Enantio- and diastereocontrolled synthesis of (+)-juvabione employing organocatalytic desymmetrisation and photoinduced fragmentation†

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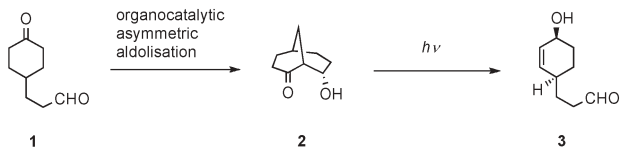
(+)-Juvabione, a natural sesquiterpene exhibiting insect juvenile hormone activity, has been synthesized from σ-symmetric 4-(2-formylethyl)cyclohexanone by employing organocatalytic asymmetric aldolisation and Norrish I-type fragmentation as the key steps.

The development of a catalytic enantioselective transformation that enables facile access to useful chiral platforms is a major goal in current synthetic organic chemistry.[1] We have recently reported the highly enantioselective construction of both enantiomeric forms of *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one (**2**) from the σ-symmetric keto-aldehyde **1** *via* intramolecular asymmetric aldolisation employing a chiral amino acid or its tetrabutylammonium salt as a catalyst,[2] and demonstrated the synthetic utility of the aldol product **2** as a chiral cyclohexanoid block based on a novel aldolisation/retroaldolisation interconversion.[3] As an alternative use of the building block **2**, we envisage the applicability of a photochemical process known as the Norrish I reaction[4] to the production of **3** from **2**, which brings about a formal intramolecular asymmetric redox transformation of **1**. We confirmed that **2** smoothly isomerises to **3** on irradiation with light (300 nm) in degassed MeOH at ambient temperature for 90 min in 60% yield (Scheme 1).



Scheme 1 Organocatalytic aldolisation and photoinduced fragmentation.

To demonstrate the synthetic utility of this methodology, we performed an enantio- and diastereocontrolled synthesis of (+)-juvabione (**4**), a natural sesquiterpene isolated together with (+)-epijuvabione (**5**) and exhibiting insect juvenile hormone activity;[5] the presence of two contiguous stereogenic centers on a ring and a side chain and the fact that the (+)-(4*R*,1′*R*) isomer exhibits the highest biological activity make this compound a fascinating target in enantio- and diastereocontrolled synthesis (Fig. 1).[6]

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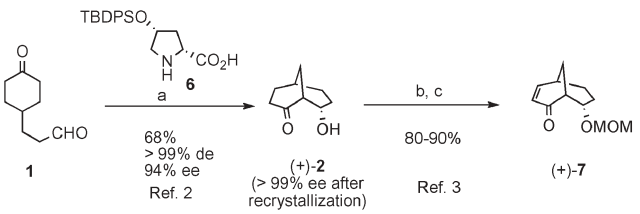
Fig. 1

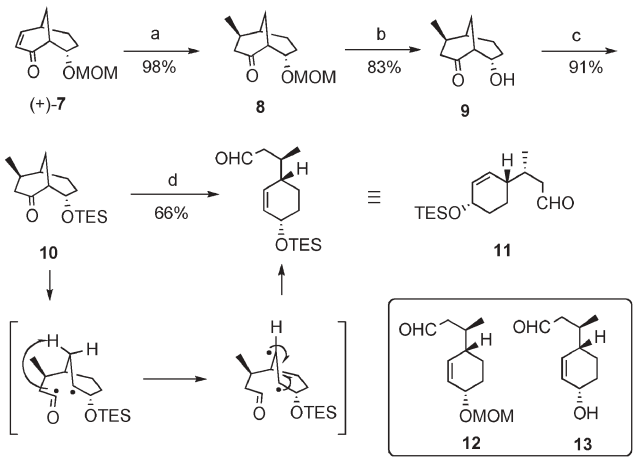
A highly enantiomerically enriched (+)-**2** was obtained *via* catalytic asymmetric aldolisation using **6** as a catalyst, and the scaffold for the installation of the C1 methyl group was generated *via* a two-step sequence involving MOM protection and IBX-mediated oxidation to give (+)-**7** (Scheme 2).[2,3]



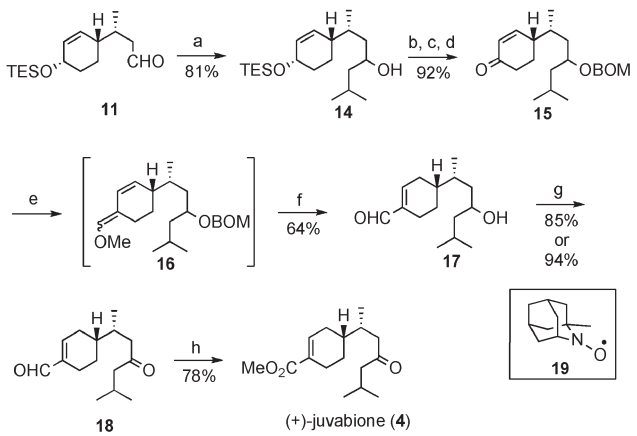
Scheme 2 *Reagents and conditions*: a) **6**, MeCN, rt, 23 h; b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 18 h; c) IBX, toluene–DMSO, 55–75 °C, 11 h.

To set the stage for the Norrish I reaction, the enone (+)-**7** (> 99% ee) was treated with Me_2CuLi to give the 1,4-adduct **8** in 98% yield exclusively. The bicyclic ketone **8** was then transformed to the TES ether **10**[7] *via* a deprotection/reprotection sequence in 76% yield over 2 steps. Having obtained the substrate for the key step, we attempted its transformation to a cyclohexenol derivative with a correct stereochemistry to (+)-juvabione (**4**) under photochemical conditions. It was found that the selective cleavage occurred smoothly to give the desired aldehyde **11** containing a cyclohexenol moiety in a good reproducible yield (66%) together with a trace amount of mechanistically predictable 3-(4-TESoxycyclohexyl) butanoic acid methyl ester *via* ketene generated *in situ* as a by-product. Note that structurally related compounds such as MOM ether **8** and free alcohol **9** furnished the corresponding aldehydes such as **12** and **13** in 69% and 60% yields, respectively, under the same conditions, indicating the potential use of this process in the synthesis of chiral cyclohexanoids. Also, note that the cleavage occurred selectively at the carbon–carbon bond connected to the bridgehead (Scheme 3).[8]

The isobutyl side chain of juvabione was introduced under Imamoto's conditions[9] using the Grignard reagent–$CeCl_3$ system to give the secondary alcohol **14** in 81% yield as a diastereomeric mixture (1 : 1).[10] Upon sequential reactions involving BOM



Scheme 3 *Reagents and conditions*: a) MeLi, CuI, THF, −40 °C, 1.5 h; b) $LiBF_4$, 1,4-dioxane, H_2O, 50–70 °C, 7 h; c) TESCl, imidazole, DMF, rt, 12 h; d) *hv* (300 nm), MeOH, rt, 1.5 h.



Scheme 4 *Reagents and conditions*: a) *i*-BuMgBr, $CeCl_3$, THF, 0 °C, 2 h; b) BOMCl, *i*-Pr_2NEt, TBAI, THF, rt, 47 h; c) TBAF, THF, rt, overnight; d) MnO_2, CH_2Cl_2, rt, 12 h; e) (methoxymethyl)triphenylphosphonium chloride, *n*-BuLi, THF, −30 °C, 2 h; f) 10% aq. HCl, THF, rt, 2 days; g) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h or cat. 1-Me-AZADO (**19**), BAIB, CH_2Cl_2, rt, 7.5 h; h) NaCN, MnO_2, AcOH, MeOH, rt, 24 h.

protection, TBAF-mediated removal of the TES group, and MnO_2 oxidation, **14** furnished the enone **15** in 92% yield. The crucial C-1 homologation of the enone **15** was attained *via* the Wittig reaction using (methoxymethyl)triphenylphosphonium chloride and *n*-BuLi in THF at −30 °C to give the methyl dienol ether **16**, which was immediately treated with aqueous 10% HCl at ambient temperature for 2 days to give the corresponding hydroxy-α,β-unsaturated aldehyde **17** in 64% yield. While the oxidation of resultant secondary alcohol **17** was carried out with Dess–Martin periodinane[11] to give the penultimate ketone **18**[6a,6b] in 85% yield, it was found that using 5 mol% 1-methyl-2-azaadamantane *N*-oxyl [1-Me-AZADO (**19**)],[12] a stable nitroxyl-radical-type oxidation catalyst that has recently been developed by our laboratory, with bis(acetoxy)iodobenzene; this improved the yield of oxidation up to 94%. Finally, according to Trost's synthesis[6b] **18** was subjected to Corey's conditions[13] using NaCN, MnO_2, and AcOH in MeOH at ambient temperature to give (+)-juvabione (**4**), $[\alpha]_D^{28}$ = +69.1 (*c* 1.00, benzene) [lit.:[6g] $[\alpha]_D^{25}$ = +66.9 (*c* 2.57, benzene)], in 78% yield and complete the synthesis (Scheme 4).

In conclusion, we have described the efficient synthesis of (+)-juvabione (**4**) with excellent stereocontrol from the σ-symmetric keto-aldehyde **1** based on "asymmetric aldolisation/Norrish I cleavage" methodology, in which the temporarily generated chiral aldol motif in **2** plays essential roles in stereochemical control. The present strategy is complementary to the aldolisation/retro-aldolisation interconversion that we established[3] and offers a versatile use of **2** as a chiral cyclohexanoid block.

Notes and references

1 Review: *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2000.
2 N. Itagaki, M. Kimura, T. Sugahara and Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4185.
3 N. Itagaki, T. Sugahara and Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4181.
4 D. S. Weiss, in *Organic Photochemistry*, ed. A. Padwa, Marcel Dekker, New York, 1981, vol. 5, p. 347.
5 For a pertinent review, see: C. H. Heathcock, S. L. Graham, M. C. Pirring, F. Plavac and C. T. White, in *Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley, New York, 1983, vol. 5, p. 1.
6 For an asymmetric total synthesis of (+)-juvabione, see: (*a*) B. A. Pawson, H.-C. Cheung, S. Gurbaxani and G. Saucy, *J. Am. Chem. Soc.*, 1970, **92**, 336; (*b*) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, 1977, **99**, 3101; (*c*) E. Nagano and K. Mori, *Biosci., Biotechnol., Biochem.*, 1992, **56**, 1589; (*d*) H. Watanabe, H. Shimizu and K. Mori, *Synthesis*, 1994, 1249; (*e*) M. Kawamura and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 2403; (*f*) H. Nagata, T. Taniguchi, M. Kawamura and K. Ogasawara, *Tetrahedron Lett.*, 1999, **40**, 4207; (*g*) E. J. Bergner and G. Helmchen, *J. Org. Chem.*, 2000, **65**, 5072. For an asymmetric formal synthesis of (+)-juvabione, see: (*h*) W. H. Miles and H. R. Brinkman, *Tetrahedron Lett.*, 1992, **33**, 589. For an asymmetric total synthesis of (−)-juvabione, see: (*i*) C. Fuganti and S. Serra, *J. Chem. Soc., Perkin Trans. 1*, 2000, 97; (*j*) A. A. Craveiro and I. G. P. Vieira, *J. Braz. Chem. Soc.*, 1992, 124; (*k*) G. Farges and H. Veschambre, *Bull. Soc. Chim. Fr.*, 1973, **11**, 3172. For recent examples of racemic synthesis of juvabione, see: (*l*) N. Soldermann, J. Velker, O. Vallat, H. S. Evans and R. Neier, *Helv. Chim. Acta*, 2000, **83**, 2266; (*m*) M. He, S. Tanimori and M. Nakayama, *Biosci., Biotechnol., Biochem.*, 1995, **59**, 900.
7 The use of the MOM group in (+)-**7** was essential for stability under IBX-mediated oxidation conditions. However, the deprotection of the MOM group in an advanced intermediate derived from **12** under several acidic conditions failed. Thus, we converted the MOM ether to TES ether before the photochemical cleavage.
8 For a detailed mechanistic consideration of the Norrish I reaction of related bicyclo[3.3.1]nonan-2-one, see: R. O. Duthaler, R. S. Stingelin-Schmid and C. Ganter, *Helv. Chim. Acta*, 1976, **59**, 307.
9 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
10 In the absence of $CeCl_3$, the reaction of **12** and *i*-BuMgBr gave the desired secondary alcohol (77%) together with an undesired primary alcohol (8%) by hydride reduction and the starting aldehyde **12** was recovered (15%).
11 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.
12 M. Shibuya, M. Tomizawa, I. Suzuki and Y. Iwabuchi, *J. Am. Chem. Soc.*, 2006, **128**, 8412.
13 E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616.

