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PII: S0040-4039(16)30806-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.06.127
Reference: TETL 47854

To appear in: *Tetrahedron Letters*

Received Date: 13 June 2016
Revised Date: 27 June 2016
Accepted Date: 28 June 2016

Please cite this article as: Panda, A., Biswas, R.G., Pal, S., A unified and common intermediate strategy for the asymmetric total synthesis of 3-deoxy-*neo*-inositol and conduritol E, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.06.127

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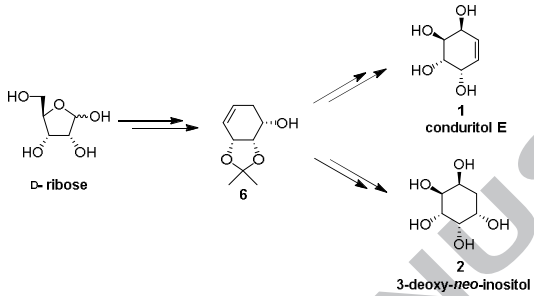

Tetrahedron Letters
journal homepage: www.elsevier.com

A unified and common intermediate strategy for the asymmetric total synthesis of 3-deoxy-*neo*-inositol and conduritol E

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
3-Deoxy-*neo*-inosotol
Conduritol E
Asymmetric synthesis
Common intermediate
Carbocycles

ABSTRACT

A competent, simplistic and unified synthetic approach has been outlined for enantiomerically pure 3-deoxy-neo-inositol and conduritol E starting from D-ribose *via* a common chiral cyclohexenol derivative. The focal attributes of the synthetic route include stereoselective Grignard reaction, Wittig olefination, ring closing metathesis (RCM) and cis dihydroxylation.

Polyhydroxy-cycloalkanes/alkenes belong to a large and supreme family of natural products known as the cyclitols.[1] Synthetic approaches to naturally occurring cyclitols and their analogues are of great significance due to their diverse biological properties, versatility as synthetic intermediates for many biologically imperative molecules and natural products and the structural challenges inherent in their syntheses.[2] The conduritols[3] and the inositols[4] are the cyclitol derivatives that evince prominently in numerous biological processes. The conduritol comprises of six diastereomers which are designated as A to F. The existence of four stereogenic C-atoms allows them to prevail in six different configurations, out of these two are *meso* compounds (conduritol A and D) while the remaining four are enantiomeric pairs (conduritol B, C, E and F). Conduritol A and F occur naturally (Figure 1). The conduritols and their derivatives have been found to possess interesting biological properties such as antibiotic, antileukemic, antifeedant, tumor inhibitory, glycosidase inhibitory and growth regulating activities etc.[5] Epoxyconduritols and aminoconduritols act as inhibitors of glycosidases[6] while the cyclophellitols have been proven to be potent inhibitors of HIV infection.[7] The conduritol A analogues regulate the insulin liberation from isolated pancreatic islets with varying concentrations of glucose.[8] Similarly, the inositols are 1,2,3,4,5,6-cyclohexanehexols and can exist as nine stereo-isomers: *myo*, *scyllo*, *cis*, D-(+)-*chiro*, L-(-)-*chiro*, *epi*, *allo*, *muco* and *neo* inositols (Figure 1). Among these the D-(+)-*chiro* and L-(-)-*chiro* are enantiomers of each other, rest of them are optically inactive having plane of symmetry and *myo*, *scyllo*, *cis*, D-(+)-*chiro*, L-(-)-*chiro* are naturally occurring inositols. The inositols as well as their structural variants like quercitols, deoxyinositols have prominent biological properties.[9] Moreover, inositol phosphate derivatives mediate intracellular signal transduction pathways,[10] several deoxy inositols have also been used for glycosidase inhibition and mediation of cellular communication.[11]

The attention in conduritols and related cyclitols has been amplified and continues to attract considerable importance due to synthetic challenge and a range of useful biological activities exhibited by them. In addition, the multifunctional nature and the stereochemical complexity of cyclitols and derivatives have made them convenient and versatile intermediates in chemical syntheses of several related natural products and biologically impressive molecules such as aminoconduritols,[12] conduritolepoxides,[13] cyclophellitol,[14] pseudosugars,[15] aminosugar analogues,[16] etc. Hence, the stereocontrolled synthesis of this class of compounds has been stimulating considerable efforts since last few decades.[17] In fact, due to the presence of several stereogenic centers in the cyclohexane moiety, many of these syntheses resulted in racemic mixtures. The general drawbacks of such methods is that, they often provide diastereomeric mixtures and lack of proper stereogenic orientation. Although several synthetic approaches to conduritols and related cyclitols have been published[17] till date, some of those have reported the use of chiral catalysts, diastereoselective catalysts, and enzymatic resolution[18] to achieve enantiomerically pure compounds while other few have employed chiral-pool strategies.[19] Still the emerging demand for this class of compounds instigates further synthetic work aimed at improving the preparative efficiency and achieving high degrees of stereo and regio control.

In this context, leveraged by the growing interest in conduritols and related cyclitols with potential biological activity, herein, we report a unified and common intermediate strategy for the asymmetric total synthesis of 3-deoxy-*neo* inositol and

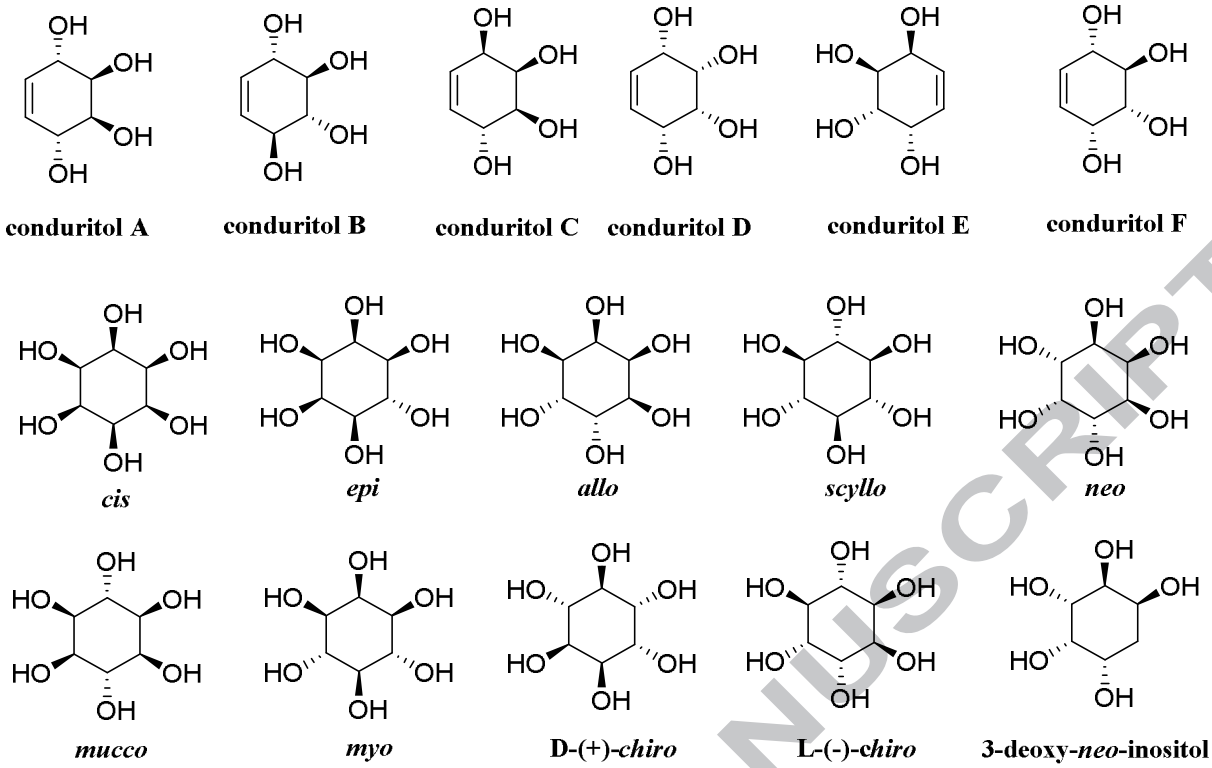


Figure 1. Conduritols A-F and inositols

conduritol-E from a readily available inexpensive starting material D-ribose *via* stereoselective Grignard reaction, Wittig olefination, ring closing metathesis (RCM) and *cis* dihydroxylation as key steps. The cornerstone of the synthetic approach has been delineated retrosynthetically in figure 2.

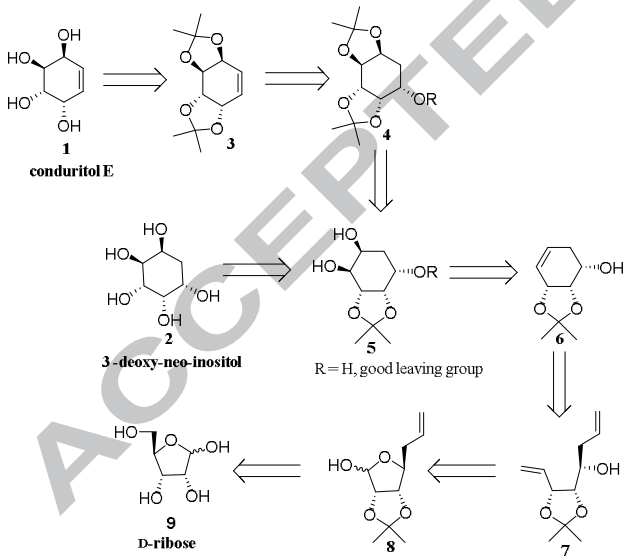
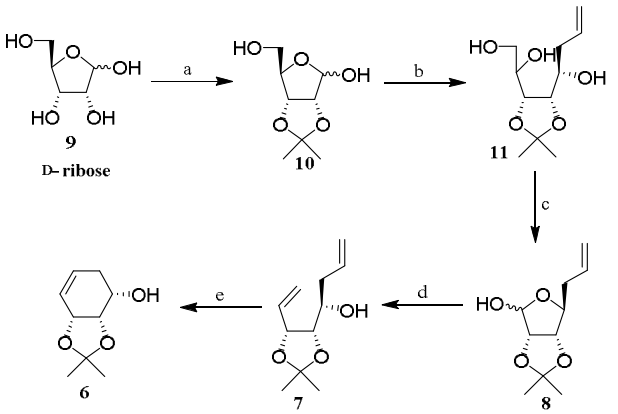


Figure 2. Retrosynthetic analysis of targer compounds

From the above retrosynthetic analysis, it was envisaged that both conduritol E **1** and 3-deoxy-*neo*-inositol **2** could be synthesized from a common intermediate **6** by implementing the following steps of reaction. 3-deoxy-*neo*-inositol **2** was contemplated to be synthesized from the key cyclohexenol **6** by *syn* dihydroxylation with OsO_4 and followed by acetonide deprotection. On the other hand, conduritol E **1** was speculated to be derived from the same cyclohexenol **6** by couple of more trasformations like *syn* dihydroxylation, protection, elimination and acetonide hydrolysis respectively. The key cyclohexenol **6**, in turn could be obtained from diene **7** *via* RCM reaction. The diene **7** was predicted to be synthesized from lactol **8** by Wittig olefination and the lactol **8** could be prepared from D-ribose **9** by acetonide protection, Grignard reaction followed by oxidative cleavage of vicinal diols.

In order to pursue the theme delineated in figure 2, the key cyclohexinol **6** was initially attempted for its synthesis commencing from D-ribose **9** by a few steps. D-ribose was treated with anhydrous acetone in presence of a catalytic amount of concentrated sulfuric acid to give the corresponding 2,3-acetonide protected diol **10**. Then the lactol **10** was subjected to



Reagents and conditions: (a) acetone, conc. H_2SO_4, rt, 4 h, 85%; (b) allylmagnesium bromide, Et_2O, –78 °C – 0 °C, 3 h, 90%; (c) aq. $NaIO_4$, DCM, 0 °C – rt, 2 h, 84%; (d) CH_3PPh_3Br, *t*-BuOK, THF, 0 °C – rt, 2 h, 85 %; (e) Grubbs' 2nd generation Catalyst, DCM, rt, overnight, 89%

Scheme 1

srereoselective Grignard reaction with allylmagnesium bromide in anhydrous ether to afford the ring opened polyhydroxylated olefin **11** predominantly over the other diastereomer [20] (Scheme 1). The stereoselectivity of Grignard reaction might be explained *via* the Felkin-Anh cyclic chelate transition model as shown in (Figure 3).[21] This chelate transition state articulates the β-attack of nucleophile from the less hindered face providing a single stereoisomer in an exclusive amount. The oxidative cleavage of the vicinal diol in compound **11** was carried out by sodium *meta* periodate in dichloromethane to obtain the desired lactol **8** in 84% yield. Wittig olefination of lactol **8** with methyl triphenylphosphonium ylide in presence of potassium-*tert*-butoxide exhibited the diene **7** in a good yield which established the platform for ring closing metathesis[22] to fabricate cyclohexene scaffold. The key cyclohexenol **6** was achieved smoothly by ring closing metathesis reaction of diene **7** with Grubbs' second generation catalyst (Scheme 1).

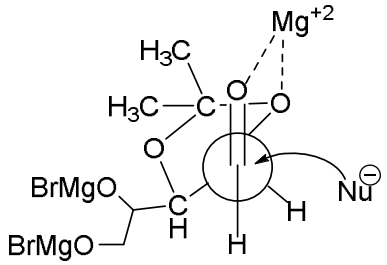
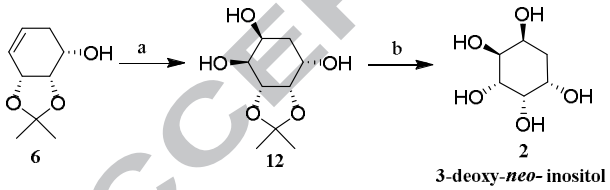


Figure 3. Felkin-Anh cyclic chelate transition model

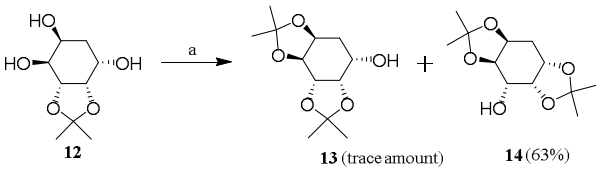
A simple, orthodox transformation was intended for the accomplishment of total synthesis of 3- deoxy-*neo*-inositol **2** from the hexenol derivative **6**. *Syn* dihydroxylation[23] of alkene in compound **6** was successfully attained by OsO_4 in presence of *N*-methylmorpholine *N*-oxide (NMO) to acquire the desired triol **12** as a sole product with high selectivity. This stereochemical predilection might be governed by the existence of the acetonide group at the α face of the cyclohexenol. Finally, the acetonide deprotection of triol **12** with trifluroacetic acid in THF-water (1:1) furnished 3-deoxy-*neo*-inositol **2** in 79% yield (Scheme 2).



Reagents and conditions: (a) OsO_4, NMO, acetone/ water, rt, 10 h, 87%; (b) Trifluoroacetic acid, THF/H_2O, rt, 4 h, 78%

Scheme 2

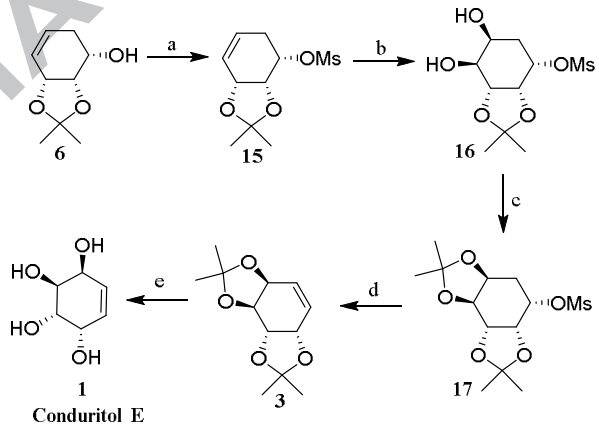
In order to execute the total synthesis of conduritol E, the triol **12** was initially strived for acetonide protection to obtain the diacetonide protected compound **13**. However, the protection led to the formation of two regioisomers **13** (trace amount) and undesired isomer **14** as a major product (Scheme 3). At this juncture, it was almost impossible to proceed further by this synthetic route. Hence, to circumvent the aforementioned draw back, the strategy was rehabilitated accordingly for the total synthesis of conduritol E.



Reagents and conditions: (a) acetone, conc.H_2SO_4, rt, 15 h,

Scheme 3

The cyclohexenol **6** was first protected to its mesylate **15** by mesyl chloride in presence of Et_3N in dichloromethane. Then the mesylate compound **15** was subjected to *cis* didydroxylation by OsO_4 to give the diol compound **16** in very good yield. The diol **16** was easily protected by 2, 2 dimethoxypropane in THF to supply the desired diacetonide compound **17** in a good yield. Further, the exposure of diacetonide **17** to potassium-*tert*-butoxide (t-BuO^- K^+) resulted the elimination of mesylate group to deliver the protected conduritol E **3**. The removal of both the acetonide group by acidic hydrolysis using TFA afforded the desired (+)-condurirol E **1** in very good yield as shown in scheme 4. All the synthesized compounds were thoroughly characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS, melting point, etc. The exact stereochemistry of both 3 deoxy-*neo*-inositol and (+)-conduritol E was further reconfirmed by the X-ray crystal structure of the diol intermediate **16** (figure 4).



Reagents and conditions :- a) MsCl, TEA, DCM, 0 °C – rt, 3 h, 88%; b) OsO_4, NMO, acetone/ H_2O, rt, 8 h, 90%; c) 2,2 dimethoxypropane, CSA, THF, rt,18 h; d) t-BuOK, DMF, 0 °C – rt, 10 h, 75% (for 2 steps); e) TFA, THF/ H_2O, rt, overnight, 79%

Scheme 4

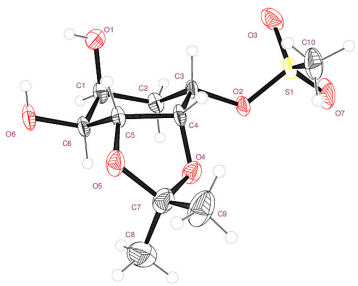


Figure 4. ORTEP of compound **16** (drawn at 50% probability)

In summary, an asymmetric total synthesis of 3-deoxy-*neo*-inositol **2** and (+)-conduritol E **1** has been successfully accomplished from a readily available inexpensive starting material D-ribose *via* a common chiral cyclohexenol intermediate. A flexible, short and proficient synthetic route has been endeavored featuring stereoselective Grignard reaction, Wittig olefination, ring closing metathesis (RCM) and *cis* dihydroxylation as the key steps for achieving the total syntheses. The adopted strategy opens opportunities for further access to several functionally embellished cyclitol derivatives by modest synthetic manipulations to explore their synthetic and biological potency.

Acknowledgements

This work was supported by the Department of Science and Technology (DST), India, FAST track Project Grant No: SERB/F/0287. We thank CIF at IIT Bhubaneswar for NMR and X-ray crystallographic data.

Supplementary data

Supplementary data (experimental details and characterization data) associated with this article can be found, in the online version, at

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Highlights

- Asymmetric total synthesis of 3-deoxy-*neo*-inositol and conduritol E *via* a common intermediate
- Stereoselective Grignard reaction, Wittig olefination, RCM reaction and *cis* dihydroxylation
- Functionalized polyhydroxylated six-membered carbocycles

A unified and common intermediate strategy for the asymmetric total synthesis of 3-deoxy-*neo*-inositol and conduritol E

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