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Remote Asymmetric Induction: Synthesis of *C*-Linked α-Galactoserine and Homoserine Derivatives by Electrophilic Amination[1]

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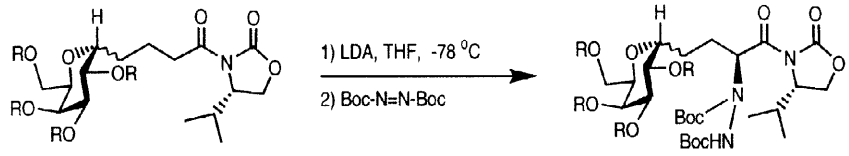
Abstract: A high diastereoselectivity (98%) for electrophilic amination of compound **9** using di-*t*-butyl azodicarboxyl ester as an electrophile was achieved. A similar reaction with compound **13** having achiral oxazolidinone was studied to examine 1,4-remote asymmetric induction. In the latter, a selectivity of 6.5:1 demonstrated the effect of α-galactosyl moiety, responsible for inducing the induction from the remote site. © 1998 Elsevier Science Ltd. All rights reserved.

Interest in the synthesis of glycopeptides is rapidly increasing due to their involvement in various cellular and biological processes.[2,3] Oxygen-linked glycosylation (i.e., glycosylation of serine and threonine amino acid moieties) is one of the primary modes for the attachment of glycosides to proteins. Due to the sensitive nature (i.e., chemical and enzymatic stability) of *O*-linked glycopeptides, several groups have reported their efforts towards the synthesis of *C*-linked analogs of *O*-linked glycopeptides.[4] *C*-linked derivatives have shown to be more stable, and exhibit similar biochemical properties when compared to *O*-linked derivatives.

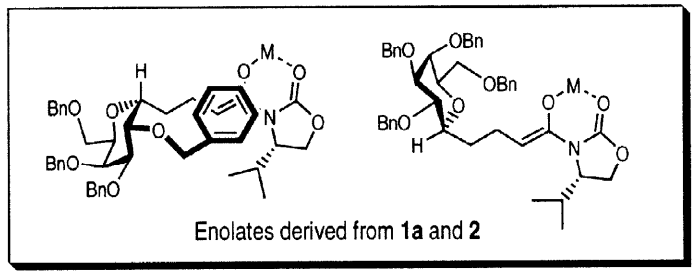
Recently, we have developed a new method utilizing asymmetric enolate chemistry for the synthesis of *C*-linked isosteres of α- or β-glycoconjugates.[4a] The key step in our approach involved the reaction of the chiral oxazolidinone enolate derived from α- or β- glycosyl derivatives (**1** and **2**) with dialkyl azodicarboxyl ester as an electrophile (Scheme 1). One of the advantages of this method is that it can be easily extended to afford the synthesis of other analogs. During our study, we were surprised by the low diastereoselectivity (72% de) for the electrophilic amination of perbenzylated α-galactosyl derivative (**1a**) with di-*t*-butyl azodicarboxyl ester (DBAD) as an electrophile. It was proposed that the benzyl-protecting group at the 2-position of α-glactosyl moiety hindered the approach of the electrophile (Scheme 1, see enolate derived from **1a**).

Scheme 1



α-isomer: **(1a)** R = Bn; **(1b)** R = Me
β-isomer: **(2)** R = Bn

α- isomer: **(3a)** R = Bn, 72% de; **(3b)** R = Me, 92% de
β- isomer: **(4)** R = Bn, 98% de



Enolates derived from **1a** and **2**

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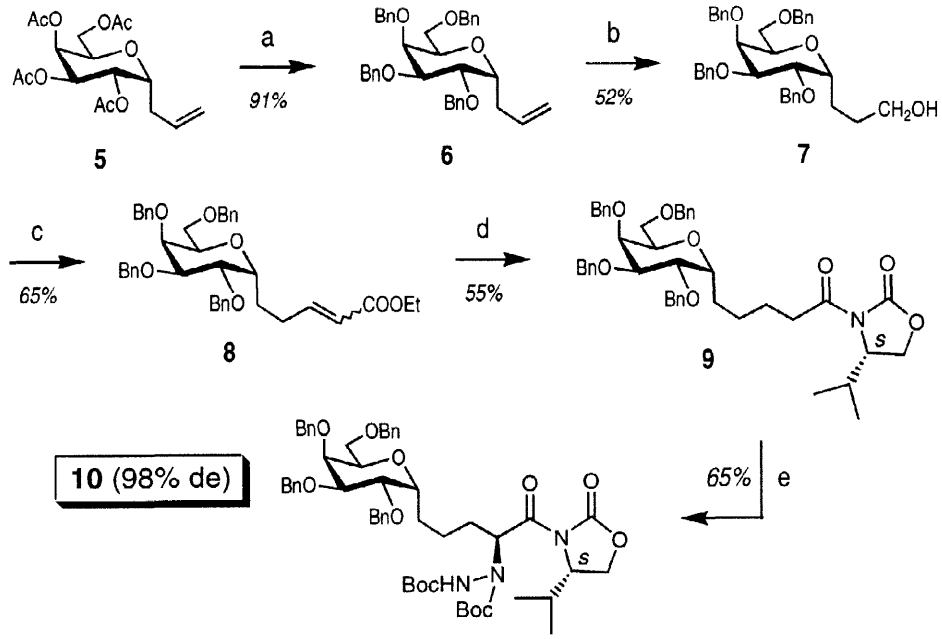
To obtain a better understanding of this unprecedented effect, electrophilic amination of the permethylated α-galactosyl derivative (**1b**) with less sterically demanding groups on α-galactosyl moiety was examined. In a second experiment, the β–isomer of perbenzylated galactosyl derivative (**2**) was studied. This experiment was designed to explore the effect of a change from 1,2-cis to 1,2-trans orientation between the anomeric position and the benzyl group at C-2 (see, enolates derived from **1a** and **2**). As expected, reaction with the permethylated α-galactosyl derivative (**1b**) gave a high diastereoselectivty (92% de). Similarly, a high diastereoselectivity (98% de) was obtained during the electrophilic amination of compound **2** using DBAD as an electrophile. This experiment indicated that by changing the relative orientation (i.e., 1,2-cis *vs* 1,2-trans), the hindrance from the galactosyl moiety could be avoided. Based upon these results, we decided to explore the effect of perbenzylated α-galactosyl moiety for inducing asymmetry at a remote site. The electrophilic amination of compounds **9** and **13** with di-*t*-butyl azodicarboxyl ester (DBAD) were studied and the results of which are described in this communication (Scheme 2 and 3). To examine the limits of the previously observed affect with compound **1a**, **9** was prepared in which an extra methylene unit is incorporated. Compound **13** differs from **1a** that it has an achiral oxazolidinone moiety. By removing the chirality of oxazolidinone in compound **1a**, the role of perbenzylated-α-galactosyl moiety in inducing 1,4-remote asymmetric induction during electrophilic amination reaction could be examined.

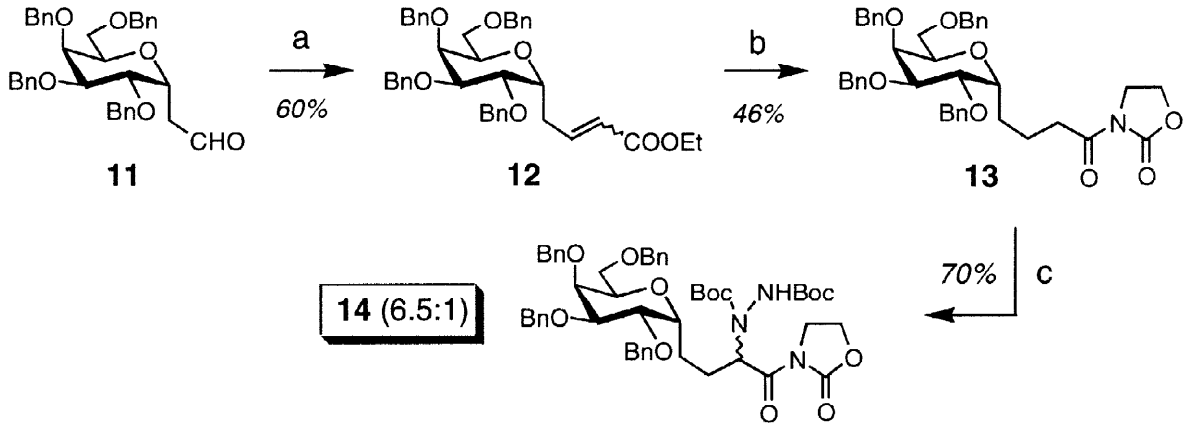
As shown in Scheme 2, synthesis of compound **6** was achieved from the α-*C*-allyl-galactosyl derivative, **5** in two steps (91%). A regioselective hydroboration of α-*C*-galactosyl derivative, **6**, followed by the oxidative work



Scheme 2: (a) (i) NaOMe, MeOH; (ii) BnBr, NaH, DMF. (b) (i) 9-BBN, THF; (ii) H_2O_2, NaOH. (c) (i) PCC, CH_2Cl_2; (ii) Ph_3P=CHCOOEt, benzene, reflux. (d) (i) H_2, 10% Pd/C, EtOH; (ii) 1M LiOH, MeOH/H_2O; (iii) pivaloyl chloride, DIPEA, CH_2Cl_2, lithio-(*S*)-isopropyl-2-oxazolidinone, THF. (e) LDA (1.1 equiv), THF, -78 °C, 30 min.; di-*tert*-butyl azodicarboxylate (DBAD, 1.3 equiv).

up gave compound **7** in 52% isolated yield. Compound **8** was obtained from **7** in the following manner, (a) PCC oxidation, and (b) Horner-Emmons reaction with the commercially available (carbethoxymethylene)-triphenylphosphorane. It was subjected to hydrogenation (H_2, 10% Pd/C), followed by alkaline hydrolysis (LiOH), and then coupled to *(4S)*-4-isopropyl-2-oxazolidinone to furnish **9** in 55% isolated yield. In contrast to the reaction of DBAD with **1a**, reaction of the enolate derived from **9** (generated under standard conditions, LDA, THF, -78 °C) gave product **10** with a high diastereoselectivity (98% de).[5] *By adding an extra methylene unit in compound* ***1a****, the perbenzylated α-galactosyl moiety did not hinder the approach of the electrophile during the reaction.*

In a separate attempt to examine the remote asymmetric induction effect by the α-galactosyl moiety, the achiral oxazolidinone derivative, **13** (Scheme 3) was subjected to electrophilic amination using DBAD as an electrophile. Compound **13** was prepared in the following way. Compound **11** was obtained from **6** upon ozonolysis followed by the reductive opening of the ozonide. Horner-Emmons reaction of the aldehyde derivative **11** with (carbethoxymethylene)-triphenylphosphorane followed by (i) hydrogenation over 10% Pd/C, (ii) hydrolysis (LiOH), and (iii) coupling with the lithium salt of oxazolidinone gave the desired compound **13**. Reaction of the enolate derived from **13** with DBAD gave the expected product **14** in 70% yield with a diastereomeric ratio of 6.5:1.[5] *It is remarkable that in the absence of a chiral oxazolidinone auxiliary, the galactose moiety can influence on the selectivity given that it is fairly remote from the newly formed C-N bond!* To our knowledge, the effect of a built-in, remote chirality on the selectivity of the electrophilic amination using DBAD as an electrophile has not previously been reported.



Scheme 3: (a) (i) Ph_3P=CHCOOEt, benzene, reflux. (b) (i) H_2, 10% Pd/C, EtOH; (ii) 1M LiOH, MeOH/H_2O; (iii) pivaloyl chloride, DIPEA, CH_2Cl_2, lithio-oxazolidinone, THF. (c) LDA (1.1 equiv), THF, -78 °C, 30 min.; di-*tert*-butyl azodicarboxylate (DBAD, 1.3 equiv).

To summarize, we have demonstrated that chiral auxiliary-based enolate method can be utilized to synthesize carbon-linked analogs of α-galactohomoserine. 1,4-remote asymmetric induction with a selectivity of

6.5:1 during the electrophilic amination of compound **13** having an achiral oxazolidinone was achieved. An advantage with the latter approach is the asymmetric induction possibility without the use of a chiral auxiliary. The effect of a built-in, perbenzylated α-galactosyl moiety on electrophilic amination represents a unique example of controlling the selectivity for the synthesis of *C*-galactosyl amino acid derivatives.

References and notes

1. NRCC publication no. 40877.

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5. (a) *General procedure for electrophilic amination:* Compound **9** or **13** (0.08 mmole) was placed in a flame dried round bottom flask with 25 mL of dry THF under a nitrogen atmosphere. This solution was then cooled to -78 ^{o}C and LDA (1.1 equiv) was added. After 30 min a THF solution of DBAD (1.2 equiv.) was added and the solution was stirred for 5 min after which time glacial acetic acid (2.6 equiv) was added and the solution was allowed to warm to room temperature overnight. Extractive work-up furnished crude yellow oil which was purified using a flash column chromatography. (b) Diastereomeric excess was measured using HPLC and HPLC-MS techniques. (c) Structure of all the compounds were fully assigned using ^{1}H, ^{13}C NMR, MS and HPLC-MS experiments. Compound **10**: ^{1}H NMR (400 MHz): δ 0.95 (6H, d, J = 6.8Hz), 1.50 (18H), 1.60-2.20 (6H, m), 2.30-2.50 (1H, m), 3.65-3.92 (4H, m), 3.95-4.05 (3H, m), 4.18-4.35 (3H, m), 4.45-4.78 (8H, m), 5.75-5.85 (1H, m), 7.20-7.42 (20H, m). ^{13}C NMR (100 MHz): δ 14.6, 17.9, 22.7, 27.0, 28.2, 29.0, 588, 61.0, 63.7, 67.7, 71.6, 72.8, 73.1, 73.2, 74.5, 77.2, 127.5, 127.9, 128.2, 128.3, 138.5, 147.0 and 153.6. MS-ES^{+} 966.4 $(M+H)^{+}$