<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Organic Letters*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Zheng, J., Margarita, C., Krajangsri, S., Andersson, P G. (2018)
Asymmetric Total Synthesis of (-)-Juvabione via Sequential Ir-Catalyzed
Hydrogenations
Organic Letters, 20(18): 5676-5679
<https://doi.org/10.1021/acs.orglett.8b02405>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:su:diva-161198>

Asymmetric Total Synthesis of (–)-Juvabione via Sequential Ir-Catalyzed Hydrogenations

Jia Zheng,^{1b} Cristiana Margarita, Suppachai Krajangsri, and Pher G. Andersson^{*1b}

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

S Supporting Information

ABSTRACT: (–)-Juvabione, a natural sesquiterpene exhibiting juvenile insect hormone activity, was synthesized constructing the two adjacent stereogenic centers via sequential Ir-catalyzed hydrogenations. The first center is generated by hydrogenation of a styrene-type double bond (99% ee). The successive monohydrogenation of a diene intermediate constitutes the key step, granting high levels of regio- and stereocontrol (94:6 dr). This novel strategy allowed the preparation of (–)-juvabione from simple starting materials in 9 steps and 17% total yield.

Regio- and stereoselective monohydrogenation proved to be a useful method for the synthesis of natural products and complex organic structures.¹ In most cases, functionalized double bonds have been hydrogenated selectively by means of coordination to Rh and Ru catalysts (see examples in Scheme 1a and 1b).^{2,3} Our group has recently reported the reverse

In this work, we present a total synthesis of (–)-juvabione (Figure 1), with installation of the two adjacent stereogenic

Scheme 1. Examples of Asymmetric Monohydrogenations with Opposite Selectivity

a) Burk, 1998

b) Zhang and Lv, 2016

c) Andersson, 2017

selectivity by using Ir–N,P catalysts, allowing the preservation of more functionalized olefinic sites over purely alkyl-substituted ones.⁴ In particular, cyclic chiral silyl enol ethers⁵ (Scheme 1c) and allylsilanes⁶ have been successfully generated and transformed into interesting building blocks.

Figure 1. Structures of (–)-juvabione and (–)-epijuvabione.

centers via Ir-catalyzed asymmetric hydrogenations. The key step consists of the diastereoselective formation of the second center by regioselective monohydrogenation, which afforded the retention of a required enol ether (Scheme 2).

Juvabione is a natural sesquiterpene isolated together with its diastereomer epijuvabione (Figure 1). It shows selective juvenile insect hormone activity, which was first detected from exposition to certain types of paper, so the compound was referred to as “the paper factor”⁷ until its structure was identified as the methyl ester of todomatuic acid by Bowers⁸ in 1965. Juvabione and epijuvabione contain two contiguous stereogenic centers on a ring and a side chain. While many syntheses of racemic juvabione have been reported,⁹ optically active juvabione has been previously prepared by a chiral pool approach starting from (+)-limonene,¹⁰ (–)-perillyl alcohol,¹¹ (+)-perillaldehyde^{12,13} or (+)-norcamphor.¹⁴ Baker’s yeast reductions,^{15–17} lipase-mediated kinetic resolution,¹⁸ and the use of chiral auxiliaries¹⁹ have also been exploited to obtain chiral precursors for juvabione.

Only a few, more recent approaches involve catalytic strategies, such as Pd-catalyzed asymmetric allylic alkylation²⁰

Received: July 28, 2018

Scheme 2. Synthesis of (–)-Juvabione

or organocatalytic asymmetric aldolization followed by a Norrish type-I photoinduced fragmentation as key steps.²¹ In our synthesis design (Scheme 2) the first stereogenic center is generated by asymmetric hydrogenation of the styrene-type conjugated ester **3**, which is easily prepared from the available starting materials.²² The saturated ethyl ester **4** is then transformed via the Weinreb amide **5** into the corresponding isobutyl ketone **6**. Following the protection of the carbonyl group as ketal (**7**), the aromatic ring undergoes Birch reduction to afford diene **8**, a suitable substrate for regio- and stereoselective monohydrogenation. The resulting monoene key intermediate **9** is converted to triflate **10**.²³ From this compound, (–)-juvabione can be obtained in two steps via methoxycarbonylation²⁴ (**11**) and acid hydrolysis, as reported by Ogasawara.¹⁸

The asymmetric hydrogenation of substrate **3** was optimized employing Ir-catalysts containing thiazole-based N,P-ligands **A** and **B** (Scheme 3). Using 0.2 mol % catalyst loading in CH₂Cl₂

Scheme 3. Asymmetric Hydrogenation of Conjugated Ester **3**

at 20 bar of H₂, both complexes furnished the corresponding saturated ester **4** with full conversion and excellent enantioselectivity (98 and 99% ee, respectively). The catalyst containing bicyclic ligand **B** was then selected as the best option for the construction of the first stereogenic center, and the reaction was further scaled up to obtain 3.57 mmol **4** (95% isolated yield).

The conversion of chiral ester **4** into the desired isobutyl ketone proceeded smoothly via preparation of the Weinreb amide (**5**, 96% yield) and its subsequent reaction with isobutyllithium in THF (ketone **6**, 76% yield). Before subjecting the aromatic ring to Birch reduction, the carbonyl functional group was protected. Compound **6** was reacted with

1,2-ethanediol in the presence of *p*-toluenesulfonic acid in refluxing toluene to give ketal **7** in 96% yield. At this point, it was possible to treat the intermediate with excess Li in liquid ammonia and *tert*-butyl alcohol, to afford the corresponding 1,4-cyclohexadiene **8** (77% yield). As shown in one of our previous reports,⁵ this cyclic motif containing an alkyl substituted double bond and a silyl enol ether is an appropriate candidate for Ir-catalyzed regio- and stereoselective monohydrogenation. We carried out a preliminary study to evaluate the method's stereoselectivity in the presence of a pre-existing stereogenic center on the side chain. The model substrate was obtained starting from (*E*)-2-(but-2-en-2-yl)naphthalene (**12**, Scheme 4), which was hydrogenated to (*S*)- or (*R*)-**13** in high enantioselectivity (99% ee) employing ligands **A** or **C**, respectively.

Scheme 4. Initial Steps for the Sequential Hydrogenation Study

Successively, the naphthalene system was transformed by Birch reduction to the triene substrate **14**. The two enantiomers of this compound were then tested in the second asymmetric hydrogenation using a range of iridium N,P-catalysts. The results of the study are summarized in Scheme 5. The occurrence of matched and mismatched pairs between the chiral substrates (*S*)- and (*R*)-**14** and the Ir-catalysts was predicted according to the reaction's selectivity model.²⁵ When using a racemic catalyst, preference over a diastereomer was still observed (3:1 dr). The hydrogenation of the triene substrates in a matched case afforded the expected product in up to 98:2 dr (ligands **H**, (*S*)-**C** and **I**). Interestingly, the

Scheme 5. Sequential Hydrogenation Study^a

^aReaction conditions: 0.05 mmol of substrate, 0.5 mol % catalyst in 0.5 mL CH₂Cl₂ at room temperature under H₂. Conversion determined by ¹H NMR spectroscopy; dr determined by GC analysis.

catalysts' high efficiency minimized the differences in reactivity, and thus it was possible to obtain good conversion even for the mismatched cases, affording the product with reverse diastereoselectivity, in up to 94:6 dr (ligand **H**). Therefore, these less favored cases displayed only a slightly lower level of diastereoselectivity (for example, 90:10 against 96:4 dr when using (*S*)- and (*R*)-**C** with substrate (*S*)-**14**). These findings show how the sequential hydrogenation path effectively makes all the product diastereomers selectively accessible by the appropriate choice of catalyst.

Consequently, the regio- and stereoselective monohydrogenation of the juvabione intermediate **8** was optimized (Table 1). The use of a base helped to prevent the silyl enol ether hydrolysis. When KHCO₃ was tested as additive, however, the reaction produced high amounts of over-reduced product **9'**, even without reaching full consumption of the starting material (entry 1). Switching to the use of K₃PO₄ aided to lower the formation of the fully saturated compound to 21% and to reach full conversion in 18 h (entry 2). The selectivity could be further improved by adjusting the base loading and hydrogen pressure. When increasing K₃PO₄ to 15 mol % loading, the

Table 1. Optimization of the Diene Monohydrogenation^a

entry	base (mol %)	H ₂ (bar)	time (h)	conv (%) ^b	9' (%)
1	KHCO ₃ (25)	10	18	92	64
2	K ₃ PO ₄ (10)	10	18	100	21
3	K ₃ PO ₄ (15)	10	24	77	11
4	K ₃ PO ₄ (15)	15	24	100	12
5	K ₃ PO ₄ (15)	15	20	100	11
6	K ₃ PO ₄ (20)	15	24	81	3
7	K ₃ PO ₄ (25)	15	24	60	3
8	K ₃ PO ₄ (20)	20	24	100	3

^aReaction conditions: 0.10 mmol of substrate, 0.5 mol % catalyst, base, in 1.0 mL PhCF₃ at room temperature under H₂. ^bDetermined by ¹H NMR spectroscopy.

hydrogenation reactivity decreased overall: only 77% conversion was observed after 24 h (entry 3). Higher hydrogen pressure was then tested (15 bar) and this resulted in full conversion both at 20 or 24 h reaction time, with a similarly limited amount of over-reduction (11–12%, entries 4 and 5). Optimal selectivity toward the monohydrogenation product was then found when using 20 mol % of base under 15 bar of H₂ (entry 6); in this case the observed amount of **9'** was only 3%. On the other hand, these conditions limited the conversion to 81%, and for higher base loading (25 mol %) the effect was even harsher, stopping it at 60% (entry 7). Gratifyingly, full conversion could be restored when 20 mol % of K₃PO₄ was used under a slightly higher pressure of H₂ (20 bar), while maintaining the low over-reduction level (entry 8). Therefore, using the catalyst containing thiazole ligand **C** (0.5 mol %) in PhCF₃ under the optimized hydrogenation conditions, monoene **9** could be prepared with satisfying selectivity and 90% yield.

Following this key step, the retained enol ether could undergo further manipulation. The conversion of the vinyl TIPS ether to the corresponding vinyl triflate was performed as reported by Corey,²³ thus, employing CsF and *N*-phenyl-trifluoromethanesulfonimide in dry dimethoxyethane (DME), compound **10** was isolated in 67% yield. GC analysis of this triflate intermediate showed a 94:6 dr. The two final steps of the (–)-juvabione synthesis were accomplished as previously demonstrated.¹⁸ Under CO balloon pressure in methanol, the Pd-catalyzed methoxycarbonylation²⁴ proceeded to yield conjugated ester **11** (60%), while acid-hydrolysis of the ketal (TFA in CH₂Cl₂) re-established the ketone (90% yield) to furnish (–)-juvabione (**1**).

In conclusion, we have demonstrated how a sequential Ir-catalyzed hydrogenation strategy can be successfully applied to the preparation of (–)-juvabione. In particular, the method proved to be highly efficient in the selective construction of the two alkylic adjacent stereogenic centers of the sesquiterpene. The key step of regio- and stereoselective monohydrogenation

allowed the retention of a fundamental enol ether function. Thus, the synthesis of (–)-juvabione could be accomplished in 9 steps with a total yield of 17%, starting from simple, achiral and available starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02405.

Experimental procedures, characterization data, ¹H, ¹³C, and ¹⁹F spectra, SFC and GC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pher.andersson@su.se.

ORCID

Jia Zheng: 0000-0003-2700-6413

Pher G. Andersson: 0000-0002-1383-8246

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge the Stiftelsen Olle Engkvist Byggmästare, the Carl Tryggers Stiftelse, the Swedish Research Council and the Knut och Alice Wallenbergs Stiftelse for supporting this work.

■ REFERENCES

- (1) Margarita, C.; Rabten, W.; Andersson, P. G. *Chem. - Eur. J.* **2018**, *24*, 8022.
- (2) Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657.
- (3) Wang, Q.; Gao, W.; Lv, H.; Zhang, X. *Chem. Commun.* **2016**, *52*, 11850.
- (4) Peters, B. K.; Liu, J.; Margarita, C.; Rabten, W.; Kerdphon, S.; Orebom, A.; Morsch, T.; Andersson, P. G. *J. Am. Chem. Soc.* **2016**, *138*, 11930.
- (5) Liu, J.; Krajangsri, S.; Singh, T.; De Seriis, G.; Chumnavej, N.; Wu, H.; Andersson, P. G. *J. Am. Chem. Soc.* **2017**, *139*, 14470.
- (6) Rabten, W.; Margarita, C.; Eriksson, L.; Andersson, P. G. *Chem. - Eur. J.* **2018**, *24*, 1681.
- (7) Sláma, K.; Williams, C. M. *Proc. Natl. Acad. Sci. U. S. A.* **1965**, *54*, 411.
- (8) Bowers, W. S.; Fales, H. M.; Thompson, M. J.; Uebel, E. C. *Science* **1966**, *154*, 1020.
- (9) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1983.
- (10) Pawson, B. A.; Cheung, H. C.; Gurbaxani, S.; Saucy, G. *J. Am. Chem. Soc.* **1970**, *92*, 336.
- (11) Farges, G.; Veschambre, H. *Bull. Soc. Chem. Fr.* **1973**, 3172.
- (12) Trost, B. M.; Tamaru, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3101.
- (13) Craveiro, A. A.; Vieira, I. G. P. *J. Braz. Chem. Soc.* **1992**, *3*, 124.
- (14) Kawamura, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2403.
- (15) Nagano, E.; Mori, K. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1589.
- (16) Watanabe, H.; Shimizu, H.; Mori, K. *Synthesis* **1994**, *1994*, 1249.
- (17) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 97.
- (18) Nagata, H.; Taniguchi, T.; Kawamura, M.; Ogasawara, K. *Tetrahedron Lett.* **1999**, *40*, 4207.

- (19) Miles, W. H.; Brinkman, H. R. *Tetrahedron Lett.* **1992**, *33*, 589.
- (20) Bergner, E. J.; Helmchen, G. *J. Org. Chem.* **2000**, *65*, 5072.
- (21) Itagaki, N.; Iwabuchi, Y. *Chem. Commun.* **2007**, 1175.
- (22) Obtained by Horner-Wadsworth-Emmons reaction of TIPS-protected 4-hydroxyacetophenone with triethyl phosphonoacetate. For experimental details, see Supporting Information.
- (23) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290.
- (24) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
- (25) Church, T. L.; Rasmussen, T.; Andersson, P. G. *Organometallics* **2010**, *29*, 6769.