Asymmetric Synthesis of the Main Pyridine Skeleton for a Macrobicyclic Antibiotic, Cyclothiazomycin

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Stoichiometric asymmetric reduction of the ketone group of a 2-acetyl-3,6-disubstituted pyridine derivative with an oxazaborolidine and *N*-ethyl-*N*-isopropyl aniline-borane complex gave the corresponding (*S*)-lactone derivative **5** in 96% ee almost quantitatively. Hydrogenolytic cleavage of **5** gave the expected (*S*)-2-(1-hydroxyethyl)pyridine derivative.

An antibiotic cyclothiazomycin (**1**),[1] isolated from the culture of *Streptomyces* NR0516, is a unique macrobicyclic peptide comprising five fragments. The main central pyridine skeleton called Fragment B features a 3,6-disubstituted (*R*)-2-(1-aminoethyl)pyridine derivative **2**. Recently, we have reported the convenient synthesis of most of the Fragments and their fragment condensations.[2–4] However, the enantioselective formation of **2** has been unsuccessful up to now, although the racemic (*RS*)-**2** has been synthesized and the configurational structure of each optical isomer separated could be confirmed.[3,4]

In connection with the total synthesis of **1**, herein we wish to report a facile asymmetric synthesis of (*S*)-6-dimethoxymethyl-2-(1-hydroxyethyl)-3-hydroxymethyl pyridine (**6**) as the important precursor of **2**.

So far, a number of stoichiometric and catalytic asymmetric reductions of the ketone group of acylbenzene and acylpyridine derivatives by using various oxazaborolidines have been reported.[5] By utilizing boron-based reducing agents, the asymmetric reduction of the ketone group of methyl 2-acetyl-6-(dimethoxymethyl)nicotinate (**3**), derived from 6-(dimethoxymethyl)-2(1*H*)-oxopyridine-3-carbonitrile,[3,4] was successfully accomplished as follows.

First, according to the method of Itsuno et al,[6] attempts to reduce **3** with (*S*)-(−)-2-amino-3-methyl-1,1-diphenyl-1-butanol as an asymmetric reagent and BH_3SMe_2 as a reductant at −20 °C gave (*S*)-2-(dimethoxymethyl)-7-methylfuro[3,4-b]-pyrid-5(7*H*)-one (**5**) with very low ee's (about 8% ee). On the other hand, similar reduction of **3** by using (*R*)-3a,4,5,6-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborole (MeCBS)[7] and BH_3SMe_2 was also carried out to give **5** in moderate ee's,[8] as summarized in Table 1. Eventually, similar stoichiometric reduction of **3** with MeCBS (1.5 molar amount) and trihydro(*N*-ethyl-*N*-isopropylamine)boron (BACH-EI) (2.0 molar amount), instead of BH_3SMe_2, proceeded smoothly to afford **5** in 96% yield and in 96% ee, by the method of Cho et al,[9] as summarized in Table 2. First, the methyl (*S*)-2-(1-hydroxyethyl)nicotinate derivative **4** formed as an unstable intermediate, and then immediately intramolecular cyclization occurred to yield the lactone ring, as shown in Scheme 1.

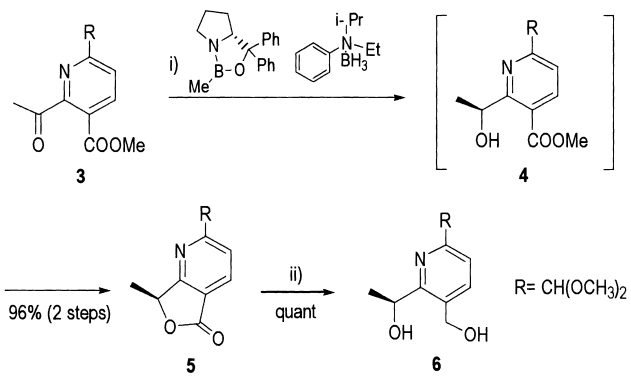
Table 1. Hydrogenation of **3** with MeCBS and BH_3SMe_2 (2.0 molar amt.) in THF for 1 h

Entry	Temp/°C	MeCBS (molar amt.)	Yield/%	ee/%
1	rt	1.5	77	54
2	rt	2.0	51	10
3	−20	1.5	62	58
4	−78	1.5	76	72

Table 2. Hydrogenation of **3** with MeCBS and BACH-EI (2.0 molar amt.) in THF for 1 h

Entry	Temp/°C	MeCBS (molar amt.)	Yield/%	ee/%
1	rt	1.0	61	26
2	rt	1.5	65	62
3	rt	2.0	98	16
4	−20	1.0	98	84
5	−20	1.5	96	96
6	−20	2.0	66	78
7	−78	1.0	85	60
8	−78	1.5	61	84
9	−78	2.0	95	30

Next, to determine the configurational structure of **5**, hydrogenolytic cleavage of the lactone ring with $NaBH_4$ in the presence of $CaCl_2$ gave the corresponding diol derivative **6**. Similarly to the case of the (*RS*)-racemate **2**,[3,4] the secondary alcohol of **6** was converted to the corresponding (*R*)-aminoethyl derivative in three steps. The obtained **2** was completely identical with the authentic sample prepared previously.[4] Conse-



Scheme 1. Reagents and conditions: i) (*R*)-2-Methyl-CBS-oxazaborolidine, BACH-EI, THF, −20 °C, 1 h, ii) $NaBH_4$, $CaCl_2$, EtOH, 0 °C, 30 min, rt, 2 h.

quently, the configurational structure of **5** could be confirmed to be the (*S*)-optical isomer.

In conclusion, a convenient asymmetric synthesis of the main central 2,3,6-trisubstituted pyridine skeleton of **1** has been sufficiently developed. Accordingly, the steps of the total synthesis will be considerably shortened.

Experimental

The IR spectra were recorded using a Hitachi EPI-G2 spectrometer in KBr. The ^{1}H NMR spectra were measured with a JEOL JNE 500 spectrometer in $CDCl_3$ solution with tetramethylsilane used as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH. High-pressure liquid chromatography (HPLC) analyses and separations were done on the following column using a mixture of hexane and isopropyl alcohol (1:9 v/v) with a flow rate of 0.25 mL min^{-1} by detecting UV (254 nm) absorption: Daicel Chemical Industries, Ltd., chiral cell OD (0.46 cm ID × 25 cm).

(*S*)-2-(Dimethoxymethyl)-7-methylfuro[3,4-b]pyrid-5(7*H*)-one (5). To a solution of MeCBS (0.40 mL, 0.40 mmol) in THF (4 mL) was added, with stirring, a solution of BACH-EI (0.27 mL, 0.52 mmol) under Ar stream at room temperature for 1 h. To the resulting solution was added a solution of **3** (6.70 mg, 0.26 mmol) in THF (2.0 mL) over a period of 1 h using a syringe pump at −20 °C. After the addition, the reaction mixture was further stirred for 1 h and then quenched with saturated NH_4Cl aqueous solution (20 mL). Concentration in vacuo gave a crude syrup, which was extracted with toluene (20 mL). The extract was washed with brine (10 mL × 3) and then dried over anhydrous Na_2SO_4. An additional concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give a residual syrup. Finally, the syrup obtained was further purified by HPLC to give **6** as a colorless syrup. Yield 96%. 96% ee. $[\alpha]_D^{26}$ −10.0° (*c* 0.98, $CHCl_3$). IR 3424, 2944, 1767, 1599 cm^{-1}. ^{1}H NMR δ 1.72 (d, 3H, CHC*H*$_3$, J = 6.0 Hz), 3.43 and 3.48 (each s, 6H, CH(OC*H*$_3$)$_2$), 5.46 (s, 1H, C*H*(OCH$_3$)$_2$), 5.59 (q, 1H, C*H*CH$_3$, J = 6.6 Hz), 7.76 (d, 1H, pyridine's H, J = 8.0 Hz), 8.22 (d, 1H, pyridine's H, J = 8.0 Hz). Found: C, 59.35; H, 5.98; N, 6.57%. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27%.

(*S*)-6-Dimethoxymethyl-2-(1-hydroxyethyl)-3-hydroxymethylpyridine (6). To a solution of **5** (380 mg, 1.70 mmol) in EtOH (20 mL) were added, with stirring, $NaBH_4$ (130 mg, 3.40 mmol) and $CaCl_2$ (380 mg, 3.40 mmol) at 0 °C for 30 min. After stirring for 2 h at room temperature, to the reaction mixture was added saturated NH_4Cl aqueous solution (20 mL). The resulting solution was concentrated in vacuo to give a residual syrup, which was extracted with EtOAc (10 mL × 3); then the combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using EtOAc to give **6** as a colorless syrup. Yield 98%. $[\alpha]_D^{26}$ −11.1° (*c* 0.98, $CHCl_3$). IR 3384, 2935, 1579 cm^{-1}. ^{1}H NMR δ 2.69 (d, 3H, CHC*H*$_3$, J = 6.4 Hz), 3.38 and 3.40 (each s, 6H, CH(OC*H*$_3$)$_2$), 3.43–3.46 (m, 1H, OH), 4.68 (s, 2H, CH$_2$), 4.81–5.00 (m, 2H, CHOH), 5.34 (s, 1H, C*H*(OCH$_3$)$_2$), 7.46 (d, 1H, pyrdine's H, J = 7.8 Hz), 7.80 (d, 1H, pyridine's H, J = 7.8 Hz). Found: C, 57.94; H, 7.98; N, 6.24%. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16%.

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