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A simple and efficient approach to 1,3-aminoalcohols: application to the synthesis of (+)-negamycin

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Abstract—A short and practical enantioselective synthesis of (+)-negamycin has been achieved in high enantio- and diastereomeric excess using an iterative Jacobsen's hydrolytic kinetic resolution as the key step.
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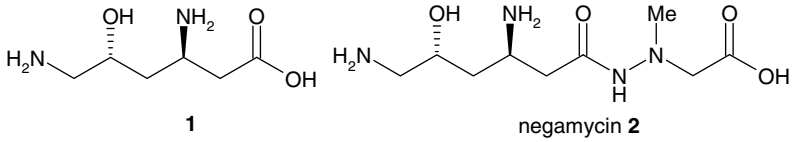
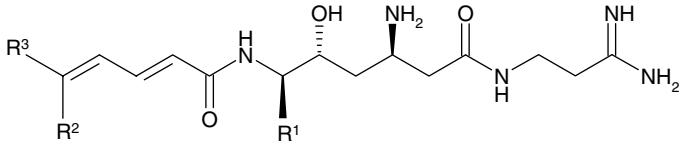
(3*R*,5*R*)-3,6-Diamino-5-hydroxyhexanoic acid **1**, is the core fragment of the pseudo-peptide antibiotics negamycin **2** and sperabillins A and C **3a** and **3c** (Fig. 1). (+)-Negamycin **2** is an unusual antibiotic which contains a hydrazine peptide linkage, and was isolated[1] by Umezawa et al. in 1970 from the culture filtrate of three strains related to *Streptomyces purpeofuscus*, and exhibits very low acute toxicity (LDm-400–500 mg/kg). It has considerable activity towards multiple drug resistant enteric Gram-positive and Gram-negative bacteria including *Pseudomonas aerginosa*.[1] Negamycin also exhibits genetic miscoding activity[2] on bacterial ribosome systems and is a specific inhibitor of protein synthesis in *Escherichia coli* K12.[3] The structure of negamycin was elucidated via degradation studies[4] and confirmed in 1972 by total synthesis from D-galacturonic acid.[5] The sperabillin family of antibiotics isolated from the culture broth of *Pseudomonas fluoresens* YK-437 shows potential in vitro and in vivo antibacterial activity, especially against Gram-positive pathogens, including



1

negamycin **2**



sperabillin A (**3a**) : R^1 = H, R^2 = Me, R^3 = H

sperabillin B (**3b**) : R^1 = Me, R^2 = Me, R^3 = H

sperabillin C (**3c**) : R^1 = H, R^2 = H, R^3 = Me

sperabillin D (**3d**) : R^1 = Me, R^2 = H, R^3 = Me

Figure 1.

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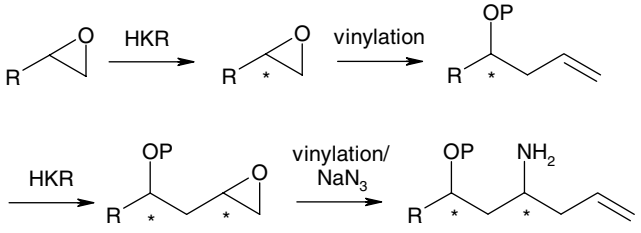
multiresistant strains of *Staphylococcus aureus*.[6] Several approaches have been reported in the literature for the synthesis of racemic[7] as well as optically active[8] negamycin. Most of the enantioselective syntheses known for negamycin derive the asymmetry from an enzymatically derived chiral building block[8a] or from chiral pool starting materials,[8] such as D-galacturonic acid, 3*R*,6-diacetamido-5*R*-hydroxyhexano lactone, amino acids, D-glucose and malic acid. However, synthetic approaches involving achiral substrates as starting materials are rather scarce.[8j,l]

As a part of our research programme aimed at developing enantioselective syntheses of naturally occurring lactones[9] and amino alcohols,[10] we have recently reported an efficient approach for the synthesis of 1,3-polyols, which was successfully applied to the synthesis of tarchonanthuslactone[11] and cryptocarya diacetate.[12] Here, we report the use of this approach for the total synthesis of (+)-negamycin from commercially available racemic epichlorohydrin.

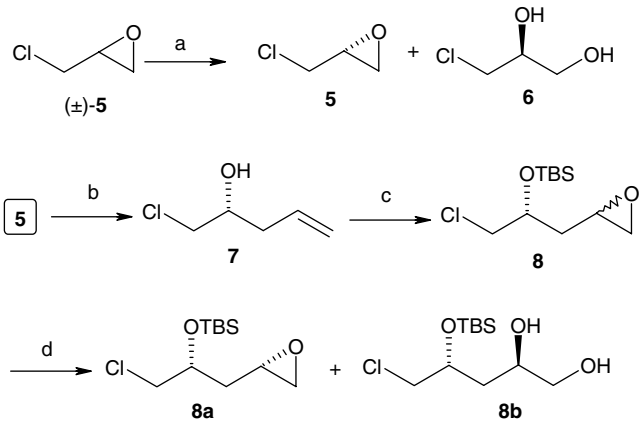
Scheme 1 shows our general synthetic strategy to construct the *syn*- and *anti*-1,3-aminoalcohol system which is based on a three-step reaction sequence employing iterative epoxidation, hydrolytic kinetic resolution (HKR)[13] and vinylation. The diastereomeric ratio in the *m*-CPBA epoxidation reaction would depend on whether the hydroxyl group is free or protected.

The *syn*- and *anti*-configuration of the 1,3-polyol/aminoalcohol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step. Our synthetic strategy for the synthesis of **2** is outlined in Scheme 2. We envisioned that (+)-negamycin **2** could be synthesized by peptide formation between **13** and l-methylhydrazineacetic acid. The bis-azido compound can be derived by regioselective opening of epoxide **8a**, which in turn could be obtained via hydrolytic kinetic resolution of epoxide **8**. Epoxide **8** could be obtained from olefin **7**, which could be derived from racemic epichlorohydrin (±)-**5** via hydrolytic kinetic resolution and vinylation. As illustrated in Scheme 3, commercially available epichlorohydrin was subjected to Jacobsen's HKR by using (*S*,*S*)-salen-Co-OAc catalyst **4** (Fig. 2) to give *R*-epichlorohydrin **5**[13d] as a single enantiomer, which was easily isolated from the more polar diol **6** by distillation. With enantiomerically pure epoxide **5** in hand our next aim was to construct the *anti*-1,3-aminoalcohol. To establish the second stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective epoxidation of a homoallylic alcohol. Thus, *R*-epichlorohydrin **5** was treated with vinylmagnesium bromide in the presence of CuI to give homoallylic alcohol **7** in good yield.

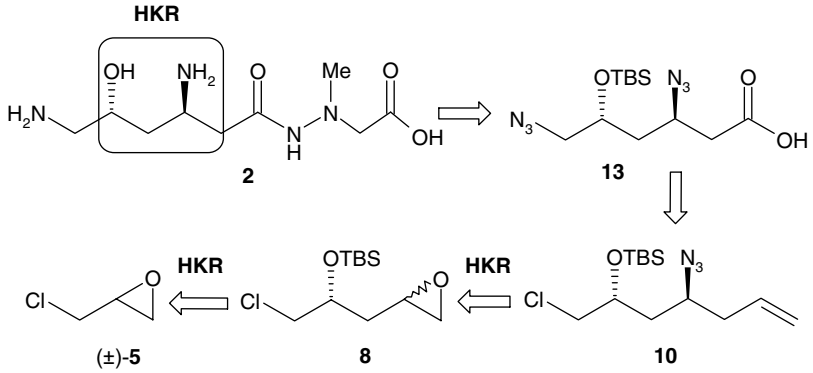
We then further proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl group protection. Towards this end, the



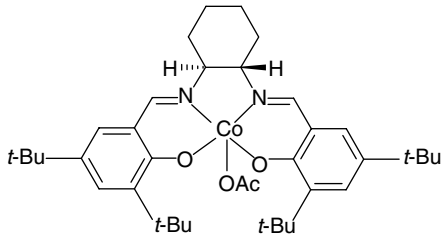
Scheme 1. General synthetic strategy for the synthesis of 1,3-aminoalcohols.



Scheme 3. Reagents and conditions: (a) *S*,*S*-salen-Co-(OAc) **4** (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 14 h, (46% for **5**, 45% for **6**); (b) vinylmagnesium bromide, ether, CuI, −78 to −40 °C, 19 h, 70%; (c) (i) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 10 h, 88%; (ii) TBDMS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 95%; (d) *S*,*S*-salen-Co-(OAc) **4** (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 24 h (46% for **8a**, 45% for **8b**).



Scheme 2. Retrosynthetic analysis of (+)-negamycin (**2**).



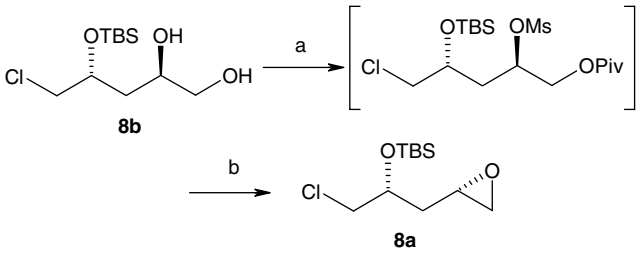
(*S*,*S*)-SalenCo(III)OAc complex (**4**)

Figure 2.

hydroxyl group of homoallylic alcohol **7** was first protected as its TBS ether, followed by epoxidation with *m*-CPBA. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti*:*syn*/3:1).

The desired *syn* isomer of **8** was obtained only as a minor component. However, when the epoxidation was carried out on alcohol **7** followed by hydroxy protection as the TBS-ether, the diastereomeric epoxide **8** was formed in favour of the desired *syn* isomer (*syn*:*anti*/1.2:1).[14] With epoxide **8** (*syn*:*anti*/1.2:1) in hand, our next aim was to synthesize the diastereomerically pure epoxide using Jacobsen's hydrolytic kinetic resolution method, the product of which could further be elaborated to the *anti*-1,3-aminoalcohol moiety.

Towards this end, epoxide **8** was treated with (*S*,*S*)-salen-Co-OAc complex **4** (0.5 mol %) and water (0.55 eq) in THF (0.55 equiv) to afford epoxide **8a** as a single diastereoisomer (determined from ^{1}H and ^{13}C NMR spectral analyses)[15] in 46% yield and diol **8b** in 45% yield. Epoxide **8a** could easily be separated from the more polar diol **8b** through silica gel column chromatography. In order to achieve the synthesis of target molecule **2**, we required epoxide **8a** in a substantial amount. As the HKR method provided the desired epoxide **8a** along with an equal amount of diol **8b**, we therefore thought it appropriate to convert diol **8b** into the required epoxide. Thus, the diol was smoothly converted into the desired epoxide **8a** via internal nucleophilic substitution of a secondary mesylate[16] (Scheme 4). Accordingly, the chemoselective pivalation of diol **8b** with pivaloyl chloride followed by mesylation of the secondary hydroxy and treatment of the crude mesylate product with K_2CO_3 in methanol led to deprotection of the pivaloyl ester to a hydroxy group.

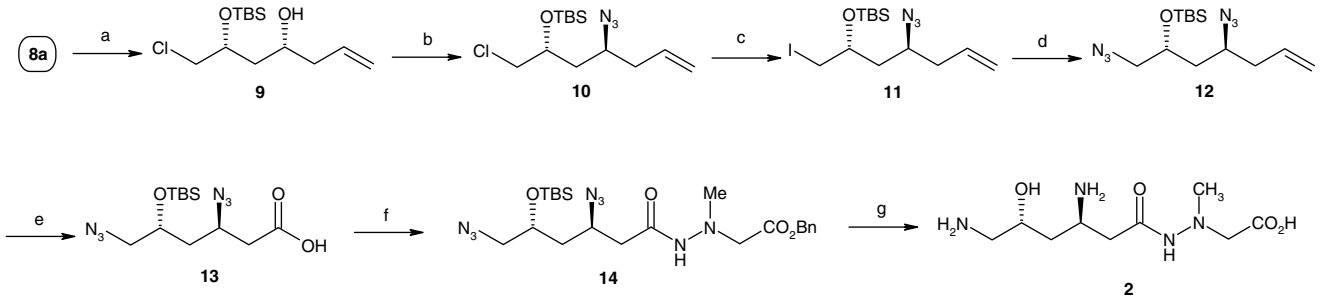


Scheme 4. Reagents and conditions: (a) (i) PivCl, Et_3N, cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 °C to rt, 1 h; (b) K_2CO_3, MeOH, rt, overnight (62% for three steps).

Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished epoxide **8a** in 62% overall yield.

With substantial amounts of **8a** in hand, we proceeded with the synthesis of **2** (Scheme 5) by opening of epoxide **8a** with vinylmagnesium bromide in the presence of CuI in THF at −20 °C to give homoallylic alcohol **9** in 86% yield. Compound **9** was then converted into an *O*-mesyl derivative, which on treatment with sodium azide in DMF furnished azide **10** with the desired stereochemistry at C-3. Treatment of **10** with a large excess of NaI in 2-butanone gave iodoazide **11** in essentially quantitative yield. Bis-azide **12** was obtained by smooth displacement of the iodo group in **11** with sodium azide. [**CAUTION**: appropriate care should be exercised when handling azides and bis-azides]. Oxidation of the olefinic bond using $RuCl_3/NaIO_4$ furnished the corresponding acid in 69% yield. Hydrazide **14** was prepared in good yield from **13** by formation of its mixed anhydride[17] with ethyl chloroformate and subsequent reaction of the activated carbonyl with benzyl (1-methylhydrazino)acetate.[8h] In the final step, the azides were reduced to amino groups by catalytic hydrogenation over Pd/C in MeOH, H_2O and AcOH with concomitant removal of the benzyl and silyl protecting groups to give (+)-negamycin **2** in 72% yield from **14**; $[\alpha]_D^{25}$ +2.1 (*c* 0.72, H_2O); lit.[8h] $[\alpha]_D^{25}$ +1.7 (*c* 0.6, H_2O); lit.[8b] +2.3 (*c* 4.07, H_2O). The physical and spectroscopic data of **2** were in full agreement with the literature data.

In conclusion, we have developed a practical and efficient strategy amenable to both *syn*- and *anti*-1,3-aminoalcohols with high degrees of enantio- and diastereoselectivities. The desired stereocentres can



Scheme 5. Reagents and conditions: (a) Vinylmagnesium bromide, THF, CuI, −20 °C, 1 h, 86%; (b) (i) MsCl, Et_3N, DMAP, 0 °C to rt, 1.5 h; (ii) NaN_3, DMF, 70 °C, 9 h, 89%; (c) NaI, 2-butanone, reflux, 6 h; (d) NaN_3, DMF, 70 °C, 4 h; (e) $RuC1_3$ (cat.), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, rt, 69%; (f) $C1CO_2Et$, NEt_3, toluene, −5 °C, then benzyl (l-methylhydrazino) acetate, 65%; (g) H_2, Pd–C, MeOH, H_2O, AcOH, rt, 72%.

simply be achieved by changing the catalyst for the HKR step. The synthetic protocol has been utilized for the synthesis of (+)-negamycin **2**. Further application of this methodology to the syntheses of all the isomers of negamycin and other biologically active compounds for structure activity relationship studies is currently underway in our laboratory.

Acknowledgements

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14. The two diastereomers could not be differentiated on TLC.
15. Spectral data of compound **8a**: colourless oil, $[\alpha]_D^{25}$ +24.0 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3017, 2959, 2932, 1859, 1469, 1376, 1258, 1216, 1108, 1006, 935, 874, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.69 (ddd, $J = 7.3$, 3.9, 2.1 Hz, 1H), 1.85 (ddd, $J = 7.3$, 4.4, 2.3 Hz, 1H), 2.53 (q, $J = 5.3$ Hz, 1H), 2.82 (t, $J = 4.4$ Hz, 1H), 3.02–3.06 (m, 1H), 3.49 (d, $J = 5.4$ Hz, 2H), 4.06–4.10 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.9, −4.6, 17.9, 25.7, 38.3, 47.5, 48.5, 49.1, 70.4. Anal. Calcd for $C_{11}H_{23}ClO_2Si$ (250.84): C, 52.67; H, 9.24; Cl, 14.13. Found C, 52.74; H, 9.11; Cl, 14.31. Spectral data of compound **9**: colourless oil, $[\alpha]_D^{25}$ +32.0 (*c* 0.41, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.80 (s, 9H), 1.61–1.95 (m, 2H), 2.13 (t, $J = 10.1$ Hz, 2H), 3.43 (d, $J = 5.2$ Hz, 2H), 3.81–3.83 (m, 1H), 4.03–4.08 (m, 1H), 5.03–5.06 (m, 2H), 5.71–5.77 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.1, −4.8, 13.9, 17.7, 25.5, 42.3, 47.9, 66.9, 70.2, 117.4, 134.2. Anal. Calcd for $C_{13}H_{27}ClO_2Si$ (278.89): C, 55.99; H, 9.76; Cl, 12.71. Found C, 56.21; H, 9.58; Cl, 12.91. Spectral data of compound **13**: yellowish oil, $[\alpha]_D^{25}$ +9.3 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3420, 2150, 1744, 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.91 (s, 9H), 1.36–1.48 (m, 2H), 2.67 (d, $J = 7.2$ Hz, 2H), 3.29 (dd, $J = 13.0$, 4.1 Hz, 1H), 3.52 (dd, $J = 13.0$, 4.0 Hz, 1H), 3.74 (m, 1H), 3.89 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.9, −4.6, 17.9, 25.7, 36.2, 37.3, 48.7, 55.8, 70.7, 176.2. Anal. Calcd for $C_{12}H_{24}N_6O_3Si$ (328.44): C, 43.88; H, 7.37; N, 25.59. Found C, 44.01; H, 7.27; N, 25.76.
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