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A Lipase-mediated Route to (+)-Juvabione and (+)-Epijuvabione from Racemic Norcamphor

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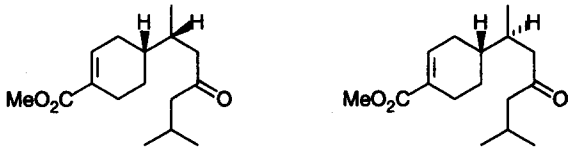
Abstract: (+)-Juvabione and (+)-epijuvabione, natural sesquiterpenes exhibiting insect juvenile hormone activity, have been synthesized from (±)-norcamphor *via* the both enantiomeric intermediates having bicyclo[3.2.1]octane framework by employing a lipase-mediated kinetic ester-hydrolysis reaction and cyclopropane ring-expansion reaction as the key steps.

Keywords: insects; enzyme and enzyme reactions; terpenes and terpenoids; resolution

(+)-Juvabione **1** and (+)-epijuvabione **2** are natural sesquiterpenes exhibiting selective insect juvenile hormone activity (**Fig. 1**).[1] These compounds have two contiguous secondary stereogenic centers on a ring and a side chain, which make their diastereodivergent synthesis from a single starting material very difficult.[2] So far, only one example carried out by us has solved the stereochemical problem to give diastereodivergently these two diastereomeric natural products using (+)-norcamphor **3** as the starting material.[3] We wish to report here an



(+)-juvabione **1** (+)-epijuvabione **2**

Fig. 1

alternative stereocontrolled construction of these two compounds from racemic norcamphor (±)-**3** by employing lipase-mediated kinetic resolution[4] and iterative use of the same ring-expansion in the key stages.

Racemic norcamphor (±)-**3** was first transformed into racemic bicyclo[3.2.1]oct-3-en-2-one (±)-**7**, on sequential silyl enol ether formation, cyclopropanation, and oxidative ring-expansion reaction,[5] in 75% overall yield (**Scheme 1**). Reduction of (±)-**7** with diisobutylaluminum hydride (DIBAL) gave diastereoselectively the

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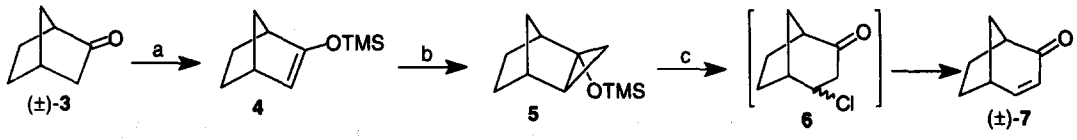
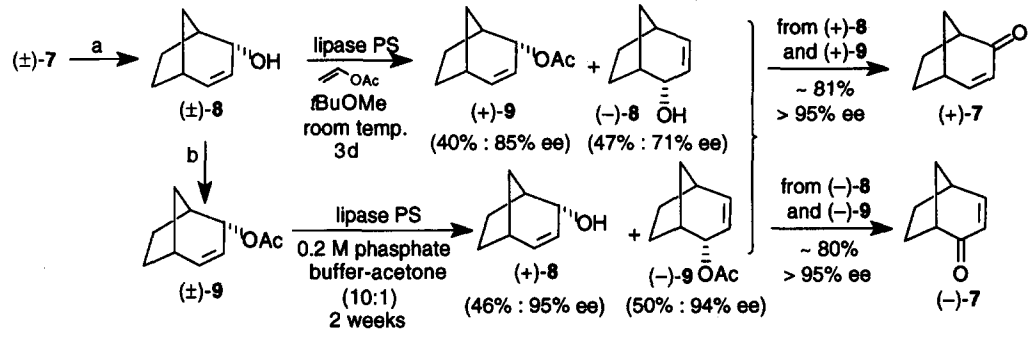


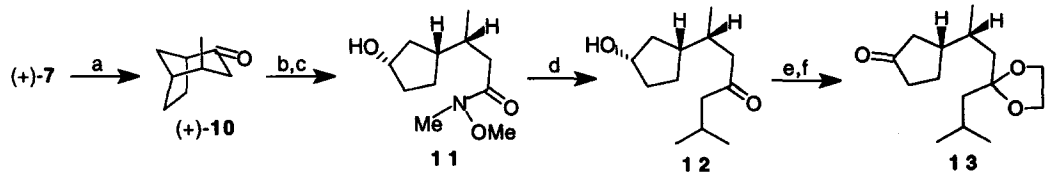
Scheme 1 *Reagents and conditions*: a) LDA, TMSCl, THF, –78 °C (82%); b) CH_2I_2, Et_2Zn, Et_2O, reflux (98%); c) $FeCl_3$, DMF, 0 °C (93%).

endo-alcohol (±)-**8**. Kinetic transesterification between (±)-**8** and vinyl acetate occurred in *tert*-butyl methyl ether in the presence of lipase PS to afford the acetate (+)-**9** and the alcohol (–)-**8** in satisfactory chemical yields, but their enantiomeric purities were less than satisfactory for practical use. On the other hand, kinetic hydrolysis of the racemic acetate (±)-**9**, generated from (±)-**8**, in a phosphate buffer in the presence of the same lipase afforded the alcohol (+)-**8** and the acetate (–)-**9**, in satisfactory chemical and enantiomerical yields, which were used for the following synthesis. The alcohol (+)-**8** gave the enone (+)-**7**, $[\alpha]_D^{29}$ +362.1 (*c* 0.6, $CHCl_3$) {lit.[3]: $[\alpha]_D^{33}$ +359.2 (*c* 1.64, $CHCl_3$)}, on Dess-Martin oxidation,[6] while the acetate (–)-**9** gave the enantiomeric enone (–)-**7**, $[\alpha]_D^{22}$ –339.0 (*c* 2.8, $CHCl_3$) {lit.[3]: $[\alpha]_D^{29}$ –346.2 (*c* 1.55, $CHCl_3$)}, on sequential K_2CO_3-mediated methanolysis and Dess-Martin oxidation. Both enantiomers of the enone **7** were identical with the authentic materials obtained from (+)-norcamphor.[3] Enatiomeric purities of the resolved products were estimated for both as > 95% ee at this stage by HPLC of both enantiomers of **7** thus obtained using a chiral column (CHIRALCEL OB, *i*PrOH-hexane 1:200) (**Scheme 2**).



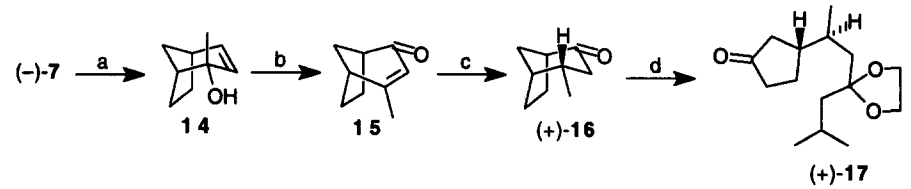
Scheme 2 *Reagents and conditions*: a) DIBAL, CH_2Cl_2, –78 °C (85%); b) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2 (97%).

To obtain the key intermediate (+)-**13** of (+)-juvabione **1**, the enone (+)-**7** was treated with the cuprate reagent generated *in situ* to give diastereoselectively the 1,4-adduct (+)-**10**, $[\alpha]_D^{27}$ +147.1 (*c* 1.0, $CHCl_3$) {lit.[3]: $[\alpha]_D^{32}$ +136.7 (*c* 1.15, $CHCl_3$)}, having *exo*-methyl stereochemistry. The bicyclic ketone (+)-**10** was then transformed into the cyclopentanone (+)-**13**, $[\alpha]_D^{25}$ +98.1 (*c* 1.1, $CHCl_3$) {lit.[3]: $[\alpha]_D^{31}$ +97.3 (*c* 1.15, $CHCl_3$)}, in 47% overall yield *via* **11** and **12** by sequential Baeyer-Villiger oxidation, Weinreb amide formation,[7] Grignard coupling, ketone protection and oxidation as shown[3] (**Scheme 3**).



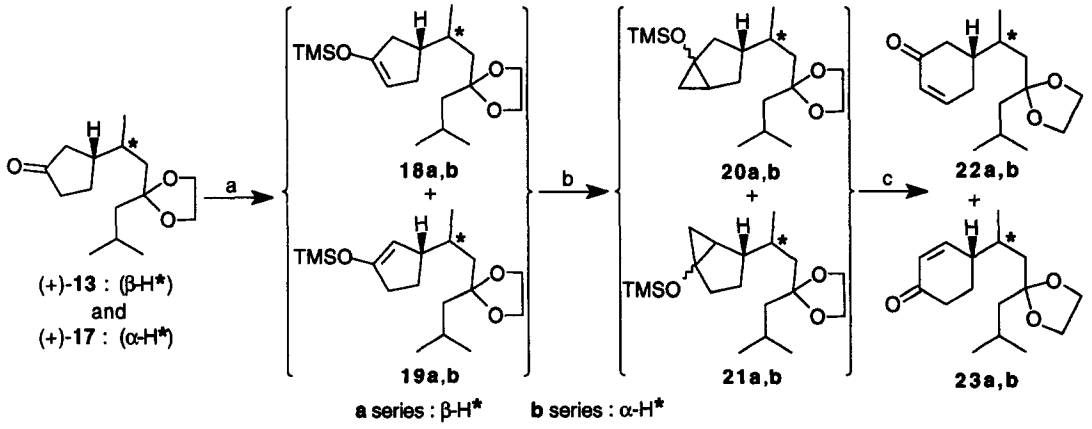
Scheme 3 *Reagents and conditions*: a) MeMgI, CuCN, LiCl, THF, – 78°C (95%); b) *m*CPBA, CH_2Cl_2, 0 °C; c) MeNHOMe·HCl, Me_3Al, CH_2Cl_2 (87%, 2 steps); d) *i*PrCH$_2$MgCl, THF (65%); e) $(CH_2OH)_2$, *p*TsOH (cat.), benzene, reflux; f) PCC, NaOAc, CH_2Cl_2 (86%, 2 steps).

On the other hand, to obtain the key intermediate (+)-**17** of (+)-epijuvabione **2**, the enantiomeric enone (–)-**7** was first treated with methyllithium to give the 1,2-adduct **14**, $[\alpha]_D^{28}$ –68.5 (*c* 1.0, $CHCl_3$). This afforded the enone **15**, $[\alpha]_D^{24}$ +274.0 (*c* 1.3, $CHCl_3$), on oxidation with pyridinium chlorochromate (PCC), which on catalytic hydrogenation, gave diastereoselectively the bicyclic ketone (+)-**16**, $[\alpha]_D^{26}$ +115.4 (*c* 1.0, $CHCl_3$), having an *endo*-methyl stereochemistry. Employing exactly the same procedure as for (+)-**10**, the diastereomeric ketone (+)-**16** was similarly transformed into the diastereomeric cyclopentanone (+)-**17**, $[\alpha]_D^{27}$ +87.3 (*c* 1.3, $CHCl_3$), in 44% overall yield (**Scheme 4**).



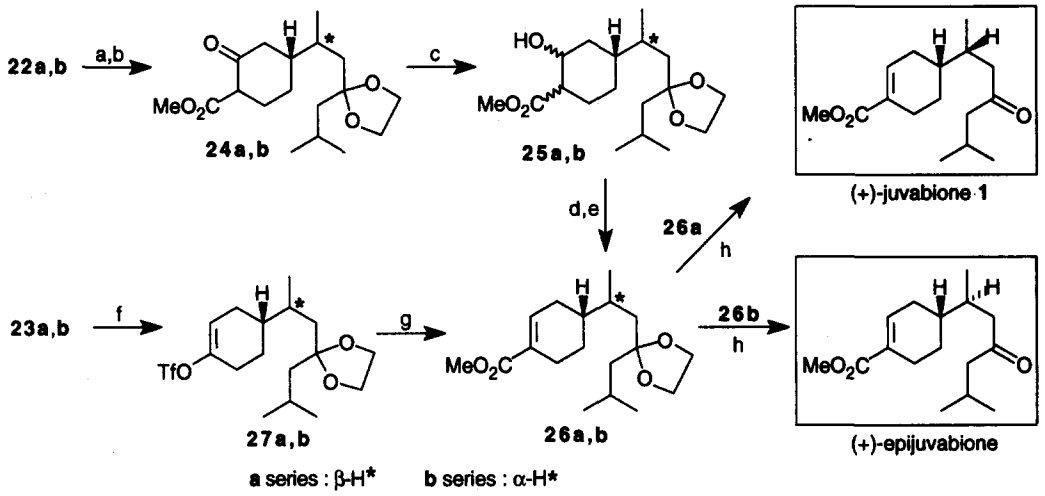
Scheme 4 *Reagents and conditions*: a) MeLi, THF (97%); b) PCC, CH_2Cl_2 (84%); c) H_2 (10%), Pd-C, AcOEt (98%); d) as Scheme 3 (44%, 5 steps).

Having obtained the two key intermediates, (+)-**13** and (+)-**17**, we examined their transformation into the target natural products, the former into (+)-juvabione **1** and the latter into (+)-epijuvabione **2**, by employing the cyclopropanation and the ring-expansion reaction that used for the conversion of norcamphor (±)-**3** into the enone precursor (±)-**7**. Since we could not find appropriate conditions to convert regioselectively both (+)-**13** and (+)-**17** into the single silyl enol ether products, we decided to use the mixtures consisted of the two regio-isomers, **18a,b** and **19a,b**, for the next step without separation. Thus, the 2.6:1 mixture consisted of **18a** and **19a** gave an inseparable mixture of the cyclopropanes, **20a** and **21a**, which on treatment with iron(III) chloride[5] followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the two isomeric cyclohexenones, **22a**, $[\alpha]_D^{27}$ –13.0 (*c* 0.3, $CHCl_3$), and **23a**, $[\alpha]_D^{31}$ +11.3 (*c* 0.3, $CHCl_3$), in overall yields of 38 and 17% after separation by silica gel column chromatography. On the same treatment, the 2.8:1 mixture consisted of **18b** and **19b** furnished the two isomeric cyclohexenones, **22b**, $[\alpha]_D^{28}$ –9.7 (*c* 0.6, $CHCl_3$), and **23b**, $[\alpha]_D^{29}$ +52.8 (*c* 0.2, $CHCl_3$), in overall yields of 37 and 14% after separation (**Scheme 5**).



Scheme 5 *Reagents and conditions*: a) LDA, TMSCl, THF, –78 °C (88% for *a*: 86% for *b*); b) CH_2I_2, Et_2Zn, CH_2Cl_2 (80% for *a* and *b*); c) $FeCl_3$, DMF then DBU, CH_2Cl_2 (51% for **22a**, 52% for **22b**; 22% for **23a**, 19% for **23b**).

To obtain the natural products, the 3-substituted cyclohexenones, **22a** and **22b**, were sequentially hydrogenated and carbomethoxylated to give the keto-esters, **24a** and **24b**, which were further transformed into the cyclohexenecarboxylates,[2] **26a**, $[\alpha]_D^{25}$ +71.3 (*c* 0.2, $CHCl_3$), and **26b**, $[\alpha]_D^{27}$ +49.3 (*c* 0.3, $CHCl_3$), by sequential reduction and dehydration, in overall yields of 48 and 53%, respectively. On the other hand, the 4-substituted cyclohexenones, **23a** and **23b**, were treated sequentially with L-selectride and *N*-(2-pyridyl)triflimide in the same flask[8] to give the enol triflates, **27a** and **27b**. On the palladium-mediated methoxycarbonylation,[9] both the triflates, **27a** and **27b**, furnished the esters, **26a** and **26b**, identical with those obtained from **23a** and **23b**, both in 35% yields. Finally, the esters, **26a** and **26b**, were acid-hydrolyzed to give (+)-juvabione **1**, $[\alpha]_D^{27}$ +65.2 (*c* 0.2, benzene) {lit.[3]: $[\alpha]_D^{27}$ +65.2 (*c* 0.46, benzene)}, and epijuvabione (+)-**2**, $[\alpha]_D^{29}$ +95.8 (*c* 0.5, benzene) {lit.[3]: $[\alpha]_D^{32}$ +96.3 (*c* 0.81, benzene)}, in yields of 84 and 82%, respectively (**Scheme 6**).



Scheme 6 *Reagents and conditions*: a) H_2, 10% Pd-C, AcOEt; b) NaH, $(MeO)_2CO$, THF (82% for **24a** and 90% for **24b**, 2 steps); c) $NaBH_4$, MeOH (65% for **25a** and 68% for **25b**); d) MesCl, Et_3N, CH_2Cl_2; e) DBU, CH_2Cl_2 (90% from **25a** and 87% from **25b**, 2 steps); f) L-selectride, THF then *N*-(2-pyridyl)triflimide (71% for **27a** and 75% for **27b**); g) CO, $Pd(OAc)_2$ (cat.), PPh_3, Et_3N, MeOH, DMF (49% from **27a**; 46% from **27b**); h) aq. CF_3CO_2H, $CHCl_3$ (84% for **1**; 82% for **2**).

In summary, a new diastereocontrolled route to (+)-juvabione and (+)-epijuvabione has been developed by lipase-mediated preparation of the key chiral building block having bicyclo[3.2.1]octane framework starting from racemic norcamphor.

References and Notes

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