Asymmetric amidation of (2*S*,3*S*)-pent-4-ene-1,2,3-triol. Total syntheses of (−)-anisomycin and (+)-polyoxamic acid

Sung Ho Kang* and Hyeong-wook Choi

Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

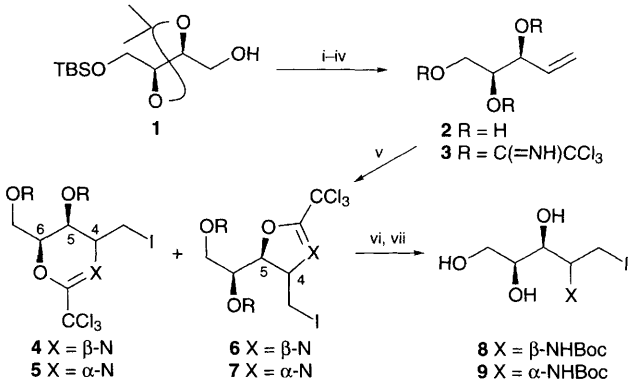
Intramolecular iodoamidation of pentenetriol 2 provides trihydroxy carbamate 8 in 94% de and was elaborated to (−)-anisomycin 15 and (+)-polyoxamic acid 19.

Optically active amino polyols are valuable building blocks for the syntheses of polyhydroxy amino acids, peptide isosteres, amino sugars, polyhydroxy pyrrolidines and piperidines, *etc.* Most commonly, they can be synthesised from carbohydrates or amino acids depending on the chiral centre(s). Since their chemical conversions and asymmetric inductions have sometimes been inefficient, it is evidently desirable to develop more facile and stereoselective synthetic routes. In this context, we planned to explore an intramolecular asymmetric iodoamidation[1] of tris(trichloroacetimidate) derived from (2*S*,3*S*)-pent-4-ene-1,2,3-triol **2**. The expected (2*S*,3*S*,4*S*)-4-amino-5-iodopentane-1,2,3-triol would serve as a useful common starting material in the syntheses of (−)-anisomycin[2] and (+)-polyoxamic acid[3] because they contain the same absolute configuration of one amino and two hydroxy groups. (−)-Anisomycin **15** exhibits potent and selective activity against pathogenic protozoa and fungi[4] by inhibiting ribosomal peptide synthesis.[5] It has been applied clinically to the treatment of trichomonas vaginitis and amebic dysentery.[6] (+)-Polyoxamic acid **19** is a common structural constituent of polyoxins[7] which act as chitin synthetase inhibitors.[8] They display prominent activities against *Candida albicans*, an infectious human fungal pathogen, as well as various phytopathogenic fungi and have been used widely as agricultural fungicides.[7,9] Here we describe an asymmetric amidation of (2*S*,3*S*)-pent-4-ene-1,2,3-triol **2** and its synthetic application to (−)-anisomycin **15** and (+)-polyoxamic acid **19**.

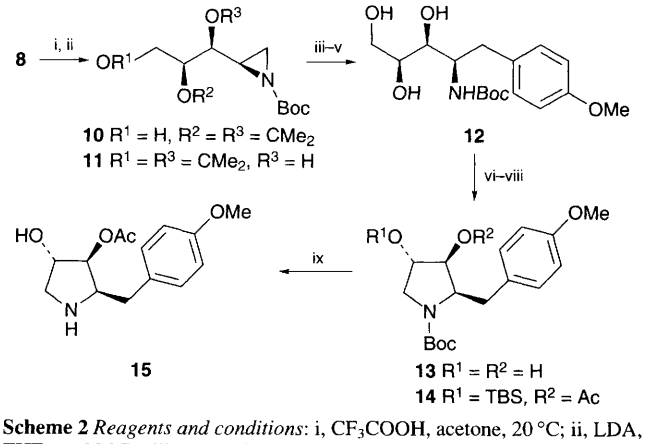
Triol **2**, $[\alpha]_D^{26}$ −37.7 (*c*. 1.00, MeOH) was prepared from the known alcohol **1**[3e] in 78% overall yield by a three step sequence of Swern oxidation,[10] Wittig methylenation and acidic hydrolysis (Scheme 1). After converting **2** into tris(trichloroacetimidate) **3** using trichloroacetonitrile and DBU, reaction with iodine in the presence of sodium bicarbonate in acetonitrile at 0 °C gave a 4–5 : 1 mixture of dihydro-1,3-oxazines (**4** and **5**) and oxazolines (**6** and **7**). Their major stereoisomers were determined to be *cis*-**4** and *trans*-**7**, respectively, based on the following spectroscopic data. **4**: C=N stretching band[11] at 1673 cm^{-1}, $J_{H\text{-}4,H\text{-}5}$ 2.9 Hz and $J_{H\text{-}5,H\text{-}6}$ 0 Hz. **7**: C=N stretching band at 1669 cm^{-1} and $J_{H\text{-}4,H\text{-}5}$ 5.7 Hz. Hydrolysis of the mixture followed by protection afforded a 12 : 1 mixture of carbamates **8** and **9** in 84% overall yield. Alternatively, when **3** reacted with iodine monobromide in the presence of potassium carbonate at −60 °C, only 6-membered heterocycles **4**, $[\alpha]_D^{26}$ −23.6 (*c* 0.50, $CHCl_3$) and **5** were formed. Their subsequent transformations produced a 37 : 1 mixture of the identical carbamates **8**, mp 86–86.5 °C, $[\alpha]_D^{27}$ +20.0 (*c* 0.80, MeOH) and **9** in 75% overall yield from **2**.

For the synthesis of (−)-anisomycin, it was necessary to introduce a 4-methoxyphenyl substituent to the C-5 position of **8**. The requisite transformation could only be achieved *via* aziridines with the hydroxy groups protected. Accordingly, **8** was treated with trifluoroacetic acid in acetone followed by lithium diisopropylamide (LDA) in THF to furnish a 3 : 1 mixture of acetonide aziridines **10** and **11** in 77% overall yield (Scheme 2). The mixture was treated with 4-methoxyphenylmagnesium bromide in the presence of a cuprous bromide–dimethyl sulfide complex in toluene, the acetonides were hydrolysed with trifluoroacetic acid and the resulting amino triol was reprotected as carbamate **12**, mp 49–49.5 °C, $[\alpha]_D^{25}$ +19.3 (*c* 0.80, $CHCl_3$) in 81% overall yield.

Since an efficient formation of the pyrrolidine ring from **12** seemed to be effected under Mitsunobu conditions,[12] it was subjected to diethyl azodicarbonate (DEAD) and triphenylphosphine, but no reaction occurred. Some experimentation revealed that unprecedentedly the addition of a few equivalents of pyridinium toluene-*p*-sulfonate (PPTS) or toluene-*p*-sulfonic acid induced the desired cyclization to provide pyrrolidine **13**, mp 140.5–141 °C, $[\alpha]_D^{25}$ −5.1 *c* 0.45, $CHCl_3$). Owing to the difficulty of separating **13** from triphenylphosphine oxide, the mixture was silylated and then acetylated to give acetate **14**,



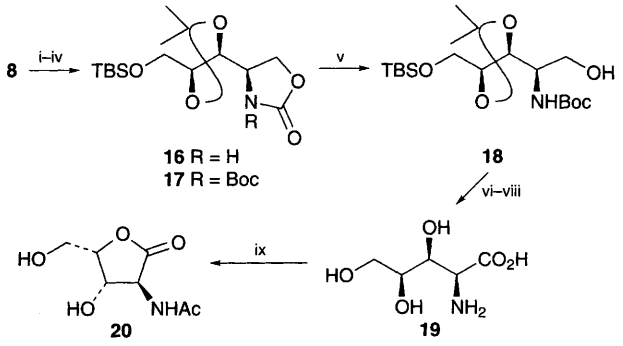
Scheme 1 *Reagents and conditions*: i, Swern oxidation; ii, $Ph_3P^+MeI^-$, BuLi, THF, HMPA, 0 °C; iii, 2 mol dm^{-3} HCl, THF, 20 °C; iv, CCl_3CN, DBU, MeCN, −30 °C; v, IBr, K_2CO_3, EtCN, −60 °C; vi, 6 mol dm^{-3} HCl, MeOH, 20 °C; vii, Boc_2O, $NaHCO_3$, MeOH, 0 °C



Scheme 2 *Reagents and conditions*: i, CF_3COOH, acetone, 20 °C; ii, LDA, THF, −20 °C; iii, *p*-$MeOC_6H_4MgBr$, CuBr–Me_2S, PhMe, −30 °C; iv, CF_3COOH, 20 °C; v, Boc_2O, $NaHCO_3$, MeOH, 0 °C; vi, DEAD, Ph_3P, PPTS, THF, 0 °C; vii, TBSCl, imidazole, DMF, 20 °C; viii, Ac_2O, DMAP, Et_3N, CH_2Cl_2, 20 °C; ix, 6 mol dm^{-3} HCl, MeOH, 20 °C

$[\alpha]_D^{25}$ +5.8 (*c* 1.14, MeOH) in 56% overall yield from **12**.[2h] Acidic hydrolysis generated (−)-anisomycin **15**, mp 142–142.5 °C, $[\alpha]_D^{30}$ −31.0 (*c* 0.49, MeOH) in 88% yield, of which the spectroscopic and physical data matched that reported in the literature.

The synthesis of (+)-polyoxamic acid was initiated by protecting the primary hydroxy group of triol **8** as the TBS ether and the two secondary hydroxy groups as an acetonide in 91% overall yield (Scheme 3). The resulting acetonide, mp 37–38 °C, $[\alpha]_D^{26}$ +25.1 (*c* 1.00, $CHCl_3$) was cyclized on treatment with sodium acetate in DMF at 120 °C to afford oxazolidinone **16**, $[\alpha]_D^{26}$ −12.1 (*c* 1.01, $CHCl_3$) in 92% yield. After converting **16** into carbamate **17**, mp 149–150 °C, $[\alpha]_D^{27}$ +32.4 (*c* 1.03, $CHCl_3$), it was hydrolysed chemoselectively[13] with methanolic potassium carbonate to provide alcohol **18**, $[\alpha]_D^{25}$ −5.3 (*c* 1.03, $CHCl_3$) in 92% overall yield. Alcohol **18** was oxidized to carboxylic acid,[14] mp 104–106 °C, $[\alpha]_D^{25}$ −12.7 (*c*, 100, $CHCl_3$) in 76% yield. Complete hydrolysis of all the protecting groups with methanolic hydrochloric acid furnished polyoxamic acid **19** in 87% yield. Treatment with acetic anhydride in methanol gave the lactone derivative **20**, mp 145.5–146.5 °C, $[\alpha]_D^{24}$ −108 (*c* 0.30, MeOH) which showed identical spectroscopic and physical data to that reported in the literature.[3b,h]



Scheme 3 *Reagents and conditions*: i, TBSCl, imidazole, DMF, −20 °C; ii, $Me_2C(OMe)_2$, *p*-TsOH, acetone, 0 °C; iii, NaOAc, DMF, 120 °C; iv, Boc_2O, DMAP, Et_3N, CH_2Cl_2, 20 °C; v, K_2CO_3, MeOH, 20 °C; vi, Swern oxidation; vii, 1 mol dm^{-3} $KMnO_4$, 5% NaH_2PO_4, Bu^tOH, 20 °C; viii, 6 mol dm^{-3} HCl, MeOH, 20 °C; ix, Ac_2O, MeOH, 20 °C

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