# Total Synthesis of Japanese Hop Ether Using an Efficient Intramolecular Pauson–Khand Reaction

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We dedicate this paper with the utmost gratitude and respect to Professor Steven V. Ley as we celebrate the occasion of his 60th birthday.

**Abstract:** The naturally occurring monoterpene Japanese Hop Ether has been synthesised in 14 steps in an overall yield of 29%. The key step of the synthesis, an intramolecular Pauson–Khand reaction, has been shown to proceed in good to excellent yield under mild *N*-oxide promotion conditions and with complete retention of alkene stereochemistry (for both *cis*- and *trans*-alkenes) in the product cyclopentenone.

**Key words:** amine *N*-oxides, cyclopentenones, natural products, Pauson–Khand cyclizations, stereoselectivity

Japanese Hop Ether **1** (Figure 1) is a monoterpene first isolated from the Japanese hop 'Shinshu-Wase' in 1968.[1] This natural product is also found to be present in Spalter hops[2] and, interestingly, it is believed to contribute to both the taste and aroma of a number of beers in which it has been identified in low concentrations.[3] The first reported synthesis of this deceptively simple molecule was by Imagawa and co-workers in 1979,[4] and since this time a small number of alternative preparative pathways have also been published.[5]

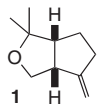

**Figure 1**

Of particular note to the study presented here is the synthesis reported by Billington et al,[5b] which employs an intermolecular Pauson–Khand (P–K) reaction[6] of the dicobalthexacarbonyl complex of acetylene **2** with the dihydrofuran **3**. Although this approach provides a rapid entry into the desired carbon skeleton, the key P–K step suffered from unselective alkene incorporation [3:2 ratio of desired (**4**) to undesired (**5**) alkene regioisomers] and a low yield of 22% (Scheme 1). However, it should be noted that this cyclisation was carried out under more traditional thermal reaction conditions and none of the more recently developed techniques, such as application of amine *N*-oxides,[7] sulfides,[8] or ultrasonication,[9] were applied to this particular transformation.

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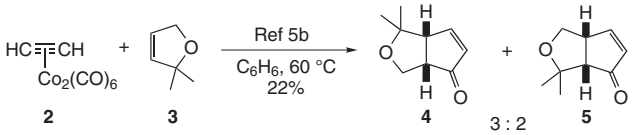
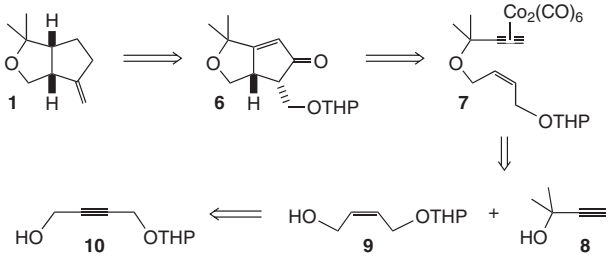


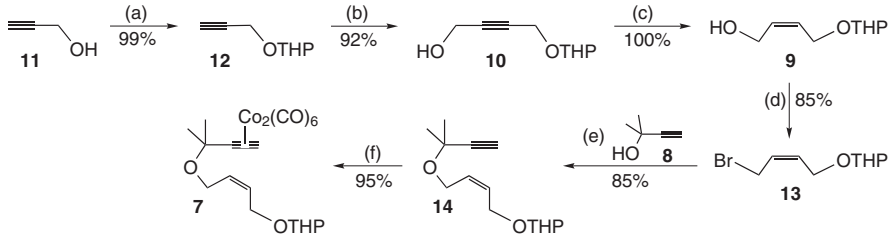

**Scheme 1**

Given the drawbacks in both yield and selectivity in the key step, shown, towards Japanese Hop Ether, as well as our interest in the application of the P–K reaction in natural product synthesis,[10] we have embarked upon a total synthesis programme towards this natural target, which would incorporate an *intra*molecular P–K reaction as the central synthetic transformation. The retrosynthetic plan presented in Scheme 2 shows how the precursor to Japanese Hop Ether **1**, cyclopentenone **6**, could be derived from P–K annulation of enyne complex **7**, which may be assembled from the propargylic alcohol **8** and the monoprotected (*Z*)-butenediol **9**. This latter alkene would itself be derived from alkyne **10**, via hydrogenation.




**Scheme 2**

This proposed synthetic route also opens up the possibility of investigating an interesting aspect of selectivity within the P–K reaction, namely the translation of alkene stereochemistry into product stereochemistry. Although the *Z*-isomer of alkene **9** is pictured in Scheme 2, the corresponding *E*-alkene could also be obtained from **10** by Red-Al® reduction, and this material could be carried through the same synthetic sequence as (*Z*)-**9** to arrive at the *E*-isomer of enyne complex **7**. If stereochemistry could be conserved, the *Z*-enyne complex **7** should cyclise to the *cis*-cyclised product **6** and the *E*-enyne complex should cyclise to the alternative *trans*-cyclic enone. However, Krafft found that, under thermal conditions, alkene stereochemistry is usually lost, with a mixture of products

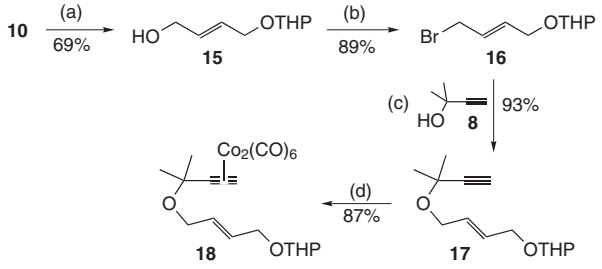



**Scheme 3** *Reagents and conditions*: (a) 3,4-DHP, *p*-TsOH, < 60 °C, 45 min; (b) *n*-BuLi, THF, $(CH_2O)_3$, ))), 75 min; (c) Pd on $CaCO_3$ poisoned with Pb, $H_2$, toluene; (d) $CBr_4$, $PPh_3$, $CH_2Cl_2$, –70 °C; (e) NaH, DMF, 3,3-dimethylbut-1-yn-3-ol, 20 h; (f) $Co_2(CO)_8$, PE, 1.5 h.

resulting.[11] Based on this, we felt that pursuing routes to Japanese Hop Ether **1** through both the *Z*- and *E*-isomers of enyne complex **7** would allow a timely evaluation of stereochemistry retention under milder methods of P–K reaction promotion, such as those employed with amine *N*-oxides.[7]

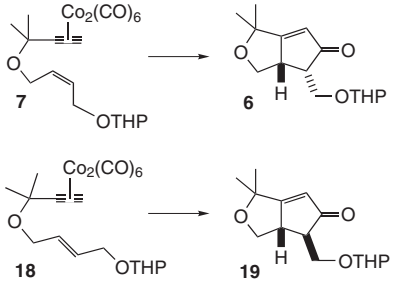
To begin with, propargyl alcohol **11** was converted to the THP-protected derivative **12** in 99% yield (Scheme 3). Deprotonation of **12**, using *n*-BuLi, followed by reaction with solid *para*-formaldehyde in an ultrasound cleaning bath, afforded the mono-protected ynediol **10** in 92% yield. For the *Z*-olefin series, alkene **9** was obtained in 100% yield by hydrogenation over Lindlar's catalyst and this allylic alcohol was converted to the bromide **13** in 85% yield by treatment with $CBr_4$ and $PPh_3$. Allyl propargyl ether **14** was then formed in 85% yield, by the action of the alkoxide anion of dimethylpropargyl alcohol **8** on bromide **13**. Finally, complexation with octacarbonyldicobalt occurred uneventfully to give **7** in 95% yield.

Turning to the *E*-alkene series, ynediol **10** was reduced using Red-Al® to give (*E*)-**15** in 69% yield (Scheme 4). This mono-protected enediol was then converted, in steps of 89% and 93% yield, to the (*E*)-allylpropargyl ether **17**, using the same chemistry as for the *Z*-isomer. Likewise, *E*-enyne complex **18** was obtained in an 87% yield.




**Scheme 4** *Reagents and conditions*: (a) Red-Al®, THF, 0 °C, 1.5 h; (b) $CBr_4$, $PPh_3$, $CH_2Cl_2$, –70 °C; (c) NaH, DMF, 3,3-dimethylbut-1-yn-3-ol, 20 h; (d) $Co_2(CO)_8$, PE, 2 h.

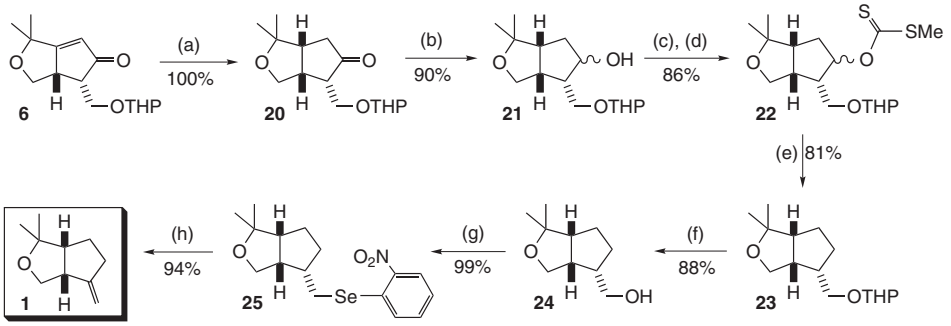
With both cobalt complexes in hand, the key P–K cyclisations were examined, using amine *N*-oxide promotion at room temperature (Scheme 5). Using a variety of *N*-oxide-based conditions, all cyclisations were complete in, at the most, a few hours and proceeded in good yields. Most notably, use of TMANO·$2H_2O$ in acetone under air with the *Z*-enyne complex **7** led to an excellent 90% yield of product **6**. The optimum yield with the *E*-enyne complex **18** was achieved when TMANO·$2H_2O$ was, again, employed as promoter, this time with a mixture of toluene and MeOH as solvent, to deliver **19** in 78% yield. Whilst, use of brucine *N*-oxide[12] did not lead to the optimum yield with either substrate, the rapid nature of the cyclisations with this promoter is worthy of note. Additionally, in terms of the potential stereoselectivity discussed within the introductory section, it was gratifying and notable that, by using such mild reaction protocols, the alkene stereochemistry was retained in the product cyclopentenone in both cases.[13]




| Reaction conditions | 7 → 6 Time | 7 → 6 Yield (%) | 18 → 19 Time | 18 → 19 Yield (%) |
|---|---|---|---|---|
| NMO·$H_2O$, $CH_2Cl_2$, THF | 1 h | 65 | 30 min | 65 |
| TMANO·$2H_2O$, acetone | 3 h | 90 | 1 h | 66 |
| TMANO·$2H_2O$, toluene, MeOH | - | - | 4 h | 78 |
| Brucine *N*-oxide acetone | < 1 min | 70 | < 1 min | 66 |

**Scheme 5**

Having secured quantities of both isomeric cyclopentenones, it was decided to continue the synthesis with the *cis*-product **6**. Thus, bicyclic enone **6** was reduced to ketone **20** in 100% yield by hydrogenation at 3 atm over Pd/C (Scheme 6). The carbonyl function in **20** was then reduced to the alcohol using $LiAlH_4$, giving a 90% yield of **21** as a 10:1 mixture of diastereomers. Separation of these diastereomers was deemed unnecessary since the alkanol stereocentre was to be removed in the following step. In this respect, Barton–McCombie deoxygenation[14] of alcohol **21** proceeded in 70% yield over the two steps of xanthate formation and reduction to cyclic ether **23**. Removal of the




**Scheme 6** *Reagents and conditions*: (a) 10% Pd on C, $H_2$ (3 atm), toluene, 75 min; (b) $LiAlH_4$, $Et_2O$, –78 °C, 10 min; (c) *n*-BuLi, $CS_2$, THF, 3 h; (d) MeI; (e) *n*-$Bu_3SnH$, AIBN, $C_6H_6$, reflux, 20 h; (f) PPTS, EtOH, 50 °C, 16 h; (g) 2-nitrophenylselenocyanate, $PPh_3$, THF, 2.5 h; (h) $H_2O_2$ (67%), THF, 5.5 h.

THP group, to give alcohol **24**, was effected using PPTS in EtOH and proceeded in 88% yield. The transformation of intermediate **24** into Japanese Hop Ether **1** makes use of selenyl oxides as intermediates in the conversion of primary alcohols to alkenes. This methodology, first developed by Sharpless and co-workers,[15] has since been applied to the formation of exocyclic alkenes by Grieco.[16] Thus, the alcohol functionality in **24** was directly replaced by treatment with *o*-nitrophenylselenyl cyanate and tri-*n*-butylphosphine, delivering the organoselenium species **25** in 99% yield. Simply treating this compound with $H_2O_2$ allowed the in situ formation of the selenoxide, which underwent elimination directly to give Japanese Hop Ether **1** in an excellent 94% yield. Pleasingly, this material displayed spectral characteristics, which were in agreement with those published following the isolation of this natural monoterpene.[1,4,5]

In conclusion, the natural product Japanese Hop Ether **1** has now been successfully synthesised in 14 steps, using an intramolecular P–K reaction as the key transformation. The overall optimum yield of 29% represents an average yield of 92% per step. Importantly, it has also been shown that, by using mild *N*-oxide methodology, the stereochemistry of the alkenes used in the intramolecular P–K reaction was retained in the cyclised product, for both the *Z*- and *E*-alkenes used.

**Pauson–Khand Cyclisation; Typical Procedure**

The cobalt complex **7** (4.15 g, 7.91 mmol) was dissolved in anhyd acetone (150 mL), and TMANO·$2H_2O$ (5.63 g, 50.65 mmol) was added in one portion. The reaction was stirred under an air atmosphere for 3 h, after which time the reaction mixture was filtered through a pad of silica, and the residues were washed with $Et_2O$. The solvents were removed in vacuo and the crude product was purified by flash column chromatography ($Et_2O$–PE, 5:1) to give 1,3,3a,4-tetrahydro-1,1-dimethyl-4-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-5*H*-cyclopenta[*c*]furan-5-one (**6**; 1.89 g, 7.10 mmol, 90% yield) exclusively as the *cis*-isomer.

IR ($CH_2Cl_2$): 3051, 2978, 2946, 2896, 2873, 1703, 1641, 1134, 1123, 1034, 1005 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.45 (s, 3 H), 1.39–1.75 (m, 6 H), 2.90–2.97 (m, 1 H), 3.36–3.58 (m, 3.5 H), 3.62–3.82 (m, 2 H), 3.91–3.95 (m, 0.5 H), 4.14–4.19 (m, 1 H), 4.46–4.56 (m, 1 H), 5.88–5.92 (m, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.5, 25.4, 26.5, 27.4, 30.6, 30.7, 48.6, 50.1, 50.6, 62.1, 62.5, 65.4, 66.3, 66.4, 78.0, 98.3, 99.8, 121.9, 122.0, 192.5, 209.4.

HMRS–EI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_4$: 267.15963; found: 267.15789.

**Cyclopentenone 19**

IR ($CH_2Cl_2$): 2981, 2951, 2874, 1723, 1640, 1461, 1444, 1385, 1368, 1327, 1245, 1187, 1158, 1140, 1076, 1036, 1006, 977, 942, 919, 872 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.44 (s, 3 H), 1.39–1.75 (m, 6 H), 2.42–2.47 (m, 1 H), 3.33–3.51 (m, 3 H), 3.65–3.71 (m, 1 H), 3.74–3.82 (m, 1 H), 3.93–4.03 (m, 1 H), 4.26–4.30 (m, 1 H), 4.54–4.59 (m, 1 H), 5.88–5.91 (m, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 19.3, 19.8, 25.5, 26.4, 27.4, 30.6, 30.7, 49.2, 49.8, 53.1, 53.4, 62.0, 62.8, 65.0, 65.2, 69.82, 69.84, 77.9, 98.6, 99.8, 122.05, 122.09, 190.5, 190.7, 208.3, 208.5.

HMRS–EI: *m/z* $[M]^+$ calcd for $C_{15}H_{22}O_4$: 266.1518; found: 267.1509.

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(13) The identity of each cyclopentenone product was initially elucidated by $^1$H NMR. In particular, the non-olefinic proton α to the carbonyl in product **19** (from *E*-enyne **18**), would be in an *endo*-position and, hence, would be more shielded; this proton appears as a multiplet at δ = 2.42–2.47 ppm. The equivalent non-olefinic proton α to the carbonyl in product **6** (from *Z*-enyne **7**), would be in an *exo*-position and, hence, would be more deshielded; this proton appears as a multiplet at δ = 2.90–2.97 ppm.
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