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Stereoselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol and formal synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxyproline☆

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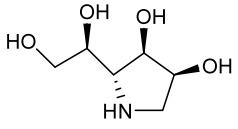
Abstract—A stereoselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol **1** and formal synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxyproline was achieved via the addition of vinylmagnesium bromide to the benzylimine derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde followed by *N*-allylation, ring-closing metathesis (RCM), and dihydroxylation.

Many natural and unnatural polyhydroxylated pyrrolidines and polyhydroxylated piperidines commonly referred to as azasugars or iminocyclitols are potent glycosidase inhibitors.[1] These azasugars represent an important class of transition state analogue inhibitors of glycosidase and glycotransferases, and they have been found to be chemotherapeutic agents for the treatment of diseases such as diabetes, cancer, inflammation and viral infections including HIV (Fig. 1).

The asymmetric inducing properties of hydroxylated pyrrolidine derivatives as chiral auxiliaries in alkylation,[2] acylation[3] and aldolisation[4] have also been demonstrated. Among these azasugars, imino furanoses, i.e. 1,4-dideoxy-1,4-imino alditols have attracted considerable attention because of their potential biological activity and structural features.

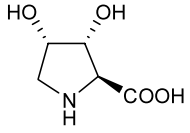
Several syntheses of these compounds have been developed, mostly based on transformation of sugar derivatives.[5] Herein we wish to report a highly efficient stereoselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol **1** via the stereoselective addition of vinyl magnesium bromide to the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde[6] based on the highly diastereoselective approach developed by Cativiela et al.,[7] followed by *N*-allylation, ring-closing metathesis and dihydroxylation. Recently this approach was utilised in our laboratory for the synthesis of (−)-cytoxazone.[8]

Compound **5** was prepared in one-pot from **3** as described by Cativiela et al.,[9] (Scheme 1) as a single diastereomer. Compound **5**, on treatment with $(Boc)_2O$ afforded **6** which under Li/liq. NH_3/THF conditions gave compound **7** as a white solid. Further treatment with allyl bromide in the presence of NaH and DMF resulted in diene **8**, $[\alpha]_D^{25} = -6.5$ (*c* 0.9, $CHCl_3$). Treatment of **8** with 10 mol% Grubbs' catalyst[10] in DCM at rt afforded **9**, $[\alpha]_D^{25} = -26.4$ (*c* 0.6, $CHCl_3$). Reaction of



1

1,4-dideoxy-1,4-imino-D-allitol



2

(2*S*,3*R*,4*S*)-3,4-dihydroxyproline

Figure 1.

Keywords: imine; Grignard reaction; *N*-allylation; ring-closing metathesis; dihydroxylation; azasugars.
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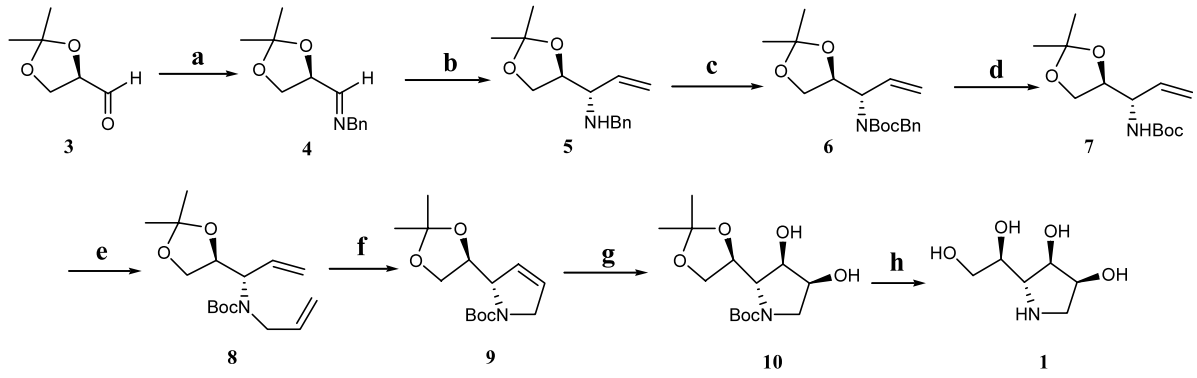
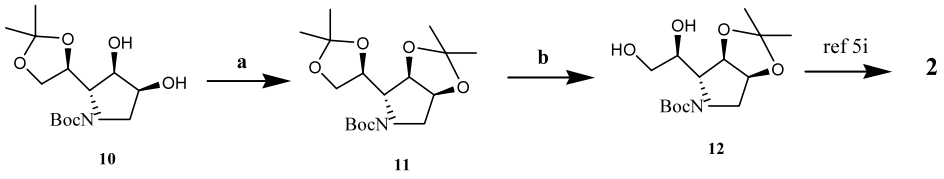


Scheme 1. *Reagents and conditions*: (a) $BnNH_2$, anhy.MgSO4, dry ether, 0°C–rt, 2 h; (b) CH_2=CH–MgBr, dry ether, 0°C–rt, 15 h, 76% (overall yield for two steps); (c) $(Boc)_2O$, Et_3N, dry DCM, 0°C–rt, 24 h, 72%; (d) Li, liq NH_3, THF, −50°C, 1 h, 81%; (e) Allyl bromide, NaH (60%), DMF, 0°C–rt, 12 h, 75%; (f) 10 mol% Grubbs' catalyst $[Cl_2(Pcy_3)_2Ru{=}CHPh]$, DCM, rt, 12 h, 75%; (g) OsO_4 (10 mol%), NMO monohydrate, acetone:H_2O (3:1), 12 h, 80%; (h) methanol–HCl, rt, 10 h, 82%.



Scheme 2. *Reagents and conditions*: (a) 2,2-DMP, cat. PTSA, dry acetone, rt, 12 h, 71%; (b) 60% AcOH, 48 h, 73%.

9 with OsO_4[11] (10 mol%), and NMO in acetone:H_2O resulted in compound **10**, $[\alpha]_D^{25}=-36.4$ (*c* 0.5, $CHCl_3$) as a single isomer. Compound **10** on treatment with MeOH–HCl[12] finally afforded the target molecule **1**, as its HCl salt, $[\alpha]_D^{25}=+25.0$ (*c* 1, H_2O) [lit.[5j] $[\alpha]_D^{25}=+25.6$ (*c* 0.9, H_2O)] whose NMR spectral data were in good agreement with the literature.[5i,j]

The synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxyproline was achieved as follows: Treatment of **10** with 2,2-DMP (cat. PTSA, acetone) under anhydrous conditions gave **11** which on selective hydrolysis of the side-chain acetonide gave compound **12** $[\alpha]_D^{25}=-34.9$ (*c* 0.9, $CHCl_3$) [lit.[5i] $[\alpha]_D^{25}=-33.5$ (*c* 0.17, $CHCl_3$)] (Scheme 2). The NMR spectral data of **12** were in agreement with those reported.[5i] Compound **12** has been converted to (2*S*,3*R*,4*S*)-3,4-dihydroxyproline **2** in three steps by Fleet et al.,[5i] so providing the formal synthesis of **2**.

In conclusion, a highly efficient stereoselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol **1** has been achieved via a strategy which may be useful for the synthesis of analogues of **1**.

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