Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8777–8780

An intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters: a very concise route to daunosamine, acosamine, ristosamine and 3-*epi*-daunosamine precursors

Yoshitaka Matsushima* and Jun Kino

Department of Chemistry, Hamamatsu University School of Medicine, Handayama, Hamamatsu 431-3192, Japan

Received 24 August 2006; revised 19 September 2006; accepted 29 September 2006
Available online 24 October 2006

Abstract—A new and very concise strategy has been formulated for the synthesis of 3-amino-2,3,6-trideoxyhexoses, daunosamine, acosamine, ristosamine and 3-*epi*-daunosamine, via *cis*- and *trans*-oxazoline intermediates assembled by a novel intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters in an acyclic system.

Amino sugars, especially deoxyamino sugars, are found in clinically important antibiotics such as antimicrobial macrolides and anthracycline antitumour antibiotics.[1] In most instances, the sugar parts of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not yet been evaluated.[2]

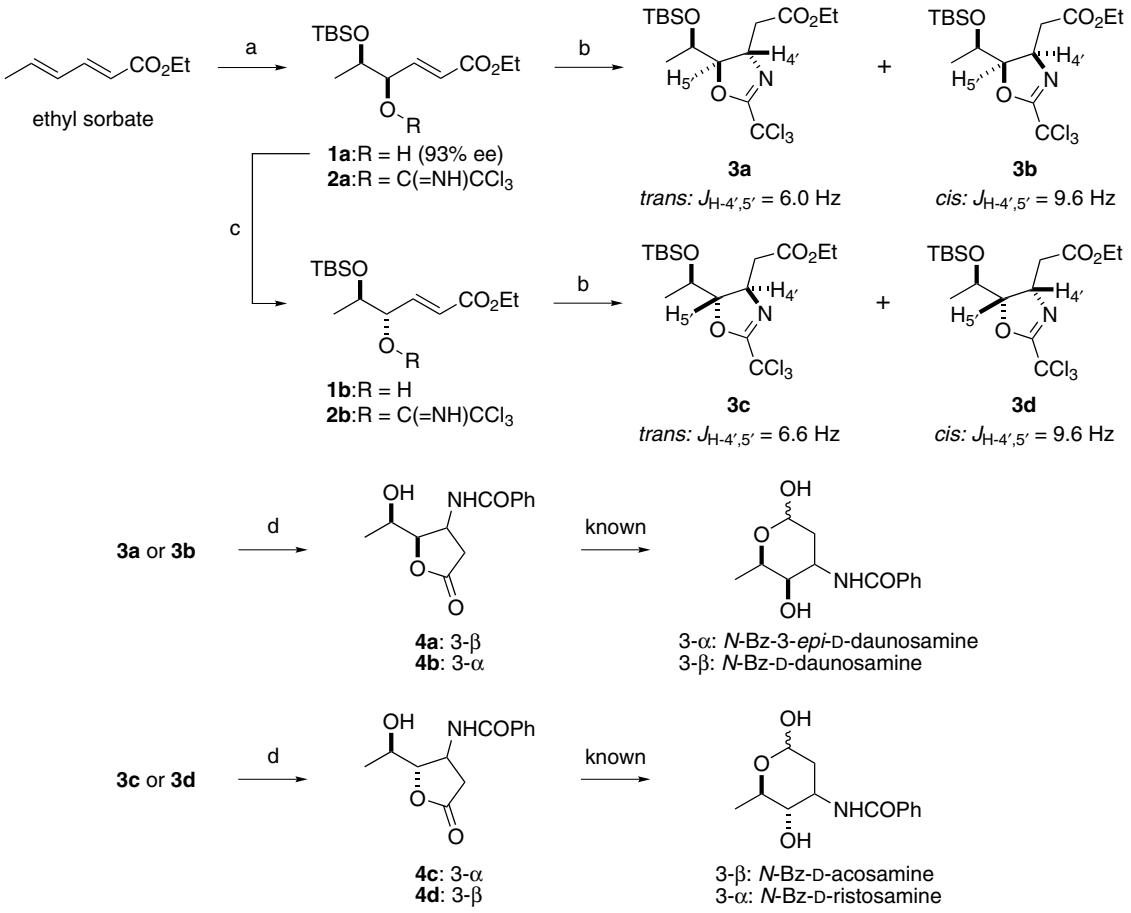
We envisaged that a modification of the sugar moieties of these antibiotics may serve as a tool for investigating the significance of amino sugars and the structure–activity relationship. For this purpose, a versatile synthetic route for deoxyamino sugars is highly desirable. Furthermore, we expected that such a route would also be beneficial for elucidating the biosynthetic route of antibiotics.[3,4] We were especially interested in developing a new synthetic route for deoxyamino sugars from non-sugar material. Recently, we reported the iodocyclisation of the carbamate based on the (*E*)-α,β-unsaturated ester moiety indigenous to the starting material (ethyl sorbate) for the synthesis of 4-amino-2,4,6-trideoxysugar.[5]

Our next target deoxyamino sugars were 3-amino-2,3,6-trideoxyhexoses[6] such as daunosamine, an amino sugar component of daunomycin. In an attempt to synthesise 3-amino-2,3,6-trideoxyhexoses effectively, we planned to develop a new nitrogen-introducing intramolecular conjugate addition expectantly with 1,2-asymmetric induction. The intramolecular conjugate additions are a well-documented method for the heterofunctionalisation of alkene; especially, the intramolecular conjugate addition of the carbamates has been used for the synthesis of 3-amino-2,3,6-trideoxyhexoses.[7] However, to our knowledge, the intramolecular conjugate addition of trichloroacetimidates involving α,β-unsaturated esters in the acyclic systems was never reported.[8] In this paper, we describe a novel intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters in an acyclic system, especially for the synthesis of the precursors of the 3-amino-2,3,6-trideoxyhexoses, D-daunosamine, D-acosamine, D-ristosamine and 3-*epi*-D-daunosamine starting from the chiral diol available by Sharpless asymmetric dihydroxylation (AD) (Scheme 1).

Starting known chiral allyl alcohol **1a**[5] was obtained from commercially available ethyl sorbate by Sharpless asymmetric dihydroxylation using dihydroquinidine phthaladine [$(DHQD)_2PHAL$] as a chiral ligand (AD-mix β)[9] and the subsequent selective protection of the 5-hydroxyl group as its 5-*tert*-butyldimethylsilyl (TBS) ether. The enantiomeric purity of **1a** was determined to be 93% ee by the ^1H NMR analysis of the corresponding ester with (+)/(−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid).[10]

Keywords: Intramolecular conjugate addition; Deoxyamino sugar; 3-Amino-2,3,6-trideoxyhexose; Oxazoline; Trichloroacetimidate.
* Corresponding author. Tel./fax: +81 53 435 2319; e-mail: ymatsu@hama-med.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.164



Scheme 1. Reagents and conditions: (a) (1) lit.[5]; (2) DBU, Cl_3CCN, CH_3CN, −20 °C (99%); (b) condition A: cat. DBU, CH_3CN (−20 °C: 67% for **3a**, 19% for **3b**; 0 °C: 92% for **3c**, 3.4% for **3d**); condition B: cat. *tert*-BuOK, THF (−78 °C: 23% for **3a**, 58% for **3b**; −62 °C: 37% for **3c**, 42% for **3d**); (c) (1) PPh_3, DEAD, HCO_2H, benzene, rt; (2) dil NH_3 aq, EtOH, rt; (61%, two steps); (3) DBU, Cl_3CCN, CH_3CN, −20 °C (94%); (d) 3 M HCl, EtOH, reflux; evaporation; PhCOCl, sat. $NaHCO_3$ aq, acetone, rt (51% for **4a**, 64% for **4b**, 19% for **4c**, 79% for **4d**).

Firstly, allyl alcohol **1a** thus obtained was dissolved in acetonitrile and treated with trichloroacetonitrile (Cl_3CCN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce trichloroacetimidate **2a**[11] in a quantitative yield. Under the usual conditions (Cl_3CCN: 1.2–3.0 equiv, DBU: 0.12–1.2 equiv, 0 °C to rt), the substantial migration of the TBS protecting group from the hydroxyl group at C-5 to that at C-4 was observed during the course of the reaction. During the course of the close analysis of by-products along with TBS migration, we fortunately found a small amount of desirable conjugate adducts, *trans*-oxazoline **3a**[12] and *cis*-oxazoline **3b**,[12] to be formed. To prevent this migration the reaction was needed to be performed in the presence of a large excess of Cl_3CCN (ca. 10 equiv) at −20 °C for several minutes. Under these conditions almost no conjugate adducts were obtained and prolonged time or increased temperature did not afford the conjugate adducts in a good yield. However, after the isolation, the trichloroacetimidate **2a** underwent a facile cyclisation with a moderate diastereoselectivity to produce these oxazolines by treatment with potassium *tertiary* butoxide (*tert*-BuOK) or DBU as the basic catalysts especially at low temperature.[13] Stereoselectivity in the cyclisation can be anticipated using the transition state (TS) models shown in Figure 1. The cyclisation is thought to proceed through the *trans*-TS model to give the *trans*-oxazoline **3a**, since *cis*-TS model is unfavourable than the *trans*-TS model due to its steric hindrance between the somewhat bulky side chain R and the alkenyl group. However, interestingly, diastereoselectivity during the attack of an imide nitrogen was found to be moderately controlled by the catalyst used in the reactions; *trans*-oxazoline was dominantly produced (**3a**:**3b** = 78:22) in the presence of a catalytic amount of DBU in acetonitrile (condition A), whereas *cis*-oxazoline was the major product in the presence of a catalytic amount of *tert*-BuOK (**3a**:**3b** = 28:72) in THF (condition B).

It was reported that in an oxazoline ring the small coupling constant (6 Hz) corresponded to trans form and the large one (9 Hz) to cis form.[14,15] Therefore, its relatively small coupling constant ($J_{H\text{-}4',5'} = 6.0$ Hz) implied the trans stereochemistry of compound **3a** and relatively large coupling constant ($J_{H\text{-}4',5'} = 9.6$ Hz) implied cis stereochemistry of the compound **3b**. Additionally, the stereochemistry of the both compounds was also confirmed by the nuclear Overhauser enhancement (NOE) experiment.[16]

In an attempt to expand our strategy to the other kinds of 3-amino-2,3,6-trideoxyhexoses, such as acosamine

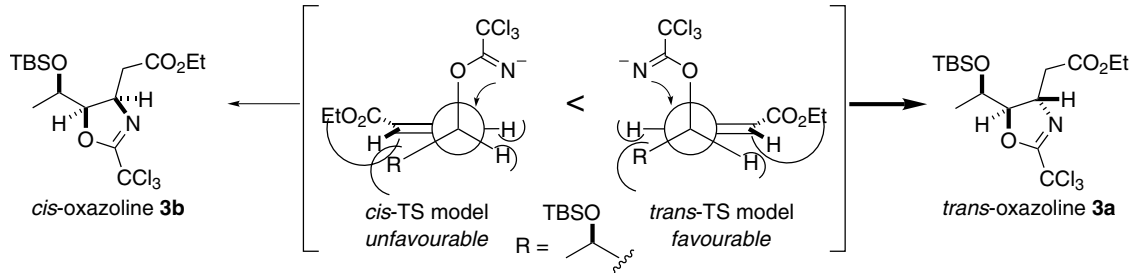


Figure 1. Proposed transition state models for cyclisation.

and ristosamine, the stereochemistry of the hydroxy group (C-4) of the starting allyl alcohol **1a** was suitably inverted by the Mitsunobu reaction, followed by the hydrolysis of the formate to afford the allyl alcohol **1b** in a 61% yield.[17] As described with **2a**, the trichloroacetimidate **2b** was produced under the same condition from **1b** in a 94% yield. In the next intramolecular conjugate addition, the reversal of diastereofacial selectivity was also observed, however, the ratios were different to some extent; namely: *trans*-oxazoline **3c**[12] was predominantly produced (**3c**:**3d** = 96:4) under condition A, whereas *cis*-oxazoline **3d**[12] was the slightly major product (**3c**:**3d** = 47:53) under condition B.

With four diastereomers in hand, the final manipulation of our work was the transformation to the known *N*-Bz-γ-lactones; the exact precursors[18a] of 3-amino-2,3,6-trideoxyhexoses. To this end,[19] the hydrolysis of the TBS protecting group and oxazoline ring of the compounds **3a**–**d** and their spontaneous lactone formation were realised by heating with 3 M hydrochloric acid in ethanol, followed by evaporation to afford the corresponding γ-lactone hydrochlorides, respectively. The crude products thus obtained were immediately suspended in acetone and treated with saturated aq sodium bicarbonate and benzoyl chloride to produce the desired *N*-Bz-γ-lactones **4a**–**d**, the precursors for the synthesis of *N*-Bz-protected 3-*epi*-D-daunosamine, D-daunosamine, D-acosamine and D-ristosamine, respectively (51% for **4a**; 64% for **4b**; 19% (not optimised) for **4c**; 79% for **4d**) for the two steps. The spectral data and optical rotation of the resulting compounds **4a**–**d** were, respectively, identical to those reported in the literature.[7,18]

In conclusion, we have succeeded in developing a very concise route for *N*-Bz-protected D-daunosamine, D-acosamine, D-ristosamine and 3-*epi*-D-daunosamine using a novel intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters, demonstrating that our synthetic strategy is applicable to the synthesis of 3-amino-2,4,6-trideoxysugars from non-sugar starting chiral diol. Further studies on this type of intramolecular conjugate additions are now in progress and will be reported in due course.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (17780089) and a 21st century COE program (Hamamatsu University School of Medicine, Medical Photonics) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors would like to thank the technical staffs (M. Suzuki and M. Toyama) for their supports.

References and notes

1. Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99–110.
2. Paloma, L. G.; Smith, J. A.; Chazin, W. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 3697–3708.
3. Nedal, A.; Zotchev, S. B. *Appl. Microbiol. Biotechnol.* **2004**, *64*, 7–15.
4. Yu, T.-W.; Müller, R.; Müller, M.; Zhang, X.; Draeger, G.; Kim, C.-G.; Leistner, E.; Floss, H. G. *J. Biol. Chem.* **2001**, *276*, 12546–12555.
5. Matsushima, Y.; Kino, J. *Tetrahedron Lett.* **2005**, *46*, 8609–8612.
6. For a recent synthesis of 3-amino-2,3,6-trideoxyhexoses, see: Ginesta, X.; Pastó, M.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001–3004, and references cited therein.
7. Hirama, M.; Nishizaki, I.; Shigemoto, T.; Itô, S. *J. Chem. Soc., Chem Commun.* **1986**, 393–394, and references cited therein.
8. Intramolecular conjugate addition of trichloroacetimidates in a cyclic system was very recently reported, see: (a) Brown, J. R.; Nishimura, Y.; Esko, J. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 532–536; For the intramolecular conjugate addition of trichloroacetimidates to vinyl sulfones, see: (b) Li, X. C.; Fuchs, P. L. *Synlett* **1994**, 629–630.
9. Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345–1376.
10. The signals due to the H-2 appeared in distinctly different fields [ester from (+)-MTPA: $\delta_{H\text{-}2}$ 5.82 (dd, $J = 1.7$, 16.0 Hz) and ester from (−)-MTPA: $\delta_{H\text{-}2}$ 5.95 (dd, $J = 1.5$, 15.8 Hz)].
11. All new compounds were fully characterised with relevant spectroscopic data and elemental analyses.
12. The data for the oxazolines (**3a**–**d**) are listed below. Compound **3a** (*trans*-oxazoline; less polar): colourless needles; mp 52.5–53.0 °C; $[\alpha]_D^{27.6}$ −78 (*c* 0.18, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2958, 2931, 2858, 1728, 1664, 1375, 1244, 1186, 1149, 1063, 1038, 941, 920, 839, 798, 777 and 663; δ_H (270 MHz, $CDCl_3$) 4.51 (dd, $J = 2.6$, 6.0 Hz, 1H), 4.48 (ddd, $J = 4.3$, 6.0, 8.1 Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.05 (dq, $J = 2.4$, 6.4 Hz, 1H), 2.84 (dd, $J = 4.3$, 16.7 Hz, 1H), 2.60 (dd, $J = 8.4$, 16.6 Hz, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.26 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H) and 0.08 (s, 3H); δ_C (67.8 MHz, $CDCl_3$) 170.5, 162.5, 91.3, 86.6, 68.8, 64.8, 60.8, 39.0, 25.6, 19.0, 17.9, 14.2, −4.2 and −5.0; Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C 44.40; H 6.52; N 3.24. Found: C 44.47; H 6.31; N 3.18. Compound **3b**

(*cis*-oxazoline; more polar): colourless oil; $[\alpha]_D^{27.3}$ −41.7 (*c* 0.620, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2958, 2931, 2858, 1732, 1664, 1329, 1255, 1184, 1093, 1030, 1001, 926, 837, 793, 777 and 671; δ_H (270 MHz, $CDCl_3$) 4.80 (dd, $J = 2.1$, 9.6 Hz, 1H), 4.72 (ddd, $J = 5.3$, 9.2, 9.6 Hz, 1H), 4.20 (dq, $J = 7.2$, 10.7 Hz, 1H), 4.17 (dq, $J = 7.2$, 10.7 Hz, 1H), 4.01 (dq, $J = 2.1$, 6.4 Hz, 1H), 3.13 (dd, $J = 9.2$, 17.3 Hz, 1H), 3.03 (dd, $J = 5.3$, 17.3 Hz, 1H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H) and 0.08 (s, 3H); δ_C (67.8 MHz, $CDCl_3$) 170.7, 162.4, 88.9, 86.8, 67.6, 64.8, 60.9, 34.3, 26.0, 20.6, 18.0, 14.2, −3.1 and −4.9; Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C 44.40; H 6.52; N 3.24. Found: C 44.77; H 6.33; N 2.99. Compound **3c** (*trans*-oxazoline; less polar): colourless oil; $[\alpha]_D^{27.4}$ +40.8 (*c* 0.495, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2931, 2858, 1736, 1664, 1375, 1257, 1182, 1159, 1115, 1078, 1032, 991, 837, 795 and 777; δ_H (270 MHz, $CDCl_3$) 4.57 (ddd, $J = 5.6$, 5.8, 6.6 Hz, 1H), 4.51 (dd, $J = 4.5$, 6.6 Hz, 1H), 4.165 (dq, $J = 7.2$, 10.8 Hz, 1H), 4.164 (dq, $J = 7.1$, 10.8 Hz, 1H), 4.02 (dq, $J = 4.4$, 6.3 Hz, 1H), 2.72 (dd, $J = 5.8$, 15.6 Hz, 1H), 2.66 (dd, $J = 5.6$, 15.8 Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 6.4$ Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H) and 0.09 (s, 3H); δ_C (67.8 MHz, $CDCl_3$) 170.1, 162.4, 91.0, 86.5, 68.6, 64.6, 60.8, 39.3, 25.8, 19.3, 17.9, 14.2, −4.1 and −4.8; Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C 44.40; H 6.52; N 3.24. Found: C 44.67; H 6.37; N 3.08. Compound **3d** (*cis*-oxazoline; more polar): colourless oil; $[\alpha]_D^{27.5}$ −40.1 (*c* 0.635, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2956, 2931, 2858, 1736, 1662, 1379, 1257, 1180, 1107, 1036, 993, 835, 793, 777 and 669; δ_H (270 MHz, $CDCl_3$) 4.83 (ddd, $J = 5.8$, 8.1, 9.6 Hz, 1H), 4.68 (dd, $J = 5.3$, 9.6 Hz, 1H), 4.194 (dq, $J = 7.2$, 10.9 Hz, 1H), 4.190 (dq, $J = 5.6$, 6.4 Hz, 1H), 4.18 (dq, $J = 7.1$, 10.8 Hz, 1H), 3.00 (dd, $J = 5.9$, 16.3 Hz, 1H), 2.65 (dd, $J = 8.0$, 16.3 Hz, 1H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 9H), 0.108 (s, 3H) and 0.105 (s, 3H); δ_C (67.8 MHz, $CDCl_3$) 171.1, 162.3, 91.0, 88.7, 67.1, 64.5, 60.8, 35.1, 25.8, 20.5, 17.9, 14.2, −3.8 and −4.7; Anal. Calcd for $C_{16}H_{28}Cl_3NO_4Si$: C 44.40; H 6.52; N 3.24. Found: C 44.63; H 6.55; N 3.09.

13. In the case of the carbamate-mediated conjugate additions, *tert*-BuOK was used as the most effective base, while DBU was not reported, see: Ref. 7 and references cited therein.
14. Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org., Chem.* **1987**, *52*, 5127–5136.
15. A similar separation of ^{1}H-coupling constants for trans (6.0–7.5 Hz) and cis (10.0–11.2 Hz) compounds was also investigated in the cases of 2-phenyl-2-oxazoline derivatives, see: Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308–3310.
16. The irradiation of methyne hydrogen adjacent to the methyl group on the compound **3a** yielded an NOE of ca. 16% on H-4′ along with H-5′, while no NOE was observed on the methylene protons (H-2). On the contrary, the irradiation of the hydrogen corresponding to compound **3b** yielded an NOE of ca. 3% on the one methylene protons (H-2), while a relatively small NOE (<1%) was observed on H-4′.
17. Sunazuka, T.; Hirose, T.; Chikaraishi, N.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Sprengeler, P. A.; Smith, A. B., III; Ōmura, S. *Tetrahedron* **2005**, *61*, 3789–3803.
18. (a) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885–891; (b) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org., Chem.* **1984**, *49*, 2236–2240.
19. For hydrolysis of the similar racemic oxazolines and subsequent manipulations, see: Ref. 14.