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A divergent approach to 3-azido-2,3,6-trideoxy-L-hexoses from rhamnal

Guisheng Zhang,* Lei Shi, Qingfeng Liu, Xiaobing Liu, Lu Li and Jingmei Wang

School of Chemical and Environmental Sciences, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, 46 East Construction Road, Xinxiang, Henan 453007, PR China

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Abstract—An alternative strategy has been developed for producing 3-azido-2,3,6-trideoxy-L-hexoses, protected forms of daunosamine, ristosamine, acosamine, and *epi*-daunosamine. This method involved $BF_3{\cdot}OEt_2$-induced peroxidation of rhamnal to construct key intermediate α,β-unsaturated lactone as the common precursor. After further derivatization, four 3-azido hexoses were successfully synthesized.

1. Introduction

Anthracycline antibiotics have received much attention because of their potent bioactivity against a wide range of human tumors.[1] Since the first isolation of doxorubicin (DOX) and daunorubicin (DNR) from *Streptomyces peucetius* in the 1960s, thousands of analogues have been reported. However, only a few of them have earned clinical approval: idarubicin (IDA),[2] epirubicin (EPI),[3] aclarubicin,[4–6] pirarubicin,[7] and valrubicin[8] (Fig. 1). These anthracyclines consist of a tetracyclic chromophore and one or more sugar residues; the first moiety is usually an amino sugar, which may be the only sugar residue, or be part of an oligosaccharide chain. Clinical studies revealed that the configuration of the amino sugar influences strongly the bioactivity of the drug. It has been reported that changing L-daunosamine of DOX to EPI (with a sugar moiety of L-acosamine) nearly suppresses the undesired toxic side effects while maintaining similar antitumor activity.[9] There have been continuing efforts on the synthesis of the not readily available four diastereomeric 3-amino-2,3,6-trideoxy-L-hexoses: daunosamine (Scheme 1, **II-1**), ristosamine (**II-3**), acosamine (**II-2**), and *epi*-daunosamine (**II-4**), key components of anthracyclines. Traditionally, the syntheses of these optical amino deoxy sugars have been initiated from carbohydrate based materials.[10] An alternative approach was using non-carbohydrate precursors.

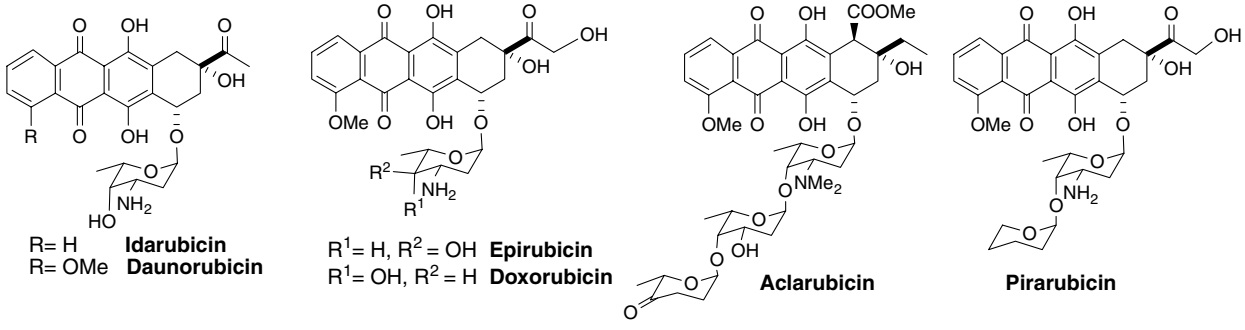

Figure 1. Clinically used anthracyclines.

* Corresponding author. Tel./fax: +86 373 3325250; e-mail: zgs6668@yahoo.com

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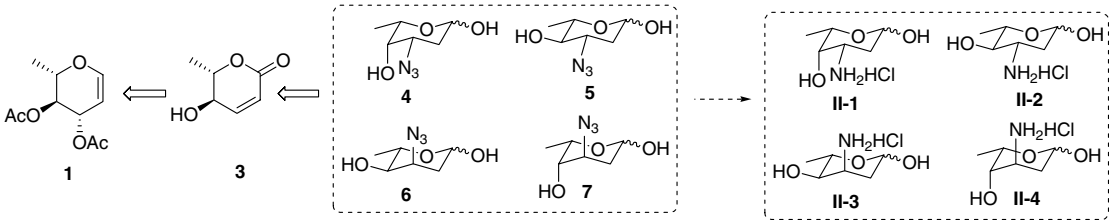
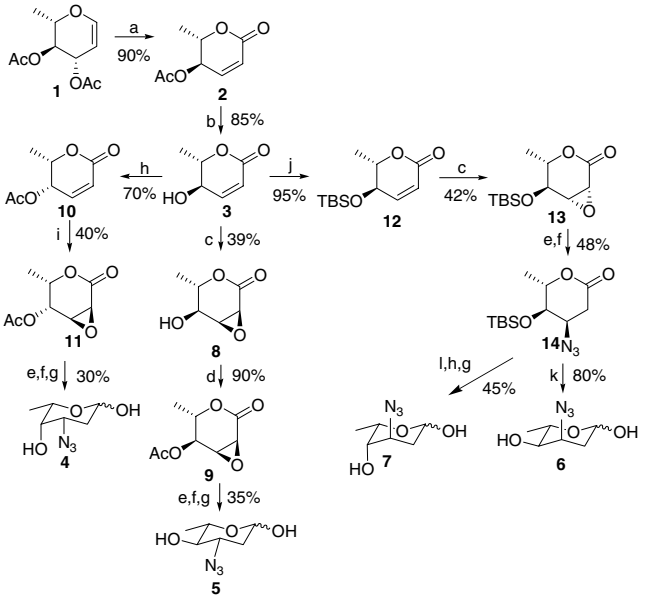


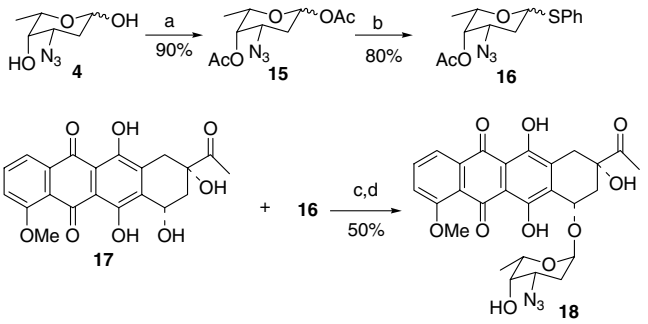
Scheme 1.

For instance, Wovkulich's group synthesized L-acosamine and L-daunosamine via an enantioselective intramolecular [3+2] cycloaddition.[11] Recently, Riera's group reported a stereodivergent approach to these four amino sugars from propargyl alcohol in 11 steps.[12]

Recently, we reported a series of anthracyclines with different uncommon sugars and their bioactivities.[13] In current research we intend to attach these aminosugars to a modified anthracycline quinone in search of new anthracycline antibiotics. Herein, we present our strategy (Scheme 1) to achieving these aminosugars from rhamnal. In this pathway 3,4-di-*O*-acetyl-L-rhamnal (**1**) was used as starting material for the preparation of key intermediate α,β-unsaturated lactone **3** via $BF_3{\cdot}OEt_2$-induced peroxidation. Finally after further derivatization, four 3-azido hexoses (**4**–**7**), protected forms of daunosamine, ristosamine, acosamine, and *epi*-daunosamine, were successfully synthesized in 7–9 steps as depicted in Scheme 2. We strategically incorporated azido group in our deoxy sugars, since the azido group can be an excellent masking group for amino functionalities and can be amplified to diversify drug-resembling moieties. These azido sugars can be converted to glycosyl donors useful for the glycosylation



Scheme 2. Reagents and conditions: (a) MCPBA, BF_3OEt_2; (b) K_2CO_3/MeOH; (c) NaClO, pyridine; (d) Ac_2O, pyridine; (e) $NaBH_4$, PhSeSePh, AcOH, ^{i}PrOH; (f) DPPA, PPh_3, DEAD; (g) K_2CO_3/MeOH then DIBAL-H; (h) HOAc, PPh_3, DEAD; (i) $PhCO_3H$, C_6H_6; (j) TBSCl, imidazole; (k) TBAF then DIBAL-H; (l) TBAF.



Scheme 3. Reagents and conditions: (a) Ac_2O, pyridine; (b) PhSH, $BF_3{\cdot}Et_2O/CH_2Cl_2$, 0 °C, 2 h; (c) TTBP, $AgPF_6/CH_2Cl_2$, 0 °C; (d) 0.1 M NaOH/THF, 0 °C.

of anthracyclinones, as exemplified by the coupling reaction of daunosamine derivative **16** with daunorubicinone **17** affording 3′-azido-3′-deamino daunorubicin **18** (Scheme 3).

2. Results and discussion

The commercially available 3,4-di-*O*-acetyl-L-rhmnal **1** was readily converted to lactone **2**[14] via the reaction with *m*-chloroperbenzoic acid (MCPBA) and $BF_3{\cdot}OEt_2$ in dichloromethane at −20 °C in excellent yield.[15] Deacetylation of compound **2** by treatment with anhydrous sodium carbonate in methanol produced the key intermediate lactone **3** in 85% yield.

Silylation of lactone **3** with *tert*-butyldimethylsilyl group in the presence of imidazole gave compound **12** in excellent yield. When compound **12** was treated with NaClO/pyridine, *trans*-epoxide **13** was obtained exclusively due to the bulky *tert*-butyldimethylsilyl group helping to force the subsequent epoxidation to happen at the *anti*-face of the existing hydroxyl group. Reduction of epoxide **13** with sodium phenylseleno(triisopropyloxy)-borate ($NaBH_4$ and PhSeSePh in acetic acid),[16] followed by treatment with diphenylphosphoryl azide (DPPA) in presence of DEAD and triphenylphosphine (Mitsunobu reaction)[17] afforded azido compound **14** in good yield. Finally, compound **14** was readily converted into the 3-azido-2,3,6-trideoxy sugar **6** after subsequent treatment with TBAF and DIBAL-H in very good yield. Meanwhile, the stereoselective approach to 3-azido-2,3,6-trideoxy sugar **7** was also achieved from **14** by taking advantage of Mitsunobu reaction, as depicted in Scheme 2. Treatment of **14** with TBAF, then with HOAc in the presence of DEAD and triphenylphosphine, and

subsequent treatment with TBAF and DIBAL-H afforded azido sugar **7**[14] in 45% overall yield from **14**.

In order to synthesize azido sugar **4**, lactone **3** was firstly converted to another lactone **10**[14] by reaction with HOAc in the presence of DEAD and triphenylphosphine as shown in Scheme 2. When the conversion of **10** to epoxide **11** was performed according to the procedure for preparation of epoxide **13**, we found it did not work well. Fortunately, the reagent $PhCO_3H$ worked well for the conversion in the benzene at 0 °C. Treatment of epoxide **11** by following the procedure for preparation of **14** from **13** afforded an azido lactone which was readily converted to azidosugar **4** after subsequent treatment with anhydrous K_2CO_3 and DIBAL-H in 30% yield (overall yield of three reaction steps).

When lactone **3** was subjected to the epoxidation conditions (NaClO/pyridine), epoxide **8** was isolated in 39% yield. Acetylation of epoxide **8** afforded another epoxide **9**. Compound **9** was converted azidosugar **5**[14] by following the procedures for the preparation of azidosugar **4** from epoxide **11** in 35% overall yield for the four reaction steps.

Recently we reported a daunorubicin analogue 3′-azido-3′-deamino daunorubicin (**18**) that shows significant anticancer activity against drug-resistant cancers in cell cultures (in vitro) and in a xenograft model in vivo, increases animal survival rate, and decreases general toxicity in the animal model.[13b] It was synthesized by treatment of daunorubicin with a TfN_3 solution in 70% yield. In this Letter we present an alternative synthetic method of the daunorubicin analogue as an example of the glycosylation of anthracyclinones with azidosugars (Scheme 3). Acetyl group was used for protecting the hydroxyl groups present in the azidosugar molecule, because they were cleavable under 0.1 M NaOH in THF at 0 °C, which allowed the acid and strong base-sensitive aglycon moiety in the anthracyclines not to be affected in the final deprotection procedures. As shown in Scheme 3, after treatment with phenylthiol in the presence of $BF_3{\cdot}Et_2O$ at 0 °C for 3 h, the desired sugar donor **16** was obtained in good yield. The thiolglycoside was obtained as a mixture of α- and β-isomers. Since both isomers are able to be used for the glycosylation to produce the desired α-linked daunorubicin derivatives, separation was not necessary. With daunorubicinone **17** and the sugar donor in hand, the glycosylation was performed subsequently. The mixture of aglycon **17** and sugar donor **16**, in the presence of TTBP (2,4,6-tri-*tert*-butylpyrimidine) and 4 Å molecular sieves, was treated with $AgPF_6$ at 0 °C for 4 h to give a unseparated mixture. The ^1H NMR data of this mixture indicated that the desired α-linkage was formed predominantly ($\alpha:\beta \approx 5:1$). Treatment of the mixture with 0.1 M NaOH in THF gave the glycosylated product **18** in 50% overall yield for the two reaction steps after purification through a silica gel column using $MeOH/CH_2Cl_2$ (1:100–50).

In summary, by utilizing the $BF_3{\cdot}OEt_2$-induced peroxidation of rhamnal, we were able to generate the α,β-unsaturated lactone conveniently in large scale. In addition, starting from this lactone, four stereoisomers of 3-azido-2,3,6-trideoxy-L-hexoses, protected forms of daunosamine, ristosamine, acosamine, and *epi*-daunosamine were successfully prepared. We have developed a new effective divergent approach to 3-amino-2,3,6-trideoxy sugars. Additional applications of these azido sugars in the preparation of new types of anthracyclines are currently undergoing in our laboratory.

Acknowledgments

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14. Spectroscopic data: Compound **2** ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, $J = 9.9$, 3.2 Hz, 1H), 6.07 (dd, $J = 9.9$, 1.5 Hz, 1H), 5.58–5.53 (m, 1H), 5.24 (dd, $J = 8.9$, 2.2 Hz, 1H), 2.10 (s, 3H), 1.39 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 143.1, 123.0, 76.6, 67.9, 21.0,

18.5; HRMS *m*/*z* calculated for $C_8H_{10}O_4$ 170.0579 (M+), found 170.0580. Compound **5** was obtained as a mixture of α/β-anomers, selected data for β-anomer ^{1}H NMR (400 MHz, CD_3OD) δ 5.15 (dd, $J = 9.3$, 2.0 Hz, 1H), 4.50 (dd, $J = 9.5$, 9.0 Hz, 1H), 3.63 (ddd $J = 12.0$, 9.5, 4.0 Hz, 1H), 3.44 (qd, $J = 9.0$, 6.5 Hz, 1H), 2.26–2.15 (m, 1H), 1.80–1.75 (m, 1H), 1.30 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 90.8, 69.6, 67.0, 63.3, 32.0, 15.4; HRMS (EI) *m*/*z* calculated for $C_6H_{11}N_3O_3$ 173.0796, found 173.0790. Compound **7** was obtained as a mixture of α/β-anomers, selected data for β-anomer ^{1}H NMR (400 MHz, CD_3OD) δ 5.01 (dd, $J = 8.9$, 2.5 Hz, 1H), 4.10 (m, 1H), 3.68 (qd, $J = 6.2$, 1.8 Hz, 1H), 3.42–3.38 (m, 1H), 2.16–2.12 (m, 1H), 1.90–1.80 (m, 1H), 1.32 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 90.8, 70.1, 67.1, 63.3, 32.1, 15.3; HRMS (EI) *m*/*z* calculated for $C_6H_{11}N_3O_3$ 173.0796, found 173.0800. Compound **10** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, $J = 9.9$, 2.2 Hz, 1H), 5.97 (dd, $J = 9.9$, 1.8 Hz, 1H), 4.50–4.42 (m, 1H), 4.23 (dd, $J = 5.8$, 3.0 Hz, 1H), 2.11 (s, 3H), 1.47 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 143.5, 124.0, 76.7, 67.9, 21.4, 18.5; HRMS *m*/*z* calculated for $C_8H_{10}O_4$ 170.0579 (M^+), found 170.0576.

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