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# Formal synthesis of dysiherbaine

Maddimsetti Venkateswara Rao, Annavareddi Naresh, Gudipati Saketh, Batchu Venkateswara Rao *

*Organic and Biomolecular Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500607, India*

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ABSTRACT

A formal synthesis of dysiherbaine was achieved from D-mannitol using Grignard addition on chiral imine, RCM and Michael addition as key steps.



(−)-Dysiherbaine isolated from a Micronesian sponge *Dysidea herbacea* by Sakai et al. is a potent neuroexcitotoxin and a selective agonist of non-NMDA (*N*-methyl-D-aspartate) type glutamate receptors in the central nervous system.[1] Similar compounds have been isolated from different sources and they have been showing excellent biological activities. Dysiherbaine **1** and neodysiherbaine A **3** have a *cis*-fused hexahydrofuro [3,2-*b*] pyran bicyclic ring system having a glutamic acid substructure. Malayamycin A **2** another member of this family exhibits potent fungicidal activity.[2] Ezomycin $A_2$ **4** is a bicyclic *N*-nucleoside and (Fig. 1) exhibits antifungal and antibiotic activities.[3] (−)-Dysiherbaine **1** which is the first example and core structure of this class of compounds has attracted the attention of many synthetic chemists.[10,11] In 2000 Masaki et al. reported the total synthesis of (−)-dysiherbaine from **17A** in 10 steps and the key intermediate **17A** was synthesized in 16 steps.[10b] In 2008 Pradilla et al. also synthesized the *ent*-**17A** in 13 steps in which *ent*-**17B** was converted into *ent*-**17A** by treating with MeI.[11] Later in 2011 Tamura et al. also synthesized **17A** in 14 steps. In our opinion the key intermediate **17** will be a good starting material not only for the synthesis of dysiherbaine but also for other related molecules. Therefore we have undertaken the synthesis of **17B** and herein we report its synthesis in 12 steps from easily available D-mannitol diacetonide with high stereoselectivity and good yielding reactions. The key features of our synthesis are a Grignard addition on chiral imine **6**[4] followed by a RCM reaction, a methodology which we have been using for the synthesis of several heterocyclic (Scheme 1). Our synthesis starts from commercially available D-mannitol (Scheme 2) which was converted into mannitol diacetonide using the literature procedure.[4a] Oxidative cleavage of mannitol diacetonide yielded aldehyde **5** which upon condensation with *p*-methoxy benzylamine in the presence of 4 Å molecular sieves afforded chiral imine **6**, which was used as such for the next step without any further purification (Scheme 2).

Treatment of imine **6** with vinyl magnesium bromide in THF at 0 °C gave *anti*-amino olefin **7** as an exclusive isomer.[4] The amino functionality in compound **7** was protected as its Cbz derivative by treatment with benzyloxy carbonyl chloride in the presence of $NaHCO_3$ in MeOH to afford compound **8** in 88% yield.[5] The isopropylidene group in compound **8** was cleaved off using 60% AcOH to give diol **9**. The *N*-Cbz protective group was advantageously

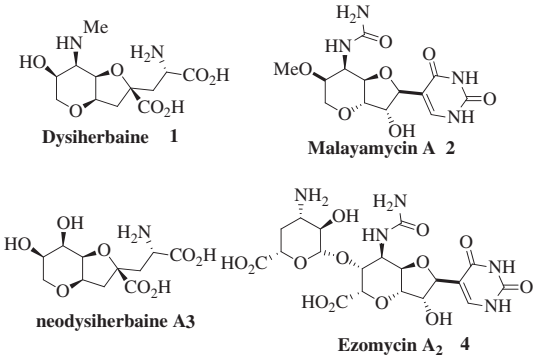


**Figure 1.**

* Corresponding author. Tel./fax: +91 40 27193003.
*E-mail addresses:* venky@iict.res.in, drb.venky@gmail.com (B.V. Rao).

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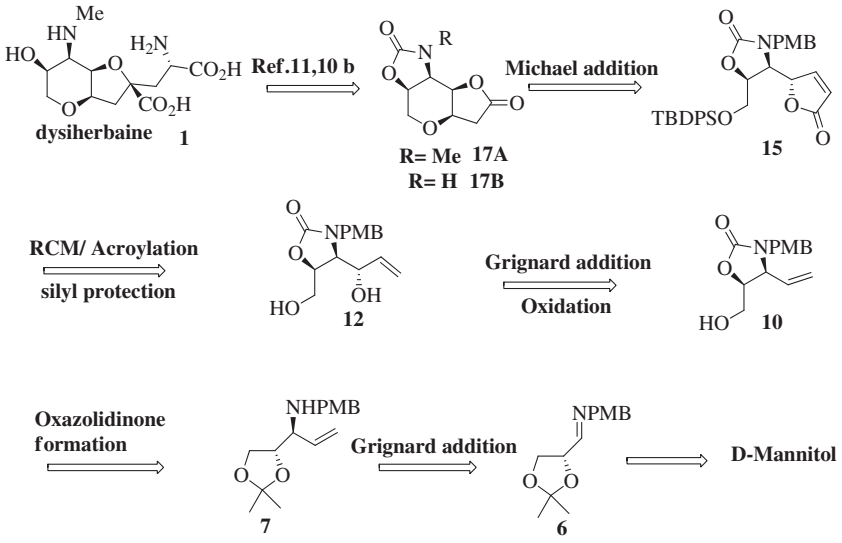
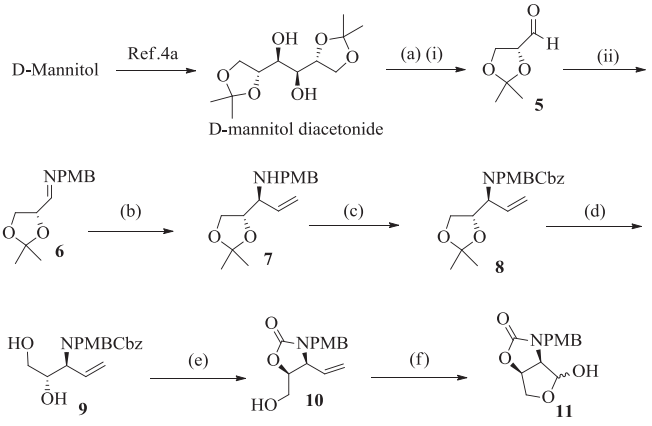
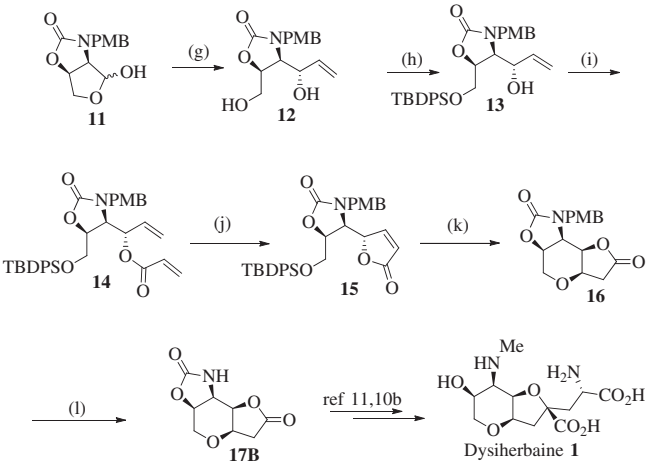



**Scheme 1.** Retro synthetic analysis of dysiherbaine.




**Scheme 2.** Reagents and conditions: (a) (i) $NaIO_4$ on silica gel, $CH_2Cl_2$, 0 °C, 2h then, (ii) $PMBNH_2$, $CH_2Cl_2$, 0 °C, over night; (b) vinyl magnesium bromide, THF, 0 °C to rt, 1 h, 92%; (c) CBzCl, $NaHCO_3$, MeOH, 0° C to rt, 2 h, 88%; (d) 60% $CH_3CO_2H$, 6 h, 80%; (e) NaH, THF, 0 °C to rt, 84%; (f) $O_3$, $CH_2Cl_2$, −78 °C, 87%.




**Scheme 3.** Reagents and conditions: (g) vinyl magnesium bromide, THF, −78 °C to rt, 6 h, 77%; (h) TBDPSCl, imidazole, 0 °C to rt, 1 h, 78%; (i) acrylic acid, DCC, DMAP, 0 °C to rt, 1 h, 80%; (j) Hoveyda–Grubbs second generation catalyst, toluene, reflux, 30 min, 85%; (k) aq HF, $CH_3CN$, 0 °C to rt for 6 h then $NaHCO_3$, 3 h, 79%; (l) $H_2$–Pd/C, MeOH, overnight, 73%.

utilized for the selective protection of the neighboring secondary hydroxyl group of **9**.[6] Thus treatment of compound **9** with NaH in THF gave oxazolidinone **10**. Oxidative cleavage of terminal double bond in **10** with $O_3$ in $CH_2Cl_2$ at −78 °C produced lactal **11** in 87% yield (Scheme 3). Treatment of **11** with vinyl magnesium bromide at −78 °C gave exclusively **12** in 77% yield. At 0 °C the formation of the other diastereoisomer is also observed. The primary alcohol in **12** was protected as silyl ether using TBDPSCl and imidazole at 0 °C to produce **13**.[7] The secondary alcohol in **13** was esterified with acrylic acid, DCC, and DMAP at 0 °C to give diene **14** in 80% yield.[8] This diene **14**, on reaction with Hoveyda–Grubbs second generation catalyst in toluene under reflux[9] afforded lactone **15**. Desilylation of **15** with aq. HF in acetonitrile at room temperature followed by Michael addition of liberated alcohol produced the tricyclic core **16** of dysiherbaine **1**[10] in 79% yield. Reduction of compound **16** with $H_2$, Pd/C in methanol afforded the core structure of dysiherbaine **17B** in 73% yield. The physical and spectroscopic data of compound **17B** are in good agreement with the literature values.[11,12]

In summary, we have developed a formal efficient synthesis of dysiherbaine from cheaply available mannitol as starting material. The conversion of the key intermediate **17A** to other related molecules will be investigated in future.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.038.

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12. *Compound* (***17***): $[\alpha]_D^{30}$ +68.3 (C 0.8, acetone), IR $\upsilon_{max}$ 2924, 2855, 1729, 1219, 772. $^1$H NMR ($CD_3OD$, 500 MHz): $\delta$ 4.53(ddd, 1H, $J$ = 8.2, 2.1, 1.3 Hz), 4.51 (dd, 1H, $J$ = 5.8, 3.9 Hz), 4.32(ddd, 1H, $J$ = 6.1, 3.6, 2.3 Hz), 4.18(dd, 1H, $J$ = 7.7, 5.8 Hz), 4.02(dd, 1H, $J$ = 13.8, 1.2 Hz), 3.64 (dd, 1H, $J$ = 14.0, 2.0 Hz), 2.85(dd, 1H, $J$ = 17.7, 5.7 Hz), 2.48(dd, 1H, J = 17.5, 2.1 Hz). $^{13}$C NMR ($CD_3OD$, 75 MHz): $\delta$ 176.5, 162.4, 76.4, 73.6, 73.5, 65.7, 50.5, 38.2. ESIMS $m/z$: 222 $[M+Na]^+$, HRMS (ESI) calcd for $C_8$ $H_9$ $O_5$ N Na = 222.0372, found 222.0371.