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A New Reaction for the Direct Conversion of 4-Azido-4-deoxy-D-galactoside into a 4-Deoxy-D-*erythro*-hexos-3-ulose

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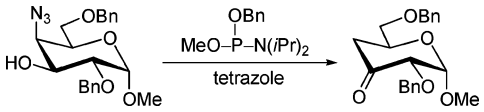
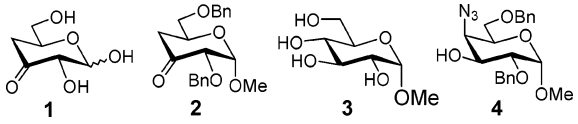
ABSTRACT



A new one-step reaction has been developed for converting 4-azido-4-deoxy-D-galactoside into 4-deoxy-D-*erythro*-hexos-3-ulose by phosphoramidites and tetrazole. It is proposed that the new reaction proceeds via an intramolecular Staudinger reaction of the phosphite intermediate and a tetrazole-catalyzed elimination reaction of the resultant phosphorimidate. Tetrazole appears to be playing a unique role by acting as a bifunctional catalyst to facilitate the elimination reaction.

Various derivatives of 4-deoxy-D-*erythro*-hexos-3-ulose (**1**) are useful intermediates for the chemical synthesis of natural and unnatural carbohydrate mimetics[1−3] and natural products such as amipurimycin[4−6] and miharamycin.[7,8] Compound **1** and related species have traditionally been prepared by the oxidation and deoxygenation of sugars[3,4] or by the Diels−Alder reaction of aldehydes and dienes.[6,9] This paper reports a novel method for preparing a protected form of **1**, namely, methyl 2,6-di-*O*-benzyl-4-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**2**), from methyl α-D-glucopyranoside (**3**). A new reaction has been invented for removing the azido group and oxidizing the hydroxyl group of methyl 4-azido-2,6-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (**4**) in one step to afford the synthetic target **2**. The mild conditions of this new reaction can circumvent one of the potential problems of ketosugar synthesis, i.e., enolization (under both acidic and basic conditions) and the resulting side reactions.



Intermediate **4** was prepared from **3** by a series of well-established transformations as shown in Scheme 1.[10] Upon treatment of **4** with phosphoramidite **10A** and tetrazole, **2** was formed in an excellent yield (90%). In an effort to identify more readily available reagents for this new reaction, other phosphoramidites were also studied. A moderate to good yield of **2** (60−70%) was obtained using **10B** and **10C**, but **10D** gave phosphite **11D** (80%) nearly exclusively. The reaction of **10E** was complex, affording a mixture of **2** and two other products, **12** and **13**. It was also observed that **4** initially transformed into the phosphites **11A**−**E** quickly (in

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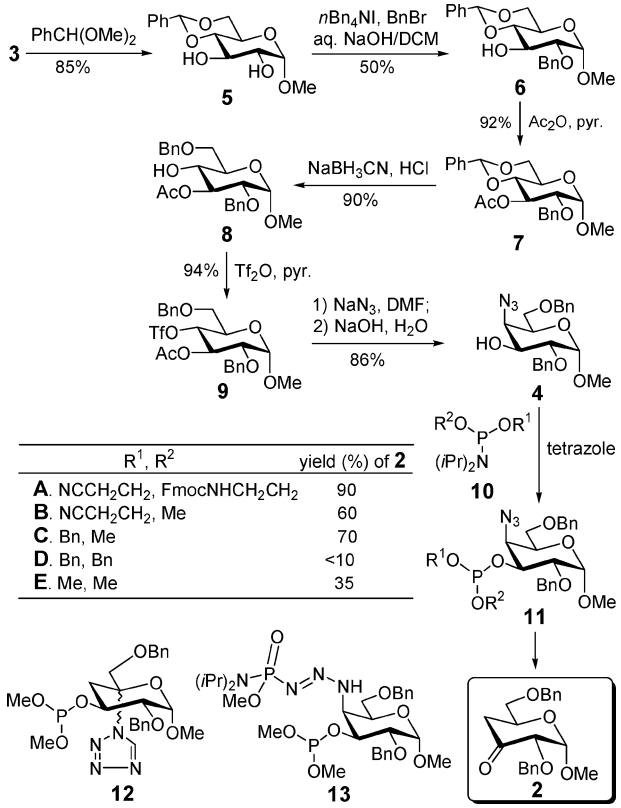
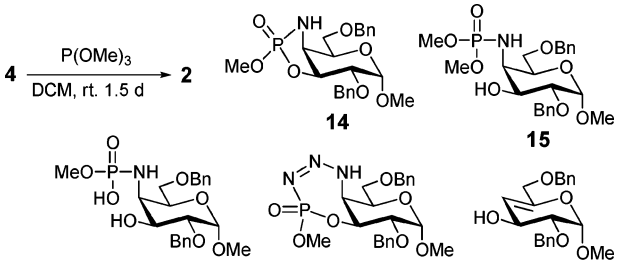
Scheme 1



R^1, R^2	yield (%) of **2**
A. $NCCH_2CH_2$, $FmocNHCH_2CH_2$	90
B. $NCCH_2CH_2$, Me	60
C. Bn, Me	70
D. Bn, Bn	<10
E. Me, Me	35

Scheme 2[a]



entry	reaction in the presence of	products and yields (%) 2	14	15	16	17	18
1	- (neutral)	-	15	75	-	-	-
2	pyridine (2 eq.)	-	10	80	-	-	-
3	DBU (5 eq.)	-	10	-	73	-	-
4	AcOH (5 eq.)	[a]	35	15	-	20	11
5	tetrazole (5 eq.)	70	3	18	-	-	-

[a] A small amount was observed by TLC.

less than 5 min). While **11A**−**C** converted into ketone **2** smoothly within 5−12 h, the conversion of **11E** into ketone **2** was much less efficient; **11D**, on the other hand, remained almost unchanged for more than 2 days. For this transformation, only reagents **10A**−**C** were of practical value, with **10C** being the most readily available reagent.

The initial formation of **11** implied that an intramolecular Staudinger reaction was occurring at a later step. Though many Staudinger-type reactions have been devised and widely used in organic synthesis,[11−22] to the best of our knowledge there have been very few examples of the intramolecular Staudinger reaction.[23]

It is a reaction that is accompanied by C−N bond fission probably through a phosphorimidate or phosphoramidate intermediate, a reaction that has never been observed previously. In fact, phosphazo compounds usually undergo Arbusov-type dealkylation by breaking of one of the C−O bonds.[24]

These results differ from those of the literature,[16,17] which report that the reactions between 2-azido alcohols and phosphites give aziridines as the major products. The literature also suggests that fission of a C−O bond and formation of a C−N bond occur concurrently. A major difference between our reaction and those of the literature is that we utilized phosphorimidates, rather than phosphites, with tetrazole as the catalyst.

To probe the role of the tetrazole (pK_a 4.70),[25] we substituted it with a simple acid, i.e., acetic acid (pK_a 4.75). It transpired that under these conditions there was almost no reaction between **4** and **10C** (3 days), which indicated that tetrazole was not simply serving as an acid.

We also studied the reaction between **4** and trimethyl phosphite, which we expected would first react with the azide rather than the hydroxyl group. As expected, the neutral reaction gave phosphoramidate **15** as the major product (entry 1, Scheme 4) as well as a significant amount of a cyclophosphoramidate **14**. Similar results were observed (entries 2 and 3) under basic conditions; however, a hydrolysis product of **15**, namely **16**, was obtained when DBU was employed. When acetic acid was included (entry 4), the reaction was complex and afforded **14**, **15**, **17**, and **18** and only a small amount of **2**. It was only when the tetrazole was employed that **2** was obtained as the major product (entry 5).

Our studies have proven that tetrazole has a special influence on the reaction course. Moreover, because the acidity of tetrazole is almost the same as that of acetic acid, this showed that tetrazole must not merely be acting as a simple acidic catalyst. Tetrazole is a unique acid, as it

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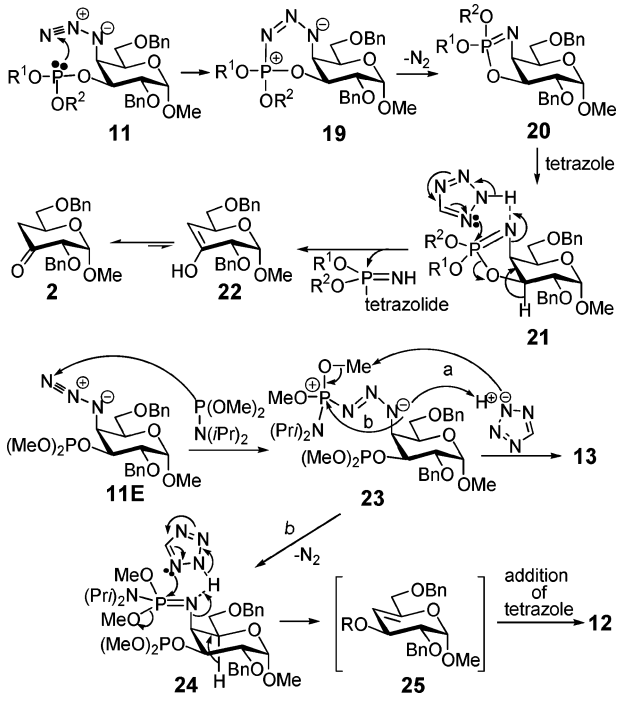
possesses three quite basic nitrogen atoms. Because of this, we propose that tetrazole is acting as a bifunctional catalyst with one of its nitrogen atoms behaving as a nucleophile; it facilitates the concerted process of elimination. Bifunctional catalysis is frequently observed in biological systems.[26,27]

Interestingly, neither the acyclic phosphoramidate **15** nor the cyclophosphoramidate **14** transformed to **2** upon treatment with tetrazole, acetic acid, or triethylamine. Instead, they gave rise to the dealkylation product **16**. No conversion of **15** into **14** was observed either. These results suggest that the engaged reactive intermediates are not phosphoramidates, a conclusion that is consistent with the literature.[17,18] Therefore, this reaction might have involved reactive phosphazo intermediates such as phosphazides or phosphorimidates before dealkylation.

Accordingly, we propose that **2** is formed from **11** via an intramolecular Staudinger reaction followed by elimination (shown in Scheme 3) and that the Staudinger reaction to form

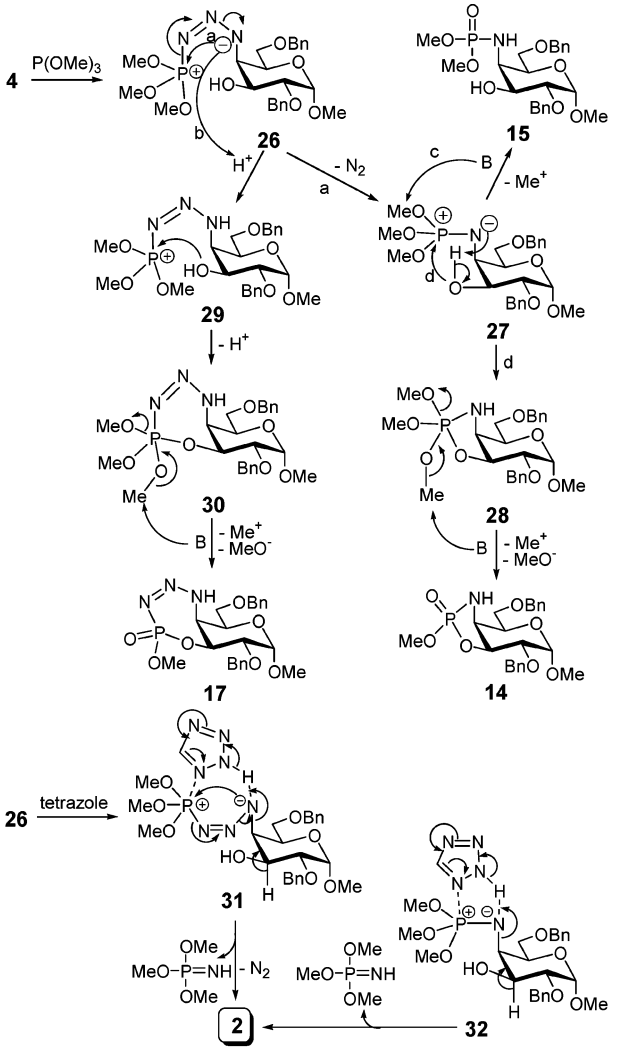
Scheme 3



phosphorimidate **20** is rate-limiting. Phosphorimidates normally experience Arbusov-type dealkylation to produce phosphoramidates,[28] but under the influence of tetrazole, a bifunctional catalyst, a concerted elimination reaction occurs through **21** to give an enol **22** and its tautomer **2**. For **10D**, probably because of steric hindrance, the intramolecular Staudinger reaction is extremely slow, and **11D** is isolated as a stable intermediate. In the case of **10E**, since a methyl group is small, the reactivity of **10E** is increased, and the intermolecular reaction to form **23** becomes competitive. As a result, besides the pathway to produce **2**, a protonation and dealkylation process (path a) can give rise to a significant amount of **13**. Meanwhile, elimination reaction followed by electrophilic addition of tetrazole to the resultant vinyl ether **25** can lead to **12** (path b).

For Scheme 2, as trimethyl phosphite does not react with alcohols, the Staudinger reaction must be happening first (Scheme 4). In entries 1−3, **26** is probably reacting through

Scheme 4



elimination of a nitrogen molecule to give an imidate **27** (path a). However, in the presence of acid (entry 4) protonation of **26** might be taking place to form a phosphonium intermediate **29** (path b). Product **15** is probably formed by the Arbusov-type dealkylation on **27** (path c). On the other hand, intramolecular proton transfer, cyclization, and dealkylation (path d) most probably give rise to **14**. Similarly, cyclization and deprotonation of **29** followed by dealkylation of **30** more than likely produces the cyclo-

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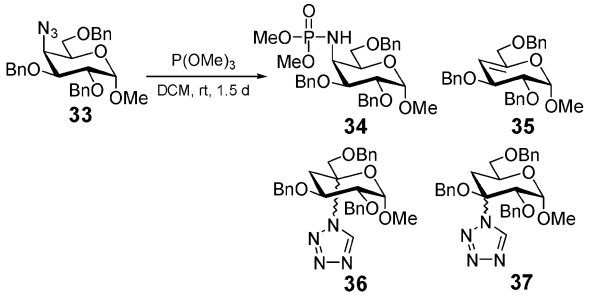
phosphazide **17**. Under the influence of tetrazole, however, a concerted process (shown in **31**) is probably favored and an elimination reaction affords **2**. Alternatively, **2** can be formed via the phosphorimidate **27**, mediated by tetrazole as shown for **32**.

The proposed reaction mechanism for **2** requires an antiperiplanar orientation of the azido group relative to the departing proton. In agreement with this, the flexible 1-azido-3-octadecanoxy-propan-2-ol and an analogue of **4** with an equatorial azido group did not form the corresponding ketone products.

As a further testament to the unique properties of tetrazole in the proposed mechanism, we also examined the reaction between trimethyl phosphite and the fully protected analogue **33** of D-galactose under various conditions (Scheme 5). The

Scheme 5



entry	reaction in the presence of	products and yields (%)			
		34	**35**	**36**	**37**
6	- (neutral)	70	-	-	-
7	AcOH (5 eq.)	63	-	-	-
8	tetrazole (5 eq.)	20	11	23	17

neutral and acetic acid-mediated reactions gave phosphoramidate **34** (entries 6 and 7), while the reaction that was conducted in the presence of tetrazole (entry 8) afforded a complex mixture consisting of **34** (20%), the elimination product **35** (11%), and two diastereoisomers of each elimination−addition product **36** (23%) and **37** (17%). Compounds **36** and **37** were not very stable and gradually decomposed in NMR tubes. The mechanisms proposed for **12** and **25** in Scheme 3 can be utilized to explain the elimination and elimination−addition products of these reactions.

In brief, this paper describes an efficient new procedure for preparing **2** and a new one-pot reaction for converting an azido galactoside into a 4-deoxy ketosugar by the reaction with readily available phosphoramidites **10A**−**C** and tetrazole. Judging by our results, this reaction looks rather like a pinacol-type rearrangement,[29] even though their mechanisms are different. To the best of our knowledge, there has been no report of the direct conversion of a 2-azido alcohol to a ketone, despite the fact that many variations of pinacol rearrangement, e.g., Demjanov[30] and Tiffeneau−Demjanov[31] rearrangements of amino alcohols, have been established.

We have also highlighted the unique impact that tetrazole can have on the Staudinger reaction of **11** and subsequent transformations. To explain why other simple acids or bases cannot be used to replace tetrazole, we have proposed that it might be acting as a bifunctional catalyst, promoting a concerted reaction process. This is somewhat supported by the findings that, in addition to being an acidic catalyst, tetrazole is also a good nucleophile, enabling the formation of reactive phosphorus tetrazolide intermediates during nucleotide synthesis.[32−34] However, in the literature it is not clear how tetrazolides are formed. Our results now provide some hints in regard to this issue.

Because the Staudinger reaction involves several steps and intermediates,[11] its reaction pathways and outcomes can be easily affected by many factors,[35] as shown by our results as well as those in the literature.[17,18,21] The reactions between phosphoramidites and other 2-azido alcohols are currently under further investigations, and the results will be reported in due course.

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Supporting Information Available: Experimental and selected NMR spectra of the intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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