Total Synthesis of (±)-3-Hydroxy-β-ionone through a Ring-Closing Enyne Metathesis

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Abstract: The total synthesis of (±)-3-hydroxy-β-ionone, a bisnorsesquiterpene having allelopathic activity, has been accomplished employing an enyne metathesis for the construction of the C1–C8 segment and two-carbon elongation via a nitrile oxide–alkene [3+2] cycloaddition as the key steps.

Key words: enyne metathesis, total synthesis, ionones, nitrile oxide, cycloaddition

The ionone-type bisnorsesquiterpenes, a widely distributed class of natural products, are known as natural aroma constituents. In 2010, 3-hydroxy-β-ionone (**1**)[1,2d] and 3-oxo-α-ionol (**2**),[2] two representatives of ionone-type natural products, were isolated from an aqueous extracts of rattail fescue (*Vulpia myuros*) by Fujii et al. and identified as growth inhibitors against lettuce, alfalfa, timothy, *D. sanguinalis*, and *L. multiflorum*, namely, allelochemicals.[3] During the course of our synthetic studies on natural products having allelopathic activity,[4] we have concentrated on developing efficient methods focused on the ionone-type bisnorsesquiterpenes. In our previous paper, we reported the first enantioselective total synthesis of 3-oxo-α-ionol (**2**).[5] Herein we describe a total synthesis of (±)-3-hydroxy-β-ionone (**1**), employing as the key step an enyne metathesis[6] of **5** for the construction of 3,5,5-trimethyl-4-vinylcyclohex-3-en-1-ol (**3**, R = H), the C1–C8 segment of **1**. Although several reports on the total syntheses of **1** have been published,[7] the syntheses starting from acyclic precursors are very few. We therefore wanted to develop a flexible synthetic method, which would enable us to assemble a library of diverse compounds analogous to **1** for biological evaluations (Figure 1).

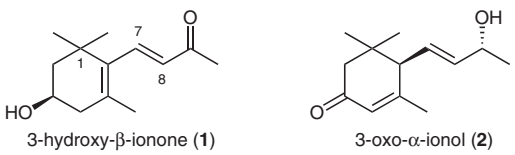
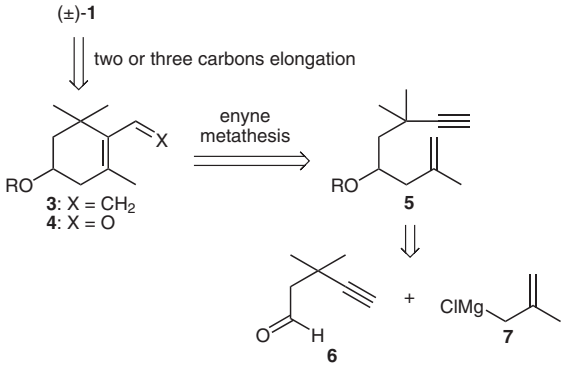


Figure 1 Structures of ionone-type allelochemicals

Our synthetic strategy is shown in Scheme 1. We envisaged the two or three carbons elongation being achieved in the last stage of the synthesis. The C1–C8 diene segment **3** would be assembled through a ring-closing enyne metathesis of the acyclic precursor **5**, which can be prepared from 3,3-dimethylpent-4-ynal (**6**)[8] and (2-methylallyl)magnesium chloride (**7**). The C1–C7 aldehyde segment **4** might be derived from **3** by oxidation. Since a ring-closing enyne metathesis directed toward the synthesis of the vinylcyclohexenes employing the substrate possessing the 1,1-disubstituted alkene and the acetylene with a quaternary carbon center at the propargylic position has never been reported so far,[9] the reaction of **5** would be synthetically challenging (Scheme 1).



Scheme 1 Retrosynthetic analysis

Reaction of **6** with the Grignard reagent **7** provided the alcohol **5a** and the alcohol moiety of which was protected as the TBS ether to give **5b**. Enyne metathesis of **5a**,**b** was examined with 10 mol% of catalyst and ethylene gas[10] in a toluene solution at 80 °C. Treatment of **5a** with the Grubbs second-generation catalyst **8** or the Hoveyda–Grubbs second-generation catalyst **9** resulted in decomposition of the starting **5a**; none of the cyclized products was found in the reaction mixture. When a solution of a mixture of **5b** and **8** in toluene was heated at 80 °C for four hours under an atmosphere of argon, the substrate **5b** was recovered. Fortunately, prolonged heating of the solution for eight hours with ethylene gas resulted in quantitative formation of the desired vinylcyclohexene **3b** along with the seven-membered diene **10b** as an inseparable 2.3:1 mixture. The reaction with the catalyst **9** provided a 3:1 mixture of the cyclized products in 73% yield (Table 1).

Desilylation of the mixture of **3b** and **10b** (Table 1, entry 4) provided a mixture of the corresponding alcohols, which was separated by HPLC to give **3a**[11] and **10a**[12] in 54% and 13% yield, respectively. With the requisite key

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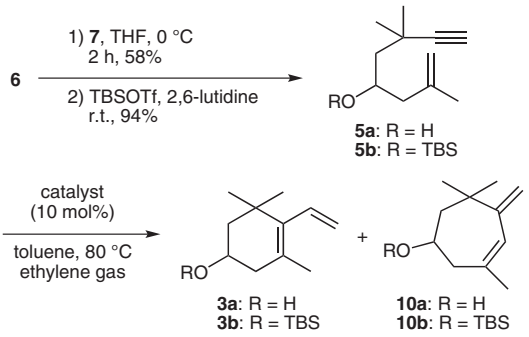
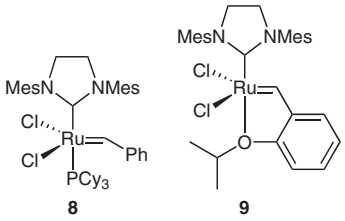
Table 1 Preparation and Enyne Metathesis of **5a**,**b**

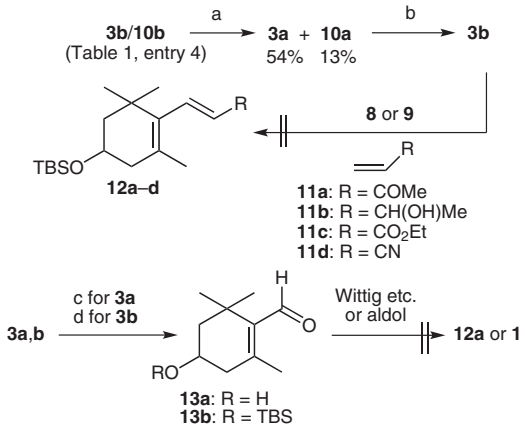


Entry	Precursor	Catalyst	Time (h)	Yield (%)	**3**/**10**[a]
1	**5a**	**8**	2	decomp.	–
2	**5a**	**9**	0.5	decomp.	–
3[b]	**5b**	**8**	4	recovered	–
4	**5b**	**8**	8	quant.	2.3:1
5	**5b**	**9**	3	73	3:1

[a] Determined by ^{1}H NMR spectroscopy.
[b] Under argon atmosphere instead of ethylene gas.



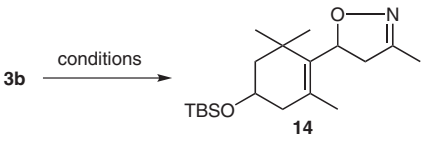
intermediates **3a**,**b** in hand, we next examined the formation of the enone part of the natural product. Attempted cross metathesis of **3a** and **3b**, derived by resilylation of **3a**, with the alkenes **11a–d** using catalysts **8** or **9** under various reaction conditions resulted in the recovery of the starting material or the decomposition and the expected **12a–d** could not be obtained at all. This result is likely due to the hindered nature of the vinyl group. The Wittig[13] and the aldol reactions[14] of the aldehyde **13a** and **13b** (prepared from **3a** and **3b** by oxidative cleavage of the vinyl group) for obtaining **12a** and **1** were also unsuccessful (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) HF·pyridine, THF–pyridine (4:1), 40 °C, 4 h then separation by HPLC, 54% for **3a**, 13% for **10a**; (b) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, r.t., 2 h, 94%; (c) OsO_4 (5 mol%), NMO, acetone–H_2O (9:1), r.t. 4 h then $NaIO_4$, MeCN–H_2O (3:2), r.t., 2 h, 66%; (d) OsO_4 (2 mol%), $NaIO_4$, MeCN–H_2O (3:1), r.t., 3 h, 72%.

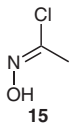
For the carbon chain elongation, it was thought that a nitrile oxide–alkene [3+2] cycloaddition[15] would be suitable. Thus, treatment of **3b** with nitroethane, a nitrile oxide precursor, in the presence of *p*-chlorophenylisocyanate and triethylamine in refluxing benzene for three hours provided the isoxazoline **14** and the recovered **3b** in 19% and 77% yield, respectively (Table 2, entry 1). A higher yield of **14** was obtained under prolonged reaction time (Table 2, entry 2). When the reaction was conducted using *N*-hydroxyacetimidoyl chloride (**15**)[16] as the nitrile oxide precursor and triethylamine in benzene at room temperature, **14** was obtained in 61% yield along with **3b** (39%). The best result was realized by treatment of a solution of **15** in dichloromethane with triethylamine at room temperature for ten hours, which provided **14** in 75% yield (Table 2, entry 5).

Table 2 Nitrile Oxide–Alkene [3+2] Cycloaddition



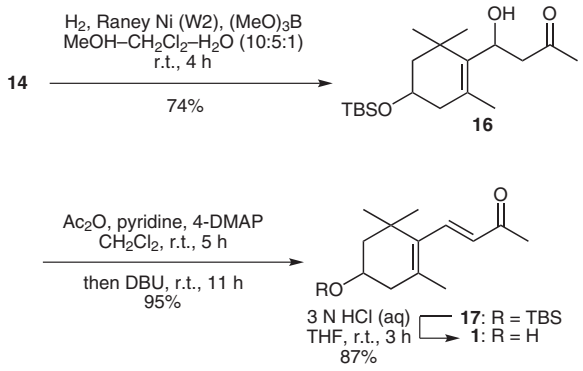
Entry	Conditions	Yield of **14** (%)[a]	Yield of **3b** (%)
1	$EtNO_2$, 4-ClC_6H_4NCO, Et_3N, benzene, reflux, 3 h	19	77
2	$EtNO_2$, 4-ClC_6H_4NCO, Et_3N, benzene, reflux, 8 h	52	34
3	**15**, Et_3N, benzene, r.t., 15 h	61	39
4	**15**, $NaHCO_3$, EtOAc, r.t., 15 h	63	–
5	**15**, Et_3N, CH_2Cl_2, r.t., 10 h	75	–

[a] Mixture of diastereoisomers (1:1 to 1:5).



The isoxazoline **14** thus prepared was exposed to the reductive hydrolysis conditions[17] under an atmosphere of hydrogen in the presence of Raney Ni (W2) and trimethyl borate in a methanol–dichloromethane–water (10:5:1) solvent mixture at room temperature for four hours and provided the β-hydroxy ketone **16** in 74% yield. Dehydration was realized by acetylation followed by DBU treatment gave the dienone **17**, which was converted into (±)-

3-hydroxy-β-ionone (**1**)[18,19] in 83% yield for the two steps. All spectral data of the synthetic material were identical to those published (Scheme 3).[7g]



Scheme 3 Conversion of **14** into **1**

In summary, we have completed the total synthesis of (±)-3-hydroxy-β-ionone (**1**) employing a ring-closing enyne metathesis for the construction of the C1–C8 segment and a two-carbon elongation via the nitrile oxide–alkene [3+2] cycloaddition as the key steps in a longest linear sequence of eight steps from 3,3-dimethylpent-4-ynal with an overall yield of 13%. In addition, it should be emphasized that the enyne metathesis of the substrate with sterically demanding alkene and alkyne functional groups was effective in producing the substituted vinylcyclohexenol in moderate yield. The synthetic route developed here is general and flexible and could be applied not only to the syntheses of other related ionone-type natural products but also for assembling a library of compounds for biological evaluations.

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References and Notes

(1) (a) Fujimori, T.; Kasuga, R.; Noguchi, M.; Kaneko, H. *Agric. Biol. Chem.* **1974**, *38*, 891. (b) Shibata, S.; Katsuyama, A.; Noguchi, M. *Agric. Biol. Chem.* **1978**, *42*, 195.

(2) (a) Aasen, A. J.; Kimland, B.; Enzell, C. R. *Acta Chem. Scand.* **1971**, *25*, 1481. (b) Kimland, B.; Aasen, A. J.; Enzell, C. R. *Acta Chem. Scand.* **1972**, *26*, 2177. (c) Aasen, A. J.; Kimland, B.; Enzell, C. R. *Acta Chem. Scand.* **1973**, *27*, 2107. (d) Fujimori, T.; Kasuga, R.; Matsushita, H.; Kaneko, H.; Noguchi, M. *Agric. Biol. Chem.* **1976**, *40*, 303. (e) Behr, D.; Wahlberg, I.; Nishida, T.; Enzell, C. R. *Acta Chem. Scand.* **1978**, *32*, 391. (f) D'Abrosca, B.; DellaGreca, M.; Fiorentino, A.; Monaco, P.; Oriano, P.; Temussi, F. *Phytochemistry* **2004**, *65*, 497. (g) Park, J. H.; Lee, D. G.; Yeon, S. W.; Kwon, H. S.; Ko, J. H.; Shin, D. J.; Park, H. S.; Kim, Y. S.; Bang, M. H.; Baek, N. I. *Arch. Pharm. Res.* **2011**, *34*, 533.

(3) Kato-Noguchi, H.; Yamamoto, M.; Tamura, K.; Teruya, T.; Suenaga, K.; Fujii, Y. *Plant Growth Regul.* **2010**, *60*, 127.

(4) For a review, see: (a) Kamei, T.; Morimoto, S.; Shishido, K. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1021. For recent synthetic studies, see: (b) Kanematsu, M.; Soga, K.; Manabe, Y.; Morimoto, S.; Yoshida, M.; Shishido, K. *Tetrahedron* **2011**, *67*, 4758. (c) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854.

(5) Kikuchi, D.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2012**, *53*, 145.

(6) For reviews, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (b) Poulson, C. S.; Madsen, R. *Synthesis* **2003**, 1. (c) Diber, S. T.; Giessert, A. *Chem. Rev.* **2004**, *104*, 1317. (d) Mori, M. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 5.

(7) For the syntheses of racemic **1**, see: (a) Loeber, D. E.; Russell, S. W.; Toube, T. P.; Weedon, C. L. *J. Chem. Soc. C* **1971**, 404. (b) Takazawa, O.; Tamura, H.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1907 . For the syntheses of optically active **1**, see: (c) Mori, K. *Tetrahedron Lett.* **1973**, *28*, 2635. (d) Mayer, H. *Helv. Chim. Acta* **1980**, *63*, 154. (e) Parry, A. D.; Neill, S. J.; Horgan, R. *Phytochemistry* **1990**, *29*, 1033. (f) Ito, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2565. (g) Khachik, F.; Chang, A. N. *J. Org. Chem.* **2009**, *74*, 3875. (h) Khachik, F.; Chang, A. N. *Synthesis* **2011**, 509.

(8) McMurry, J. E.; Mats, J. R.; Kees, K. L. *Tetrahedron* **1987**, *43*, 5489.

(9) For the syntheses of five-membered hetero- and carbocyclic dienes from the precursors with a 1,1-disubstituted alkene and an acetylene with a quaternary carbon center at the propargylic position, see: (a) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258. (b) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678. (c) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.

(10) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

(11) **Analytical Data**
IR (neat): 3334, 2922, 1460, 1362, 1049, 918 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.16 (ddd, *J* = 13.2, 7.2, 1.6 Hz, 1 H), 5.26 (dd, *J* = 7.2, 2.4 Hz, 1 H), 4.98 (dd, *J* = 13.2, 2.4 Hz, 1 H), 4.05–3.92 (m, 1 H), 2.35 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.01 (dd, *J* = 16.8, 6.8 Hz, 1 H), 1.75 (ddd, *J* = 12.0, 3.2, 2.0 Hz, 1 H), 1.71 (s, 3 H), 1.45 (t, *J* = 12.0 Hz, 1 H), 1.35 (br s, 1 H), 1.05 (s, 3 H), 1.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (Cq), 134.7 (CH), 125.6 (Cq), 118.7 (CH_2), 65.1 (CH), 48.3 (CH_2), 42.2 (CH_2), 36.6 (Cq), 30.0 (CH_3), 28.3 (CH_3), 21.2 (CH_3). ESI-HRMS: *m/z* calcd for $C_{11}H_{18}ONa$ $[M + Na]^+$: 189.1255; found: 189.1255.

(12) **Analytical Data**
IR (neat): 3345, 2965, 2925, 1041, 892 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.99 (s, 1 H), 4.98 (s, 1 H), 4.79 (s, 1 H), 3.99–3.92 (m, 1 H), 2.37 (dd, *J* = 16.4, 3.2 Hz, 1 H), 2.30 (dd, *J* = 16.4, 9.6 Hz, 1 H), 1.84 (ddd, *J* = 13.2, 3.6, 1.6 Hz, 1 H), 1.81 (s, 3 H), 1.70 (dd, *J* = 13.2, 9.6 Hz, 1 H), 1.45 (br s, 1 H), 1.15 (s, 3 H), 1.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (Cq), 133.1 (Cq), 127.9 (CH), 111.7 (CH_2), 67.7 (CH), 52.0 (CH_2), 43.9 (CH_2), 37.2 (Cq), 31.8 (CH_3), 29.4 (CH_3), 26.7 (CH_3). ESI-HRMS: *m/z* calcd for $C_{11}H_{18}ONa$ $[M + Na]^+$: 189.1255; found: 189.1258.

(13) The Wittig and Horner–Wadsworth–Emmons reactions of **13a**,**b** were examined under various conditions; however, only starting aldehyde was recovered.

(14) It has been reported that the aldol reaction of **13a** with acetone provided **1**; however, the yield was not described.[7e] When the reaction was attempted under the same conditions as reported, **1** was not produced at all.
(15) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
(16) Zhang, Z.; Curran, D. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2627.
(17) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4042.
(18) **Analytical Data**
IR (neat): 3409, 2960, 2926, 1672, 1606, 1363, 1257, 1051 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 16.4 Hz, 1 H), 6.11 (d, *J* = 16.4 Hz, 1 H), 4.06–3.95 (m, 1 H), 2.44 (dd, *J* = 17.6, 5.2 Hz, 1 H), 2.30 (s, 3 H), 2.09 (dd, *J* = 17.6, 9.6, 1 H), 1.80 (ddd, *J* = 12.4, 3.2, 2.0 Hz, 1 H), 1.78 (s, 3 H), 1.49 (t, *J* = 12.4 Hz, 1 H), 1.25 (br s, 1 H), 1.12 (s, 3 H), 1.11 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (Cq), 142.3 (CH), 135.7 (Cq), 132.4 (CH), 132.2 (Cq), 64.5 (CH), 48.4 (CH_2), 42.8 (CH_2), 36.9 (Cq), 30.1 (CH_3), 28.6 (CH_3), 27.3 (CH_3), 21.5 (CH_3). ESI-HRMS: *m/z* calcd for $C_{13}H_{21}O_2$ $[M + H]^+$: 209.1542; found: 209.1539.
(19) The optical resolution has been successfully achieved by Khachik et al.[7h]

