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# Concurrent resolution and oxidation of an allylic acetate and its utilization in the diastereocontrolled synthesis of some cyclopentanoid monoterpenes

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**Abstract**

Racemic *endo*-4-acetoxybicyclo[3.2.1]oct-2-ene furnishes enantiopure (+)-bicyclo[3.2.1]oct-3-en-2-one and its dihydro derivative leaving enantiopure (+)-*endo*-4-acetoxybicyclo[3.2.1]oct-2-ene in a phosphate buffer solution in the presence of a lipase (*Candida antarctica*) and palladium(II) chloride. Utilizing the products, a diastereocontrolled route to some cyclopentanoid monoterpenes has been established. 

*Keywords:* enzymes; enzymatic reaction; oxidation; palladium; palladium compounds; resolution; terpenes; terpenoids.

Despite their small molecules, enantio- and diastereo-controlled construction of the loganin type monoterpenoids is not an easy task owing to the difficulty in introduction of three or four contiguous stereogenic centers in their molecules.[1] In order to develop an efficient route to these monoterpenes, we decided to use bicyclo[3.2.1]oct-3-en-2-one **2** which we have obtained in both enantiomeric forms, employing lipase-mediated kinetic resolution[2b] of *endo*-4-acetoxybicyclo[3.2.1]oct-2-ene (±)-**1**. In this study, we encountered an interesting result which led to a direct generation of enantiopure (+)-**2** accompanied with its dihydro derivative (+)-**3** and enantiopure (+)-**1** in a lipase–palladium-mediated reaction of the racemic acetate (±)-**1** and we have established a new route to four natural monoterpenes utilizing these enantiopure products thus obtained. Herein, we wish to report an unprecedented concurrent resolution and oxidation of (±)-**1** and a new enantio- and diastereo-controlled entry into the cyclopentanoid monoterpenes, (+)-mitsugashiwalactone **4**, (+)-*cis,cis*-dihydronepetalactone **5**, (+)-iridomyrmecin **6**, and (−)-isoiridomyrmecin **7** (Fig. 1).

Since it was reported that certain racemic allyl acetates are enantioselectively converged into single enantiomeric alcohols in the presence of a lipase and a palladium catalyst in a buffer solution via concurrent palladium-assisted dynamic allylic 1,3-acetoxy rearrangement and lipase-mediated kinetic resolution,[3] we treated (±)-**1** with immobilized lipase (*Candida antarctica*, Novo Nordisk) and

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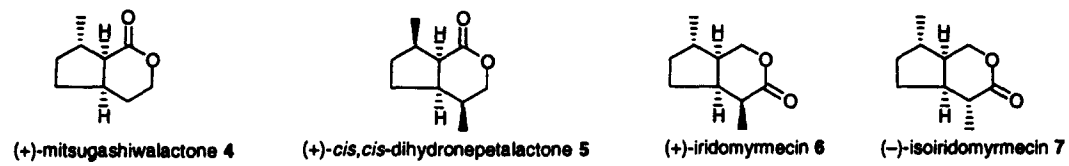
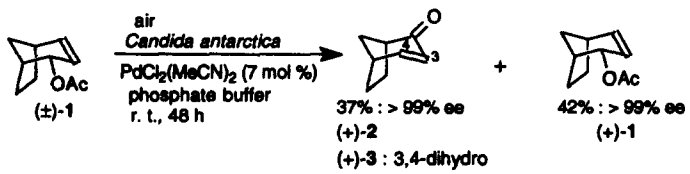



Figure 1.

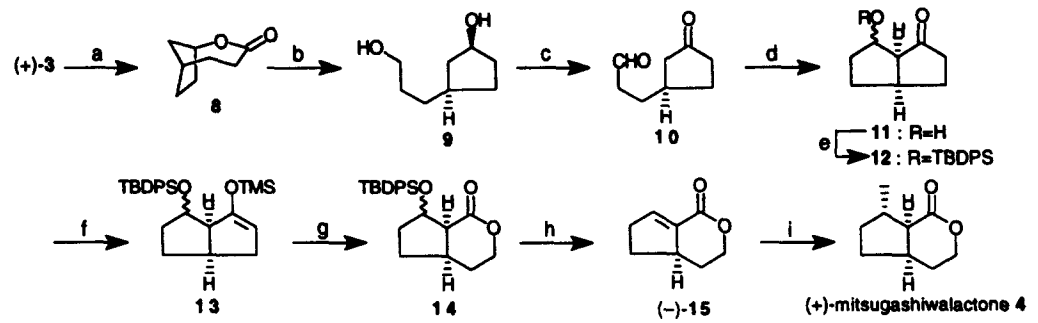
$PdCl_2(MeCN)_2$ (7 mol%) in a phosphate buffer under air at room temperature in expectation of obtaining a single enantiomeric hydrolysis product. However, instead of giving the single product, the reaction furnished a mixture of three readily separable products consisting of (+)-**1**, $[\alpha]_D^{25}$ +32.1 (*c* 0.8, $CHCl_3$), (+)-**2**, $[\alpha]_D^{27}$ +340.5 (*c* 0.6, $CHCl_3$) [lit.[2] $[\alpha]_D^{33}$ +359.2 (*c* 1.64, $CHCl_3$)], and (+)-**3**, mp 58–60°C, $[\alpha]_D^{29}$ +129.6 (*c* 0.3, $CHCl_3$), in 42, 37, and 6% yield, respectively, after separation by silica gel column chromatography. Enantiomeric purity of the former two products could be determined to be >99% ee by HPLC using a column with a chiral stationary phase (Chiralcel OB, $Pr^i$-OH:hexane, 1:200). The structure of the third product (+)-**3** was determined by correlation to the second product (+)-**2** which gave (+)-**3**, mp 58–60°C, $[\alpha]_D^{28}$ +127.0 (*c* 0.7, $CHCl_3$), quantitatively, on catalytic hydrogenation. The result indicated that the palladium catalyst did not initiate the expected dynamic acetoxy rearrangement, but it induced oxidation[4] of the resolved alcohol (–)-**26** to give the latter two compounds (Scheme 1).




Scheme 1.

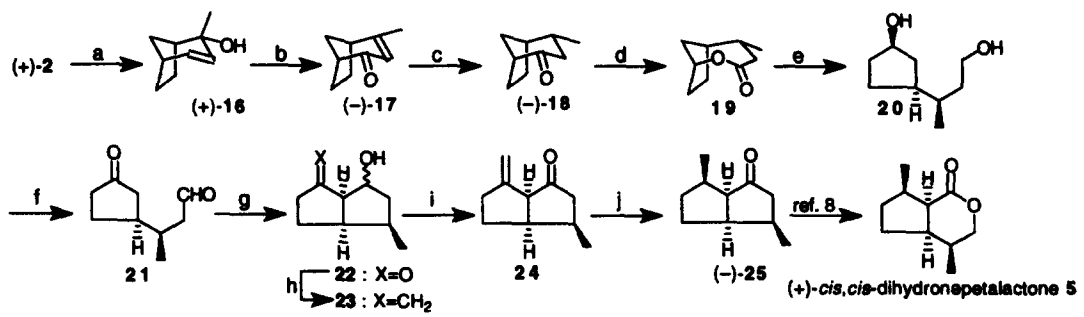
Although our initial intention of obtaining a single enantiomeric product could not be realized, we next examined transformation of the three products into the cyclopentanoid monoterpenes, **4**–**7**. To obtain (+)-mitsugashiwalactone **4**,[5] a component of *Boschniakia rossica*,[6] having three contiguous stereogenic centers, (+)-**3** was subjected to Baeyer–Villiger oxidation to give a mixture of two lactones, quantitatively, containing **8** as a major component (ca. 10:1) which, without separation, was converted into the ketol **11** on sequential reduction, Swern oxidation, and intramolecular aldolization via the diol **9** and the keto-aldehyde **10**. Compound **11** was converted into the silyl enolether **13**, via **12**, which was transformed into the δ-lactone **14** by single-flask ozonolysis-reduction followed by acid treatment. Exposure of **14** to tetrabutylammonium fluoride (TBAF), induced elimination to give the known lactone[5] (–)-**15**, $[\alpha]_D^{30}$ –118.5 (*c* 0.5, $CHCl_3$) [lit.[5] $[\alpha]_D^{31}$ –116.6 (*c* 0.93, $CHCl_3$)], which gave (+)-mitsugashiwalactone **4**, $[\alpha]_D^{29}$ +5.1 (*c* 0.4, $CHCl_3$) [lit.[5] $[\alpha]_D^{32}$ +5.3 (*c* 0.92, $CHCl_3$)], diastereoselectively, on 1,4-addition[5] (Scheme 2).

The route to the remaining three diastereomeric monoterpenes **5**–**7**, having four contiguous stereogenic centers, was established on the basis of the inherent convex-face selectivity of the bicyclic enone **2**. Thus, (+)-**2** was treated with methyllithium to give the 1,2-adduct (+)-**16**, $[\alpha]_D^{29}$ +69.9 (*c* 1.3, $CHCl_3$) [lit.[2b] for the enantiomer: $[\alpha]_D^{28}$ –68.5 (*c* 1.0, $CHCl_3$)], which was then oxidized with pyridinium chlorochromate[2] to give the β-methylenone (–)-**17**, $[\alpha]_D^{26}$ –272.9 (*c* 0.6, $CHCl_3$) [lit.[2b] for the enantiomer: $[\alpha]_D^{24}$ +274.0 (*c* 1.3, $CHCl_3$)]. Catalytic hydrogenation occurred diastereoselectively from the convex-face to give the *endo*-methyl-ketone (–)-**18**, $[\alpha]_D^{27}$ –118.5 (*c* 1.0, $CHCl_3$) [lit.[2b] for the enantiomer: $[\alpha]_D^{26}$ +115.4 (*c* 1.0, $CHCl_3$)]. On sequential Baeyer–Villiger oxidation, reduction, Swern oxidation, and intramolecular aldolization, the ketone (–)-**18** furnished the ketol **22** via the lactone **19**, the diol **20**, and the keto-aldehyde **21**. On treatment with diiodomethane and zinc in the presence of titanium tetrachloride,[7] **22** furnished




Scheme 2. *Reagents and conditions*: (a) *m*CPBA, $CH_2Cl_2$, 0°C. (b) $LiAlH_4$, THF. (c) Swern oxidation. (d) 2% aq. KOH:MeOH (1:1), rt (50%, 4 steps). (e) TBDPS-Cl, imidazole, DMF (96%). (f) LDA, TMS-Cl, $Et_3N$, THF, −78°C (97%). (g) $O_3$, MeOH, −78°C then $NaBH_4$ then *p*TsOH, $CH_2Cl_2$ (44%). (h) TBAF, THF, rt (88%). (i) $Me_2CuLi$, $Et_2O$, −30°C (80%)

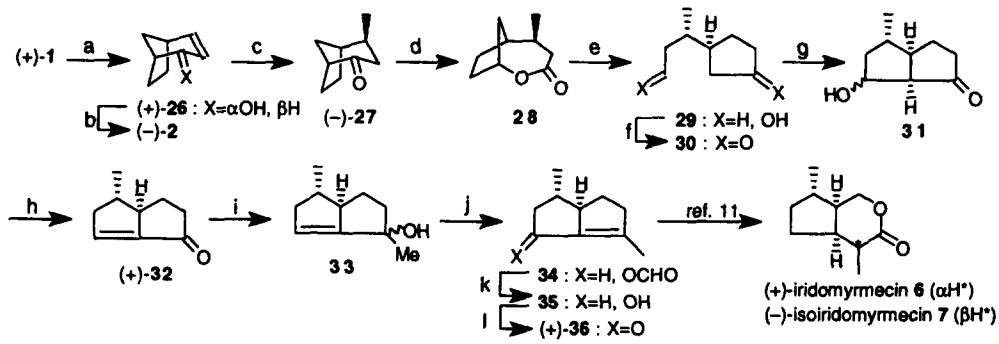
the *exo*-methylene derivative **23** which was transformed diastereoselectively into the ketone (−)-**25**,[8] $[\alpha]_D^{26}$ −272.1 (*c* 0.6, $CHCl_3$) [lit.[8] $[\alpha]_D^{17}$ −243 (*c* 0.113, $CHCl_3$)], via **24** on sequential oxidation and catalytic hydrogenation. Since (−)-**25**, obtained from (−)-limonene,[8] has been transformed into (+)-*cis,cis*-dihydronepetalactone **5**, isolated from *Boschniakia rossica*,[6] the present acquisition of (−)-**25** constitutes a formal synthesis (Scheme 3).




Scheme 3. *Reagents and conditions*: (a) MeLi, THF, −78°C (97%). (b) PCC, $CH_2Cl_2$ (84%). (c) $H_2$, 10% Pd-C, AcOEt (98%). (d) *m*CPBA, $CH_2Cl_2$. (e) $LiAlH_4$, THF. (f) Swern oxidation. (g) 2% aq. KOH:MeOH (1:1), rt (52%, 4 steps). (h) $CH_2I_2$, Zn, $TiCl_4$, THF, 0°C–rt (47%). (i) PCC, $CH_2Cl_2$ (71%). (j) $H_2$, $PtO_2$, MeOH (79%)

On the other hand, to establish a route to the remaining two terpenes, the acetate (+)-**1** was first transformed into the enone (−)-**2**, $[\alpha]_D^{25}$ −331.7 (*c* 0.6, $CHCl_3$) [lit.[2] $[\alpha]_D^{22}$ −339.0 (*c* 2.8, $CHCl_3$)], via the alcohol (+)-**26**, $[\alpha]_D^{27}$ +11.1 (*c* 0.6, $CHCl_3$), on sequential methanolysis and oxidation. Compound (−)-**2** was then converted to the *exo*-methyl-ketone (−)-**27**, $[\alpha]_D^{31}$ −129.8 (*c* 0.8, $CHCl_3$) [lit.[2b] for the enantiomer: $[\alpha]_D^{27}$ +147.1 (*c* 1.0, $CHCl_3$)], by convex-face selective 1,4-addition. Employing the same procedure as for the diastereomer (−)-**18**, (−)-**27** was transformed into the ketol **31** in four steps via **28**, **29**, and **30**. On sequential mesylation and base treatment, **31** gave the enone (+)-**32**, $[\alpha]_D^{27}$ +25.8 (*c* 0.7, $CHCl_3$), which was reacted with methyllithium in the presence of ceric trichloride[9] to give the 1,2-adduct **33**. As the oxidative conditions that transformed **16** into **17** were not effective for the conversion of **33** into **36**, **33** was first treated with formic acid[10] to give the rearranged formate **34** which gave the β-methylenone (+)-**36**, $[\alpha]_D^{29}$ +43.2 (*c* 1.1, $CHCl_3$) [lit.[11] $[\alpha]_D^{24}$ +39.7 (*c* 0.98, $CHCl_3$)], on sequential methanolysis and oxidation. Since (+)-iridomyrmecin **6** and (−)-isoiridomyrmecin **7**, both the components of *Iridomyrmex humilis*,[12] have been synthesized[11] from (+)-**36**, a formal route to these natural products was established at this stage (Scheme 4).

In short, we have found an unprecedented lipase–palladium-mediated concurrent resolution and




Scheme 4. *Reagents and conditions*: (a) $K_2CO_3$, MeOH, rt. (b) $MnO_2$, $CH_2Cl_2$ (82%, 2 steps). (c) MeMgI, CuCN, LiCl, THF, −78°C (95%). (d) *m*CPBA, $CH_2Cl_2$. (e) $LiAlH_4$, THF. (f) Swern oxidation. (g) 2% KOH:MeOH (1:1) (53%, 4 steps). (h) MesCl, $Et_3N$, $CH_2Cl_2$, then DBU, $CH_2Cl_2$ (59%). (i) MeLi, $CeCl_3$, THF, −78°C (87%). (j) $HCO_2H$, dioxane, 0°C (80%). (k) $K_2CO_3$, MeOH (98%). (l) Dess–Martin oxidation (78%)

oxidation of *endo*-4-acetoxy[3.2.1]oct-2-ene and have established a diastereocontrolled route to some cyclopentanoid monoterpenes utilizing the enantiopure products obtained.

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