

First total synthesis of (–)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid

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Abstract—The first total synthesis of (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid was accomplished from commercially available 1-bromo-3-methylbutane in 11 steps and 25.8% overall yield. The key steps were asymmetric allylic alkylations via allyl-diisopinocampheylborane and hydroboration–oxidation.

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The asymmetric synthesis of β -hydroxy carboxylic acid with no substituents at $C\alpha$ systems remains a formidable challenge despite the progress that has been achieved in this area in recent years.¹ Favorable elimination of β -hydroxy and poor ee impede their preparation; once they are formed, further functionalization is difficult due to their susceptibility to acid and base. Compound **1** (Fig. 1) has attracted particular attention because of its β -hydroxyl acid skeleton. This compound and its trimer **2** (as their methyl ester derivatives **1a** and **2a**) were

isolated from the chloroform extract of aerial parts of *Lafuentea rotundifolia* Lag.²

Gross structure of **1a** was determined on the basis of spectroscopic methods and the configuration of the chiral center was determined using Mosher's method.³ Limited isolation and purification of acid **1** were reported due to its polarity and nature. However, containing β -hydroxyl in **1a**, the substance has not been hydrolyzed to produce acid **1**. Interestingly, **1** holds a β -hydroxyl acid skeleton connected with unique 1,4-dihydroxyl. In this letter, we wish to report our results on the asymmetric total synthesis of (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid by using asymmetric allylic alkylations via allyl-diisopinocampheylborane as a key reaction.

The general strategy for our asymmetric total synthesis of acid **1** and its methyl ester **1a** was detailed in Scheme 1. The synthesis of **1** was started from commercially available isopentyl bromide **3**. The corresponding 5-methylhexanal **4** was readily prepared by Grignard reaction of isopentylmagnesium bromide with ethylene oxide in ethyl ether⁴ followed by Swern oxidation in 79% yield (two steps). Reaction of aldehyde **4** with ^dIpc₂B(allyl) reagent under Brown's conditions⁵ afforded homoallylic alcohol **5a** in 90.3% ee (determined by Mosher ester **5b**), which was protected as its corresponding TBS ether with TBSCl and imidazole to provide **5c** in 76% overall yield after these two operations. TBS ether **5c** was followed by hydroboration–oxidation reaction to give alcohol **6** in 85% yield. Alcohol **6** was oxidized by Dess–Martin reagent to give aldehyde **7** in 95% yield. Aldehyde **7** reacted with ^dIpc₂B(allyl) reagent

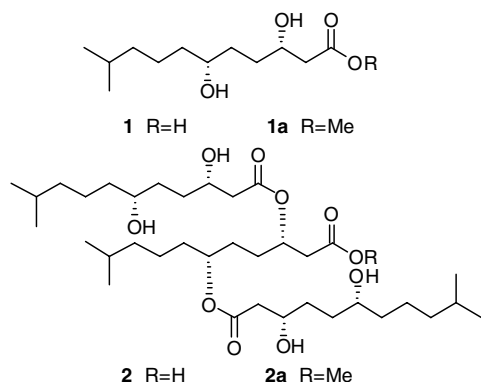
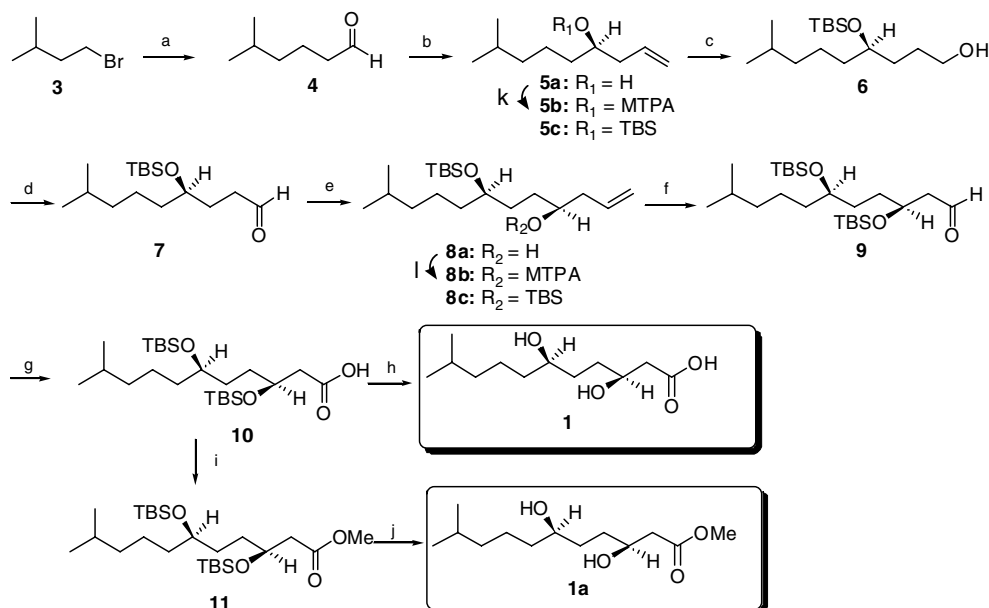


Figure 1. (–)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid (**1**) and trimer **2**.

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Scheme 1. Reagents and conditions: (a) 1) i. Mg, Et₂O; ii. ethylene oxide, Et₂O, 0 °C-reflux, 3 h, 90%; 2) DMSO, (COCl)₂, CH₂Cl₂, -78 to 0 °C, 30 min, 88%; (b) 1) i. ⁴Ipc₂B(allyl), Et₂O, -100 to 23 °C, 5 h; ii. 3 M NaOH, H₂O₂, reflux, 1 h, 80%; 2) TBDMSCl, imidazole, DMF, 30 °C, 24 h, 95%; (c) i. BH₃·SMe₂, THF, -78 to 0 °C, 2.5 h; ii. 3 M NaOH, H₂O₂, 3.5 h, 20 °C, 85%; (d) Dess–Martin reagent, CH₂Cl₂, rt, 2 h, 95%; (e) i. ⁴Ipc₂B(allyl), Et₂O, -100 to 23 °C, 5 h; ii. 3 M NaOH, H₂O₂, reflux, 1 h, 72%; 2) TBDMSCl, imidazole, DMF, 30 °C, 24 h, 98%; (f) i. O₃, CH₂Cl₂, -78 °C; ii. PPh₃, rt, 4 h, 90%; (g) 5% ^tBuOH–aqueous NaH₂PO₄, 2 M KMnO₄, aq ^tBuOH, rt, 30 min, 90%; (h) BF₃·Et₂O, MeCN, 0 °C, 2 h, 93%; (i) diazomethane, Et₂O, rt, 5 min, 98%; (j) TBAF, THF, rt, 12 h, 90%; (k, l) (*R*)-(-)-MTPA chloride, DMAP, Et₃N, CH₂Cl₂, rt, 1 h, 95%.

under Brown's conditions to provide homoallylic alcohol **8a** in 92.6% de (determined by Mosher ester **8b**), the newly formed homoallylic alcohol was then protected as its corresponding TBS ether **8c** with TBSCl and imidazole in 71% overall yield. Aldehyde **9** was formed by ozonolysis of **8c** followed by treatment with PPh₃ in 90% yield.⁶ The precursor, two TBS protected acid **10** was derived from oxidation of aldehyde **9** with KMnO₄ in 5% ^tBuOH–aqueous NaH₂PO₄ buffer solution at room temperature in 90% yield.⁷

Removing two TBS groups of **10** using TBAF was unsuccessful. We then attempted the method reported by Newton⁸ using pyridine/HF or HF in CH₃CN to remove the two TBS groups which was also a failure. Reaction of **10** with *tetra-n*-butylammonium chloride and potassium fluoride dehydrate in CH₃CN under Carpino's conditions did not give the expected dihydroxy acid **1** either, instead one TBS removed product was formed.⁹ The removal of two TBS groups was finally achieved using the method described by King¹⁰ (Scheme 1). Treatment of **10** with 2 equiv BF₃·Et₂O in MeCN gave (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid **11** in 93% yield.¹⁰ The two TBS protected acid **10** was treated with diazomethane in ethyl ether to afford methyl ester **11**. The application of one of the most common removing TBS groups reaction procedures, the two TBS groups were removed with TBAF in THF leading to the methyl ester derivative **1a**¹². The ¹H NMR data of **1a** were identical with those reported.²

The first asymmetric synthesis of (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid was accomplished from commercially available 1-bromo-3-methylbutane in 11 steps

and 25.8% overall yield. The synthetic route presented here allows an access to the other compounds of the β-hydroxy carboxylic acid with no substituents at Cα.

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11. Compound (–)-**1**: White powder mp 149–151 °C, $[\alpha]_{\text{D}}^{20}$ –7 (*c* 0.9, CHCl₃). ¹H NMR (300 MHz, CDCl₃, δ ppm): 0.87 (d, 6H, *J* = 6.6 Hz, H-11, H-12); 1.25–1.68 (m, 11H, H-4, H-5, H-7, H-8, H-9, H-10); 2.56–2.65 (m, 2H, H-2); 3.68–3.72 (m, 1H, H-6); 4.04–4.11 (m, 1H, H-3); ¹³C NMR (75 MHz, CDCl₃, δ ppm): 182.1, 72.6, 68.5, 38.9, 37.9, 37.3, 33.8, 29.7, 27.9, 23.5, 22.6. HRMS calcd for C₁₂H₂₄O₄Na (M+Na) 255.1567, found 255.1572.
12. Compound (–)-**1a**: $[\alpha]_{\text{D}}^{20}$ –9.5 (*c* 0.4, CHCl₃) {lit.,² $[\alpha]_{\text{D}}$ –11.1 (*c* 1.0, CHCl₃)}. ¹H NMR (300 MHz, CDCl₃, δ ppm): 0.87 (d, 6H, *J* = 6.6 Hz, H-11, H-12); 1.14–1.67 (m, 11H, H-4, H-5, H-7, H-8, H-9, H-10); 2.47–2.50 (m, 2H, H-2); 3.63–3.65 (m, 1H, H-6); 3.71 (s, 3H, Me); 4.03–4.05 (m, 1H, H-3). HRMS calcd for C₁₃H₂₆O₄Na (M+Na) 269.1723, found 269.1729.