Stereo- and Enantio-controlled Synthesis of (+)-Juvabione and (+)-Epijuvabione from (+)-Norcamphor

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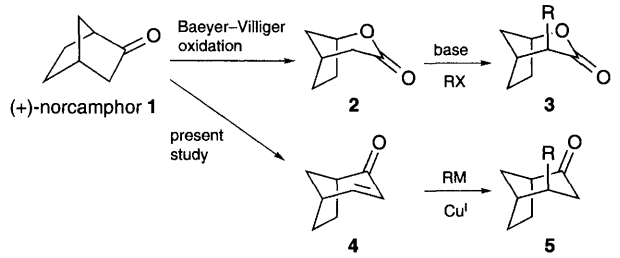
(+)-Juvabione and (+)-epijuvabione, natural sesquiterpenes exhibiting insect juvenile hormone activity, have been synthesized with complete stereo- and enantio-control using (+)-norcamphor as the chiral precursor *via* both the enantiomeric bicyclo[3.2.1]octenone intermediates.

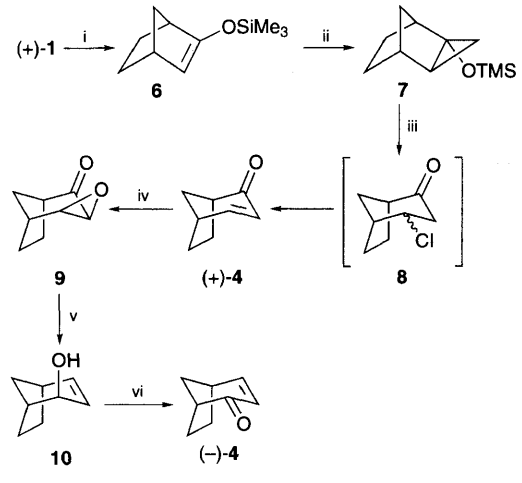
Convex face selective introduction of an electrophile to 2-oxabicyclo[3.2.1]octan-3-one **2**, obtained by oxidation of norcamphor **1**, is well established.[1] It is, however, very difficult to retain the original stereoselectivity owing to facile epimerization under the basic conditions employed.[2] We, therefore, prepared optically active bicyclo[3.2.1]oct-3-en-2-one[3] **4** so as to prevent epimerization *via* the convex face selective 1,4-nucleophilic addition pathway (Scheme 1). Here we report a preparation of both enantiomeric forms of bicyclo[3.2.1]oct-3-en-2-one **4** from the same (+)-norcomphor[2] **1** and their complete stereocontrolled conversion into (+)-juvabione **23** and (+)-epijuvabione **29**, natural sesquiterpenes exhibiting selective insect hormone activity,[4,5] employing convex face selective 1,4-addition as a key step.

(+)-Norcamphor† **1**, presently the only commercially available enantiomer, was easily converted into the silyl enol ether[6] **6**. Compound **6** was then treated with diiodomethane and diethyl zinc[7] to stereoselectively give the cyclopropane **7** in excellent yield. On treatment with iron(III) chloride in dimethylformamide,[7] compound **7** afforded directly (+)-bicyclo[3.2.1]oct-3-en-2-one‡,§ **4**, $[\alpha]_D^{33}$ + 359.2 (*c* 1.64, $CHCl_3$), [lit.,[3b]: + 334 (*c* 1.1, $CHCl_3$), 93% ee], in excellet yield with concomitant dehydrochlorination of the transient β-chloroketone intermediate **8**. To invert the stereochemistry,[8] (+)-**4** was first treated with alkaline hydrogen peroxide to stereoselectively give the *exo*-epoxide **9**, $[\alpha]_D^{31}$ + 31.1 (*c* 1.71, $CHCl_3$). Compound **9** was then treated with hydrazine hydrate, followed by the Dess–Martin periodinate[9] to give the enantiomeric (−)-enone **4**, $[\alpha]_D^{29}$ −346.2 (*c* 1.55, $CHCl_3$), in 57% overall yield *via* the allyl alcohol **10**, $[\alpha]_D^{33}$ −207.5 (*c* 1.48, $CHCl_3$) [lit:[3a] + 219 (*c* 0.6, $CHCl_3$) for the (+)-enantiomer] (Scheme 2).

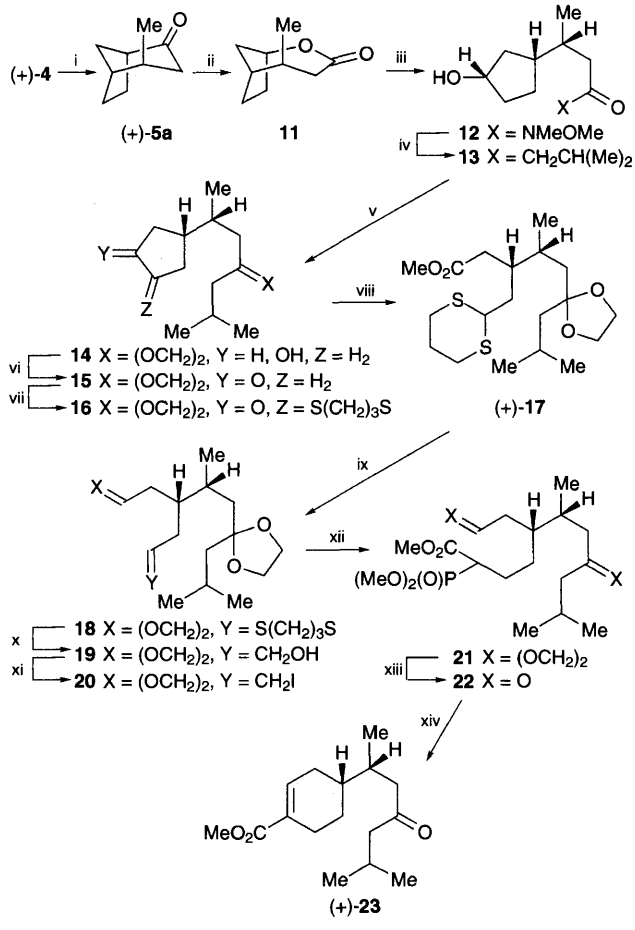
To demonstrate its convex face selectivity, we chose two epimeric natural sesquiterpenes (+)-juvabione **23** and (+)-epijuvabione **29** as target molecules whose stereocontrolled construction is known to be exceedingly difficult.[4a] The present synthesis of (+)-juvabione **23** began with 1,4-addition of the Grignard reagent to (+)-enone **4** to selectively give the methyl product (+)-**5a**, $[\alpha]_D^{23}$ + 136.7 (*c* 1.14, $CHCl_3$) [lit.,[3b] + 124



Scheme 1



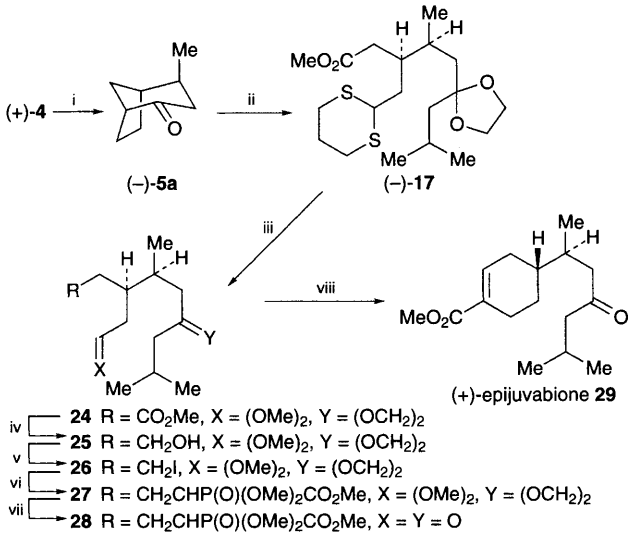
Scheme 2 *Reagents and conditions*: i, Me_3SiCl, LDA THF; ii, CH_2I_2, Et_2Zn, Et_2O (94% from **1**); iii, $FeCl_3$, DMF, 85%; iv, 30% H_2O_2, MeOH, NaOH (1 mol dm^{-3}) 97%; v, $NH_2NH_2{\cdot}H_2O$, AcOH (cat.), MeOH, 72%; vi, Dess–Martin periodinate oxidation, 81%



Scheme 3 *Reagents and conditions*: i, MeMgI, CuCN, LiCl, THF, 92%; ii, MCPBA, CH_2Cl_2; iii, MeNHOMe·HCl, Me_3Al, CH_2Cl_2 (86% after separation); iv, Pr^iCH_2MgCl, THF, 70%; v, $(CH_2OH)_2$, *p*-toluenesulfonic acid (p-TsOH), benzene, 91%; vi, pyridinium chlorochromate (PCC), NaOAc, CH_2Cl_2, 94%; vii, pyrrolidine then $TsS(CH_2)_3STs$, 70%; viii, KOH, acid workup, then CH_2N_2, 92%; ix, diisobutylaluminum hydride, then $(CH_2OH)_2$, *p*-TsOH, benzene, 77%; x, $Hg(ClO_4)_2$, $CaCO_3$, then $NaBH_4$, 83%; xi, I_2, PPh_3; imidazole; xii, $(MeO)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6-MeCN, DMF (94% from **19**); xiii, aq. TFA; xiv, LiCl, DBU, MeCN (57% from **21**)

(*c* 2.3, $CHCl_3$), 93% ee]. Although the Baeyer–Villiger oxidation did not occur regioselectively, (+)-**5a** afforded a mixture of lactones, mostly consisting of the desire **11** in nearly quantitative yield. The mixture was then treated, without separation with a complex[10] generated *in situ* from *N*-methoxymethylamine hydrochloride and trimethylaluminium in dichloromethane to give the hydroxamate **12**, $[\alpha]_D^{28}$ + 11.5 (*c* 1.10, $CHCl_3$), in 86% yield after separation of the undesired isomer, $[\alpha]_D^{30}$ −3.5 (*c* 1.04, $CHCl_3$), in 9% yield. Treatment of **12** with the Grignard reagent[10] gave the ketone **13**, $[\alpha]_D^{31}$ −3.9 (*c* 1.02, $CHCl_3$), which after ketalization was oxidized to the cyclopentanone **15**, $[\alpha]_D^{31}$ + 97.3 (*c* 1.15, $CHCl_3$), *via* the alcohol **14**, $[\alpha]_D^{30}$ + 4.7 (*c* 1.13, $CHCl_3$). Treatment of **15** with trimethylene dithiotosylate[11] furnished regioselectively the α-diketone monothioketal **16**, $[\alpha]_D^{31}$ −68.2 (*c* 1.21, $CHCl_3$), which on cleavage[12] followed by esterification furnished the dithian-ester (+)-**17**, $[\alpha]_D^{31}$ +0.1 (*c* 1.10, $CHCl_3$), in 39% overall yield from **12**. The ester **17** was partially reduced, followed by acetalized, to give the bis-dioxolane **18**, $[\alpha]_D^{30}$ −1.3 (*c* 1.94, $CHCl_3$), whose dithian functionality was sequentially hydrolysed[13] and reduced to give the primary alcohol **19**, $[\alpha]_D^{30}$ −9.2 (*c* 1.04, $CHCl_3$). The alcohol **19** was first transformed[14] into the iodide **20** which was then coupled with the phosphonate[15] to give the ester **21**, $[\alpha]_D^{30}$ −1.2 (*c* 0.61, $CHCl_3$), in 60% overall yield from **17**. Finally, **21** was acid-hydrolysed to give the keto-aldehyde **22** which was immediately subjected to intramolecular Horner–Emmons reaction[16] to give (+)-juvabione¶ **23** $[\alpha]_D^{27}$ +65.2 (*c* 0.46, benzene) [lit:[17] $[\alpha]_D^{25}$ +65.09 (*c* 0.89, benzene)], in 57% yield.

(+)-Epijuvabione **29** was synthesized starting with the same 1,4-addition reaction of the enantiomeric (−)-enone **4** to give the enantiomeric *exo*-methyl product (−)-**5a**, $[\alpha]_D^{31}$ −129.8 (*c* 0.82, $CHCl_3$). Exactly the same way as for the (+)-enantiomer, (−)-**5** was converted into the enantiomeric dithian-ester (−)-**17** in a comparable overall yield. On stirring with bis(trifluoroacetoxy)iodobenzene in methanol,[18] (−)-**17** furnished the dimethyl acetal **24** by methanolysis of the dithian functionality. The ester group of **24** was then reduced to give the primary alcohol **25** $[\alpha]_D^{31}$ −6.1 (*c* 1.06, $CHCl_3$), which was transformed into the phosphonate ester **27**, $[\alpha]_D^{31}$ +5.3 (*c* 1.21, $CHCl_3$), *via* the iodide **26** as above. Finally, **27** was sequentially hydrolysed and cyclized as above to yield (+)-epijuvabione **29**, $[\alpha]_D^{32}$ +96.3 (*c* 0.81, benzene)[lit:[17] $[\alpha]_D^{25}$ −94.14 (*c* 0.64, benzene) for (−)-enantiomer] *via* the keto-aldehyde **28**. Overall yield of the natural product **29** from **17** was 35%.



Scheme 4 *Reagents and conditions*: i, MeMgI, CuCN, LiCl, THF, 88%; ii, see Scheme 3; iii, $PhI(OCOCF_3)_2$, MeOH; iv, LAH, THF (67% from **17**); v, I_2, PPh_3, imidazole, 89%; vi, $(MeO)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6-MeCN, DMF, 92%; vii, aq. TFA; viii, LiCl, DBU, MeCN (64% from **27**)

In conclusion, we have succeeded in converting (+)-norcamphor into bicyclo[3.2.1]oct-3-en-2-one in both its enantiomeric forms. Owing to its biased and rigid structure, the latter allowed convex face selective nucleophilic 1,4-addition leading to stereocontrolled construction of (+)-juvabione from the (+)-enantiomer in 10% overall yield and (+)-epijuvabione from the (−)-enantiomer in 18% overall yield.

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Footnotes

† Prepared from (+)-endo-norborneol, kindly provided by Chisso Corporation, Japan, in *ca.* 95% ee.

‡ Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, ^1H NMR, and MS) data were obtained for all new compounds.

§ Optical purity was determined to be >95% ee by HPLC analysis using a chiral column (CHIRALCEL OB, elution: Pr^iOH–hexane 1 : 200).

¶ Optical purity was determined to be >95% ee by HPLC analysis using a chiral column (CHIRALCEL OB, elution: Pr^iOH–hexane 1 : 100).

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