NEW ASYMMETRIC SYNTHESES OF (-)-ISOIRIDOMYRMECIN AND (+)-LOGANIN AGLUCON 6-ACETATE UTILIZING C_2-SYMMETRIC DIMETHYL 3,7-DIHYDROXY-*CIS*-BICYCLO[3.3.0]OCTA-2,6-DIENE-2,6-DICARBOXYLATE

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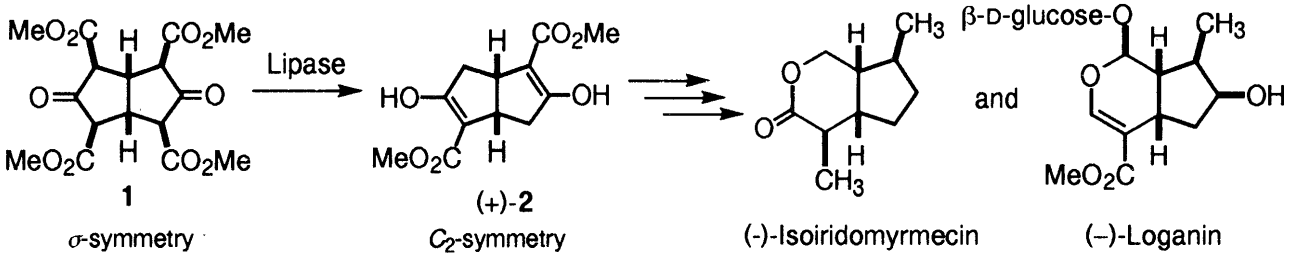
The first asymmetric synthesis of (-)-isoiridomyrmecin and formal synthesis of (-)-loganin were done using chiral C_2-symmetric building block dimethyl 3,7-dihydroxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,6-dicarboxylate (**2**) which was prepared by the lipase-catalyzed asymmetric demethoxycarbonylation of tetramethyl 3,7-dioxo-*cis*-bicyclo-[3.3.0]octane-2,4,6,8-tetracarboxylate (**1**).

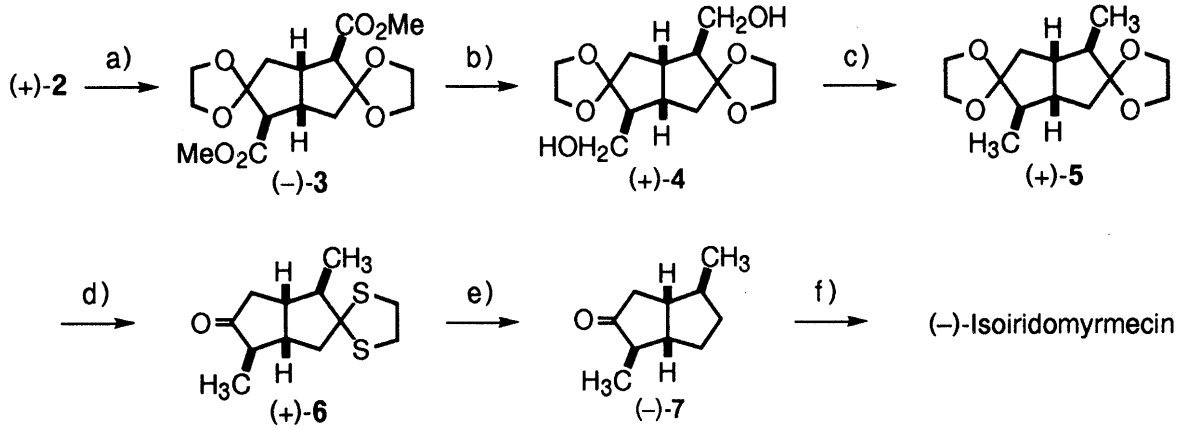
KEY WORDS lipase catalyst; asymmetric synthesis; (-)-isoiridomyrmecin; (+)-loganin aglucon 6-acetate

We have recently been involved in studies on the lipase-catalyzed asymmetric demethoxycarbonylation[1] of σ-symmetric tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**1**) prepared from dimethyl 3-oxoglutarate and glyoxal by the one-pot Weiss reaction.[2] In this reaction, both enantiomers of C_2-symmetric dimethyl 3,7-dihydroxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,6-dicarboxylate (**2**) are obtained in an enantiomerically pure form by double differentiation depending on the lipases used. As a part of this program, we have attempted to synthesize biologically active compounds and natural products from **2** for the promotion of the usefulness of this reaction. Here we report the first asymmetric synthesis of (-)-isoiridomyrmecin and formal synthesis of (-)-loganin utilizing C_2-symmetric dimethyl ester (+)-**2**.



(-)-Isoiridomyrmecin, an iridoid monoterpene lactone isolated from *Iridomyrmex nitidus* MAYR.,[3] is used by the ant as an agent of defense against preying insects and possibly as a means of communication. It is also a component of matatabilactone, which is a cat-attracting oil isolated from *Actinidia polygama* MIQ.[4] Although several syntheses of both enantiomers of isoiridomyrmecin from chiral pools have been studied so far,[5] no asymmetric synthesis of natural (-)-isoiridomyrmecin has been reported. Our synthetic route for (-)-isoiridomyrmecin is shown in Chart 1.

Chart 1. New Total Synthesis of (–)-Isoiridomyrmecin



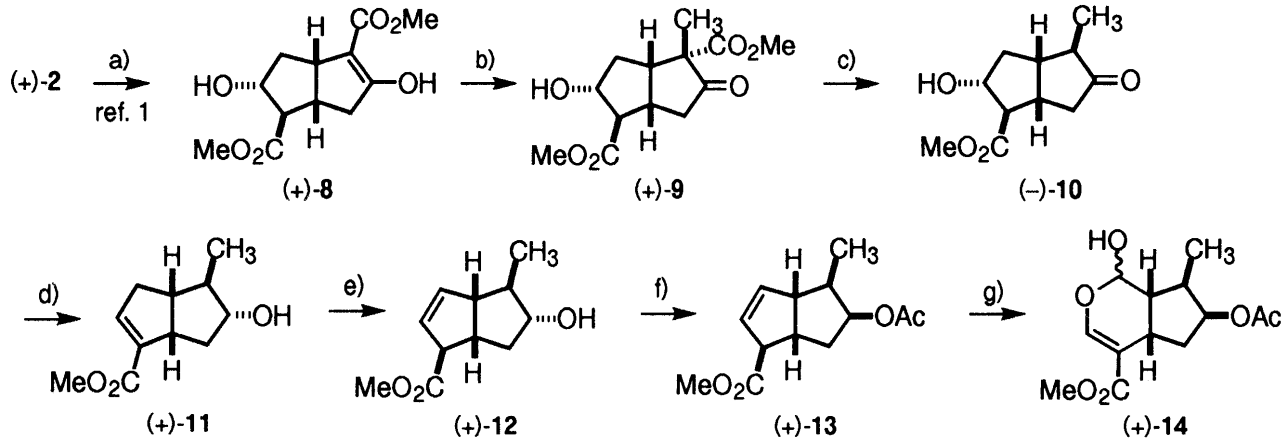
a) BTSE, Me_3SiOTf, CH_2Cl_2, -78°C→30°C, 99%; b) DIBAH, THF, -50°C, 99%; c) 1) TsCl, py, 2) $LiAlH_4$, 77%; d) 1) BF_3-Et_2O, ethanedithiol (1 eq.), 2) HCl-acetone, 81%; e) Raney Ni, EtOH, r.t., 58%; f) 1) LDA, TMSCl, 2) O_3 then $NaBH_4$, 44%

The C_2-symmetric dimethyl (1*S*,5*S*)-3,7-dihydroxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,6-dicarboxylate [(+)-**2**] (97%ee) which was obtained by PPL-catalyzed demethoxycarbonylation of **1** and subsequent alkaline hydrolysis and decarboxylation,[1] was acetalized with bis(trimethylsilyloxy)ethane and trimethylsilyl triflate to give diacetal (-)-**3**, according to Noyori's method,[6] while the usual acetalization failed with ethylene glycol and *p*-toluenesulfonic acid under azeotropic conditions. The two methyl esters of (-)-**3** were reduced with diisobutylaluminum hydride to give diol (+)-**4** in quantitative yield. The two hydroxymethyl groups of (+)-**4** were reduced to methyl substituents *via* its ditosylate. One acetal of diacetal (+)-**5** was exchanged for dithioacetal with ethanedithiol and boron trifluoride etherate, and subsequent hydrolysis of the remaining acetal with hydrochloric acid to the carbonyl group gave (+)-**6**. The dithioacetal in (+)-**6** was desulfurized reductively to the methylene group with Raney nickel to give bicyclic ketone (-)-**7**. The ketone (-)-**7** was converted into kinetic enol silyl ether, and ozonolysis of the enol ether followed by reduction with sodium borohydride afforded the desired (-)-isoiridomyrmecin, according to Sakai's procedure, of which the specific rotation {$[\alpha]_D^{24}$ -57.5 (0.55, CCl_4), lit. $[\alpha]_D^{27}$ -60.1 (0.18, CCl_4)} and spectroscopic data were identical with those reported.[7]

(-)-Loganin, originally isolated from *Strychnos nux vomica*,[8] is an important iridoid glucoside for plant metabolism and the biosynthesis of indole alkaloids.[9] The first asymmetric synthesis of (-)-loganin was reported by Partridge *et al.* utilizing asymmetric hydroboration.[10] In addition, reports on the synthesis of (-)-loganin from the chiral pool or through optical resolution have been published by several groups.[11] Our synthetic route for its synthetic precursor loganin aglucon 6-acetate (+)-**14**[10,11d,e] is shown in Chart 2. The *C*-methylation of the β-ketoester of (+)-**8**, prepared by the half reduction of enantiomerically pure (+)-**2**, which was obtained by double differentiation by PPL and lipase M-catalyzed demethoxycarbonylation,[1] was done using Shono's method[12] to give (+)-**9** in high yield. Hydrolysis of methyl esters and decarboxylation of the β-ketoacid formed with 6*N*-hydrochloric acid followed by methylation of the remaining carboxylic acid with diazomethane afforded ketoalcohol (-)-**10**. Elimination of the hydroxyl group *via* mesylate and reduction of the ketone with sodium borohydride gave (+)-**11** in high yield. Isomerization of α,β-unsaturated ester in (+)-**11** to β,γ-unsaturated ester (+)-**12** was successfully conducted by Michael addition of benzenethiolate anion and β-*cis*-elimination of the corresponding sulfoxide. The configuration of the

hydroxyl group in (+)-**12** was inverted by the Mitsunobu reaction[13] to give acetate (+)-**13**. Final ozonolysis of the double bond of (+)-**13** afforded the desired loganin aglucon 6-acetate (+)-**14**, of which the specific rotation {$[\alpha]_D^{21}$ +1.1 (0.18, $CHCl_3$), lit. $[\alpha]_D^{25}$ +2.0 (1.17, $CHCl_3$)} and spectroscopic data were identical with those reported.[10] This transformation constitutes the formal total synthesis of (-)-loganin.

Chart 2. New Synthesis of (+)-Loganin Aglucon 6-Acetate



a) $NaBH(OEt)_3$, THF; b) tetrabutylammonium 2-pyrrolidonate, CH_3I, DMF, 96%; c) 1) 6*N*-HCl, Δ, 2) CH_2N_2, 89%; d) 1) MsCl, DBU, $CHCl_3$, 99%, 2) $NaBH_4$, MeOH, 0°C, 96%; e) 1) PhSLi, 2) $NaIO_4$, then Δ, 60%; f) DEAD, Ph_3P, AcOH, THF, r.t., 92%; g) O_3 then Me_2S, 32%

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