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A Simple, Divergent, Asymmetric Synthesis of All Members of the 2,3,6-Trideoxy-3-aminohexose Family

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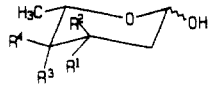
Several deoxyaminosugars constitute the glycosidic fragments of many anticancer antibiotics, such as anthracyclines,[1] glycopeptides,[2] and the recently reported esperamicin.[3] Interest in synthesizing these compounds, especially the 2,3,6-trideoxy-3-aminohexoses, has been apparent in the last 2 decades. More than 200 synthetic references relating to this subject were comprehensively reviewed in 1986.[1] A recent structure-activity study of antibiotics revealed the importance of aminosugars, for example, replacement of daunosamine (**1**) by acosamine (**2**) in daunorubicin

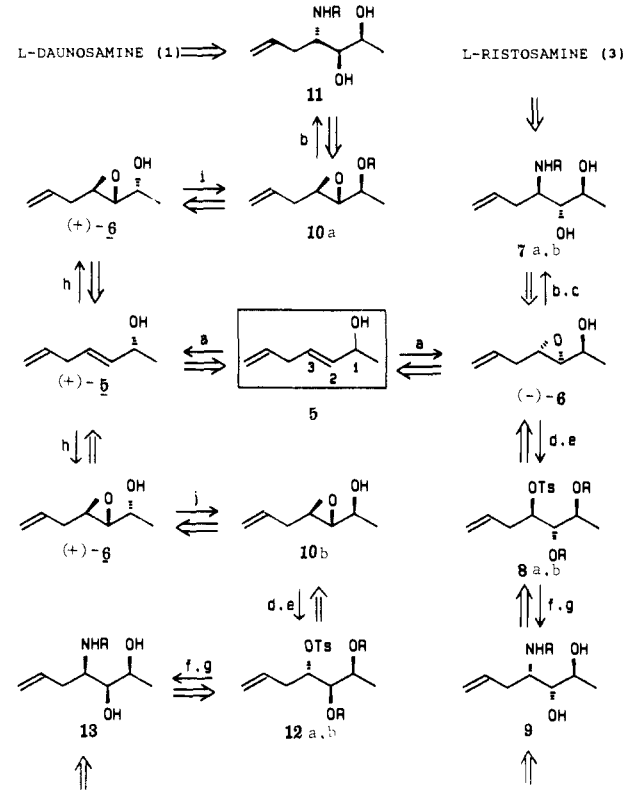


L-daunosamine (lyxo), R^2, R^4 = H; R^1 = NH_2; R^3 = OH, **1**
L-acosamine (arabino), R^2, R^3 = H; R^1 = NH_2; R^4 = OH, **2**
L-ristosamine (ribo), R^1, R^3 = H; R^2 = NH_2; R^4 = OH, **3**
L-3-*epi*-daunosamine (xylo), R^1, R^4 = H; R^2 = NH_2; R^3 = OH, **4**

and adriamycin produces analogues which are nearly devoid of cardiotoxicity but retain the anticancer activity.[4] Most of the syntheses of these aminosugars have been initiated from carbohydrate based materials and other natural chiral pools, but substantial efforts also have focused on the asymmetric synthesis from achiral compounds.[5,6]

We report here a simple, divergent synthesis of all four configurational isomers of 2,3,6-trideoxy-3-aminohexose (lyxo, arabino, ribo, and xylo) from the racemic 3,6-heptadien-2-ol. The synthetic strategy, depicted in Scheme I, relies mainly on the Sharpless epoxidation and a subsequent highly regiospecific ring-opening reaction. This strategy has been adopted by Masamune and Sharpless[7] as well as by Kishi[8] and by Roush[9] in the synthesis of monosaccharides. The crucial step here is installing the amino group with the right configuration to attain the three requisite contiguous chiral centers.

Scheme I. Retrosynthetic Analysis and Synthesis of L-2,3,6-trideoxy-3-amino-hexoses



[a] (a) Ti(O-i-Pr)$_4$ (0.14 equiv), L-(+)-DIPT (0.21 equiv, *t*-BuOOH (0.42 equiv), CH_2Cl_2, −25 °C; (b) NH_3–MeOH, 100 °C, 10 h; (c) PhCOCl, K_2CO_3, water–acetone; (d) PTS-LPTS, CH_2Cl_2, 0 °C; (e) cyclohexanone dimethyl ketal, CH_2Cl_2, PTS; (f) NaN_3/NH_4Cl, 100 °C, 15 h; (g) i, LAH, diethyl ether reflux, 1 h; ii, MeOH-H$^+$, 100 °C, 1 h; iii, PhCOCl, K_2CO_3, water–acetone; (h) Ti(O-*i*-Pr)$_4$, (1 equiv), D-(−)-DIPT (1.2 equiv), *t*-BuOOH (0.9 equiv), CH_2Cl_2, −25 °C; (i) PhCOOH, DEAD, Ph_3P, CH_2Cl_2; (j) i, *p*-NO_2-C_6H_4COOH, DEAD, Ph_3P, toluene, ii, MeOH/NaOMe, H$^+$.

Scheme I also presents synthetic details. Thus, kinetic resolution of the racemic **5** by the Sharpless method,[10] expeditiously afforded the epoxy alcohol (−)-**6** in 43.5% yield with more than 90% ee and the dienol (+)-**5** in 35% yield and 90% ee. Treatment of (−)-**6** with methanolic ammonia at 100 °C in a sealed tube, gave the required aminodiol, **7a** (R = H), which was converted to the known benzoylaminodiol **7b** (R = PhCO) [mp 137–138 °C, $[\alpha]_D^{10}$ −3.9° (*c* 1, EtOH) (lit.[5b,11] mp 137–138 °C $[\alpha]_D^{20}$ +6.4° (*c* 1, EtOH))] in 61% yield (two steps).[12] The observation that the ammonia opening occurred only at C_3 was not our expectation. In general, the nucleophilic opening of primary epoxyalcohols usually gives mixtures of products resulting from C_2 and C_3 attack, and high regioselectivity at C_3 can only be achieved with the aid of Ti(O-*i*-Pr)$_4$ or other chelating reagents.[13] Exclusive C_3 opening of (−)-**6** also occurred with NaN_3 to furnish the azido diol **14** (75% yield). **7b**, obtained in 60% yield by successive reduction and benzoylation of **14**, has been previously transformed to one of our targets, L-ristosamine (**3**).[11,12]

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For the route to L-acosamine, the amino group should be disposed in an opposite configuration of that of **7b**. This was realized by opening of the epoxide ring of (−)-**6** with tosylate to give **8a** (R = H) (78% yield, [mp 51–52 °C, $[\alpha]_D^{10}$ +7.4° (*c* 0.6, $CHCl_3$)]. Ketal protection of the diol **8a** with cyclohexanone followed by displacement with NaN_3 afforded in 74% yield the ketal protected azidodiol **15**, which was further treated with LAH and followed by acid hydrolysis and benzoylation to yield **9** [65% yield, $[\alpha]_D^{20}$ −13.8° (*c* 0.5, EtOH), (lit.[11] $[\alpha]_D^{20}$ −14.5° (*c* 1, EtOH))], a known precursor of acosamine.[11] The tosylate opening of the epoxyalcohol (−)-**6** proceeded very slowly with the conventional LPTS-Ti(O-*i*-Pr)$_4$. This reaction can only be effected by LPTS-PTS reagent.[18] The tosylate opening here again occurs exclusively at C_3.

The routes to daunosamine and epidaunosamine comprise entirely the same reactions with an only exception of an added Mitsunobu transformation of the C_1 configuration[14] (procedures i and j of Scheme I). The epoxybenzoate **10a** (R = PhCO) [$[\alpha]_D^{10}$ +35.4° (*c* 0.5, $CHCl_3$)] was obtained in 86% yield, which was transformed to **11** [47% yield, mp 134–135 °C, $[\alpha]_D^{10}$ +20.5° (*c* 0.5, EtOH) (lit.[11] $[\alpha]_D^{20}$ +21° (*c* 1, EtOH))]. An intramolecular migration of a benzoyl group from O to N was involved in this step. The epoxyalcohol **10b** [$[\alpha]_D^{20}$ +40.5° (*c* 0.5, CH_2Cl_2)] was obtained in 73% yield and underwent oxirane opening by tosylate to a monotosylate **12a** (R = H) [82% yield, mp 83–85 °C, $[\alpha]_D^{20}$ +12.1° (*c* 0.5, $CHCl_3$)]. In four steps and 49% overall yield, **12a** was transformed to **13** $[\alpha]_D^{10}$ +30° (*c* 0.5, EtOH)]. Compound **11** can be transformed to daunosamine (**1**) by a known ozonolysis procedure.[11] **13**[15] was subjected to ozonolysis and afforded an *N*-benzoyl-**4** [77% yield, mp 216–217 °C, $[\alpha]_D^{10}$ −55.0° (*c* 0.1, EtOH) (lit.[16] $[\alpha]_D^{20}$ −58.5° (*c* 0.25, EtOH) mp 215–218 °C)].

The D-isomers of the whole family can also be obtained either by exchanging L-(+)-DIPT in procedure a with D-(−)-DIPT in procedure h or by adding a Mitsunobu transformation in the right-hand side of Scheme I (that is transform (−)-**6** to (+)-**11**) and omit the Mitsunobu reaction in the left-hand side of Scheme I. Indeed, the antipode of **11** was obtained in 52% yield from (−)-**10a**, with an opposite rotation value of that of **11**, $[\alpha]_D^{10}$ −19.5 (*c* 0.5, EtOH).

In addition, the *N*-methyl or *N*,*N*-dimethyl isomers (namely, rhodasamine, R^1 = *N*,*N*-dimethyl in L-**1**, actinosamine, R^1 = *N*-methyl in L-**2**, megosamine, R^2 = *N*,*N*-dimethyl in L-**3**, angolosamine, R^1 = *N*,*N*-dimethyl in D-**2**) can be produced by opening of the epoxide ring with methyl or dimethylamine instead of opening by methanolic ammonia. One of them, a precursor of megosamine was prepared by treating (−)-**6** with dimethylamine in a sealed tube and after benzoylation, yielded a monobenzoyl-dimethylamino analogue of **7a** in 52% yield, $[\alpha]_D^{10}$ +18.3° (*c* 1.5, EtOH).[17]

Acknowledgment. This project is supported by The National Natural Science Foundation of China and Chinese Academy of Sciences.

(12) Owing to the discrepancy of the specific optical rotations, **7b** was subjected to ozonolysis and gave the benzoylristosamine on further treatment in 75% yield [$[\alpha]_D^{10}$ −15.3° (*c* 0.5, EtOH) 5 min, (lit.[11] $[\alpha]_D^{20}$ −12.5° (*c* 1, EtOH) 10 min)]. The ^{13}C NMR of benzoylristosamine obtained here showed the same spectra with known data. On correlating the value of the specific optical rotations of **7b**, **9**, **11**, and **13**, we are further convinced that the [α] value of −3.9 of **7b** is correct.

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(15) **13** has been obtained[11] as a minor component and has been transformed to a mixture of *N*-benzoyl derivatives of **1** and **4**. No data of **13** has been given.

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(17) Satisfactory spectroscopic data and elemental compositions were obtained for all new compounds.

(18) LPTS = 2,6-lutidinium *p*-toluenesulfonate; DEAD = diethyl azodicarboxylate.

Stereocontrolled Total Synthesis of (±)-Quinocarcin

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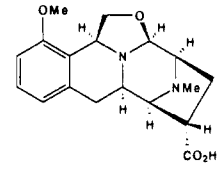
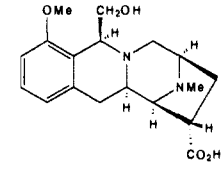
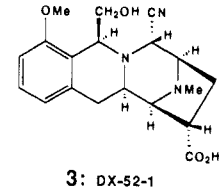
Since its initial isolation by Takahashi and Tomita[1] in 1983, the antitumor antibiotic quinocarcin (**1**) and its inactive congener quinocarcinol (**2**), have attracted considerable synthetic attention.[2]



1: Quinocarcin



2: Quinocarcinol



3: DX-52-1

Although little is known of the mechanism of action of quinocarcin, it seems likely that the compound may act as a site specific catalyst for superoxide generation, much like the quinone antibiotics. As a result, it exhibits strong activity against P388 lymphocytic leukemia in mice while displaying a rather restricted antibacterial spectrum.[3] Although the synthesis of quinocarcinol was achieved in 1985,[2a] the instability inherent in the oxazolidine of the title compound proved a demanding obstacle to the successful synthesis of quinocarcin. Herein we report the first total synthesis of the novel molecule via the key intermediate DX-52-1 (**3**), a cyano derivative first synthesized from the natural product by investigators at Kyowa Hakko in Japan.[2b] DX-52-1 afforded an excellent subtarget, possessing the requisite stability for appropriate skeletal manipulations while providing easy access to the aforementioned oxazolidine of this complex structure.

Condensation of the readily available aldehyde **4**[4] and piperazinedione **5**[5] (*t*-BuOK/*t*-BuOH, THF, −78 °C),[6] followed by ammonolysis (NH_3, MeOH), provided the unsymmetrical piperazinedione **6** in 81% yield (Scheme I). Selective activation of the amide nitrogen (CbzCl, DMAP, Et_3N, CH_2Cl_2, −20 °C, 24 h, 82%) to give **7** allowed for the construction of a diazabicyclo[3.2.1] system utilizing a three-step protocol. First, partial amide carbonyl reduction ($NaBH_4$, MeOH/CH_2Cl_2, −20 °C), followed by acyliminium ion-mediated cyclization ($HgCl_2$, CSA, CH_3CN/H_2O, 40 °C, 20 min), and finally reduction of the resultant aldehyde ($NaBH_4$, MeOH/CH_2Cl_2, 0 °C) gave the alcohol **8** in 59% yield. With the bicyclic system in place, reduction of the exocyclic double bond (Ra–Ni (W2), H_2 (2000 psi), EtOH, 100 °C, 1.5 h) could be effected from the less hindered α-face of the molecule. Immediate in situ reprotection of the amine[7]

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(4) Prepared from commercially available *m*-hydroxybenzaldehyde (dimethylthexylsilyl chloride (DMTSCl), *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 70 °C).

(5) Prepared in seven steps from commercially available diethylacetamidomalonate in 39% overall yield: (1) propargyl bromide, NaH, DMF; (2) 3 N HCl, reflux; (3) MeOH, 12 N HCl, reflux; (4) $ClCH_2COCl$, $NaHCO_3$, Et_2O/H_2O; (5) NH_3, MeOH, 140 °C; (6) Ac_2O, reflux; (7) PhSH, AIBN, benzene.

(6) A modification of the original procedure which provided improved yields. See: Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667.

(7) For subsequent opening of the bicyclic lactam it was crucial that some electron-withdrawing group be affixed to this amine nitrogen.

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