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Enantio- and Diastereocontrolled Synthesis of (−)-Iridolactone and (+)-Pedicularis-lactone

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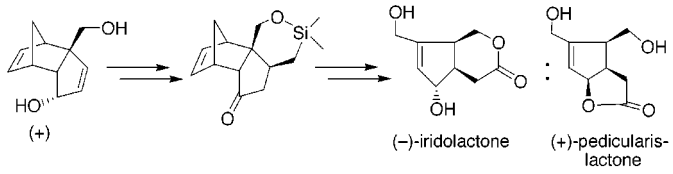
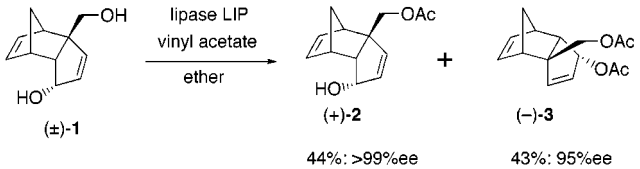
ABSTRACT



Two iridoid lactones, (−)-iridolactone and (+)-pedicularis-lactone, have been synthesized in an enantio- and diastereocontrolled manner starting from a tricyclic chiral building block serving as a synthetic equivalent of chiral 3-(hydroxymethyl)cyclopenta-2,4-dien-1-ol.

We have recently disclosed[1,2] lipase-mediated resolution of the tricyclic diol (±)-**1** in ether under transesterification conditions to give rise to enantiopure monoacetate (+)-**2** and highly enantioenriched diacetate (−)-**3**, both in good yields. Since these compounds exhibit inherent convex-face selectivity owing to their biased framework and since they undergo thermal retro-Diels−Alder reaction to leave a substituted cyclopentene with removal of a cyclopentadiene molecule, they may be taken as a synthetic equivalent of chiral 3-(hydroxymethyl)cyclopenta-2,4-dien-1-ol allowing diastereocontrolled modification, (Scheme 1).

Scheme 1



To explore their potential as a versatile chiral building block, we used one of the resolution products as the substrate for a radical cyclization reaction leading to two monoterpenoid natural products. We chose two iridoid lactones, (−)-iridolactone[3,4] (−)-**4** and (+)-pedicularis-lactone[4,5] (+)-**5**, isolated from *Pedicularis* and *Vitex* plants used in folk medicine in Asia, as the target molecules of the present study for utilization of enantiopure monoacetate (+)-**2** (Figure 1).

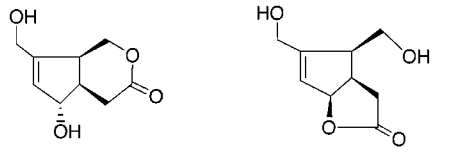


Figure 1.

Although these two natural products have been synthesized quite recently in racemic forms,[6,7] the method employed in the present synthesis is fundamentally different and is carried out in an enantiocontrolled manner.

Thus, monoacetate (+)-**2** (>99% ee) was first transformed into enone (+)-**6**, mp 130−132 °C, $[\alpha]^{30}_{D}$ +13.7 (*c* 1.1,

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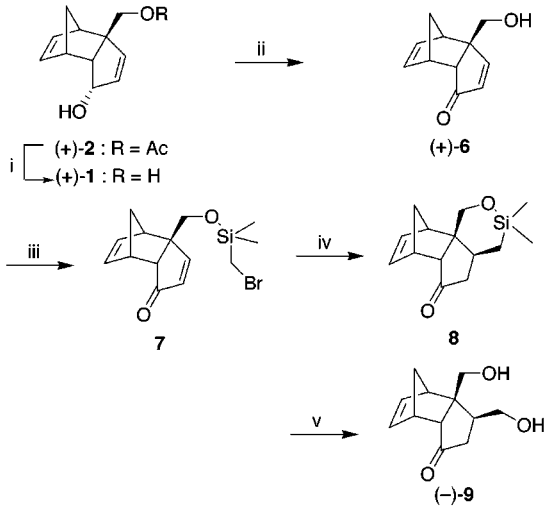
$CHCl_3$), via diol (+)-**1** by sequential alkaline methanolysis and chemoselective oxidation. The primary hydroxy functionality of (+)-**6** was silylated with bromomethyldimethylsilyl chloride[8−10] to give silyl ether **7**. On reflux with tributylstannane in benzene in the presence of a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN), **7** afforded cyclic silyl ether **8** which, without purification, was oxidized with 30% aqueous hydrogen peroxide in the presence of potassium hydrogen carbonate[11,12] to give diol (−)-**9**, $[\alpha]^{29}_D$ −54.4 (*c* 0.7, $CHCl_3$), diastereoselectively, as a single diastereomer. Very interestingly, no tandem cyclization by participation of the neighboring olefin functionality was observed under these radical-mediated conditions,[13] leaving the other cyclopentene olefin intact. The overall yield of (−)-**9** from (+)-**6** was 61% in three steps (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (i) K_2CO_3, MeOH (95%); (ii) MnO_2, CH_2Cl_2 (96%); (iii) $BrCH_2Si(Me)_2Cl$, DMAP (catalytic), Et_3N, CH_2Cl_2; (iv) Bu_3SnH, AIBN (catalytic), benzene; (v) 30% H_2O_2, $KHCO_3$, THF−MeOH, reflux (61% from **6**).

Although the diastereocontrolled introduction of the hydroxymethyl functionality required for the target molecules was accomplished as expected, it was found that alkylation of (−)-**9** for the introduction of the acetic acid moiety was unexpectedly difficult and was strongly affected by the protecting group of the diol functionality. Thus, the acetonide of (−)-**9** did not show diastereoselection to give a mixture of two epimers, while the bis-TBS and other silicon protecting groups afforded the dialkylated product as a major product on reaction with an allyl halide under basic conditions. Diastereoselective *exo*-face monoalkylation took place to give the desired product **11** in acceptable 59% yield only when the bis-ethoxyethyl ether **10** was treated with allyl iodide in the presence of potassium hydride in THF at 0 °C. To transform the product into (−)-iridolactone (−)-**5**, the ketone functionality was reduced from the convex face to give diastereoselectively *endo*-alcohol **12** whose hydroxy and cyclopentene olefin functionalities were blocked simultaneously to form a bromo-ether linkage. Thus, on exposure to *N*-bromosuccinimide (NBS) in dichloromethane in the presence of triethylamine, **12** afforded the bromo-ether **13** whose side-chain olefin functionality was then cleaved sequentially[14,15] to give the carboxylic acid **15** via aldehyde **14**. During the oxidation of **14** under acidic conditions,[15] concurrent removal of the ethoxyethyl protecting group occurred to liberate the dihydroxy functionalities. Although direct lactonization of **15** did not take place, the lactone (+)-**16**, mp 178−181 °C, $[\alpha]^{30}_D$ +23.0 (*c* 0.3, MeOH), could be obtained in excellent yield on exposure to diazomethane in acetone which brought about spontaneous lactonization.

Having introduced the requisite functionalities on the chiral building block, the bromo-ether linkage was removed by treating (+)-**16** with zinc in methanol containing acetic acid to give the penultimate tetracyclic diol (−)-**17**, mp 160−162 °C, $[\alpha]^{27}_D$ −7.3 (*c* 0.2, MeOH), with regeneration of the secondary hydroxy and the cyclopentene olefin functionalities. Finally, this was subjected to thermolysis in diphenyl ether at refluxing temperature to give (−)-iridolactone (−)-**4**, $[\alpha]^{27}_D$ −15.3 (*c* 0.3, MeOH) {lit.[4] $[\alpha]^{28}_D$ −15.4 (*c* 2.0, MeOH)}, whose spectroscopic data were identical with those reported for the natural product. The overall yield of (−)-**4** from the starting monoacetate (+)-**2** was 14% in 14 steps (Scheme 3).

Synthesis of pedicularis-lactone (+)-**5** could be achieved using the same intermediate (+)-**16** obtained above. Thus, (+)-**16** was first acylated and the resulting acetate (+)-**18** was treated with zinc in methanol containing acetic acid to give the secondary alcohol (+)-**19**, $[\alpha]^{24}_D$ +23.5 (*c* 0.7, $CHCl_3$), which was oxidized with perruthenate reagent (TPAP)[16] to afford the ketone (+)-**20**, mp 131−132 °C, $[\alpha]^{25}_D$ −125.1 (*c* 1.4, $CHCl_3$). On thermolysis in diphenyl ether at refluxing temperature, (+)-**20** furnished the cyclopentenone (−)-**21**, $[\alpha]^{25}_D$ −0.7 (*c* 0.9, $CHCl_3$), having a *δ*-lactone moiety. Reduction of (−)-**21** with sodium borohydride in the presence of cerium(III) chloride[17] at −78 °C took place diastereoselectively from the convex face to give the *endo*-alcohol **22** which on alkaline methanolysis followed

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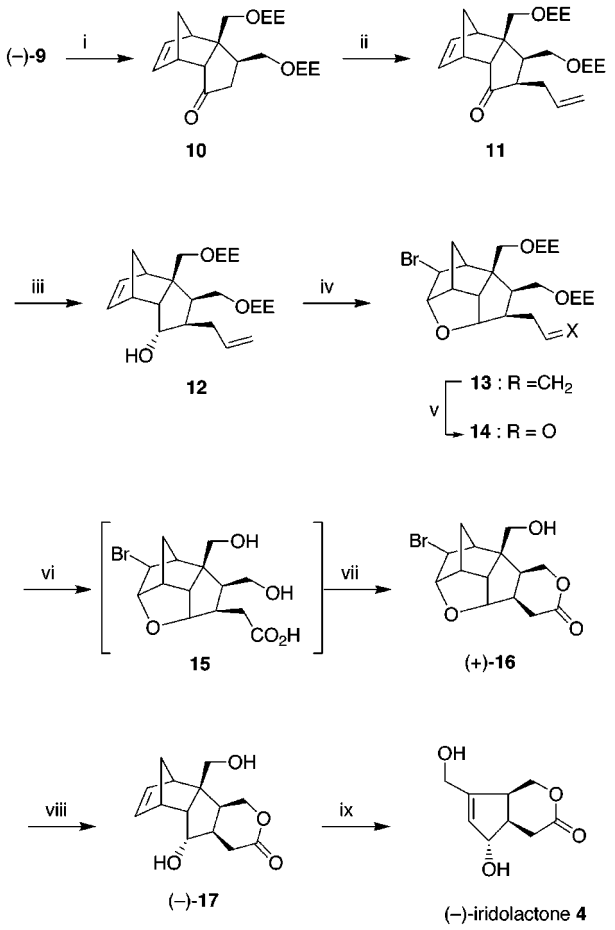
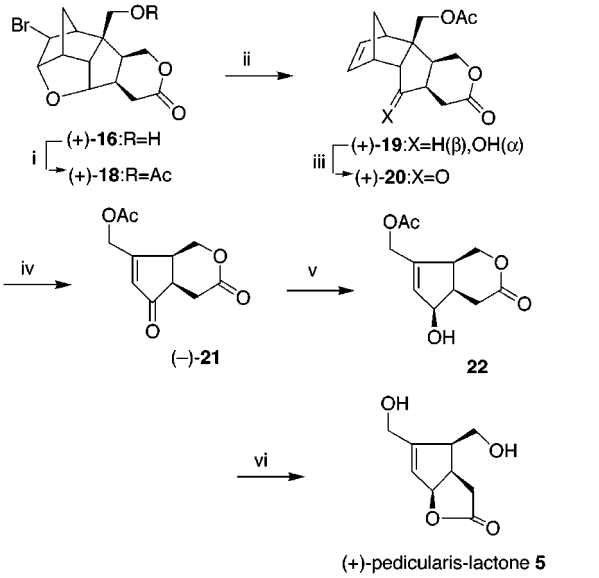
Scheme 3[a]



[a] Reagents and conditions: (i) ethyl vinyl ether, PPTS (catalytic), CH_2Cl_2 (96%); (ii) allyl iodide, KH, THF, rt (59%); (iii) $LiAlH_4$, Et_2O (92%); (iv) NBS, Et_3N, CH_2Cl_2 (98%); (v) OsO_4 (catalytic), NMO, aqueous THF, then $NaIO_4$ (97%); (vi) $NaClO_2$, NH_2SO_3H, aqueous dioxane; (vii) CH_2N_2, acetone (92% from **14**); (viii) Zn, AcOH−MeOH, reflux (92%); (iv) Ph_2O, reflux (60%).

by acidic workup afforded (+)-pedicularis-lactone[18] (+)-**5**, $[\alpha]^{27}_D$ +7.6 (*c* 0.2, MeOH) {lit. $[\alpha]^{28}_D$ +7.5 (*c* 0.6, MeOH);[4] $[\alpha]^{15}_D$ +45.5 (*c* 0.154, MeOH)[5]}, by concurrent isomerization of the δ-lactone linkage into the γ-lactone linkage. The overall yield of (+)-**5** from (+)-**2** was 12% in 16 steps (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (i) Ac_2O, pyridine; (ii) Zn, AcOH−MeOH, reflux (91% from **16**); (iii) TPAP (catalytic), NMO, 4A sieves, MeCN (93%); (iv) Ph_2O, reflux (93%); (v) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; (vi) K_2CO_3, MeOH, then aqueous HCl (60% from **21**).

In summary, we have demonstrated the utilization of a chiral tricyclic acetate having a biased framework for the first enantiocontrolled synthesis of two iridoid monoterpenes, (−)-iridolactone and (+)-pedicularis-lactone, serving as a synthetic equivalent of chiral 3-(hydroxymethyl)cyclopenta-2,4-dien-1-ol.

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(18) Spectroscopic data of (+)-pedicularis-lactone **5**: IR (film) ν = 3378, 2920, 1753, 1658, 1177 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ = 5.85 (1H, br s), 5.43 (1H, d, J = 7.4 Hz), 4.23 and 4.15 (each 1H, d, J = 15.2 Hz), 3.73 (1H, dd, J = 11.2, 4.5 Hz), 3.64 (1H, dd, J = 11.2, 6.0 Hz), 3.00 (1H, m), 2.72 (1H, dd, J = 18.4, 6.0 Hz), 2.63 (1H, dd, J = 18.4, 9.9 Hz).