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Site-selective Benzoin-type Cyclization of Unsymmetrical Dialdoses Catalyzed by N-Heterocyclic Carbenes for Divergent Cyclitol Synthesis

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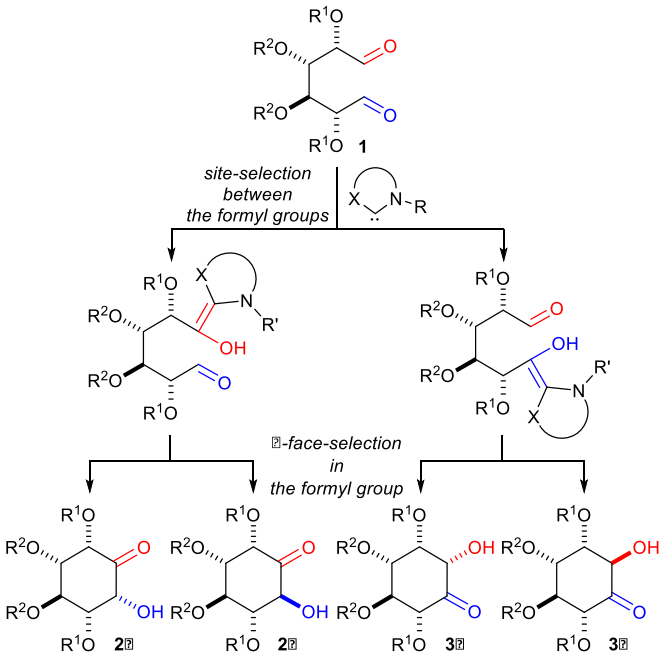
A highly site-selective N-heterocyclic carbene (NHC)-catalyzed benzoin-type cyclization of unsymmetrical dialdoses is developed to enable a divergent cyclitol synthesis. The choice of chiral NHCs and protecting groups affects the site-selectivity. The resulting inososes are converted into *epi*-, *muco*- and *myo*-inositol, and their chiral protected derivatives are formed in good yields.

Cyclitols, polyhydroxylated cycloalkanes, and their derivatives have attracted widespread interest in the fields of medicinal, biological and synthetic chemistry[1] due to their various biological properties[2] as well as their value as building blocks.[3,4] The most extensively studied are *myo*-inositol and its derivatives, including phosphates because they are ubiquitous and are reported to have numerous biological properties. In contrast, other stereoisomers (*allo*-, D-*chiro*-, L-*chiro*-, *cis*-, *epi*-, *muco*-, *neo*- and *scyllo*-inositols) and their derivatives are relatively unexplored due to their unavailability in nature. Consequently, their potential utilities are unknown. Although many methods to synthesize inositol derivatives have been reported,[1, 5] a new method to supply potentially bioactive unprecedented derivatives remains considerably valuable.

Recently, we developed synthetic methodologies utilizing organocatalysts.[6] As a part of the study, a new strategy for a divergent synthesis of cyclitol derivatives was reported.[7] We demonstrated that inososes, which are produced by an N-heterocyclic carbene (NHC)-catalyzed benzoin-type cyclization of dialdoses,[8] are versatile intermediates for various cyclitol derivatives. To selectively obtain inosose via the benzoin-type cyclization of an unsymmetrical dialdose such as **1**, two factors must be controlled: (1) the site-selectivity where one of the two formyl groups preferentially reacts with an NHC and is converted into a nucleophilic species, or the so-called Breslow intermediate, and (2) the π-face-selectivity of the acceptor formyl group, which determines the stereochemistry of the forming hydroxy group (Scheme 1).



Scheme 1 Required selectivity in NHC-catalyzed benzoin-type cyclization of dialdoses **1** to give inososes **2α**, **2β**, **3α** and **3β**.

Previously we utilized C_2-symmetric dialdoses with two equivalent formyl groups to avoid issues with site-selectivity, and the π-face-selectivity was successfully controlled, realizing the selective synthesis of *allo*-, *chiro*-, *myo*-, *neo*-, *scyllo*-inositol derivatives. Herein we report more challenging site- and π-face-selective benzoin-type cyclizations of unsymmetrical dialdoses **1** to selectively give inosose **2α**, **2β**, **3α** or **3β**, which can be converted to *epi*-, *muco*- and *myo*-inositol derivatives. To the best of our knowledge, this report presents the first examples of

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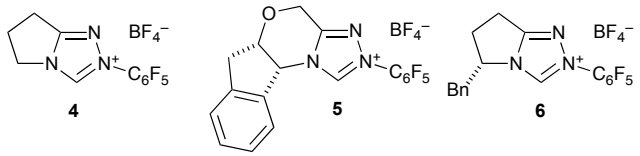
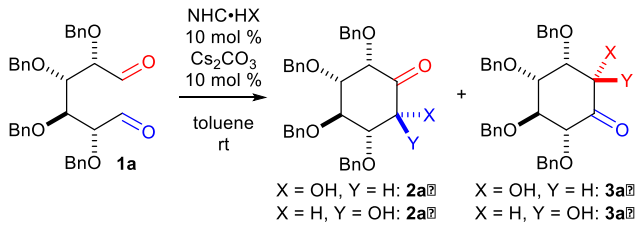


Figure 1. Structures of NHC precursors (NHC·HX).

Table 1 Benzoin-type cyclization of tetrabenzyl dialdose **1a**[a]



entry	NHC·HX	time/h	yield/%	**2a**:**3a**	**2a** (α:β)	**3a** (α:β)
1	**4**	20	51	41:59	66:34	31:69
2	**5**	9	59	69:31	28:72	>99:1
3	*ent*-**5**	20	89	48:52	73:27	33:67
4	**6**	16	74	74:26	68:32	>99:1
5	*ent*-**6**	20	54	40:60	78:22	42:58

[a] The reaction was performed using 0.2 mmol **1a**. The yields and ratios were determined by ^{1}H NMR of the crude products using Ph_3CH as an internal standard.

a highly selective cross benzoin-type reaction [9] between aliphatic aldehydes with similar steric bulkiness.

Initially, we tested several achiral and chiral NHCs generated from NHC precursors (Figure 1). A solution of tetrabenzyl dialdose **1a** (0.2 mmol), which was derived from D-sorbitol, in toluene (4 mL) was added to a suspension of **4** and Cs_2CO_3 (10 mol% each) in toluene (4 mL). The resulting mixture was stirred at rt (Table 1, entry 1). After 20 h, inososes **2a** and **3a** were produced in 51% yield with a slight preference for **3a** (**2a**:**3a** = 41:59; site-selectivity). The site-selectivity was almost the same as those previously reported for the same NHC with different bases and solvents,[8a] although **3a** did not epimerize at the α-position under this condition. The epimer ratios were moderate for both **2a** and **3a** (α:β = 66:34 and 31:69, respectively).

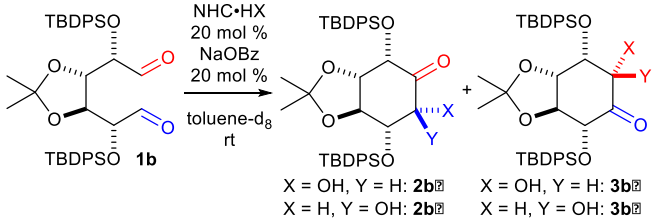
Then we tested chiral NHCs derived from **5** and **6** and their enantiomers. Although the site- and face-selectivity were affected by the utilized NHC, satisfactory site-selectivity was not achieved to produce **2a** and **3a**. At most, a 74:26 selectivity was achieved (entries 2–5).

We speculated that the lack of site- and face-selectivity in the reaction of **1a** was due to the small difference between the steric environment of the two formyl groups and the conformational flexibility in the transition states of the cyclization, respectively. Therefore, we hypothesized that a bulky protective group at the α-position (R^1) and a cyclic protection at the β-position (R^2) would improve the selectivity. We tested the NHCs in the reaction of 3,4-*O*-acetonide protected **1b** bearing TBDPSO groups at the α-positions (Table 2). In the reaction of **1b**, using less basic NaOAc instead of Cs_2CO_3 was important to prevent undesired side reactions such as β-elimination and epimerization. The observed selectivity completely differed from that with **1a** (Table 1). As expected, the site- and face-selectivity generally improved, but it was difficult to fully explain the effects of NHCs. The face-selectivity was strongly influenced by the chirality of the NHCs (entries 2 vs 3 and 4 vs 5). In contrast, the site-selectivity seemed to be affected by the structures, possibly the bulkiness, of the NHCs rather than the chirality (entries 2 and 3 vs. 4 and 5). Among the tested NHCs, *ent*-**6** showed the best performance to preferentially give **2bα** with an 84:16 site-selectivity and an almost perfect face-selectivity (entry 5).

The products were unstable on silica gel. Because they decomposed and isomerized during purification by column chromatography, isolation was accomplished after removal of the acetonide. Thus, the reaction of **1b** with *ent*-**6** was conducted on a 1.5 mmol scale (Scheme 2). After the benzoin-type reaction, the crude product was hydrolyzed by treatment with HF in aqueous acetonitrile to give **2cα** in 40% isolated yield. Interestingly, the TBDPS groups were inert under hydrolysis conditions.

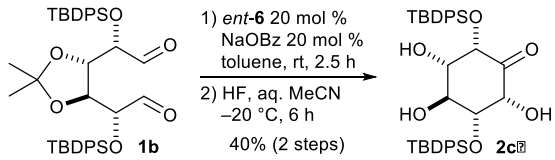
Unexpectedly, the site-selectivity was reversed when dialdose **1d** with a carbonate as cyclic protection was utilized to give **3dα** as the major product (Table 3). Except for the reaction with achiral NHC **4** (entry 1), **3dα** was formed with high to perfect site- and face-selectivities (entries 2–5). Among the tested NHCs, the best yield of 67% was produced with *ent*-**6** (entry 5). After purification by column chromatography using DIOL silica gel, **3dα** was obtained in 58% yield in a diastereomerically pure form. The use of conventional silica gel chromatography led to significant decomposition and epimerization of the products.

Table 2 Benzoin-type cyclization of 2,5-*O*-diTBDPS-3,4-*O*-isopropylidene dialdose **1b**[a]



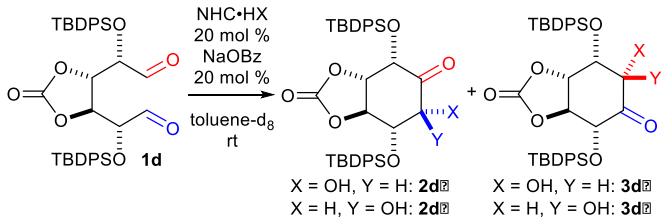
entry	NHC·HX	time/h	yield/%	**2b**:**3b**	**2b** (α:β)	**3b** (α:β)
1	**4**	12	57	70:30	43:57	>99:1
2	**5**	12	48	21:79	<1:99	>99:1
3	*ent*-**5**	12	20	35:65	>99:1	>99:1
4	**6**	12	83	67:33	85:15	>99:1
5	*ent*-**6**	2.5	63	84:16	>99:1	>99:1

[a] The reaction was performed using 0.2 mmol **1b**. The yields and ratios were determined by ^{1}H NMR of the crude products using Ph_3CH as an internal standard.



Scheme 2. Synthesis of **2cα** in diastereomerically pure form.

Table 3 Benzoin-type cyclization of 2,5-*O*-diTBDPS-3,4-*O*-carbonyl dialdose **1d**[b]



entry	NHC·HX	time/h	yield/%	**2d**:**3d**	**2d** (α:β)	**3d** (α:β)
1	**4**	12	57	56:44	<1:99	>99:1
2	**5**	20	11	<1:99	-	>99:1
3	*ent*-**5**	20	38	<1:99	-	>99:1
4	**6**	9	9	<1:99	-	>99:1
5[b]	*ent*-**6**	2	67 (58)[c]	6:94	<1:99	93:7

[a] The reaction was performed using 0.2 mmol **1d**. The yields and ratios were determined by ^{1}H NMR of the crude products using Ph_3CH as an internal standard unless otherwise noted. [b] The reaction using 0.5 mmol **1d** in toluene. [c] Isolated yield of **3dα** in the parentheses.

Figure 2 depicts the possible transition states for the benzoin-type cyclization on the basis of the hydrogen bond assisted 6-membered ring model.[7,8a,10] **TS$_{2α}$**, **TS$_{2β}$**, **TS$_{3α}$** and **TS$_{3β}$** were probably responsible for the formation of **2α**, **2β**, **3α** and **3β**, respectively. The transition states to give β-epimers **2β** and **3β** were apparently unstable, especially when bulky substituents were at the α-positions due to the increased unfavorable interactions, 1,3-allylic strain and 1,3-diaxial repulsion, respectively (**TS$_{2β}$** and **TS$_{3β}$**). This was one reason for the observed face-selectivity in the cyclization. As clearly indicated in Table 2, entry 2, the face-selectivity was also strongly induced by chirality of NHC. Although it was not easy to fully understand the observed opposite site-selectivity between the reactions of **1b** and **1d**, we speculated that one possible reason was the steric repulsion between one of the TBDPS groups and the *gem*-dimethyl moiety of the acetonide in **TS$_{3bα}$**, resulting in the unfavorable formation of **3b** in the reaction of **1b**, while **TS$_{3dα}$** without such a steric repulsion was preferred over **TS$_{2dα}$** in the reaction of **1d** due to less axial substituents as well as minimum allylic strain.

Scheme 3 depicts the stereoselective reduction of the obtained inososes to inositols. Although the reduction of **2cα** with $NaBH_4$ in methanol suffered from the migration of the TBDPS group, the use of BH_3·THF gave *epi*-**7c** in 80% yield as a single diastereomer. The other diastereomer *muco*-**7c** was also obtained by the β-hydroxy-directed reduction with $Me_4N(AcO)_3BH$.[5d,11] Reduction of **3dα** with BH_3·THF also stereoselectively produced *epi*-**7d** in 83% yield. The sense of reduction was reversed by using our previously developed protocol,[7] TES protection followed by reduction with *t*-$BuNH_2$·BH_3 produced *myo*-**7d** in 70% yield as the sole diastereomer. The stereochemistries of *epi*- and *muco*-**7c**, and *epi*- and *myo*-**7d** were confirmed by conversion into known hexaacetates[12,13,14] in 99%, 93%, 70% and 99% yields, respectively.

In summary, we develop the first highly site-selective cross benzoin-type cyclization of unsymmetrical dialdoses to give inosose derivatives selectively. The choices of NHCs and the protective groups are important to control the site- and face-selectivity of the cyclization. The resulting inososes can be converted into chirally protected derivatives of *epi*-, *muco*-, and *myo*-inositol in good yields.

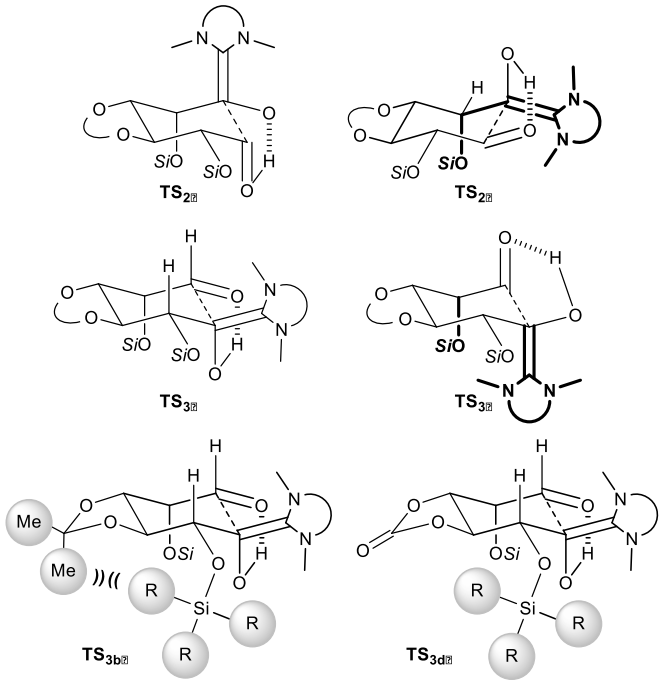
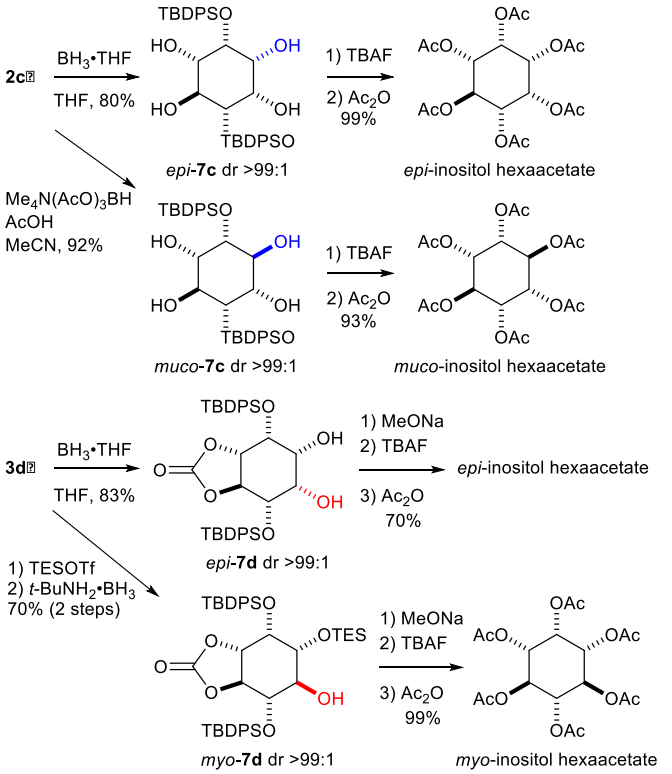


Figure 2 Possible transition states **TS$_{2α}$**, **TS$_{2β}$**, **TS$_{3α}$**, **TS$_{3β}$**, **TS$_{3bα}$** and **TS$_{3dα}$** give **2α**, **2β**, **3α**, **3β**, **3bα** and **3dα**, respectively. The *Si* represents a TBDPS group.



Scheme 3 Stereodivergent syntheses of *epi*-, *muco*-, *myo*-inositols from **2cα** and **3dα**.

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