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Regio- and stereospecific synthesis of DL-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol

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Abstract:

The regio- and stereospecific synthesis of DL-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol is reported. Bromination of *p*-benzoquinone followed by reduction of the carbonyl groups with $NaBH_4$ gave the corresponding *trans*-dibromodiol compound, which was reacted with sodium methoxide to produce dimethoxy conduritol-B. Regiospecific bromination of the alkene moiety furnished the desired *chiro*-inositol derivative.

Keywords: *chiro-inositol, methoxy conduritol-B, methoxy inositol, regio- and stereospecific synthesis*

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1. Introduction

Inositol **1** and its derivatives are an important class of biologically active natural products. Among the nine theoretically possible inositols, six are known to occur in Nature.[1] Interestingly, inositols containing one or more methyl ethers have been isolated from plants, and these methyl inositols are presumed to have important functions in plant biology.[1b,1c] D-*chiro*-Inositol **2**, a naturally occurring inositol, is clinically used for the treatment of polycystic ovary syndrome.[2] Additionally, *myo*-inositol and D-*chiro*-inositol have been shown to possess insulin-mimetic properties, acting as secondary messengers in the insulin intracellular pathway.[3] Recently, their methyl-inositol or methoxy-inositol derivatives (pinitol,[4a,4b] 1,4-di-*O*-methyl-*chiro*-inositol **3**,[4c] 1,2-di-*O*-methyl-*chiro*-inositol[4d]) have also been synthesized. Moreover, halo-substituted inositols (dimethoxydichloro **4,**[5] methoxydibromo **5**,[6] methoxyfluoro **6**[7]) have also gained importance over the last decade (Fig. 1).

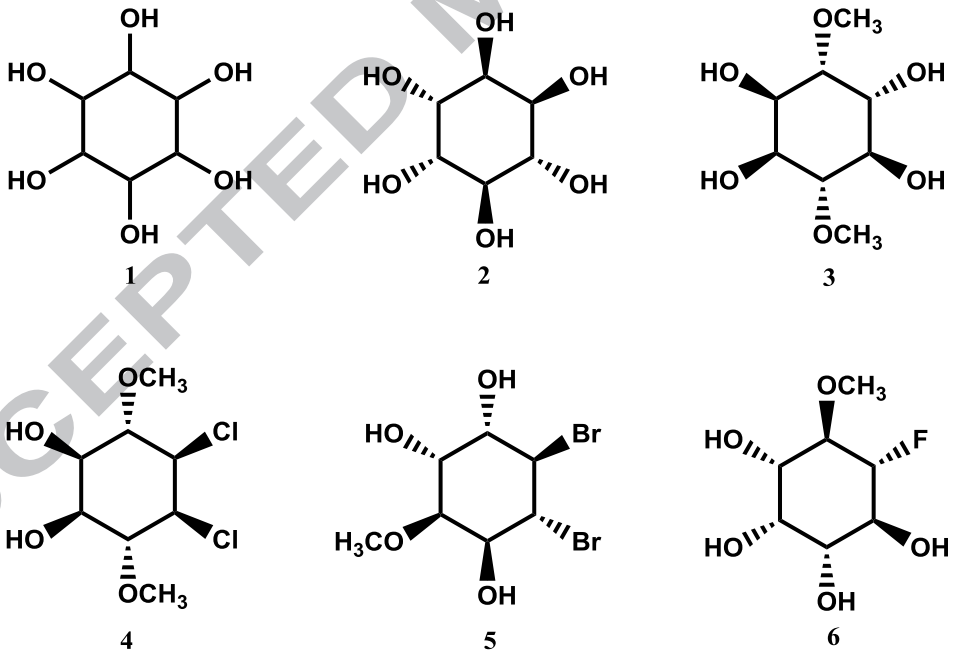


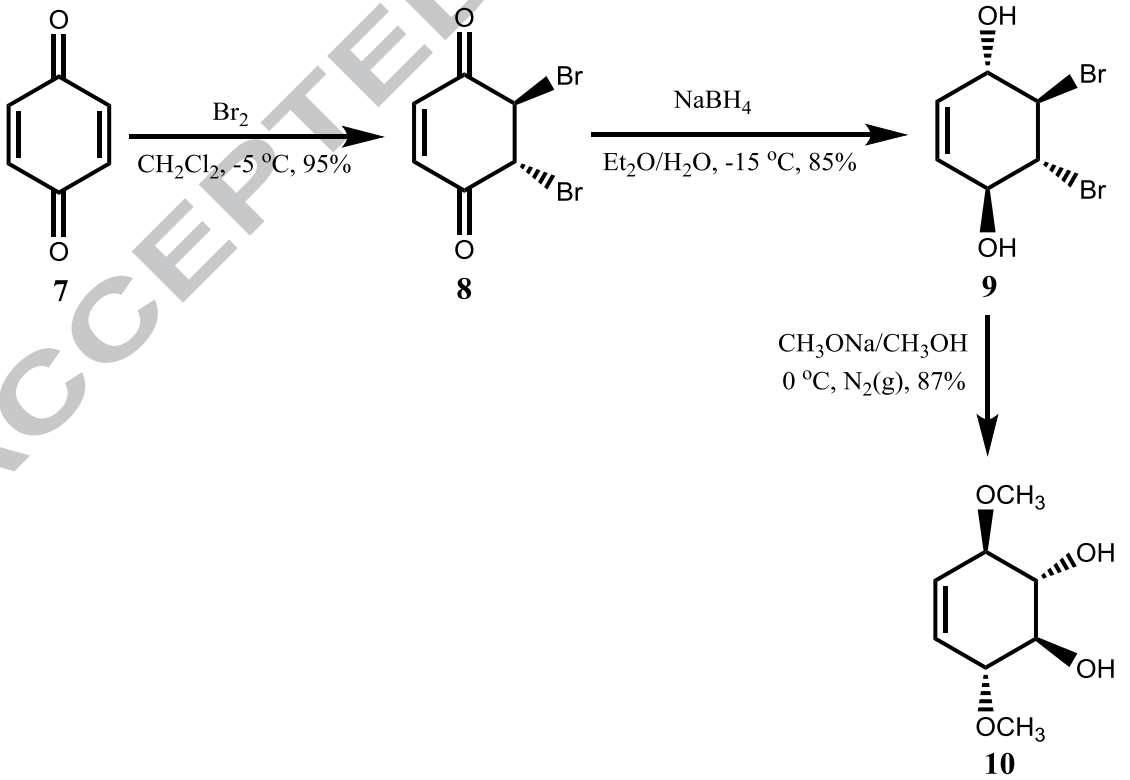
Figure 1. Selected inositol derivatives

The preparation of cyclitols and their analogues is challenging due to the numerous hydroxy bearing stereocenters. Recently, we reported the stereospecific synthesis of polyhydroxylated compounds.[8] Consequently, based on these results, we aimed to synthesize

novel halogenated deoxyinositols containing methyl groups. Due to the important biological activity of methoxyinositols and the interesting structural features of halogenated deoxyinositols, we focused on the synthesis of a dimethoxydibromo deoxyinositol, namely DL-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol **11**.

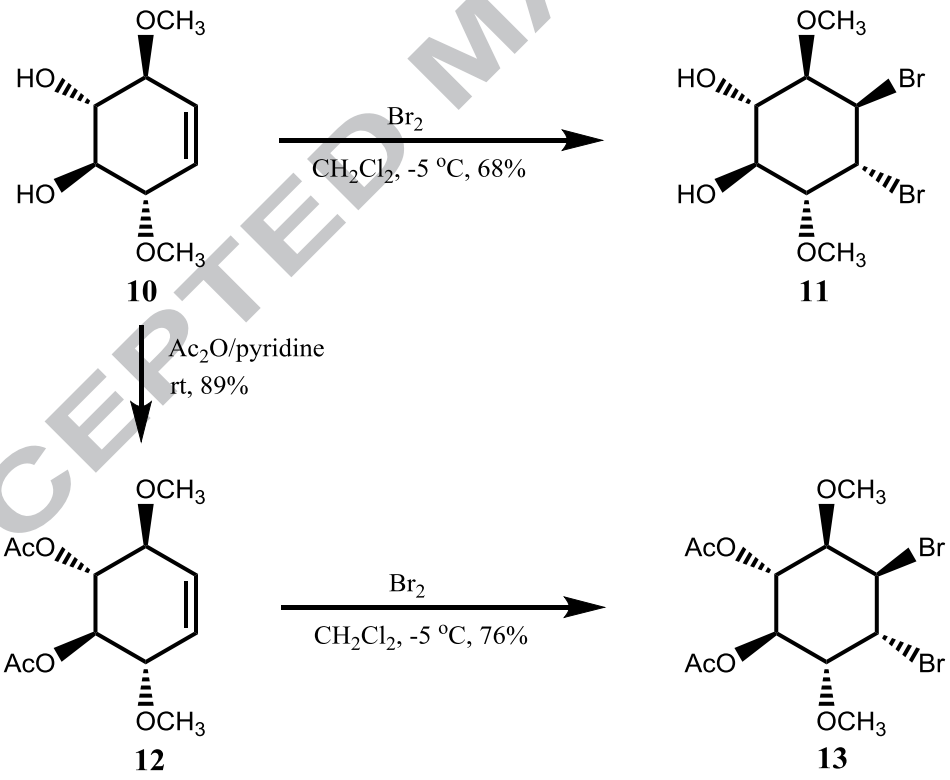
2. Results and Discussion

p-Benzoquinone **7** was brominated at low temperature to give only the *trans*-dibromo compound **8** in high yield. The required key intermediate, allylic *trans*-diol **9**, was obtained as the sole product by the stereoselective reduction of the carbonyl groups with $NaBH_4$ in diethyl ether.[9] The stereochemical course of the reduction was as shown and was proven by NMR and X-ray analysis of a later intermediate. Treatment of dibromodiol **9** with a metallic sodium-methanol system (MeONa/MeOH)[10] under a N_2 atmosphere led to the stereocontrolled transformation to conduritol-B derivative **10** in 76% yield (Scheme 1). The structure of compound **10**, which possesses C_2-symmetry, was unambiguously deduced by ^1H and ^{13}C NMR spectroscopy.



Scheme 1. Synthesis of dimethoxy conduritol-B **10**

Treatment of dimethoxydiol **10** with bromine in CH_2Cl_2 at low temperature for 2 days afforded DL-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol **11** as the sole product in 68% yield. Regio- and stereoselective addition of bromine to compound **10** resulted in product **11**, a *chiro*-inositol derivative. The structure of compound **11** was unambiguously deduced by ^1H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum consisted of four carbon resonances owing to the C_2-symmetry. Furthermore, selective decoupling experiments allowed the connectivity of **11** to be determined. In the ^1H NMR spectrum, irradiation of -CHOH (4.83 ppm) caused the H-6 signal (3.36 ppm) to change. The irradiation of -CHBr (3.95 ppm) resulted in the -CHOMe signal (3.73 ppm) changing from a triplet doublet into a doublet. Upon irradiation of -CHOMe (3.73 ppm), both the -CHOH signal (4.83 ppm) and the -CHBr signal (3.95 ppm) changed from a doublet into a singlet and from a doublet of doublet into a singlet, respectively. These results clearly indicate that the connectivity of 11 is as shown.



Scheme 2. Synthesis of dimethoxydibromo inositol **11**

Next, we focused on the bromination reaction of compound **12**, including the larger acetate groups. For this purpose, acetylation of **10** with the Ac_2O/pyridine system gave

compound **12**[10a] as the sole product in 89% yield. The reaction of **12** with bromine in CH_2Cl_2 under the same conditions produced the desired *chiro*-inositol dibromodiacetoxy **13** as the sole product in 76% yield. A six-line pattern in the ^{13}C NMR spectrum of **13** confirmed the proposed structure due to the C_2-symmetry in the molecule. However, NMR spectroscopic studies did not allow configurational assignment of the bromine groups. Therefore, single crystal X-ray analysis of *chiro*-inositol derivative **13** (Fig. 2) was required to confirm the structural assignment. Compound **13** crystallizes in the monoclinic $P2_1/c$ space group with four molecules in the unit cell. C-C bond lengths of the cyclohexene unit are in the range of 1.516(3)-1.534(3) Å. In this cyclic unit, the bromine and acetate groups are *trans* to each other. The structure contains six asymmetric carbon atoms and all have (*R*)-stereogenic centers.

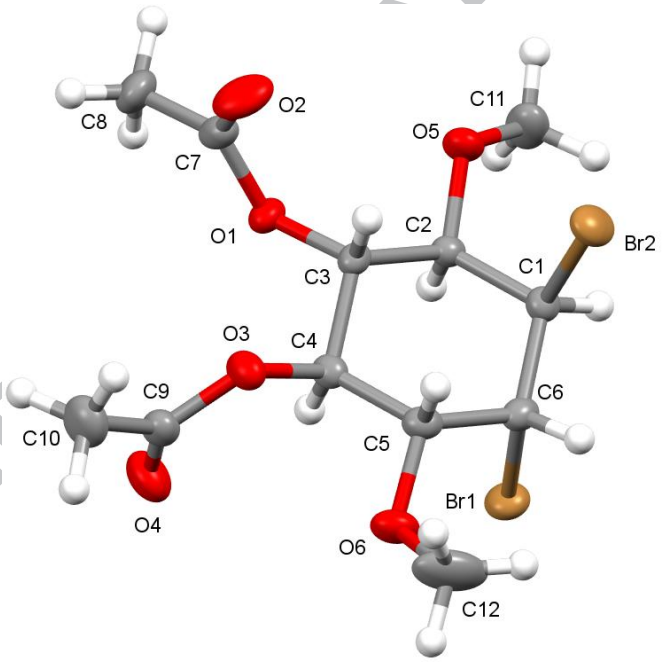
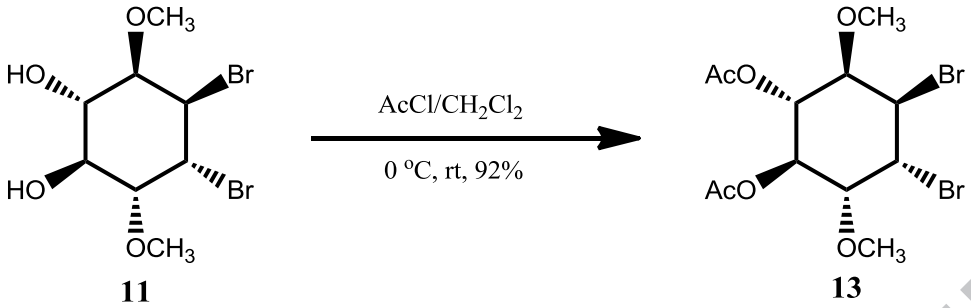


Figure 2. Molecular structure of the *chiro*-inositol derivative **13.** Thermal ellipsoids are drawn at the 30% probability level.

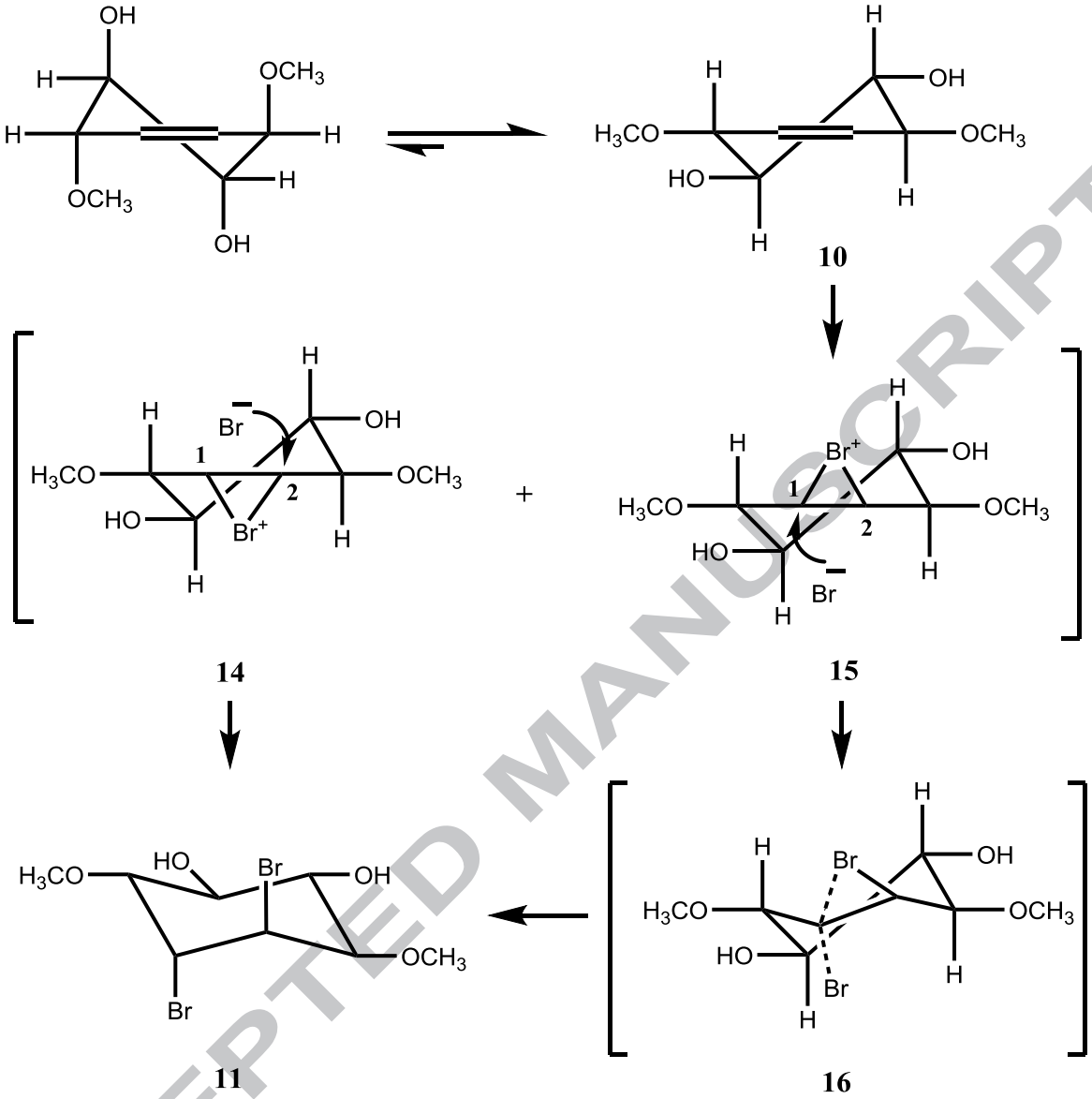


11 **13**

Scheme 3. Acetylation of dibromodiol **11**

Additionally, to test the potential of this approach, dibromodiacetate **13** was obtained in one-step from dibromodiol **11** by treatment with CH_3COCl in CH_2Cl_2 at room temperature. After crystallization from AcOEt/hexane, compound **13** was obtained in 92% yield, as the only isomer detected by NMR spectroscopy.

We suggest the following mechanism for the regio- and stereospecific synthesis of **11** (Scheme 4). In general, the electrophilic bromination reaction of olefins is stereoselective and leads to *trans*-1,2-dibromides *via* a three-membered bromonium ion intermediate. Since the diequatorial arrangement predominates as the favoured conformation of **10**, the bromination reaction progresses from this conformation. Here the bromonium ion may form on both faces of the ring (e.g. **14** and **15**), but in both cases the same diaxial product occurs due to ring-opening progressing according to the Fürst-Plattner rule.[11] In the light of these findings, the electrophilic bromine can attack the double bond in **10** at both sides of the double bond to form cyclic bromonium ions **14** and **15**, respectively (Scheme 4). The formation of intermediate **15** is important not only in terms of the synthetic aspect, but also in view of the mechanism of compound **11** which was regioselectively obtained as the sole product. It is evident from the configuration of the bromine atoms in **11** that attack of the bromide through the *trans*-diaxial chair conformation is preferred at C-1, which gave DL-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol.



Scheme 4. Proposed mechanism for the formation of dibromdimethoxy deoxyinositol **11**

3. Conclusion

The regio- and stereospecific synthesis of a novel dimethoxy-dibromo-deoxyinositol possessing *chiro*-inositol stereochemistry is reported. As shown by the efficient preparation of **11** and **13**, these compounds have potential to be used as precursors for the synthesis of methoxy-, azido- and aminoinositol derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at…

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Concise route to a chiro-inositol derivative ingluding bromine groups was developed.
Precursors of methoxy-, azido-, and aminoinostols were efficiently synthesized.

GRAPHICAL ABSTRACT

Regio- and stereospecific synthesis of (DL)-4,5-dibromo-4,5-dideoxy-3,6-*O*-methyl-*chiro*-inositol

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