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Stereoselective synthesis of (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-tetradecyl-4-butanolide starting from 2,5-anhydro-D-mannitol

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Abstract—A novel approach to natural β-hydroxy-γ-lactone **2** from 2,5-anhydro-D-mannitol (**1**) is described. The key reactions in this synthesis include stereoselective methylation of aldehyde **3** with lithium dimethylcuprate, an intramolecular radical cyclization of seleno carbonate **11** and an intermolecular cross-metathesis of 3-allyl-4-hydroxy-γ-lactone **16** with 1-tridecene.

1. Introduction

Carbohydrates and their related compounds have been well recognized as a chiral pool for the syntheses of optical active natural products.[1] 2,5-Anhydro-D-mannitol (**1**),[2] however, has not been employed as a starting material for such syntheses[†] (Fig. 1). One of the reasons seems to stem from the difficulties of desymmetrization of **1**. For example, mono acylation or alkylation of **1** under restricted conditions is reported to result in a mixture of di- and mono protected mannitol derivatives along with **1**.[3] In the course of our synthetic studies on mucocin, we have developed a highly efficient method for desymmetrization of **1**.[4] As part of our continuing studies in this field, we describe herein the stereocontrolled synthesis of (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-tetradecyl-4-butanolide (**2**) starting from **1**. The lactone **2** was isolated from the methanol extract of fruits of *Trichila claussenii* in admixture with its 7′-dehydro form.[5] Its biological activities, which remain unclear, are of interest in connection with annonaceous acetogenins having prominent biological properties such as cytotoxity and antitumor activity.[6] Structurally, the butanolide **2** has three *cis*-substituents on the γ-lactone ring, and such sterically congested compounds are prone to elimination of the hydroxyl group during synthesis. Therefore, several synthetic methods to overcome such a problem have been devised, and total syntheses have been reported.[7]

2. Results and discussion

Synthesis of **2** began from the preparation of **1**. Although **1** had been prepared from D-glucosamine,[10] we newly found that **1** was also obtainable from a readily available polysaccharide, chitosan. Thus, chitosan was treated with sodium nitrite in aqueous acetic acid and subsequently reduced with sodium borohydride to give **1** in 67% yield (Scheme 1). The compound **1** was transformed into aldehyde **3** in good overall yield according to the procedure previously reported.[4] Stereoselective methylation[11] of **3** was accomplished by the action of lithium dimethylcuprate in

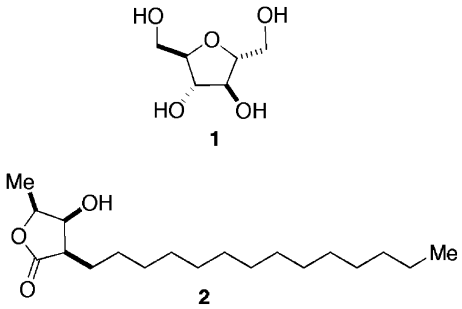

Figure 1.

Keywords: 2,5-Anhydro-D-mannitol; Intramolecular radical cyclization; Intermolecular cross-metathesis.
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† Because of its unique C_2-symmetrical structure, **1** served as a chiral ligand of catalysts for asymmetric hydrogenation,[8] and a central core of chiral dendrimers.[9]

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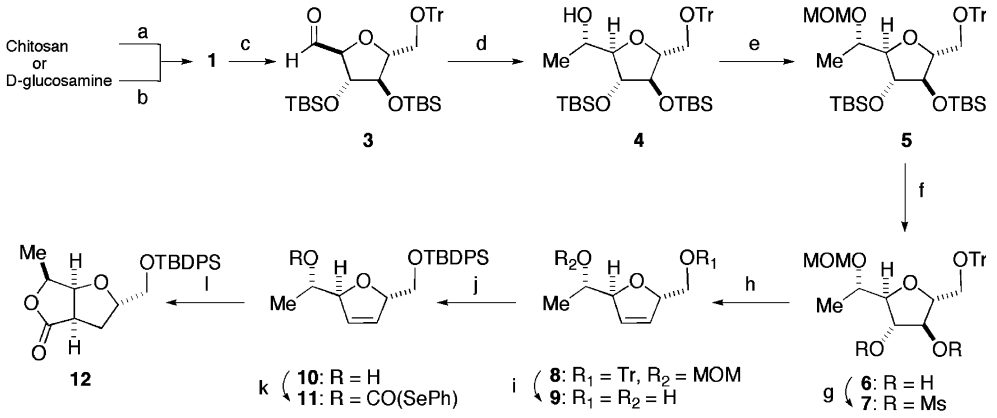
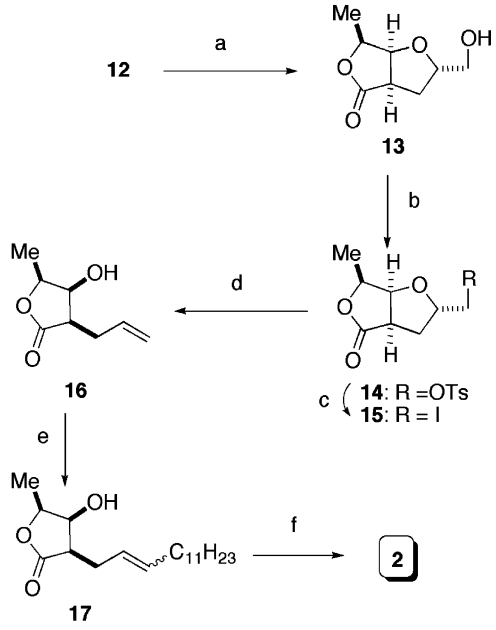


Scheme 1. (a) $NaNO_2$, 5% aqueous AcOH, 0 °C, and $NaBH_4$, MeOH, 67%; (b) Ref.10; (c) Ref. 4; (d) Me_2CuLi, Et_2O, −78 °C, 70% (>92% de); (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt,; (f) TBAF, THF, rt, 83% (two steps from **4**); (g) MsCl, Et_3N, CH_2Cl_2, rt, 74%; (h) Zn, NaI, DMF, 140 °C, 89%; (i) 10%HCl–MeOH, CH_2Cl_2, rt, 97%; (j) TBDPSCl, imidazole, DMF, rt, 81%; (k) triphosgene, pyridine, CH_2Cl_2, 0 °C∼rt and then PhSeH, Et_3N, 0 °C∼rt, 95%; (l) Bu_3SnH, AIBN, toluene, 100 °C, 93%.

ether at −78 °C to give **4** in high selectivity (>92% de, by ^{1}H NMR analyses) while reaction with methylmagnesium iodide–zinc chloride in dichloromethane–ether decreased both yields and selectivities. The newly created stereochemistry was determined by the modified Mosher's method[12] of the corresponding MTPA esters. Furthermore, this result was also confirmed by the chemical conversion of **4** into the final product **2**. The stereoselectivity would be explained by the formation of cyclic chelate[13] involving the aldehyde carbonyl and the ring oxygen. The free hydroxyl group in **4** was temporarily protected as methoxymethyl (MOM) ether with MOMCl and *N*,*N*-diisopropylethylamine, and the resulting compound **5** was treated with tetrabutylammonium fluoride, affording diol **6** in 83% yield from **4**. For deoxygenation of the tetrahydrofuran ring, **6** was mesylated to give dimesylate **7** in 74% yield. Upon treatment with zinc powder–sodium iodide,[14] **7** led to olefin **8** in 89% yield. The compound **8** reacted with hydrogen chloride in methanol–dichloromethane to provide diol **9**, which was silylated with *tert*-butylchlorodiphenylsilane to give alcohol **10** in 79% yield (two steps). Successive treatment of **10** with triphosgene[15] and benzeneselenol[16] in a one-pot manner afforded seleno carbonate **11** in 95% yield. Radical cyclization of **11** with tributyltin hydride proceeded nicely to give γ-lactone **12** as a single isomer in 93% yield. This complete stereoselection reflects the stereochemical requirement of a 2,7-dioxabicyclo[3.3.0] octane ring system.

Having completed the construction of the γ-lactone ring, we next turned to the final C–C bond formation (Scheme 2). Prior to the elaboration, the silyl group in **12** was removed to afford alcohol **13** in 89% yield. As direct iodination of **13** with iodine, triphenylphosphine, and imidazole resulted in a low yield (∼50%) of iodide **15**, the alcohol **13** was initially transformed into the corresponding tosylate **14** with *p*-TsCl-triethylamine in the presence of *N*,*N*-dimethylaminopyridine, and then **15** (sodium iodide, acetone) in high yield. Zinc-mediated elimination reaction of **15** furnished olefin **16** in 93% yield from **14**. Intermolecular cross-metathesis[17] of **16** with 1-tridecene was effected by treatment with a catalytic amount of Grubbs catalyst 1st generation in dichloromethane at 40 °C to give γ-lactone **17** (*E*/*Z*=ca.



Scheme 2. (a) TBAF, THF, rt, 89%; (b) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C∼rt, 94%; (c) NaI, acetone, 55 °C; (d) Zn, aqueous THF, 65 °C, 93% (two steps form **14**); (e) 1-tridecene, Grubbs catalyst 1st generation, CH_2Cl_2, 40 °C, 45%; (f) $(Ph_3P)_3RhCl$, H_2, benzene, rt, 95%.

7/1, by ^{1}H NMR analysis) in 45% yield (52% yield based on **16** consumed). The production of dimers derived from **16** was traced judging by TLC analysis. Unexpectedly, the use of Grubbs catalyst 2nd generation gave unsatisfactory results arising from the yields (20–25%).‡ Finally, **17** underwent hydrogenation with Wilkinson's catalyst to give the γ-lactone **2** in 95% yield. The spectroscopic and physical properties of **2** were consistent with those of **2** previously reported.[5,7]

In summary, we succeeded in the stereoselective synthesis of **2** employing 2,5-anhydro-D-mannitol (**1**) as a starting

‡ A considerable amount of a β-hydroxy lactone carrying a 1′-tridecenyl group was isolated as a major side product. The compound was estimated to be produced from an isomerization of the double bond in **16** followed by the cross-metathesis with 1-tridecene.