An Enantio- and Diastereocontrolled Route to Mintlactone and Isomintlactone Using A Chiral Cyclohexadienone Equivalent

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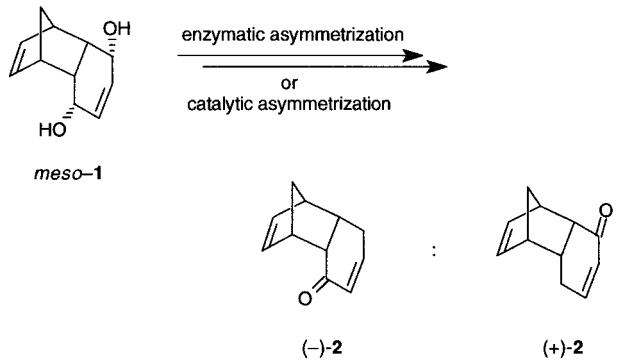
Abstract: An enantio- and diastereocontrolled route to mintlactone and isomintlactone, aroma components of important commercial flavoring materials, has been established using a chiral cyclohexadienone synthetic equivalent.

We prepared both enantiomeric tricyclic dienones **2** in high enantiomeric excess from *meso* tricyclic diol **1** by either enzymatic[1] or catalytic asymmetrization[2] as the key step. Because **2** allows diastereoselective functionalization of its enone functionality under various conditions as well as generating a cyclohexene functionality with removal of cyclopentadiene on thermolysis, optically active **2** may be used as a chiral cyclohexadienone synthetic equivalent[3] (**Scheme 1**). Actually, we have so far been constructing a variety of natural products enantio- and diastereoselectively using optically pure **2** as the starting material[4]. In this paper we wish to report an enantio- and diastereocontrolled synthesis of two monoterpene lactones, (–)-mintlactone (–)-**3** and (–)-isomintlactone (–)-**4**, starting from the (+)-enantiomer of chiral cyclohexadienone synthetic equivalent **2**.



meso–**1** (–)-**2** (+)-**2**

Scheme 1

(–)-Mintlactone (–)-**3** and (+)-isomintlactone (+)-**4** were isolated from an important commercial flavoring material, American peppermint oil, the essential oil of *Mentha piperita*, both as minor constituents[5]. The enantiomeric (+)-mintlactone (+)-**3** and (–)-isomintlactone (–)-**4** were recently isolated from the essential oil of the woods of *Bursera graveolens* as key aroma components[6] (**Fig. 1**).

Although several syntheses of optically active mintlactone[7] **3** and isomintlactone[7] **4** have been reported, no procedure capable of producing these two monoterpene lactones in both enantiomeric forms in a highly enantio- and diastereoselective way has appeared to date besides the procedure using a chiral citronellal.[7c] We, therefore, investigated chiral construction of mintlactone **3** and isomintlactone **4** intending to develop an enantio- and diastereodivergent route to either of the two natural products in optically pure forms using either (+)- or (–)-**2** as the starting material.

To realize our intention, we chose (+)-cyclohexadienone equivalent[1] (+)-**2** as the starting material. Thus, treatment of (+)-**2** with lithium dimethylcuprate gave the *exo*-methyl ketone **6**, $[\alpha]_D^{29}$ +184 (*c* 1.0, $CHCl_3$), stereoselectively. Reduction of **6** with diisobutylaluminum hydride (DIBAL) also proceeded selectively from the *exo*-face to give

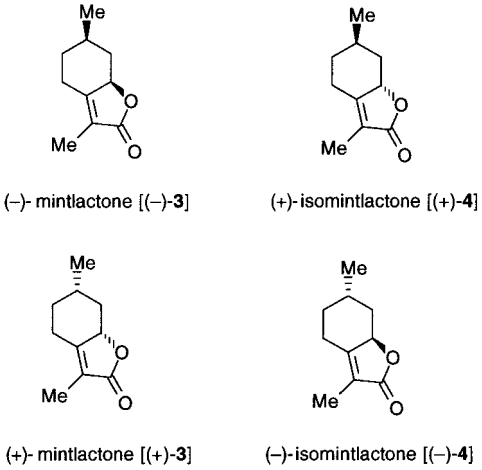


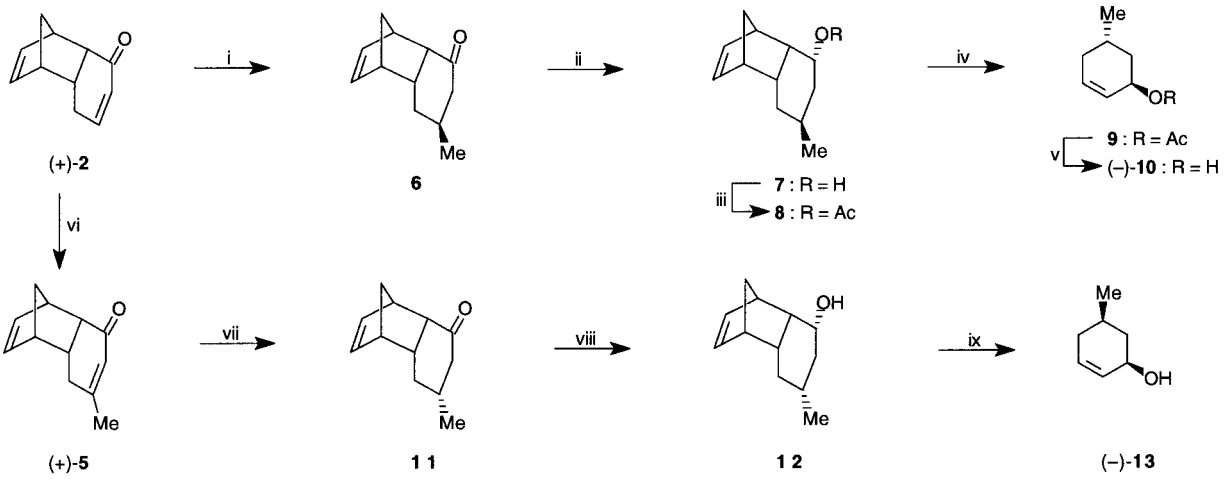
Figure 1

the *endo*-alcohol **7**, $[\alpha]_D^{27}$ –59.8 (*c* 1.0, $CHCl_3$), as a single product. Since thermolysis of the alcohol **7** gave a complex mixture, **7** was first transformed into the acetate **8**, $[\alpha]_D^{29}$ +26.8 (*c* 1.1, $CHCl_3$), which, on thermolysis in diphenyl ether at 260 °C, afforded the cyclohexenyl acetate **9**, excellently, as the single product. Hydrolysis of **9** gave the *trans*-substituted cyclohexenol (–)-**10**, $[\alpha]_D^{29}$ +196 (*c* 0.7, $CHCl_3$), in 50% overall yield from (+)-**2**.

On the other hand, the same cyclohexadienone equivalent (+)-**2** was first transformed into the β-methylenone (+)-**5** *via* a one-pot four-step sequence[4b,8] in 78% yield. Thus, (+)-**2** was treated with triphenylphosphine and *tert*butyldimethylsilyl triflate (TBSOTf) in THF at –78 °C to generate the 3-phosphonium-silylenol ether which, in the same flask, was sequentially treated with butyllithium and formaldehyde to furnish (+)-**5**, $[\alpha]_D^{30}$ +280 (*c* 0.9, $CHCl_3$), after acid-hydrolytic workup. Treatment of (+)-**5** with diisobutylaluminum hydride[9,10] (DIBAL) in the presence of copper (I) iodide[11] in THF containing hexamethylphosphoric triamide (HMPA) (20%) at –78 °C allowed stereoselective 1,4-reduction to give the *endo*-methyl ketone **11**, $[\alpha]_D^{27}$ +226 (*c* 1.2, $CHCl_3$), in 80% yield. Reduction of **11** with DIBAL gave stereoselectively the *endo*-alcohol **12**, mp 47.5 °C, $[\alpha]_D^{26}$ –40.8 (*c* 1.1, $CHCl_3$), which, in contrast to the *exo*-methyl counterpart **7**, gave the *cis*-substituted cyclohexenol (–)-**13**, $[\alpha]_D^{29}$ –29.9 (*c* 1.5, $CHCl_3$), in 71% yield without decomposition on thermolysis (**Scheme 2**). The observed neat reaction of **12** was presumed to be due to repulsive 1,3-interaction between the two *endo*-substituents which, at the same time, forces the hydroxy group farther away from the cyclopentene olefin functionality in the molecule to prevent undesirable side reactions such as ether formation.

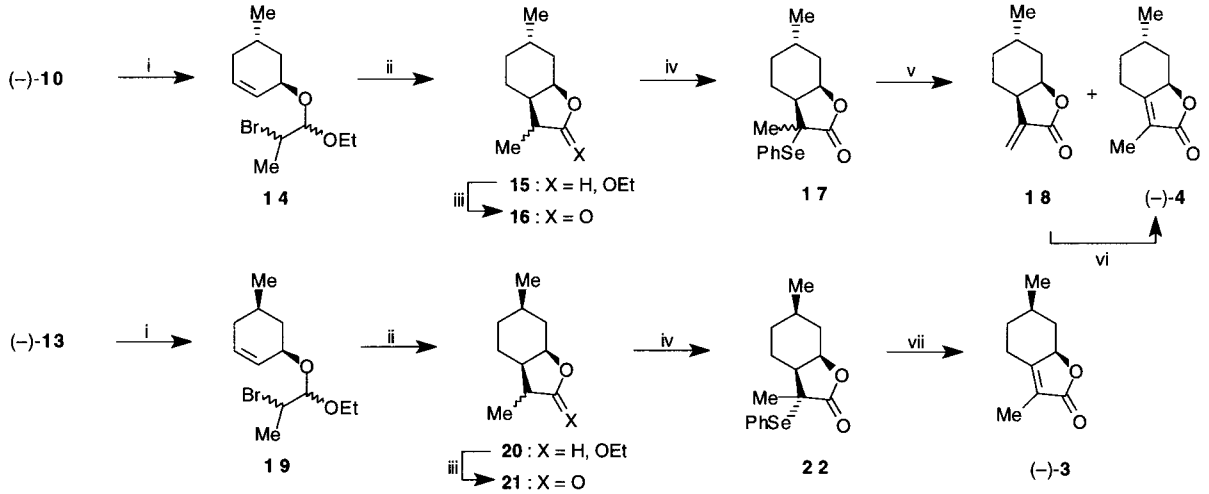
The described preparation of the diastereomeric cyclohexenols (–)-**10** and (–)-**13** from the same cyclohexadienone equivalent (+)-**2** implies formal acquisition of their enantiomers (+)-**10** and (+)-**13** as we have also obtained[1,2] the enantiomeric cyclohexadienone equivalent (–)-**2**.

Having established the route to the two diastereomeric cyclohexenols (–)-**10** and (–)-**13** in enantiomerically pure forms, their conversion into (–)-mintlactone (–)-**3** and (–)-isomintlactone (–)-**4** was next examined.



Reagents and conditions: i) MeLi, CuI, THF, –78 °C (98%). ii) DIBAL, CH_2Cl_2, –78 °C (82%). iii) Ac_2O, 4-(*N*,*N*-dimethylamino)pyridine (cat.), Et_3N, CH_2Cl_2, (97%). iv) diphenyl ether, reflux. v) $LiOH·H_2O$, 50% MeOH (64% from **8**). vi) Ph_3P, TBSOTf, THF, –78 °C, then BuLi, then HCHO (gas), then 5% HCl, (78%). vii) DIBAL, CuI, THF-HMPA (5:1), –78 °C (80%). viii) DIBAL, CH_2Cl_2, –78 °C (94%). ix) diphenyl ether, reflux (71%)

Scheme 2



Reagents and conditions: i) NBS, EtOCH=CHMe, Et_2O (95% for **14** and 94% for **19**). ii) Bu_3SnCl (cat.), AIBN (cat.), $NaBH_4$, ^tBuOH, reflux. iii) *m*-CPBA, $BF_3·OEt_2$ (cat.), CH_2Cl_2, 0 °C (71% from **14** for **16** and 72% from **19** for **21**). iv) LDA, PhSeCl, THF, 0 °C. v) 30% H_2O_2, AcOH (cat.), CH_2Cl_2, 0 °C [**18** (25 %) and (–)-**4** (30%) from **16**]. vi) $RhCl_3·3H_2O$ (15 mol %), EtOH, reflux (90%). vii) 30% H_2O_2, AcOH (cat.), CH_2Cl_2, 0 °C (45% from **21**)

Scheme 3

Reaction of (–)-**10** with ethyl 1-propenyl ether (1.2 equiv.) in the presence of *N*-bromosuccinimide[12] (NBS) (1.1 equiv.) in ether produced the bromo-acetal **14** excellently as a mixture of diastereomers. The mixture without separation was next refluxed with sodium borohydride[13] in butanol in the presence of a catalytic amount each of tributylstannyl chloride (5 mol %) and azobisisobutyronitrile (AIBN) (0.3 mol %) to give the cyclic acetal **15** as a mixture of four diastereomers. The mixture without separation was then reacted with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of a catalytic amount of boron trifluoride etherate[14] ($BF_3·OEt_2$) (10 mol %) in dichloromethane to give the α-methyl-γ-lactone **16** in 71% yield as a 55:45 mixture at the α stereogenic center of the γ-lactone moiety. Without separation, the mixture was treated with phenylselenyl chloride[15] in the presence of lithium diisopropylamide (LDA) to give the selenide **17** as a diastereomeric mixture which immediately was treated with 30% hydrogen peroxide in THF containing a catalytic amount of acetic acid (4%) to give (–)-isomintlactone[7a,b,d] (–)-**4**, mp 78.5-80.5 °C, $[\alpha]_D^{30}$ –75.9 (*c* 0.7, EtOH) [natural for (+)-enantiomer[5c]:mp 77-79 °C, $[\alpha]_D^{25}$ +76.9 (*c* 5, EtOH)], and its *exo*-olefin isomer[7d] **18**, $[\alpha]_D^{31}$ +111.0 (*c* 0.9, EtOH) [natural[7b]: for (–)-enantiomer, $[\alpha]_D$ –120 (*c* 0.5, $CHCl_3$)[7b]] in yields of 30 and 25%, respectively, after separation. The latter compound was isomerized to the former compound[7a,d] in 90% yield on reflux with a catalytic amount of Rh(III) chloride[7d,16] (15 mol %) in ethanol. Thus, total yield of (–)-isomintlactone (–)-**4** from **16** was 51 %.

On the other hand, (–)-**13** was transformed in the same way into the γ-lactone **21** in 67% overall yield through the bromo-acetal **19** and the cyclic acetal **20**. In contrast to **16**, the same two-step dehydrogenation step of **21** proceeded in a regioselective manner[7a,d] to give (–)-mintlactone[17] (–)-**3**, $[\alpha]_D^{29}$ –56.3 (*c* 0.7, EtOH) [natural[5b]: $[\alpha]_D$ –51.8 (*c* 10, EtOH); synthetic[7d]: $[\alpha]_D$ –56.6 (*c* 2.2, EtOH)], in 45% overall yield as a single product *via* the single selenide **22** (**Scheme 3**).

In summary, we have developed an enantio- and diastereoselective route to enantiomeric mintlactone and isomintlactone, both of which are present in nature, starting from an appropriate enantiomer of the chiral cyclohexadienone synthetic equivalent.

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