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The stereoselective synthesis of α-substituted β-amino secondary alcohols based on the proline-mediated, asymmetric, three-component Mannich reaction and its application to the formal total synthesis of nikkomycins B and B_x

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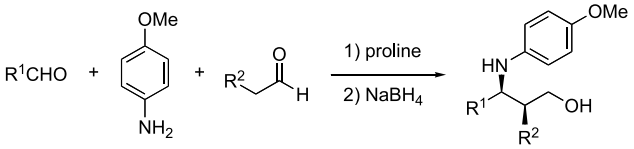
Abstract—A general method for the asymmetric synthesis of α-substituted β-amino secondary alcohols is described, which comprises the four-reaction sequence (1) the proline-mediated, asymmetric, three-component Mannich reaction of two different aldehydes, (2) nucleophilic carbon addition to aldehyde, (3) oxidation of the resulting alcohol to the corresponding ketone, and (4) diastereoselective reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ or catecholborane. The former reductant afforded the 1,2-*syn* isomer, while the latter gave the 1,2-*anti* isomer stereoselectively. The present method was successfully applied to the efficient asymmetric synthesis of the N-terminal amino acid moiety of nikkomycin B and B_X.

1. Introduction

β-Amino alcohols are not only found in many natural products[1] and potent drugs,[2] but are also used as a component of ligands in asymmetric catalysts.[3] In spite of this synthetic utility, there are few methods for their asymmetric synthesis, which remains a considerable challenge.[4] Recently, Ellman and co-workers reported an asymmetric synthesis of both *syn* and *anti* β-amino alcohols based on the diastereoselective reactions of metallo-enamines derived from chiral *N*-sulfinyl imines, followed by the diastereoselective reduction, for which an equimolar amount of the chiral auxiliary is necessary.[4d] The development of a general and practical method for the synthesis of chiral β-amino alcohols based on catalytic asymmetric reactions is an important goal.

List reported a proline-mediated asymmetric Mannich reaction in 2000,[5] after which organocatalyst-mediated asymmetric Mannich reactions have been investigated by several research groups.[6] Our group have applied high-pressure induced by water freezing to the proline-mediated Mannich reaction, widening the generality of the reaction.[7] During the application of the high pressure to other proline-mediated reactions, we have discovered a proline-mediated, one-pot, three-component, cross-Mannich reaction involving two different aldehydes and *p*-anisidine proceeding at ambient pressure.[8] That is, in the presence of proline an aldehyde and anisidine react to give the corresponding imine, which reacts with a second, different aldehyde, affording an α-substituted β-amino aldehyde. As this β-aminoaldehyde is unstable, it is reduced immediately to give an α-substituted β-amino primary alcohol in good yield with excellent *syn* selectivity and enantioselectivity (Eq. 1). The similar Mannich reaction has been reported also by Barbas'[6i] and Cordova's[6k,u] groups, independently. The α-substituted β-amino aldehyde that was generated is a versatile synthetic intermediate, which can be further transformed to give the corresponding α-substituted β-amino secondary alcohols with a generation of a new chiral center by formation of a carbon–carbon bond. The utility of the present method is further demonstrated by an efficient formal asymmetric total synthesis of nikkomycin, which is also described in this full paper.



(1)

Keywords: Proline; Mannich reaction; Asymmetric synthesis; Nikkomycin; Three-component reaction.
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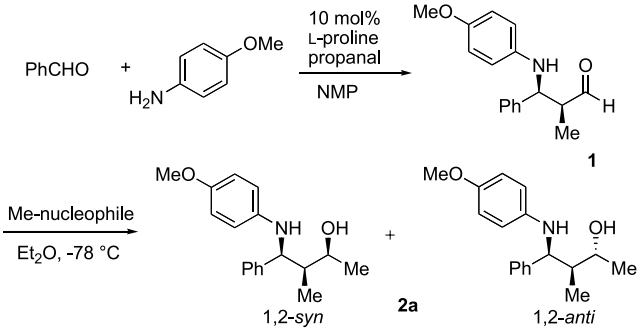
2. Results and discussion

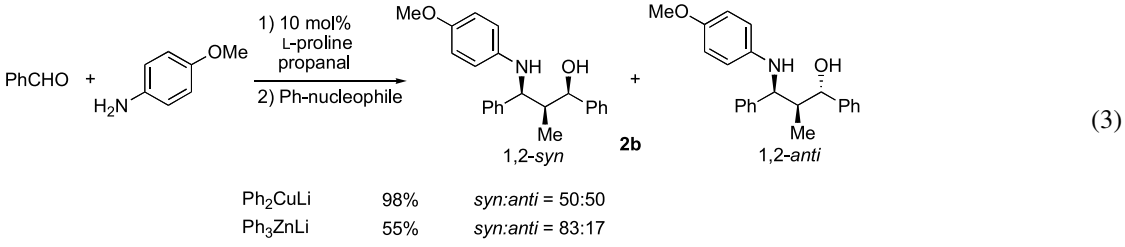
We have reported the proline-mediated, three component coupling Mannich reaction of benzaldehyde, propanal, and anisidine to afford an unstable, α-substituted β-amino aldehyde, which was reduced to an α-substituted β-amino primary alcohol with $NaBH_4$ in 90% yield with high *syn* selectivity and excellent enantioselectivity (Eq. 1, $R^1=Ph$, $R^2=Me$, *syn*/*anti* = >95:5, 98% ee).[8] This result indicates that the β-amino aldehyde is generated as intermediate in very high optical purity. By employing an organo-metallic nucleophile instead of $NaBH_4$, a β-amino secondary alcohol would be prepared, generating a new chiral center. With this scenario in mind, in a preliminary trial we examined the introduction of a methyl group, using MeMgI as nucleophile (Eq. 2). The reaction was performed as follows: the crude β-amino aldehyde generated as above was treated with MeMgI in Et_2O at −78 °C for 4 h, generating 4-amino-butan-2-ol derivative **2a** in 30% yield, as a 1:1 mixture of *syn* and *anti* isomers (Table 1, entry 1). As both the yield and diastereoselectivity of this reaction were insufficient, other organometallic reagents were examined, with the results summarized in Table 1.



(2)

Though the moderate yields were obtained in the cases of MeLi and $MeTi(O\text{-}i\text{-}Pr)_3$,[9] diastereoselectivity was low (entries 2 and 3). The *anti* isomer was obtained predominantly in good yield in the case of Me_2CuLi[10] (entry 4), while the *syn* isomer was generated predominantly in the reactions of $MeCeCl_2$[11] and Me_4AlLi[12] (entries 5 and 6). When Me_3ZnLi[13] was used, the *syn* isomer was generated selectively (83:17) in good yield (entry 7). Thus either *anti* or *syn* isomers could be selectively synthesized by the proper choice of metal. Namely, Me_2CuLi gave *anti* isomer, and Me_3ZnLi afforded *syn* isomer predominantly, though the selectivities were only moderate.

However, in spite of the successful results using methyl nucleophiles, aryl nucleophiles such as phenyl metal reagents gave disappointing results (Eq. 3). Though the *syn* isomer predominated with Ph_3ZnLi, the use of Ph_2CuLi gave equal amounts of *syn* and *anti* isomers. As *anti*-selective introduction of the aryl group had not proved successful, a new general method for the stereoselective formation of *syn* and *anti* β-amino secondary alcohol was investigated. Thus, the two-step protocol of oxidation followed by stereoselective reduction was investigated, for which phenyl-substituted β-amino alcohol **2b** was selected as a model.



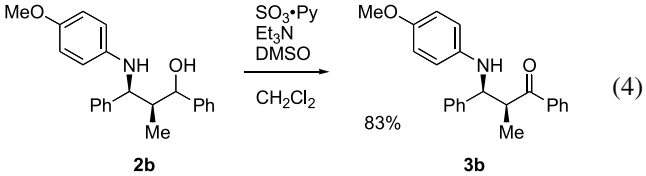
(3)

Table 1. The effect of reagent on diastereoselectivity[a]

Entry	Reagent	Time (h)	Yield (%)[b]	*Syn*:*anti*[c]
1	MeMgI	4	30	50:50
2	MeLi	4	52	33:67
3[d]	$MeTi(O\text{-}i\text{-}Pr)_3$	18	60	33:67
4	Me_2CuLi	4	83	25:75
5[e]	$MeCeCl_2$	4	77	67:33
6	Me_4AlLi	4	71	67:33
7	Me_3ZnLi	4	82	83:17

[a] The reaction was performed at −78 °C in Et_2O, unless otherwise noted.
[b] Isolated yield.
[c] The diastereomeric ratio was determined by ^1H NMR.
[d] The reaction was performed at −20 °C.
[e] THF was used as solvent.

Oxidation of **2b** was successfully carried out using $SO_3\cdot$pyridine[14] to afford β-amino ketone **3b** in 83% yield (Eq. 4). Diastereoselective reduction of **3b** was investigated with a variety of reducing reagents (Eq. 5), the results of which are summarized in Table 2. When $NaBH_4$, $LiAlH_4$, and DIBAL were employed, the *anti* isomer was predominantly obtained (entries 1–3). In the presence of $LiAlH(O\text{-}t\text{-}Bu)_3$, the reaction took place with excellent *anti* selectivity and quantitative yield (entry 4). On the other hand, borane reagents afforded the *syn* isomer stereoselectively. In the case of catecholborane the *syn* isomer was obtained in good yield and excellent diastereoselectivity (98:2) (entry 6). As both *anti* and *syn* isomers had been synthesized in high stereoselective manner by the use of $LiAlH(O\text{-}t\text{-}Bu)_3$ and catecholborane, respectively, the generality of these conditions was then examined.



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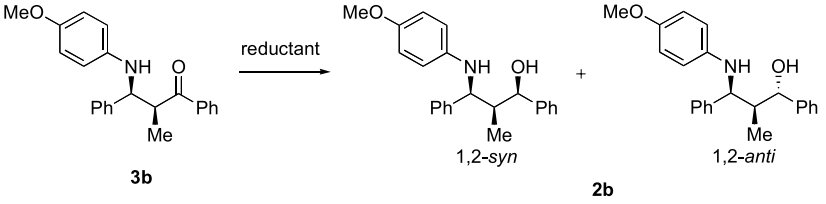


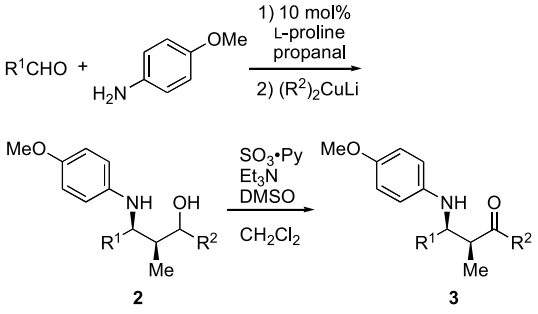
(5)

Table 2. The effect of reducing agent on the diastereoselectivity of **2b** formation

Entry	Reductant	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	*syn*:*anti*[b]
1	$NaBH_4$	MeOH	−20	2	96	17:83
2	$LiAlH_4$	THF	−78	3	96	13:87
3	*i*-Bu_2AlH	CH_2Cl_2	−78	2	86	7:93
4	$LiAlH(O\text{-}t\text{-}Bu)_3$	THF	−78	0.5	Quant.	5:95
5	$BH_3\cdot THF$	THF	0	0.1	76	96:4
6	Catecholborane	THF	0	3	90	98:2

[a] Isolated yield.
[b] The diastereomeric ratio was determined by ^1H NMR.

First the synthesis of the starting β-amino ketone **3** was examined. The β-amino aldehyde was generated according to our asymmetric three-component Mannich reaction conditions, and then immediately treated with a lithium dialkyl- or diarylcuprate to afford β-amino alcohol **2**. The oxidation of **2** with $SO_3\cdot$pyridine gave β-amino ketone **3** (Eq. 6). The yields of **2** and **3** are summarized in Table 3, which shows that **3** was easily obtained in good yield from commercially available compounds.



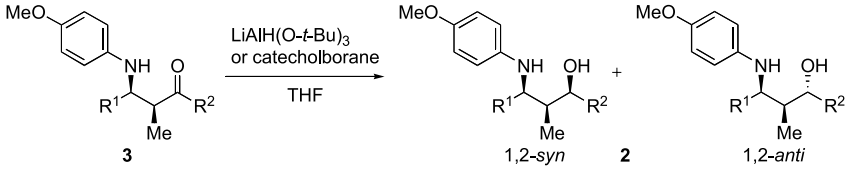
(6)

Table 3. Generality of the synthesis of β-amino alcohol **2** and β-amino ketone **3**

Entry	R^1	R^2	Yield of **2** (%)[a]	Yield of **3** (%)[b]
1	Ph	Me	83 (**2a**)	94 (**3a**)
2	Ph	Ph	98 (**2b**)	83 (**3b**)
3	Ph	Bu	78 (**2c**)	78 (**3c**)
4	4-BrC_6H_4–	Me	70 (**2d**)	86 (**3d**)
5	4-BrC_6H_4–	Bu	62 (**2e**)	93 (**3e**)
6	4-BrC_6H_4–	Ph	73 (**2f**)	77 (**3f**)

[a] Isolated yield over two steps.
[b] Isolated yield.

The stereoselective reduction of β-amino ketones was examined using $LiAlH(O\text{-}t\text{-}Bu)_3$ and catecholborane (Table 4). In the case of $LiAlH(O\text{-}t\text{-}Bu)_3$, the 1,2-*anti* isomer was obtained stereoselectively in quantitative yield. This *anti* selectivity can be rationalized by intramolecular hydride transfer, as shown in Figure 1. A similar model was proposed by Evans and co-workers for the *anti*-selective reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride.[15] When catecholborane was employed as reducing reagent, the 1,2-*syn* isomer was generated, also with high to exellent diastereoselectivities and in good yield. The *syn*-selective reduction of β-hydroxy ketone with catecholborane[16] can be explained using six-membered chelation model (Fig. 2).



(7)

Table 4. Generality of the reduction of **3** with $LiAlH(O\text{-}t\text{-}Bu)_3$ or catecholborane

Entry	R^1	R^2	$LiAlH(O\text{-}t\text{-}Bu)_3$		Catecholborane	
			Yield (%)[a]	*Syn*:*anti*[b]	Yield (%)[a]	*Syn*:*anti*[b]
1	Ph	Me	Quant.	14:86	90	98:2
2	Ph	Bu	Quant.	11:89	67	75:25
3	Ph	Ph	Quant.	5:95	90	98:2
4	4-BrC_6H_4–	Me	Quant.	20:80	65	73:27
5	4-BrC_6H_4–	Bu	84	16:84	97	73:27
6	4-BrC_6H_4–	Ph	Quant.	6:94	86	99:1

[a] Isolated yield.
[b] The diastereomeric ratio was determined by ^1H NMR.

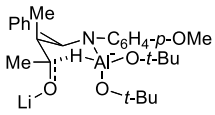


Figure 1. Transition state structure for the reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$.

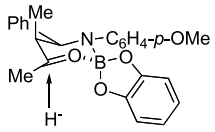


Figure 2. Transition state structure for the reduction with catecholborane.

2.1. The determination of the stereochemistry

As reported in our previous paper (Eq. 1),[8] the optical purity of the Mannich reaction of benzaldehyde, anisidine, and propanal, and that of *p*-bromobenzaldehyde, anisidine, and propanal were both excellent (98% ee). As the optical purity does not change during the oxidation and reduction processes, the α-alkyl β-amino secondary alcohols are also obtained in excellent enantiomeric purity, as was confirmed for compound **15** (vide infra).

The relative stereochemistry of the alkyl and hydroxy groups of **2a** was determined as following: the mixture of *syn* and *anti* isomers **2a** was treated with $ClCO_2Me$ and DMAP, affording **4a** as a mixture of diastereomers, which were separated by TLC. When **4a** was treated with NaH in THF, no reaction occurred with the more polar isomer. On the other hand, the less polar isomer gave a cyclic urethane **5a**, the stereochemistry of which was determined by NOESY spectra (Fig. 3). Thus, the configuration of the less polar isomer was determined to be 1,2-*syn*. The stereochemistry of phenyl-substituted **2b** was also determined using the same method.

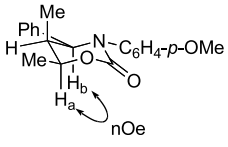
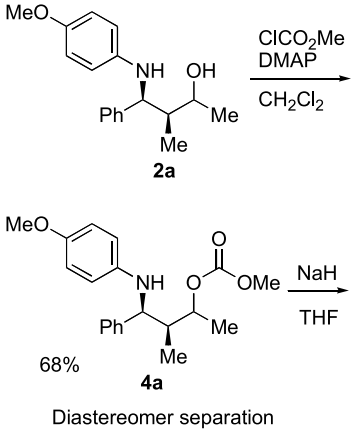


Figure 3. NOE observed in **5a**.



(8)

2.2. Formal total synthesis of nikkomycin

Nikkomycins B and B_X are nucleoside peptide antibiotics isolated from the culture broth of *Streptomyces tendae*.[17] They are potent chitin synthetase inhibitors, exhibiting fungicidal, insecticidal, and acaricidal activities.[18] Because of these important biological properties, nikkomycins are attractive synthetic targets. The Konig[19] and Barrett[20] groups have accomplished the total synthesis of nikkomycins B and B_X, respectively. The nikkomycins can be divided into two structural units, the C-terminal nucleoside amino acid and the N-terminal amino acid **8**. The N-terminal amino acid **8** and its synthetic equivalent **9** contain the three contiguous stereocenters of an α-methyl β-amino secondary alcohol moiety, the stereoselective synthesis of which is a synthetic challenge. Several methods to prepare this moiety in either racemic[21] or optically active form[22] have been reported. We have synthesized the N-terminal amino acid moiety **9** based on the method developed above, as will be described below (Fig. 4).

The synthesis starts with the Mannich reaction of 2-furylaldehyde. We had already found that the enantioselectivity of the Mannich reaction of 2-furylaldehyde was not satisfactory (84% ee).[8] In order to improve the enantioselectivity, we investigated this particular reaction in detail and found that addition of pyridine increased the enantioselectivity (Eq. 9). That is, while 84% ee was obtained under the standard reaction conditions, excellent enantioselectivity (92% ee) was realized in the presence of

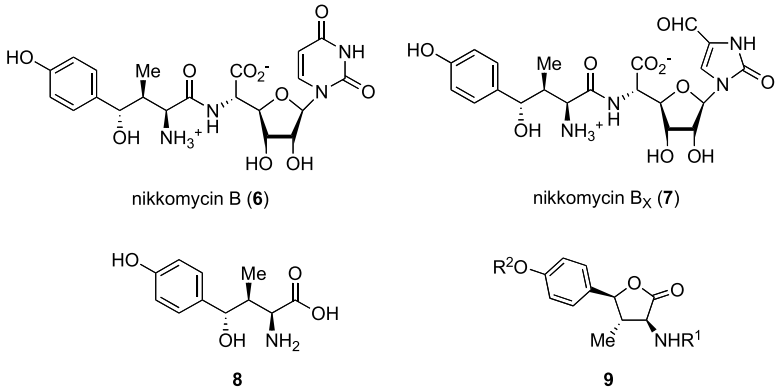
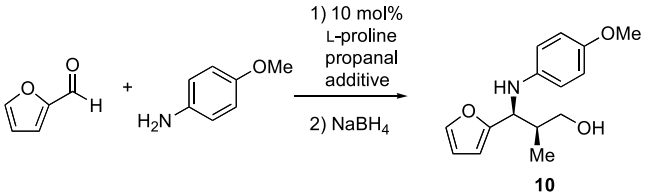


Figure 4. The structures of nikkomycin B and B_X, and of the N-terminal amino acid **8** and its synthetic equivalent **9**.

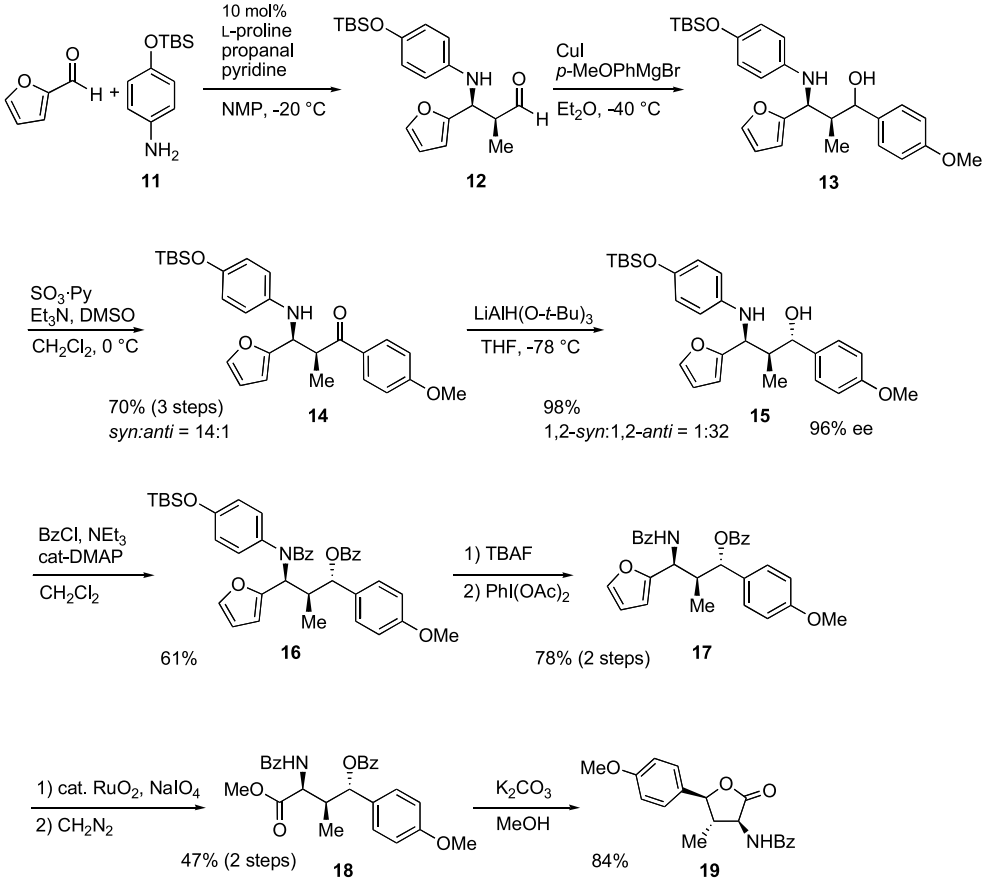
1.5 equiv of pyridine. It should be noted that this effect of pyridine was observed only in the reaction of 2-furylaldehyde, and no improvement in ee was seen for other aldehydes.



(9)

In the total synthesis of nikkomycin, we employed 4-*tert*-butyldimethylsiloxyaniline (**11**) instead of anisidine because the 4-*tert*-butyldimethylsiloxyphenyl moiety is easily cleaved from an amine under nearly neutral conditions (vide infra).[7] The Mannich reaction of 2-furylaldehyde, propanal, and 4-*tert*-butyldimethylsiloxyaniline proceeded with high diastereo- and enantioselectivities (96% ee, vide infra). Crude β-amino aldehyde **12** was immediately treated with $(p\text{-MeOC}_6H_4)_2CuMgBr$ in THF at −40 °C to give β-amino alcohol **13**. The crude mixture of *syn* and *anti* alcohols **13** was oxidized with $SO_3\cdot$pyridine to afford β-amino ketone **14** in 70% yield over three steps. These reactions could be easily scaled up because purification was performed only after the oxidation. Diastereoselective reduction of β-amino ketone **14** with $LiAlH(O\text{-}t\text{-}Bu)_3$ at −78 °C for 1 h proceeded smoothly, generating 1,2-*anti* alcohol **15** in excellent yield and diastereoselectivity (98%, 1,2-*syn*/1,2-*anti*=1:32). The optical purity of the alcohol **15** was determined by chiral HPLC analysis and shown to be 96% ee.[23] As the three continuous stereocenters had been established in a highly diastereo- and enantioselective manner, all that remained was oxidation of the furan to a carboxy group and transformations of the functional groups. However, the order of the reactions and the protecting groups used were found to be crucial for the successful transformation of **15** to **19**, because of the presence of three oxidatively-labile moieties, the furan, *p*-methoxyphenyl and *p*-*tert*-butyldimethylsilyloxyaniline groups.

First, the hydroxy and amino groups were protected with the electron-withdrawing benzoyl group by treatment with benzoyl chloride, Et_3N and a catalytic amount of DMAP, affording **16** in 61% yield. The *p*-*tert*-butyldimethylsiloxyphenyl substituent on nitrogen was successfully removed by successive treatment with TBAF and iodobenzene diacetate in 78% yield over two steps.[7] Iodobenzene diacetate is a mild oxidant, which afford the successful removal of the *p*-*tert*-butyldimethylsiloxyphenyl moiety without affecting the oxidatively-labile *p*-methoxyphenyl group and furan. In spite of several precedents for the conversion of furan into carboxy group, the oxidative modification of furan of **15** was found to be difficult. Though ozonolysis[24] gave the product in low yield, the reaction of **17** with sodium periodate and a catalytic amount of ruthenium dioxide[25] afforded the carboxylic acid, which was treated with diazomethane to



Scheme 1. Total synthesis of the N-terminal of amino acid equivalent **19** of nikkomycin B and B_X.

afford methyl ester **18** in 47% yield over two steps. Even under these conditions over-oxidation at the *p*-methoxyphenyl moiety proceeded to some extent. Treatment of **18** with K_2CO_3 in MeOH gave lactone **19** in 84% yield, which was identical to the literature [21d] (Scheme 1).

3. Conclusion

In summary, we have accomplished a general method for the synthesis of α-substituted β-amino secondary alcohols based on the following sequence of four reactions. (1) The proline-mediated, asymmetric, one-pot, three-component cross Mannich reaction of two different aldehydes to generate α-substituted β-amino aldehydes. (2) The nucleophilic addition reaction of R_2CuLi. (3) Oxidation of alcohol to ketone. (4) Diastereoselective reduction with LiAlH(O-*t*-Bu)$_3$ or catecholborane to generate the 1,2-*syn* or 1,2-*anti* isomer. This synthetic method was successfully applied to the formal total synthesis of the N-terminal amino acid moiety of nikkomycins B and B_X.

4. Experimental

4.1. Typical experimental procedures for the preparation of 2 (Table 3, entry 1)

To a solution of benzaldehyde (53 μL, 0.5 mmol) and *p*-anisidine (67.8 mg, 0.55 mmol) in NMP (0.5 mL) was added L-proline (5.8 mg, 0.05 mmol) and the reaction mixture was stirred for 2 h at room temperature. To this reaction mixture was added propanal (60.5 μL, 1.5 mmol) at −20 °C, which was further stirred for 20 h at this temperature. After addition of phosphate buffer, the organic materials were extracted with Et_2O three times and the combined organic phase was washed with brine three times, dried over $MgSO_4$. After filtration, the volatile materials were removed under reduced pressure to afford a crude β-amino aldehyde, which was used immediately in the next reaction.

To a suspension of CuI (238 mg, 1.25 mmol) in Et_2O (2.5 mL) was added MeLi (1.14 M in Et_2O, 2.19 mL, 2.5 mmol) at −20 °C over 5 min and the reaction mixture was stirred for 30 min at that temperature. To a Me_2CuLi solution was added a solution of crude β-amino aldehyde in Et_2O (1 mL) at −78 °C over 15 min and the reaction mixture was stirred for 3 h at this temperature. After addition of phosphate buffer and filtration of the insoluble materials via Celite pad, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were obtained, which was purified by thin-layer chromatography (TLC) (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** in 83% yield.

4.1.1. (2*S*,3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-ol (*syn*-2a). Yellow solid; mp: 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, d, *J*=8.0 Hz), 1.20 (3H, d, *J*=6.4 Hz), 1.73–1.86 (1H, m), 3.66 (3H, s), 4.15 (1H, dq, *J*=1.8, 6.4 Hz) 4.54 (1H, d, *J*=3.6 Hz), 6.53 (2H, d, *J*=8.8 Hz), 6.66 (2H, d, *J*=8.8 Hz), 7.10–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.5, 21.7, 45.5, 55.6, 63.6, 71.6, 114.6, 116.0, 126.6, 126.8, 128.4, 140.8, 142.2, 152.6; IR (neat): ν 3367, 2927, 2918, 1512, 1450, 1234, 1039, 820, 702 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1721.

4.1.2. (2*R*,3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-ol (*anti*-2a). Yellow solid; mp: 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, *J*=7.1 Hz), 1.26 (3H, d, *J*=6.3 Hz), 1.92 (1H, d of quintet, *J*=3.3, 7.1 Hz), 3.67 (3H, s), 3.77 (1H, quintet, *J*=6.3 Hz), 4.69 (1H, d, *J*=3.3 Hz), 6.52 (2H, br d, *J*=8.9 Hz), 6.67 (2H, br d, *J*=8.9 Hz), 7.15–7.25 (1H, m), 7.26–7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 21.9, 45.9, 55.7, 59.5, 70.3, 114.8, 115.4, 126.7, 127.1, 128.3, 141.2, 142.0, 152.3; IR (neat): ν 3380, 2968, 2931, 2360, 1512, 1452, 1232, 1037, 820, 702 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1691; $[\alpha]_D^{20}$ −34.5 (*c* 0.10, $CHCl_3$).

4.1.3. (1*R*,2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-ol (*syn*-2b). Yellow solid; mp: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, d, *J*=7.1 Hz), 2.13 (1H, tq, *J*=3.6, 7.1 Hz), 3.65 (3H, s), 4.56 (1H, d, *J*=3.6 Hz), 5.01 (1H, d, *J*=3.7 Hz), 6.49 (2H, br d, *J*=8.9 Hz), 6.66 (2H, br d, *J*=8.9 Hz), 7.13–7.37 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.2, 47.0, 55.6, 62.5, 77.4, 114.6, 115.9, 125.8, 126.6, 126.8, 127.1, 128.2, 128.4, 140.7, 142.2, 143.4, 152.5; IR (neat): ν 3379, 2933, 2908, 1512, 1452, 1234, 1036, 820, 740, 702 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{25}NO_2$ 347.1885, found 347.1862; $[\alpha]_D^{22}$ −5.4 (*c* 0.81, MeOH).

4.1.4. (1*S*,2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-ol (*anti*-2b). Yellow solid; mp: 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, d, *J*=7.2 Hz), 2.25–2.35 (1H, m), 3.68 (3H, s), 4.65–4.71 (2H, m), 6.53 (2H, br d, *J*=8.8 Hz), 6.67 (2H, br d, *J*=8.8 Hz), 7.14–7.23 (3H, m), 7.23–7.32 (3H, m), 7.32–7.40 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.7, 45.8, 55.6, 58.6, 77.6, 114.7, 115.9, 126.2, 126.7, 126.9, 127.5, 128.3, 128.5, 140.6, 141.6, 143.9, 152.5; IR (neat): ν 3419, 2912, 1612, 1512, 1448, 1234, 1030, 822, 746, 702 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{26}NO_2$ 348.1964, found 348.1992; $[\alpha]_D^{22}$ +0.5 (*c* 0.88, MeOH).

4.1.5. (1*S*,2*S*,3*S*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-ol (*syn*-2c). Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.83–0.95 (6H, m), 1.20–1.42 (4H, m), 1.45–1.65 (2H, m), 1.80–1.90 (1H, m), 3.66 (3H, s), 3.88–3.95 (1H, m), 4.51 (1H, d, *J*=3.3 Hz), 6.53 (2H, br d, *J*=8.2 Hz), 6.66 (2H, br d, *J*=8.2 Hz), 7.15–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.6, 14.1, 22.7, 28.3, 35.3, 43.9, 55.6, 64.0, 75.8, 114.6, 116.0, 126.6, 126.7, 128.4, 140.9, 142.3, 152.5; IR (neat): ν 3363, 2956, 2931, 1514, 1493, 1452, 1261, 1234, 1037, 976 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$ 328.2277, found 328.2263.

4.1.6. (1*S*,2*S*,3*R*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-ol (*anti*-2c). Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (3H, d, *J*=7.2 Hz), 0.89 (3H, t, *J*=7.0 Hz), 1.25–1.63 (6H, m), 1.91 (1H, d of quintet, *J*=3.2, 7.0 Hz), 3.55–3.72 (1H, m), 3.65 (3H, s), 4.69 (1H, d, *J*=3.2 Hz),

6.49 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.17 (1H, t, J=7.0 Hz), 7.22–7.29 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.5, 14.1, 22.8, 28.1, 35.1, 44.0, 55.6, 58.9, 74.7, 114.7, 115.5, 126.6, 126.9, 128.3, 141.0, 142.1, 152.3; IR (neat): ν 3379, 2956, 2931, 1618, 1601, 1514, 1464, 1452, 1234, 1039 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$ 328.2277, found 328.2286.

4.1.7. (2*S*,3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-ol (*syn*-2d). Yellow solid; mp: 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, J=7.2 Hz), 1.21 (3H, d, J=6.3 Hz), 1.72–1.80 (1H, m), 3.67 (3H, s), 4.10 (1H, dq, J=2.3, 6.3 Hz), 6.46 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.14 (2H, br d, J=8.4 Hz), 7.40 (2H, br d, J=8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.1, 21.1, 44.8, 55.7, 63.3, 72.4, 114.9, 116.7, 120.7, 128.3, 131.6, 139.8, 140.7, 153.1; IR (neat): ν 3369, 2970, 1510, 1485, 1403, 1234, 1178, 1039, 1008, 520 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{22}^{79}BrNO_2$ 363.0834, found 363.0832.

4.1.8. (2*R*,3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-ol (*anti*-2d). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (3H, d, J=7.1 Hz), 1.26 (3H, d, J=6.3 Hz), 1.87 (1H, d of quintet, J=3.2, 7.1 Hz), 3.67 (3H, s), 3.76 (1H, quintet, J=6.7 Hz), 4.65 (1H, d, J=3.2 Hz), 6.45 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.17 (2H, br d, J=8.3 Hz), 7.40 (2H, br d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 22.0, 45.9, 55.7, 59.0, 70.2, 114.8, 115.2, 120.4, 128.8, 131.4, 141.0, 141.3, 152.3; IR (neat): ν 3379, 2968, 2931, 2360, 1512, 1485, 1234, 1178, 1037, 1008 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{18}H_{23}^{79}BrNO_2$ 364.0912, found 364.0917.

4.1.9. (1*S*,2*S*,3*S*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-ol (*syn*-2e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.94 (6H, m), 1.20–1.65 (6H, m), 1.76–1.85 (1H, m), 3.67 (3H, s), 3.82–3.88 (1H, m), 4.42 (1H, d, J=4.0 Hz), 6.46 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.14 (2H, br d, J=8.4 Hz), 7.41 (2H, br d, J=8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.7, 14.0, 22.7, 28.2, 35.4, 43.9, 55.6, 63.5, 75.6, 114.6, 115.7, 120.4, 128.4, 131.5, 140.8, 141.7, 152.5; IR (neat): ν 3367, 2931, 1514, 1484, 1465, 1234, 1039, 1008, 819, 524 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{28}^{79}BrNO_2$ 405.1303, found 405.1298.

4.1.10. (1*S*,2*S*,3*R*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-ol (*anti*-2e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, J=6.9 Hz), 0.90 (3H, t, J=8.4 Hz), 1.25–1.42 (4H, m), 1.43–1.66 (2H, m), 1.90 (1H, d of quintet, J=3.0, 6.9 Hz), 3.58 (1H, ddd, J=4.0, 6.3, 8.2 Hz), 4.65 (1H, d, J=3.0 Hz), 6.45 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.15 (2H, br d, J=8.3 Hz), 7.40 (2H, br d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.5, 14.1, 22.7, 28.0, 35.1, 44.0, 55.6, 58.6, 74.6, 114.7, 115.3, 120.3, 128.8, 131.4, 140.8, 141.4, 152.3; IR (neat): ν 3367, 2954, 2931, 1532, 1484, 1234, 1039, 1008, 820, 526 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd $C_{21}H_{29}^{79}BrNO_2$ 406.1382, found 406.1353.

4.1.11. (1*R*,2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-ol (*syn*-2f). Colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (3H, d, J=7.0 Hz), 2.05–2.12 (1H, m), 3.68 (3H, s), 4.49 (1H, d, J=3.2 Hz), 5.00 (1H, d, J=3.7 Hz), 6.45 (2H, d, J=8.8 Hz), 6.67 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.3 Hz), 7.23–7.26 (1H, m), 7.30–7.33 (4H, m), 7.39 (2H, d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.4, 47.0, 55.6, 61.9, 77.3, 114.7, 115.6, 120.5, 125.8, 127.4, 128.3, 128.4, 131.5, 140.6, 141.6, 143.3, 152.5; IR (neat): ν 3374, 2931, 2908, 1512, 1484, 1234, 1178, 1035, 1008, 819 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{23}H_{25}^{79}BrNO_2$ 426.1069, found 426.1089; $[\alpha]_D^{20}$ −7.7 (*c* 0.75, $CHCl_3$).

4.1.12. (1*S*,2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-ol (*anti*-2f). Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (3H, d, J=7.1 Hz), 2.25 (1H, d of quintet, J=2.5, 7.1 Hz), 3.68 (3H, s), 4.62–4.66 (2H, m), 6.47 (2H, br d, J=8.9 Hz), 6.67, (2H, br d, J=8.9 Hz), 7.09 (2H, br d, J=8.5 Hz), 7.25–7.35 (5H, m), 7.38 (2H, br d, J=8.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.7, 45.8, 55.6, 58.3, 77.5, 114.7, 115.5, 120.4, 126.3, 127.7, 128.5, 128.8, 131.4, 140.5, 140.9, 143.5, 152.4; IR (neat): ν 3388, 2931, 1512, 1484, 1234, 1072, 1037, 1009, 819, 702 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{23}H_{25}^{79}BrNO_2$ 426.1069, found 426.1040; $[\alpha]_D^{20}$ −30.5 (*c* 0.55, $CHCl_3$).

4.2. Typical experimental procedures for the preparation of 3 (Table 3, entry 1)

To a solution of β-amino alcohol **2a** (205 mg, 0.59 mmol) in CH_2Cl_2 (0.6 mL) was added Et_3N (0.41 mL, 2.96 mmol), DMSO (0.6 mL) and SO_3·pyridine (278 mg, 1.78 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at that temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:3) to afford β-amino ketone **3a** in 94% yield.

4.2.1. (3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-one (3a). Colorless solid; mp: 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (3H, d, J=7.0 Hz), 2.08 (3H, s), 2.98 (1H, dq, J=5.4, 7.0 Hz), 3.66 (3H, s), 4.00 (1H, br s), 4.65 (1H, d, J=5.4 Hz), 6.44 (2H, br d, J=8.9 Hz), 6.65 (2H, br d, J=8.9 Hz), 7.18–7.24 (1H, m), 7.27–7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 29.3, 53.1, 55.7, 59.7, 114.7, 113.8, 114.7, 114.9, 126.9, 127.2, 128.6, 141.1, 141.3, 152.2; IR (neat): ν 3403, 2933, 1708, 1514, 1452, 1355, 1243, 1002, 796, 648 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1597; $[\alpha]_D^{20}$ +55 (*c* 0.85, $CHCl_3$).

4.2.2. (2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-one (3b). Colorless solid; mp: 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, J=7.0 Hz), 3.64 (3H, s), 3.92 (1H, dq, J=4.8, 7.0 Hz), 4.22 (1H, br s), 4.64 (1H, d, J=4.8 Hz), 6.39 (2H, br d, J=8.9 Hz), 6.60 (2H, br d, J=8.9 Hz), 7.19 (1H, t, J=7.4 Hz), 7.29 (2H, t, J=7.4 Hz), 7.37 (2H, d, J=7.4 Hz), 7.43 (2H, t, J=7.4 Hz), 7.54 (1H, t, J=7.4 Hz), 7.91 (2H, d, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.3, 46.9, 55.6, 59.9, 114.5, 114.9,

126.9, 127.2, 128.3, 128.6, 128.8, 133.3, 136.2, 141.4, 141.8, 152.0, 202.8; IR (neat): ν 3394, 2974, 1672, 1514, 1448, 1294, 1257, 1039, 974, 812 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1748; $[\alpha]_D^{22}$ −0.1 (*c* 0.88, MeOH).

4.2.3. (1*S*,2*S*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-one (3c). Colorless solid; ^1H NMR (400 MHz, CDCl3): δ 0.80 (3H, t, J=7.3 Hz), 1.08 (3H, d, J=7.0 Hz), 1.17 (2H, septet, J=7.2 Hz), 1.42 (2H, m), 2.27 (1H, dt, J=7.3, 17.2 Hz), 2.35 (1H, dt, J=7.3, 17.1 Hz), 2.96 (1H, quintet, J=5.9 Hz), 3.66 (3H, s), 4.57 (1H, d, J=5.7 Hz), 5.43 (2H, br d, J=8.8 Hz), 6.64 (2H, br d, J=8.8 Hz), 7.15–7.24 (1H, m), 7.26–7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 13.8, 22.1, 25.5, 42.0, 52.5, 55.7, 60.0, 114.7, 114.9, 126.9, 127.2, 128.5, 141.3, 141.5, 152.2, 213.0; IR (neat): ν 3396, 2929, 1702, 1518, 1454, 1295, 1267, 1247, 1232, 1036 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{27}NO_2$ 325.2042, found 325.2039; $[\alpha]_D^{21}$ +49.9 (*c* 0.27, $CHCl_3$).

4.2.4. (3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-one (3d). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.06 (3H, d, J=7.1 Hz), 2.09 (3H, s), 2.94 (1H, dq, J=5.4, 7.1 Hz), 3.66 (3H, s), 3.98 (1H, br s), 4.60 (1H, d, J=5.4 Hz), 6.40 (2H, br d, J=8.9 Hz), 6.65 (2H, br d, J=8.9 Hz), 7.18 (2H, br d, J=8.4 Hz), 7.41 (2H, br d, J=8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 10.9, 29.3, 52.8, 55.6, 59.1, 114.7, 114.9, 121.0, 128.7, 131.7, 140.5, 140.7, 152.4, 210.2; IR (neat): ν 3392, 2933, 1708, 1514, 1486, 1357, 1241, 1234, 1039, 1009 cm^{-1}; HRMS (FAB): $C_{18}H_{20}^{79}BrNO_2$ 361.0677, found 361.0647; $[\alpha]_D^{20}$ +21.3 (*c* 0.84, $CHCl_3$).

4.2.5. (1*S*,2*S*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-one (3e). Colorless solid; ^1H MNR (600 MHz, $CDCl_3$): δ 0.81 (3H, t, J=7.4 Hz), 1.05 (3H, d, J=7.0 Hz), 1.16 (1H, dq, J=2.9, 7.5 Hz), 1.19 (1H, dq, J=2.9, 7.5 Hz), 1.40–1.44 (2H, m), 2.30 (1H, td, J=7.3, 14.9 Hz), 2.37 (1H, td, J=7.4, 14.9 Hz), 2.92 (1H, quintet, J=6.7 Hz), 3.66 (3H, s), 4.07 (1H, br s), 4.52 (1H, d, J=5.4 Hz), 6.39 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.18 (2H, br d, J=8.3 Hz), 7.41 (2H, br d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCL_3$): δ 11.3, 13.8, 22.1, 25.4, 42.1, 52.1, 55.6, 59.3, 114.6, 114.9, 120.9, 128.7, 131.6, 140.7, 140.8, 152.2, 212.8; IR (neat): ν 3407, 2960, 2931, 1701, 1513, 1460, 1408, 1010, 813, 738 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{26}^{79}BrNO_2$ 403.1147, found 403.1138; $[\alpha]_D^{20}$ +33.5 (*c* 0.29, $CHCl_3$).

4.2.6. (2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-one (3f). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, J=7.0 Hz), 3.64 (3H, s), 3.87 (1H, dq, J=5.0, 7.0 Hz), 4.22 (1H, br s), 4.59 (1H, d, J=5.0 Hz), 6.37 (2H, br d, J=8.9 Hz), 6.62 (2H, br d, J=8.9 Hz), 7.26 (2H, br d, J=8.3 Hz), 7.41 (2H, br d, J=8.3 Hz), 7.45 (2H, d, J=7.8 Hz), 7.55 (1H, t, J=7.3 Hz), 7.89 (2H, d, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 46.8, 55.7, 59.6, 114.7, 115.1, 121.0, 128.2, 128.7, 128.8, 131.7, 133.4, 136.2, 141.0, 141.1, 152.4, 202.5; IR (neat): ν 3380, 2931, 1676, 1512, 1448, 1241, 1236, 1038, 1010, 971 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{22}^{79}BrNO_2$ 423.0834, found 423.0807; $[\alpha]_D^{20}$ +51.7 (*c* 1.83, $CHCl_3$).

4.3. Typical experimental procedures for the preparation of 2-*anti* by the reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ (Table 4, entry 1)

To a solution of **3a** (10 mg, 0.035 mmol) in THF (0.5 mL) was added a solution of $LiAlH(O\text{-}t\text{-}Bu)_3$ (1 M in THF, 0.175 mL, 0.175 mmol) at −78 °C and the reaction mixture was stirred for 1 h at that temperature. After addition of a saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine three times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were purified by TLC (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** quantitatively (**2a**-*anti*/**2a**-*syn*=86:14). The ratio of *anti*/*syn* was determined by ^1H NMR measurement.

4.4. Typical experimental procedures for the preparation of 2-*syn* by the reduction with catecholborane (Table 4, entry 1)

To a THF solution (1.5 mL) of **3a** (50 mg, 0.15 mmol) was added catecholborane (155 μL, 1.5 mmol) at −10 °C and the reaction mixture was stirred for 3 h at that temperature. After addition of MeOH and a saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine five times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were purified by TLC (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** in 90% yield (**2a**-*anti*/**2a**-*syn*=2:98). The ratio of *anti*/*syn* was determined by ^1H NMR measurement.

4.5. The determination of the relative stereochemistry

4.5.1. (1*S*,2*S*,3*S*)-Carbonic acid 3-(*p*-anisidino)-1,2-dimethyl-3-phenylpropyl ester methyl ester (*syn*-4a). To a solution of **2a** (75.7 mg, 0.29 mmol) in CH_2Cl_2 (2.9 mL) was added DMAP (715.9 mg, 5.86 mmol), $ClCO_2$-Me (453 mL, 5.86 mmol) at 0 °C and the reaction mixture was stirred for 2.5 h at room temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:3) to afford *syn*-**4a** and *anti*-**4a** in 68% yield. *Syn*-**4a** and *anti*-**4a** were separated by TLC.

Yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, d, J=6.8 Hz), 1.32 (3H, d, J=6.4 Hz), 1.93–2.02 (1H, m), 3.66 (3H, s), 3.71 (3H, s), 4.40 (1H, d, J=4.8 Hz), 4.81 (1H, dq, J=5.2, 6.4 Hz), 6.41 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.17–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 8.8, 18.4, 29.7, 45.1, 54.7, 55.7, 60.4, 114.5, 114.6, 126.7, 127.0, 128.5, 141.3, 142.4, 151.8, 155.3; IR (neat): ν 3415, 2981, 2954, 1743, 1514, 1442, 1271, 1234, 1038, 820 cm^{-1}; HRMS (FAB): calcd for $C_{20}H_{25}NO_4$ 343.1784, found 343.1816; $[\alpha]_D^{21}$ −8.5 (*c* 0.17, MeOH).

4.5.2. (4*S*,5*S*,6*S*)-3-(*p*-Anisidino)-5,6-dimethyl-4-phenyl-[1,3]oxazinan-2-one (5a). To a solution of *syn*-**4a** (25.6 mmol) in THF (0.8 mL) was added NaH (8.95 mmol, 0.373 mmol) at room temperature and the reaction mixture was stirred for 12 h at that temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:1) to afford **5a** in 25% yield.

Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, J=7.0 Hz), 1.38 (3H, d, J=6.5 Hz), 2.17–2.25 (1H, m), 3.66 (3H, s), 4.85 (1H, dq, J=1.1, 6.5 Hz), 5.26 (1H, d, J=5.0 Hz), 6.68 (2H, br d, J=8.6 Hz), 7.06–7.22 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.8, 18.1, 37.8, 55.2, 67.3, 75.9, 113.7, 127.5, 127.9, 128.3, 133.8, 137.2, 154.2, 157.5; IR (neat): ν 2937, 1689, 1515, 1454, 1402, 1247, 1170, 1033, 1025, 833 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{19}H_{22}NO_3$ 312.1600, found 312.1622; $[\alpha]_D^{20}$ −53.8 (*c* 0.47, $CHCl_3$).

4.6. Experimental procedures of the formal total synthesis of nikkomycin

4.6.1. (2*S*,3*S*)-3-(*N*-*p*-*tert*-Butyldimethylsiloxyphenyl-amino)-3-(2-furyl)-2-methyl-1-(*p*-methoxyphenyl)propan-1-one (14). To a solution of 2-furylaldehyde (0.25 mL, 3.0 mmol) and *p*-*tert*-butyldimethylsiloxyaniline (737 mg, 3.3 mmol) in NMP (3.0 mL) was added L-proline (34.5 mg, 0.03 mmol) and the reaction mixture was stirred for 2 h at room temperature. To this reaction mixture was added pyridine (0.363 mL, 4.5 mmol) and propanal (0.972 mL, 4.5 mmol) at −20 °C, which was further stirred for 20 h at this temperature. After addition of phosphate buffer, the organic materials were extracted with Et_2O three times and the combined organic phase was washed with brine three times and dried over $MgSO_4$. After filtration, the volatile materials were removed under reduced pressure to afford a crude β-amino aldehyde, which was used without further purification in the next reaction.

To a suspension of CuI (2.85 g, 15 mmol) in Et_2O (10 mL) was added a solution of *p*-MeOPhMgBr (2.15 M in Et_2O, 14 mL, 30 mmol) at −7 °C over 5 min and the reaction mixture was stirred for 30 min at this temperature. To this reaction mixture was added a solution of crude β-amino aldehyde in Et_2O (20 mL) at −7 °C and the reaction mixture was stirred for 3 h at this temperature. After addition of phosphate buffer and filtration of the insoluble materials via Celite pad, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was obtained, which was further oxidized.

To a solution of crude amino alcohol **13** in CH_2Cl_2 (2 mL) was added Et_3N (1.3 mL, 10 mmol), DMSO (2 mL) and SO_3·pyridine (937 mg, 6 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at this temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by column chromatography (AcOEt/hexane=1:25) to afford β-amino ketone **14** in 70% yield over three steps.

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (6H, s), 0.92 (9H, s), 1.27 (3H, d, J=6.9 Hz), 3.84 (3H, s), 4.03 (1H, quintet, J=6.9 Hz), 4.75 (1H, d, J=6.5 Hz), 6.09 (1H, d, J=3.2 Hz), 6.17 (1H, dd, J=2.0, 3.2 Hz), 6.44 (2H, br d, J=8.7 Hz), 6.58 (2H, d, J=8.7 Hz), 6.90 (2H, d, J=8.8 Hz), 7.25 (1H, d, J=2.0 Hz), 7.90 (2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5, 13.3, 18.1, 25.7, 44.3, 55.46, 55.49, 107.2, 110.2, 113.8, 115.3, 120.4, 129.3, 130.6, 141.4, 141.6, 148.0, 154.6, 163.6, 200.7; IR (neat): ν 3381, 2956, 2929, 1672, 1601, 1510, 1254, 1173, 924, 841 cm^{-1}; HRMS (FAB): calcd for $C_{27}H_{35}NO_4Si$ 465.2335, found 465.2332; $[\alpha]_D^{22}$ −37.6 (*c* 0.39, $CHCl_3$).

4.6.2. (1*S*,2*S*,3*S*)-3-(*N*-*p*-*tert*-Butyldimethylsiloxyphenyl-amino)-3-(2-furyl)-2-methyl-1-(*p*-methoxyphenyl)propan-1-ol (15). To a solution of **14** (673 mg, 1.44 mmol) in THF (14.4 mL) was of $LiAlH(O\text{-}t\text{-}Bu)_3$ (1 M in THF, 7.2 mL, 7.2 mmol) at −78 °C and the reaction mixture was stirred for 1 h at that temperature. After addition of the saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by column chromatography (AcOEt/hexane=1:15) to afford β-amino alcohol **15** in 98% yield.

The ee was determined by the chiral HPLC analysis: Chiralpak AD-H column (hexane/2-propanol=30:1), 0.5 mL/min, major tr=16.9 min, minor tr=21.5 min.

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (6H, s), 0.84 (3H, d, J=7.4 Hz), 0.94 (9H, s), 2.41 (1H, d of quintet, J=2.5, 7.4 Hz), 3.80 (3H, s), 4.60 (1H, d, J=7.4 Hz), 4.79 (1H, d, J=2.5 Hz), 6.05 (1H, d, J=3.2 Hz), 6.23 (1H, dd, J=1.8, 3.2 Hz), 6.57 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 6.87 (2H, br d, J=8.7 Hz), 7.27 (2H, d, J=8.7 Hz), 7.29 (1H, d, J=1.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ −4.5, 12.5, 18.1, 25.7, 43.4, 54.6, 55.2, 106.7, 110.1, 113.8, 116.0, 120.6, 127.5, 128.3, 136.0, 141.2, 141.4, 148.4, 155.4, 158.9; IR (neat): ν 3388, 2956, 2929, 1610, 1508, 1250, 1009, 910, 837, 779 cm^{-1}; HRMS (FAB): calcd for $C_{27}H_{37}NO_4Si$ 467.2492, found 467.2493; $[\alpha]_D^{22}$ −22.4 (*c* 0.81, $CHCl_3$).

4.6.3. (1*S*,2*S*,3*S*)-Benzoic acid 3-{benzoyl-[4-(*tert*-butyl-dimethylsiloxy)-phenyl]-amino}-3(2-furyl)-1-(4-methoxy-phenyl)-2-methylpropyl ester (16). To a solution of **15** (253.1 mg, 0.541 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.679 mL, 4.87 mmol), benzoyl chloride (0.377 mL, 3.25 mmol) and catalytic amount of DMAP at 0 °C. After stirring the reaction mixture for 18 h at room temperature, the reaction was quenched by the addition of phosphate buffer. The organic materials were extracted with AcOEt three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude

material was purified by thin-layer chromatography (AcOEt/hexane=1:3) to afford **16** in 61% yield.

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.88 (9H, s), 1.34 (3H, d, J=6.7 Hz), 3.05–3.17 (1H, m), 3.77 (3H, s), 5.85 (1H, d, J=10.7 Hz), 6.10 (1H, d, J=4.5 Hz), 6.24–6.28 (1H, m), 6.41 (1H, d, J=4.1 Hz), 6.45–6.54 (4H, m), 6.84 (2H, d, J=8.2 Hz), 7.05–7.20 (7H, m), 7.28 (1H, s), 7.41 (2H, t, J=7.4 Hz), 7.53 (1H, t, J=7.4 Hz), 8.02 (2H, d, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ −4.5, 11.7, 18.2, 25.6, 39.1, 55.16, 55.20, 76.6, 110.4, 110.5, 113.6, 120.2, 127.4, 128.29, 128.31, 128.6, 128.7, 129.0, 129.6, 130.4, 133.0, 136.5, 141.7, 151.6, 154.6, 159.3, 165.3, 170.7; IR (neat): ν 1718, 1686, 1655, 1647, 1508, 1269, 1252, 912, 711 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{34}H_{40}NO_4Si$ 554.2726, found: 554.2714; $[\alpha]_D^{22}$ −68.9 (c 0.79, $CHCl_3$).

4.6.4. (1*S*,2*S*,3*S*)-Benzoic acid 3-benzoylamino-3-(2-furyl)-1-(4-methoxyphenyl)-2-methylpropyl ester (17). To a solution of **16** (251 mg, 0.371 mmol) in THF (7 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 0.445 mL, 0.445 mmol) at 0 °C. After stirring the reaction mixture for 10 min at this temperature, the reaction was quenched by the addition of saturated NH_4Cl. The organic materials were extracted with AcOEt three times, and the combined organic phase was washed with brine, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were used directly in the next reaction. To a CH_3CN (1.02 mL) solution of crude phenol derivative was added water (0.5 mL) and iodobenzene diacetate (119.5 mg, 0.371 mmol) at 0 °C. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of solution of $NaHCO_3$ and $Na_2S_2O_3$. The organic materials were extracted with AcOEt three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by thin-layer chromatography (Et_2O/benzene=1:3) to afford **17** in 78% yield over two steps.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, d, J=7.1 Hz), 2.85 (1H, d of quintet, J=3.5, 7.1 Hz), 3.74 (3H, s), 5.63–5.67 (2H, m), 6.23 (1H, d, J=3.3 Hz), 6.27 (1H, dd, J=1.8, 3.3 Hz), 6.80–6.88 (3H, m), 7.23–7.42 (7H, m), 7.45–7.58 (2H, m), 7.68 (2H, d, J=8.0 Hz), 7.98 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 42.3, 50.1, 55.2, 78.5, 107.3, 110.3, 113.9, 127.1, 128.4, 128.5, 128.7, 129.5, 130.6, 131.1, 132.8, 134.4, 142.2, 152.6, 159.5, 165.3, 166.4; IR (neat): ν 3346, 2935, 1720, 1657, 1514, 1269, 1252, 1111, 808, 712 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{22}H_{22}NO_3$ 348.1600, found 348.1610; $[\alpha]_D^{22}$ +10.5 (c 0.58, MeOH).

4.6.5. (1*S*,2*S*,3*S*)-Benzoic acid 3-benzoylamino-3-methoxycarbonyl-1-(4-methoxyphenyl)-2-methylpropyl ester (18). To an aqueous solution (AcOEt 1.0 mL and water 0.25 mL) of **17** (8.1 mg, 0.017 mmol) was added RuO_2 (1.0 mg, 0.0075 mmol) and $NaIO_4$ (46 mg, 0.22 mmol) at −6 °C. After stirring the reaction mixture for 2 h at this temperature, the reaction was quenched by the addition of 1 N HCl solution. The organic materials were extracted with $CHCl_3$ three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were dissolved in Et_2O. To an Et_2O solution of crude carboxylic acid was added an Et_2O solution of diazomethane at 0 °C. After 10 min at this temperature, the volatile materials were removed under reduced pressure and the crude methyl ester was purified by thin-layer chromatography (Et_2O/HCO_2H/benzene=1:1:3) to afford methyl ester **18** in 47% yield over two steps.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, J=7.1 Hz), 2.86 (1H, dqd, J=2.8, 7.1, 9.8 Hz), 3.75 (3H, s), 3.77 (3H, s), 5.31 (1H, dd, J=2.8, 9.0 Hz), 5.69 (1H, d, J=9.8 Hz), 6.66 (1H, d, J=9.0 Hz), 6.84 (2H, d, J=8.7 Hz), 7.30–7.45 (6H, m), 7.47–7.55 (2H, m), 7.72 (2H, d, J=7.2 Hz), 8.02 (2H, d, J=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.7, 41.3, 52.7, 53.6, 55.2, 77.4, 113.9, 127.1, 128.4, 128.5, 129.6, 130.4, 131.7, 132.9, 134.0, 159.5, 165.4, 167.3, 172.3; IR (neat): ν 3375, 2926, 1739, 1724, 1668, 1514, 1252, 1215, 1109, 1026, 837, 712 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{20}H_{22}NO_4$ 340.1549, found: 340.1526; $[\alpha]_D^{22}$ +22.0 (c 0.19, $CHCl_3$).

4.6.6. (3*S*,4*S*,5*R*)-*N*-[5-(4-Methoxyphenyl)-4-methyl-2-oxo-tetrahydro-furan-3-yl]-benzamide (19). To a solution of **18** (5.0 mg, 0.011 mmol) in MeOH (0.5 mL) was added K_2CO_3 (6.0 mg, 0.044 mmol) at room temperature. After stirring the reaction mixture for 2.5 h at this temperature, the reaction was quenched by the addition of phosphate buffer. The organic materials were extracted with $CHCl_3$ three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by thin-layer chromatography (Et_2O/HCO_2H/benzene=1:1:3) to afford lactone **19** in 84% yield.

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24 (3H, d, J=6.4 Hz), 2.52 (1H, qdd, J=6.4, 10.1, 11.8 Hz), 3.80 (3H, s), 4.80 (1H, dd, J=7.7, 11.8 Hz), 4.93 (1H, d, J=10.1 Hz), 6.71 (1H, d, J=7.2 Hz), 6.90 (2H, d, J=7.7 Hz), 7.33 (2H, t, J=8.8 Hz), 7.42 (2H, t, J=8.0 Hz), 7.52 (1H, t, J=6.5 Hz), 7.81 (2H, d, J=8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8, 47.2, 55.3, 57.0, 85.3, 114.2, 127.1, 128.0, 128.27, 128.31, 128.7, 132.1, 133.0, 160.3, 167.7, 174.4; IR (neat): ν 2926, 2854, 1780, 1647, 1516, 1250, 1174, 831, 712 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{19}H_{20}NO_4$: 326.1392, found: 326.1400; $[\alpha]_D^{23}$ +9.5 (c 0.13, $CHCl_3$).

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