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A Formal Total Synthesis of Nikkomycin B Based on Enzymatic Resolution of a Primary Alcohol Possessing Two Stereogenic Centers

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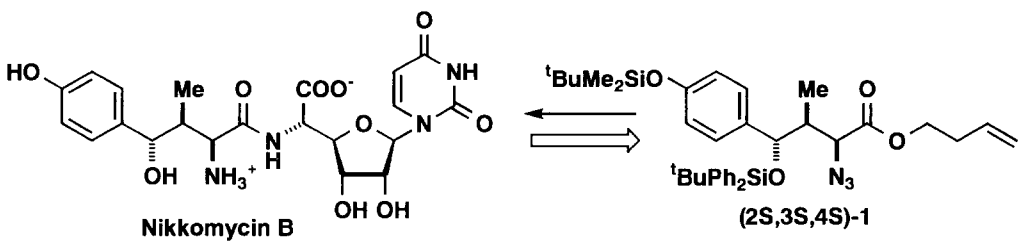
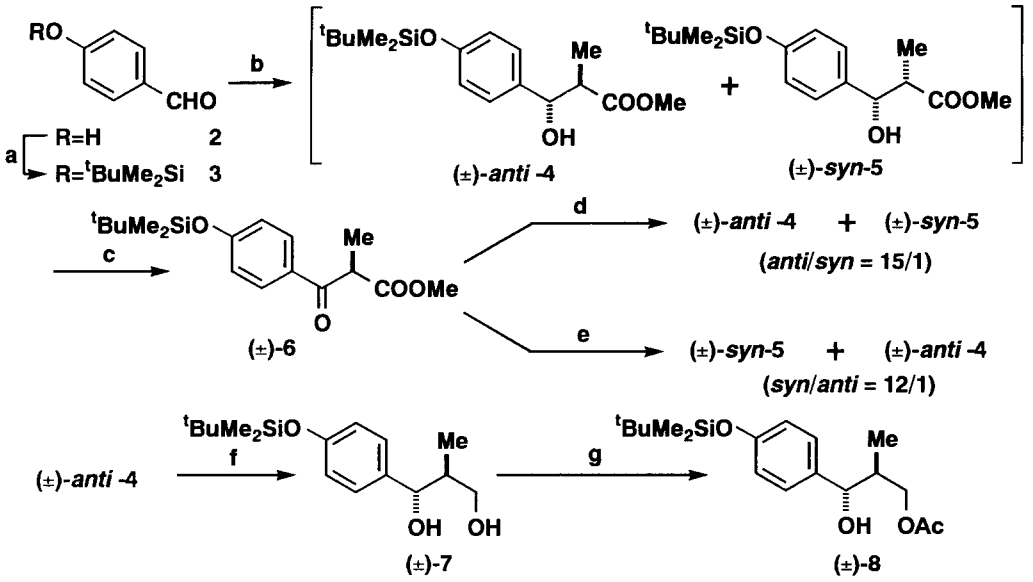
Abstract: A highly stereoselective synthesis of the versatile chiral synthon possessing two stereogenic centers, (2S,3S)-**8** (>99% ee) was achieved and the conversion of (2S,3S)-**8** into the homochiral intermediate (2S,3S,4S)-**1** for the synthesis of nikkomycin B is described.

Nikkomycins, peculiar antibiotics isolated from the culture broths of *Streptomyces tendae* exhibit fungicide and insecticide activity due to an inhibition of cell wall chitin biosynthesis.[1] From the point view of fungal infections, chitin synthetase inhibition seems to be a useful approach for the sake of safer antifungal agents. The total synthesis of nikkomycin B has already been achieved from an optically active γ-hydroxy-β-methyl-α-azidobutanoic acid congener (-)-**1** which was synthesized using (-)-(*E*)-crotyldiisopinocampheylborane as the key chiral induction process.[2] We now report a highly stereoselective synthesis of (2S,3S,4S)-**1** based on a combination of chemical diastereoselectivity and enzymatic enantioselectivity by a lipase in organic solvent.



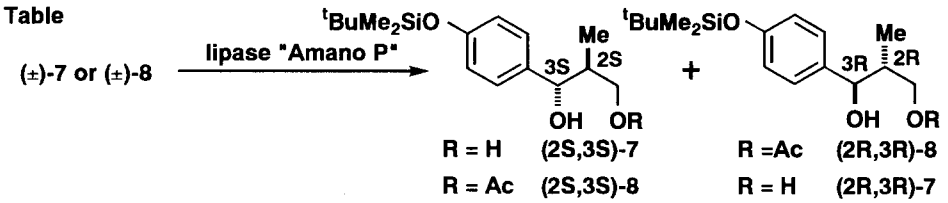
Reformatsky reaction of *p*-siloxybenzaldehyde **3** (85%) obtained by the silylation of *p*-hydroxybenzaldehyde **2** and α-bromopropionate gave a mixture of (±)-*anti*-**4** and (±)-*syn*-**5** in 97% yield, which was oxidized with Jones reagent to afford the β-keto ester (±)-**6** (86%). Reduction of (±)-**6** with n-Bu4NBH4[3] gave the (±)-*anti*-**4** (71.3%)[4] along with a small amount of the (±)-*syn*-**5** (4.8%) with high *anti*-diastereoselectivity (*anti*/*syn* = 15/1). In order to confirm the reaction products, minor (±)-*syn*-**5** was also obtained in 81.2% yield by the Zn(BH4)2 reduction of (±)-**6** with high *syn*-diastereoselectivity (*syn*/*anti* = 12/1), because Zn(BH4)2 reduction of α-methyl-β-keto esters has been reported to give predominantly the *syn*-α-methyl-β-hydroxy ester **5**.[5] Reduction of (±)-**4** with LiAlH4 provided (±)-*anti* diol **7** in 76% yield, which was treated with one equivalent of Ac2O in pyridine to afford (±)-mono acetate **8** in 43% yield. Intially, (±)-**7** was subjected to screening experiments using several kinds of commercially available lipases. Among them, lipase "Amano P" from *Pseudomonas* sp. was found to give the (2R,3R)-mono acetate **8** (53%, 75% ee, $[\alpha]_D$ +11.0 (c=1.88, CHCl3) and the unchanged (2S,3S)-**7** (36%, 81% ee, $[\alpha]_D$ -20.0 (c=1.29, CHCl3) in the presence of isopropenyl

chart 1



a; $^tBuMe_2SiCl$/imidazole b; MeCHBrCOOMe/Zn/PhH c; CrO_3/H^+ d; n-Bu_4NBH_4
e; $Zn(BH_4)_2$ f; $LiAlH_4$ g; Ac_2O/pyridine

Table



Entry	Substrate (g)	Products %(% ee)	%(% ee)
1	(±)-7 (1.66)	(2S,3S)-7 36(81)	(2R,3R)-8 53(75)
2	(±)-8 (3.06)	(2S,3S)-8 49(77)	(2R,3R)-7 44(70)
3*	(2S,3S)-8 (1.43)	(2S,3S)-8 84(>99)	(2R,3R)-7 13(37)

* Optically active (2S,3S)-8 (77% ee) was employed.

chart 2

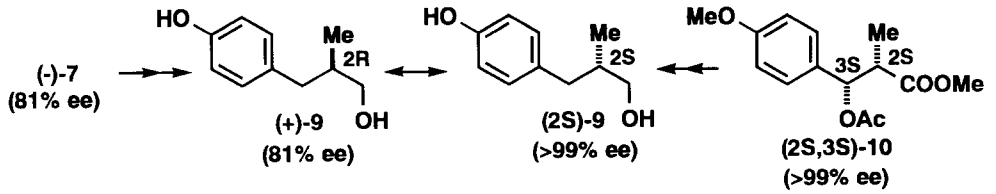
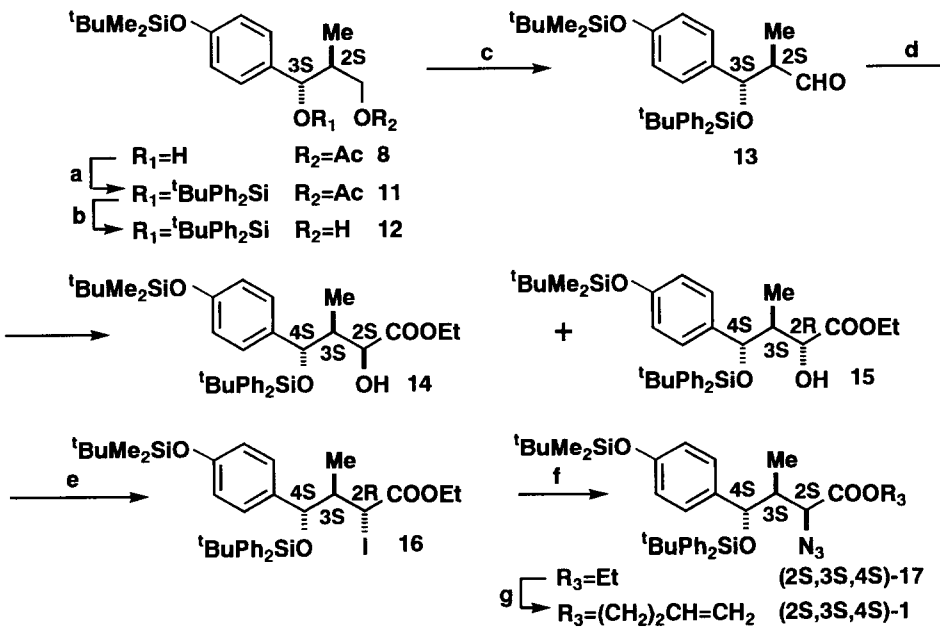


chart 3



a; ^{t}BuPh$_2$SiCl/imidazole/CH$_2$Cl$_2$ b; HAl(*i*-Bu)$_2$ c; (COCl)$_2$/DMSO/Et$_3$N/CH$_2$Cl$_2$
d; 1) ethyl vinyl ether/^{t}BuLi 2) O$_3$ 3) Me$_2$S e; I$_2$/Ph$_3$P/imidazole/CH$_3$CN/Et$_2$O
f; NaN$_3$/DMF g; 3-buten-1-ol/Ti(O-*i*-Pr)$_4$/PhH

acetate as an acyl donor in isopropyl ether as shown in table. On the other hand, stereoselective hydrolysis of (±)-**8** using "Amano P" in water saturated isopropyl ether gave (2S,3S)-**8** (49%, 77% ee) and (2R,3R)-**7** (44%, 70% ee). The recovered (2S,3S)-**8** having 77% enantiomeric excess was again subjected to the enzymatic hydrolysis using "Amano P" for 18 hour to give (2S,3S)-**8** (84%, $[\alpha]_D$ -14.1 (c=0.93, $CHCl_3$); corresponds to >99% ee) and (2R,3R)-**7** (13%, 37% ee). The enantiomeric purity of the enzymatic reaction products was determined by HPLC on a CHIRALCEL OD (250 X 4.6 mm) column. In order to confirm the absolute configuration of the present (-)-**7**, (-)-**7** was successfully converted to the mono alcohol (+)-**9** ($[\alpha]_D$ +7.41 (c=1.39, $CHCl_3$); correponds to 81% ee), whose sign of $[\alpha]_D$ was opposite in comparison with that ($[\alpha]_D$ -9.72 (c=1.08, $CHCl_3$); corresponds to >99% ee) of (2S)-mono alcohol **9** derived from (2S,3S)-**10** previously reported by us.[6] Consequently, absolute configuration of (+)-**9** was determined to be 2R, and thence absolute configurations of (-)-**7** and (+)-**8** were confirmed to be 2S,3S and 2R,3R, respectively. Silylation (**11**, 97%) of the optically pure (2S,3S)-**8** followed by reductive deacetylation gave mono alcohol (2S,3S)-**12** ($[\alpha]_D$ -90.4 (c=1.81, $CHCl_3$), which was subjected to the Swern oxidation provided the aldehyde **13**. Without further purification, **13** was subjected to the Felkin Ahn controlled addition of lithiated ethyl vinyl ether under dry-ice acetone cooling. The generated vinyl ether was directly ozonolyzed and subsequently treated with Me_2S to yield a 6:1 mixture of α-hydroxy ethyl ester **14** and **15**. Chromatographic separation of a mixture gave **14**($[\alpha]_D$ -61.7 (c=0.92, $CHCl_3$), 42% overall yield from **12**) and **15** ($[\alpha]_D$ +74.4 (c=0.81, $CHCl_3$), 7% overall yield from **12**). Conversion of **14** to the iodide **16** ($[\alpha]_D$ -10.6 (c=1.05, $CHCl_3$), 77%) followed by nucleophilic displacement with NaN_3 provided the desired (2S)-α-azido ethyl ester **17** ($[\alpha]_D$ -45.4 (c=1.21, $CHCl_3$), 88%) as a single diastereoisomer. Transesterification of **17** in the presence of 3-buten-1-ol and Ti(O-*i*-Pr)$_4$ gave the corresponding ester **1** ($[\alpha]_D$ -40.7 (c=1.38, $CHCl_3$), 90%), whose spectral data ($[\alpha]_D$, ^{1}H-NMR, IR and FAB-MS) were identical with those reported by Barrett.[2] The total synthesis of nikkomycin B from (2S,3S,4S)-**1** has already been achieved by Barrett.[2]

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References and Notes

1) For a recent review about Nikkomycins, see A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, **55**, 5818 (1990), and references cited therein.
2) A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, **56**, 4875 (1991).
3) M. Taniguchi, H. Fujii, K. Oshima, and K. Uchimoto, *Tetrahedron*, **49**, 11169 (1993).
4) Satisfactory analytical data were obtained for all new compounds.
5) T. Nakata and T. Oishi, *Tetrahedron Lett.*, **21**, 1641 (1980).
6) H. Akita, Cheng Yu Chen and S. Nagumo, *Tetrahedron; Asymmetry*, **5**, 1207 (1994).
A detailed conversion procedure will be reported in the forthcoming paper.

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