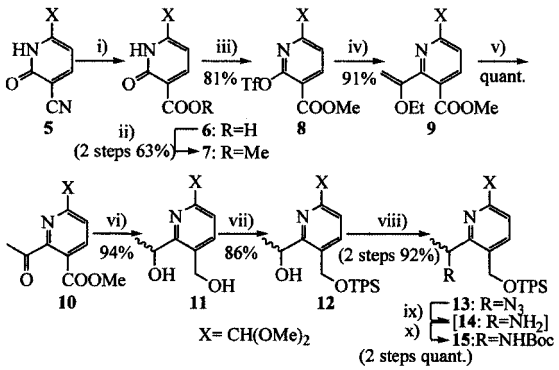


Figure 1. Retrosynthesis of **1**.

First of all, to synthesize the Fragment B derivative, 3-cyano-6-(dimethoxymethyl)-2-pyridone (**5**)[4] was converted to the corresponding 3-methyl ester **7** via the 3-carboxylic acid **6**. Triflation of **7** with triflic anhydride (Tf_2O) gave the 2-trifloxypyridine derivative **8**, the TfO group of which was then treated with ethyl vinyl ether in the presence of $Pd(OAc)_2$ and dppp[5] to give the 2-(ethoxyvinyl)pyridine derivative **9**. Conversion of the ethoxyvinyl group to an acetyl group by using 70% AcOH, followed by simultaneous reduction of both the acetyl and methoxycarbonyl groups with $NaBH_4$ in the presence of $CaCl_2$ gave the 2-(1-hydroxyethyl)-3-(hydroxymethyl)pyridine derivative **11** as a racemate. Subsequent protection of the primary alcohol with *t*-butyldiphenylsilyl chloride (TPSCl) gave the 3-(TPSO-methyl)pyridine derivative **12**, and then the secondary alcohol was azided with mesyl chloride (MsCl) and NaN_3 to give the 2-(1-azidoethyl)pyridine derivative **13**. Hydrogenolysis of the azido group with 10% Pd-C/H_2 gave the 2-(1-aminoethyl)pyridine derivative **14**, the amino group of which was protected with Boc_2O to give the expected 2-[1-(*N*-Boc)aminoethyl]pyridine derivative **15**, as shown in Scheme 1.

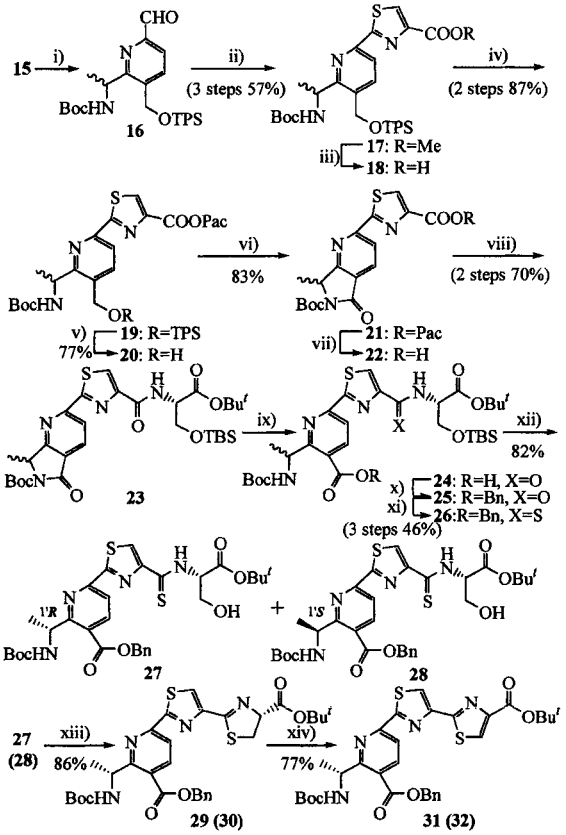


Scheme 1. Reagents: i) 6 M KOH, EtOH, ii) H^+, MeOH, iii) Tf_2O, DMAP, pyridine, iv) $Pd(OAc)_2$, dppp, Ethyl vinyl ether, Et_3N, toluene, v) 70% AcOH, THF, vi) $NaBH_4$, $CaCl_2$, EtOH, vii) TPSCl, Et_3N, DMAP, $CHCl_3$, viii) a) MsCl, Et_3N, CH_2Cl_2, b) NaN_3, DMF, ix) H_2, 10% Pd-C, EtOH, x) Boc_2O, Et_3N, $CHCl_3$.

Furthermore, hydrolysis of the 6-acetal group of **15** with 2 M HCl, followed by thiazolation of the formed 6-formylpyridine derivative **16** with H-L-Cys-OMe and then oxidation with MnO_2 by the Shioiri method[6] gave the (pyridin-6-yl)thiazole-4-carboxylate **17**. After hydrolysis of the methyl ester with 1 M LiOH, the obtained free acid **18** was esterified again with phenacyl bromide (PacBr) to give the Pac ester **19**. Deprotection of the TPS group by using tetrabutylammonium fluoride (TBAF), followed by oxidation with the Jones reagent gave the corresponding lactam derivative **21**. After hydrolysis of the Pac ester with K_2CO_3 aq solution, coupling with H-L-Ser(TBS)-OBu^t (TBS=*t*-butyldimethylsilyl) by the diphenylphosphinic azide (DPPA) method gave the dipeptide derivative **23** as a diastereomeric mixture. Then, ring cleavage of the lactam with 1 M LiOH gave the 3-carboxylic acid **24**, which was esterified with BnBr and then thioamidated with Lawesson's reagent to give the expected thiocarbonyl derivative **26**. Subsequently, after deprotection of the TBS group of **26** with 2 M HCl, separation of the obtained mixture on a silica-gel column using a mixture of $CHCl_3$ and acetone (50 : 1 v/v) gave each diastereomer **27** and **28**. Thiazolination of the two isomers with the Mitsunobu reagent gave the corresponding (pyridin-6-yl)thiazolylthiazoline derivatives **29**[7] and **30** respectively. In order to examine whether **29** and **30** are diastereomers or not, further oxidation of the thiazoline ring with TBAF gave the corresponding bithiazole derivatives **31** and **32** respectively, as

shown in Scheme 2. As a result, it was found that the physical (IR and ^{1}H NMR) and chemical constants (mp and elemental analysis) were completely identical, but the signs of the specific rotation were reversed. These facts clearly indicate that the compounds **29** and **30** as well as **27** and **28** are diastereomeric isomers; further, **31** and **32** are enantiomer to each other.

Furthermore, in order to determine the configuration of the 2-(1-aminoethyl) group of the synthetic **29** and **30**, (*R*)- and (*S*)-configurational 2-(1-aminoethyl)pyridines **36** were synthesized, and the CD spectra of **36** were compared with those of **29** and **30**.

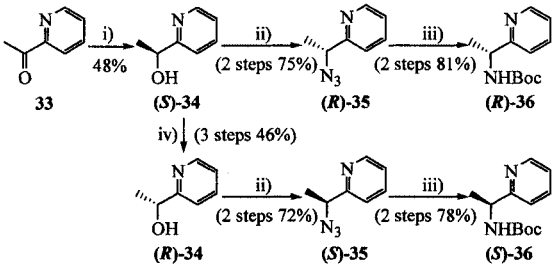


Scheme 2. Reagents: i) 2 M HCl, THF, ii) a) HCl·H-Cys-OMe, Et_3N, toluene, b) MnO_2, toluene, iii) 1 M LiOH, H_2O-dioxane (1:1 v/v), iv) PacBr, Et_3N, DMF, v) TBAF, THF, vi) Jones reagent, acetone, vii) K_2CO_3, THF, H_2O, viii) H-Ser(TBS)-OBu^t, DPPA, Et_3N, DMF, ix) 1 M LiOH, THF, H_2O, x) BnBr, Et_3N, DMF, xi) Lawesson's reagent, DME, xii) 2 M HCl, THF, xiii) Ph_3P, DEAD, THF, xiv) MnO_2, toluene.

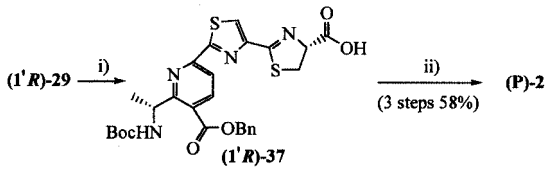
Asymmetric reduction of 2-acetylpyridine (**33**) with Baker's Yeast gave (*S*)-2-(1-hydroxyethyl)pyridine **34**, which was converted to (1'*R*)-2-[1-(*N*-Boc)aminoethyl]pyridine **36** via (1'*R*)-(1-azidoethyl)pyridine **35**. The specific rotation value of **34** thus obtained was $[\alpha]_D^{26}$ –55.5° (*c* 1.6, EtOH) {lit.[8] $[\alpha]_D$ –55.5° (*c* 1.5, EtOH)}, showing high optical purity (96% ee). Similarly, (*S*)-**36** was also obtained from (*S*)-**34** via successive (*R*)-**34** and (*S*)-**35**, as shown in Scheme 3.

The CD spectra of optically active **29** and (*R*)-**36** showed strong negative Cotton effects at 373 and 270 nm, respectively, while those of **30** and (*S*)-**36** showed positive Cotton effects in the same region. Therefore, it could be determined that the absolute structure of **29** was (*R*,*S*)-configuration and identical with that of the natural **1**.

Finally, hydrolysis of the *t*-butyl ester of (1'*R*)-**29** with TFA, accompanying deprotection of the Boc group, followed by protection once more with Boc_2O gave the corresponding free acid derivative (1'*R*)-**37**, which was then coupled with the indepenedently prepared precursor of (**P**)-**3**[3] by the BOP method to give first the protected Fragment A-B derivative **(P)-2**.[9]



Scheme 3. Reagents: i) Baker's Yeast, D-Glucose, H_2O, ii) a) MsCl, Et_3N, $CHCl_3$, b) NaN_3, DMF, iii) a) H_2, 10% Pd-C, EtOH, b) Boc_2O, Et_3N, $CHCl_3$, iv) a) MsCl, Et_3N, $CHCl_3$, b) NaOAc, 15-Crown-5-ether, DMF, c) K_2CO_3, MeOH, H_2O.



Scheme 4. Reagents: i) a) TFA-$CHCl_3$ (3:2 v/v), b) Boc_2O, Et_3N, $CHCl_3$, ii) **(P)-3**, BOP, (*i*-Pr)$_2$NEt, DMF.

In conclusion, a convenient synthetic method for the main central 2,3,6-trisubstituted pyridine skeleton of **1** has been sufficiently developed.

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References and Notes

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5 dppp = 1,3-bis(diphenylphosphino)propane.
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7 **29:** Colorless syrup. $[\alpha]_D^{26}$ –50.9°(*c* 0.7, $CHCl_3$). IR 3435, 3113, 2977, 2931, 2360, 1719, 1606, 1583 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 1.43 (s, 9H, Boc), 1.46 (d, 3H, C*H*$_3$CH, *J* = 6.3 Hz), 1.53 (s, 9H, Bu^t), 3.63 (d, 2H, C*H*$_2$SCH, *J* = 9.2 Hz), 5.22 (t, 1H, CHN=C, *J* = 9.2 Hz), 5.39 (s, 2H, PhC*H*$_2$), 5.62–5.89 (m, 2H, C*H*NH), 7.34–7.49 (m, 5H, Ph), 8.17 (s, 1H, pyridine ring-H, *J* = 8.3 Hz), 8.20 (s, 1H, thiazole ring-H), 8.34 (d, 1H, pyridine ring-H, *J* = 8.3 Hz).
8 M. Takeshita, K. Terada, N. Akutsu, S. Yoshida, and T. Sato, *Heterocycles*, **26**, 3051 (1987).
9 **(P)-2**: Colorless syrup. $[\alpha]_D^{22}$ +11.1°(*c* 0.3, $CHCl_3$). IR 3389, 2929, 2333, 1715, 1684, 1582, 1489, 1438 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 0.93 and 0.95 (each s, 9H, TPS's Bu^t), 1.29–1.65 (m, 12H, Boc, C*H*$_3$CH), 3.62–3.85 (m, 4H, thiazoline's CH$_2$ × 2), 3.86 (s, 3H, OMe), 3.94–4.14 (m, 2H, CH$_2$O), 4.32–4.40 (m, 1H, C*H*CH$_2$O), 5.28–5.39 (m, 2H, thiazoline's CH × 2), 5.40 (s, 2H, Bn's CH$_2$), 5.46–5.54 (m, 1H, CONH), 5.63–5.85 (m, 2H, BocNH, CH$_3$C*H*), 7.20–7.60 (m, 15H, TPS's Ph × 2, Bn's Ph), 7.98–8.10 (m, 3H, thiazole ring-H × 3), 8.15–8.34 (each d, 2H, pyridine ring-H, *J* = 7.5 Hz).