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A practical enantioselective synthesis of massoialactone via hydrolytic kinetic resolution

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Abstract—An efficient enantioselective synthesis of (*R*)- and (*S*)-massoialactone has been achieved. The key steps are the hydrolytic kinetic resolution of a racemic epoxyheptane with (*R*,*R*)-(salen)–Co^{III}OAc complex and ring-closing metathesis of homoallylic alcohol derived acrylate esters using Grubb's catalyst.

δ-Lactones possessing alkyl side chains have attracted much attention from synthetic and medicinal chemists due to their biological activity. One such compound is massoialactone,[1,2] isolated for the first time from the bark of *Cryptocarya massoia*, by Abe[3] in 1937. It has been used for many centuries as a constituent of native medicines. It is a powerful skin irritant and produces systolic standstill in frog heart muscles.[1] This lactone has also been isolated from cane molasses[4] and jasmine blossoms[5] as a flavour substance. Later it was isolated from the secretion of the two species of Formicin ants[6] of the genus *Componotus*, collected in Western Australia.

Various methods for the synthesis of massoialactone (Fig. 1) have been described.[2,7] The asymmetric syntheses reported in the literature for the natural **1a** and unnatural **1b** isomers of massoialactone either utilize the chiral pool as a starting material[8] or the chromatographic resolution of the diastereomeric derivative of the lactone precursor.[9] A recent report describes the synthesis via asymmetric allylboration of an aldehyde with β-allyldiisopinocampheylborane.[10] As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[11] and amino alcohols[12] we recently reported the synthesis of (*S*)-massoialactone using the Sharpless asymmetric dihydroxylation approach.[11a] However the enantiomeric purity of the diol obtained was not high due to the terminal olefin employed as a substrate in the dihydroxylation

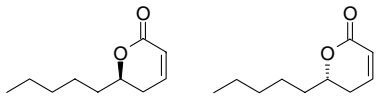

Figure 1.

step. Herein we report a new and highly enantioselective synthesis of (*R*)- and (*S*)-massoialactone using Jacobsen's hydrolytic kinetic resolution (HKR) of a terminal epoxide.[13] The HKR method uses readily accessible cobalt-based chiral salen complex **2** (Fig. 2) as catalyst and water as the only reagent to resolve a racemic epoxide into the enantomerically enriched epoxide and diol in high enantiomeric excess. These advantages have made it a very attractive asymmetric synthetic tool.

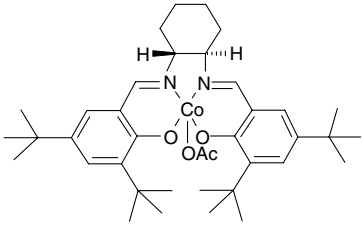

Figure 2.

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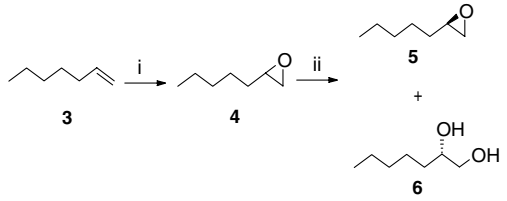
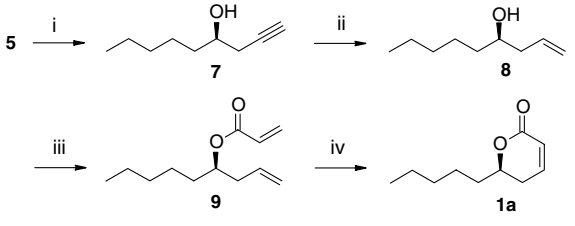


Scheme 1. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 10 h, 92%; (ii) *R*,*R*-salen–Co-(OAc) (0.5 mol%), distd H_2O (0.55 equiv), 0 °C, 16 h, (45% for **5**, 43% for **6**).

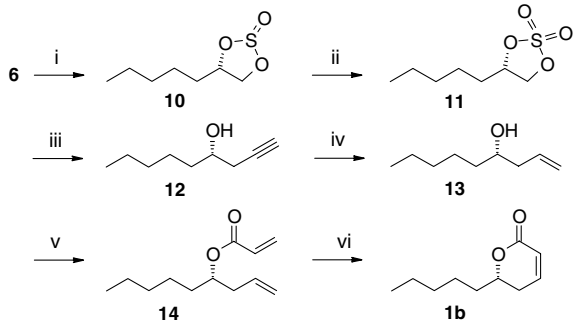
The racemic epoxide **4**, a substrate for HKR was prepared from commercially available 1-heptene **3** using *m*-CPBA. The HKR was performed on **4** with (*R*,*R*)-salen–Co-(OAc) complex **2** (0.5 mol%) and water (0.55 equiv) to give the *R*-epoxide **5** in 45% yield with >99% ee,[14] $[\alpha]_D^{25}$ +9.6 (*c* 1, $CHCl_3$) [lit.[15] +9.8 (*c* 1, $CHCl_3$)] and the *S*-diol **6** in 43% yield with 99.5% ee,[16] $[\alpha]_D^{25}$ −15.9 (*c* 1.67, EtOH) [lit.[8a] $[\alpha]_D^{22}$ −15.2 (*c* 1.67, EtOH)] (Scheme 1).

The synthesis of (*R*)-massoialactone **1a** started from the enantiomerically enriched epoxide **5** as illustrated in Scheme 2. Thus opening of **5** with an excess of lithium acetylide followed by partial hydrogenation of the resultant acetylene **7** with Lindlar's catalyst furnished the homoallylic alcohol **8**. Compound **8** was esterified with acryloyl chloride in the presence of triethylamine to afford **9** in 89% yield. The subsequent ring-closing metathesis[17] in dichloromethane under reflux in high dilution conditions using the first generation Grubbs's catalyst, bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride and catalytic amount of Ti(*i*-PrO)$_4$ afforded (*R*)-massoialactone in 84% yield, $[\alpha]_D^{25}$ −115.2 (*c* 1, $CHCl_3$) [lit.[10] $[\alpha]_D^{29}$ −113.6 (*c* 1.36, $CHCl_3$)]. The physical and spectroscopic data were in full agreement with the literature.[8c]

Scheme 3 summarizes the synthesis of (*S*)-massoialactone **1b** from the diol **6**. Thus treatment of **6** with thionyl chloride in the presence of triethylamine gave the cyclic sulfite **10**, which was further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **11** in essentially quantitative yield.[18] The essential feature of our synthetic strategy shown in Scheme 3 was based on the presumption



Scheme 2. Reagents and conditions: (i) LiC≡CH–ethylene diamine, DMSO, rt, 12 h, 86%; (ii) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 92%; (iii) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 5–6 h, 89%; (iv) $(PCy_3)_2$ Ru(Cl)$_2$=CH–Ph (20 mol%), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 12 h, 84%.



Scheme 3. Reagents and conditions: (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 20 min, 99%; (ii) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0 °C, 2 h, 100%; (iii) LiC≡CH–ethylene diamine, DMSO, 0 °C to rt, 10 h, 80%; (iv) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 86%; (v) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 5–6 h, 84%; (vi) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (20 mol%), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 12 h, 85%.

that the nucleophilic opening of the cyclic sulfate **11** would occur in a regioselective manner at the terminal carbon. Indeed the cyclic sulfate **11** on treatment with lithium acetylide furnished the desired alcohol **12**, which on hydrogenation followed by ring-closing metathesis afforded the target molecule **1b**, $[\alpha]_D^{25}$ +110.1 (*c* 2.0, $CHCl_3$) [lit.[9] $[\alpha]_D^{22.6}$ +109.6 (*c* 2, $CHCl_3$)]. The physical and spectroscopic data were in full agreement with the literature.[8c]

In conclusion we have demonstrated that the enantioselective synthesis of both the isomers of massoialactone can be accomplished using hydrolytic kinetic resolution of a racemic epoxide and ring-closing metathesis. The synthetic strategy described has significant potential for further extension to a variety of other 6-substituted chiral lactones, which serve as important synthons for several naturally occurring and biologically active molecules. Currently studies are in progress in this direction.

Acknowledgements

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