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Total Synthesis of (±)-Waihoensene

Hongsoo Lee, Taek Kang, and Hee-Yoon Lee*[a]

Dedicated to Professor Paul A. Wender on the occasion of his 70th birthday.

Abstract: The first total synthesis of waihoensene, a tetracyclic diterpene containing an angular triquinane and a six-membered ring, with four contiguous quaternary carbon atoms, was achieved through the tandem cycloaddition reaction of an allenyl diazo substrate containing a six-membered ring via trimethylenemethane (TMM) diyl intermediate.

A tetracyclic diterpene, waihoensene (**1**) was isolated from the New Zealand podocarp, *Podocarpus totara var waihoensis* by Rex T. Weavers and co-workers in 1997 (Figure 1).[1a] It is closely related to compounds **3**, which are acid-induced rearrangement products[1] of laurenene (**2**), the only natural product with C-C fenestrane ring structure.[2] Waihoensene is presumed to be the product derived from the extended biosynthetic pathway of laurenene and has as challenging structure as laurenene with four contiguous quaternary carbon centres of highly congested tetracyclic structure. Thus, waihoensene was recognized in a recent review[3] of structurally challenging natural products against total synthesis as one of the natural products waiting for creative synthetic strategies to conquer the total synthesis, and has not been explored by the synthetic organic chemistry community much.[4]

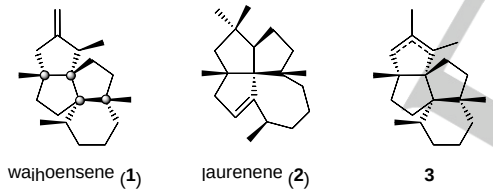
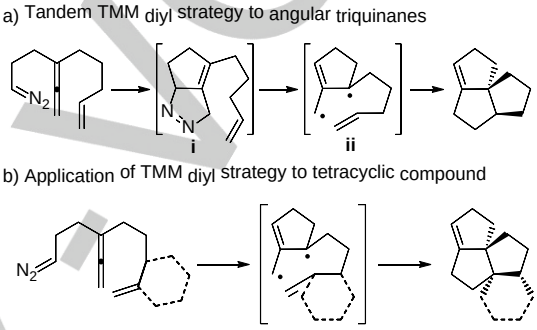


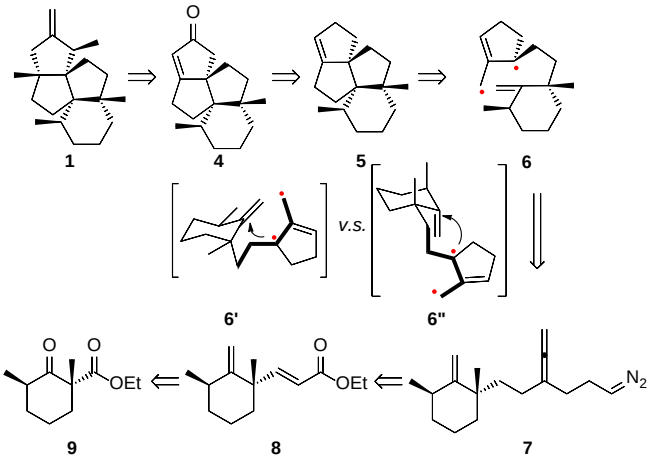
Figure 1. Natural products and derivatives from podocarp

This challenging structural feature of waihoensene makes it an excellent target for the tandem cycloaddition strategy via trimethylenemethane (TMM) diyl intermediate, which we have developed for synthesis of polyquinanes from linear substrates and have applied to the total synthesis of various natural products with complex and congested structural features.[5] In the tandem synthetic methodology, the skeleton of angular triquinane is assembled through [2+3] cycloaddition between olefin and TMM diyl (**ii**) generated from nitrogen extrusion of tetrahydropyrazole (**i**) formed by [2+3] cycloaddition of diazo group and allene (Scheme 1). If we place a six-membered ring at the proper location in the starting material, we can set a test ground to construct tetracyclic skeleton of waihoensene in one-pot. Herein, we report the first total synthesis of waihoensene where TMM diyl mediated tandem cycloaddition reaction constructs the tetracyclic ring skeleton of waihoensene.



Scheme 1. Tandem cycloaddition strategy via TMM diyl to polycyclics.

Recently, we have successfully applied the synthetic strategy to the first total synthesis of (-)-crinipellin A[5k], a tetraquinane compound. In the case of the synthesis of crinipellin A, the anticipated tetraquinane skeleton was obtained stereoselectively owing to the fact that the cis-fused ring system was highly favoured due to strain at the ring junctions. On the other hand, for construction of the core skeleton of waihoensene, presence of the six-membered ring does not guarantee the regiochemical and stereochemical outcome of the tandem cycloaddition reaction as it could form isomers including the [3.2.1]bicyclic containing tetracyclic structure or the undesired *trans*-hydrindane structure.



Scheme 2. Retrosynthetic analysis for waihoensene.

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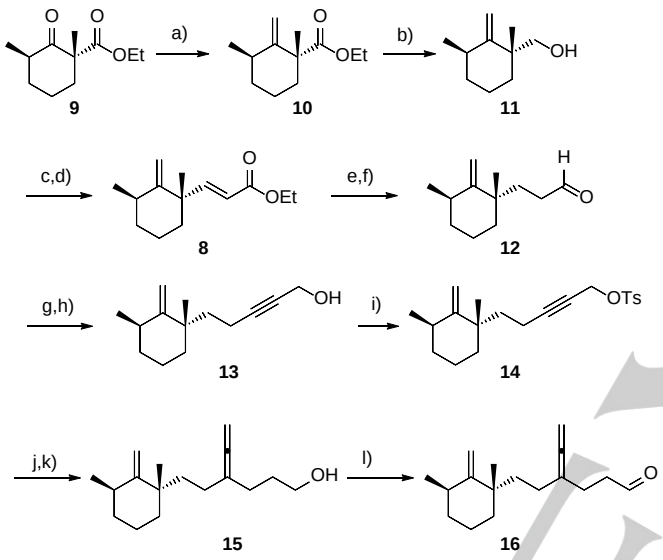
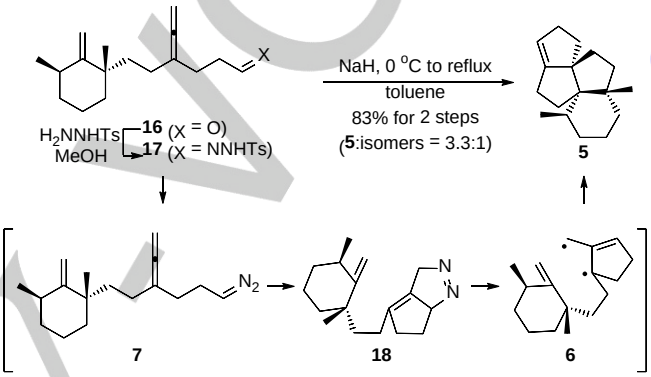
We envisioned that waihoensene **1** could be derived from enone compound **4** that could be obtained through allylic oxidation of the corresponding tetracyclic compound **5** The tetracyclic compound **5** could be assembled from the allenyl diazo compound **7** through the tandem cycloaddition reaction via TMM diyl intermediate **6** (Scheme 2). Examination of the transition state model of the reaction intermediate **6**' between TMM diyl and olefin, hinted that the desired tetracyclic compound containing a *cis*-hydrindane would be the major product as the transition state **6'** appeared to be more stable than **6"** by avoiding 1,3-diaxial interaction of two methyl groups. The substrate **7** would be readily obtained from the α,β-unsaturated ester **8** that can be obtained from the keto-ester **9**.



Scheme 3. Reagents and conditions: a) Zn, $TiCl_4$, CH_2I_2, THF, DCM, 0 °C to r.t., 60%; b) LAH, Et_2O, 0 °C to r.t., 91%; c) $(COCl)_2$, DMSO, TEA, DCM, -78 °C to r.t.; d) $EtO_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 93% for 2 steps; e) Mg, MeOH, r.t., 99%; f) DIBAL, DCM, -78 °C to r.t., 97%; g) CBr_4, PPh_3, DCM, 0 °C, 93%; h) n-BuLi, $(CH_2O)n$, THF, -78 °C to r.t., 91%; i) TsCl, KOH, Et_2O, 0 °C to r.t., 94%; j) Mg, 1,2-dibromoethane, $Br(CH_2)_3OTBS$, CuCN, THF, 0 °C; k) TBAF, THF, 0 °C to r.t., 95% for 2 steps; l) $(COCl)_2$, DMSO, TEA, DCM, -78 °C to r.t., 94%. LAH = lithium aluminium hydride, DMSO = dimethyl sulfoxide, TEA = triethylamine, DIBAL = diisobutylaluminum hydride, TsCl = toluenesulfonyl chloride, TBAF = tetrabutyl ammonium fluoride.

The total synthesis started with the known racemic keto-ester compound **9** that was readily prepared from commercially available ethyl 2-cyclohexanonecarboxylate through a 2-step literature sequence.[6] Conversion of the ketone in **9** into the exo-olefin of **10** was achieved using Lombardo-Takai olefination[7] as Wittig reaction was unsuccessful and it was known that the titanium mediated olefination well tolerated steric hindrance around carbonyl groups (Scheme 3). Another advantage of the reaction was the neutral nature of the reaction condition that prevented a possible isomerization of the methyl group of **9**.[8] Reduction of **10** with lithium aluminium hydride produced the alcohol **11**. Swern's oxidation of **11** followed by Horner-Wadsworth-Emmons olefination gave the α,β-unsaturated ester **8**. **8** was converted to the aldehyde **12** through the selective reduction of the conjugated double bond using magnesium in methanol[9] followed by diisobutylaluminum hydride mediated partial reduction at -78 °C. Preparation of the propargylic alcohol **13** was achieved through the Corey-Fuchs procedure,[10] 1,1-dibromoolefination followed by the *in situ* hydroxymethylation of the corresponding alkynyl anion. Tosylation of **13** with p-toluenesulfonyl chloride and potassium hydroxide furnished the activated propargylic alcohol **14**. **14** was converted to the allenyl alcohol **15** by copper(I) catalysed S_N2' reaction with the Grignard reagent generated from 3-bromopropoxy-tert-butyldimethylsilane followed by desilylation with TBAF and oxidized to the aldehyde **16** using Swern's oxidation condition.



Scheme 4. Synthesis of the tetracyclic compound **5**.

The hydrazone **17** which is the precursor for **7** that would spontaneously undergo the tandem cycloaddition reaction, was obtained by *p*-toluenesulfonyl hydrazide treatment, and used for the tandem cycloaddition reaction immediately due to its instability (Scheme 4). Heating the sodium salt of the hydrazone initiated the formation of the tetracyclic products by converting **17** into diazo compound **7**[11] (Scheme 4). Subsequent intramolecular [2+3] cycloaddition reaction of the diazo group with the allene moiety provided methylenepyrazole intermediate **18**[12] that immediately lost nitrogen molecule to generate the TMM diyl intermediate **6**.[13] The highly reactive diyl intermediate **6** underwent final [2+3] cycloaddition reaction with the olefin despite of high steric congestion during the cycloaddition reaction to yield the tetracyclic compounds. Fortunately, the desired tetracyclic product **5** was obtained as the major product as an inseparable mixture with minor isomeric products. Based on the signature peaks at the olefinic region in NMR spectrum, the minor products were presumed to be stereoisomer **5'** along with regioisomers **5e** and/or **5'e** (Scheme 5). Though the formation of **5** was not exclusive as in the case of tetraquinane formation, the transition state conformation **6'** for the formation of **5** was presumed to be highly favoured over other transition states as anticipated in the scheme 2. Structure of the major isomer was firmly confirmed after purification at the enone (**4**) or tosylated dihydroxide (**20**) stage.

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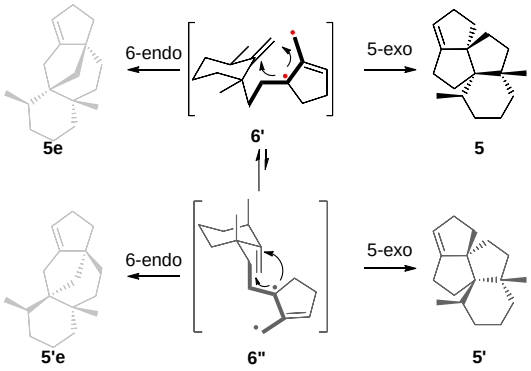
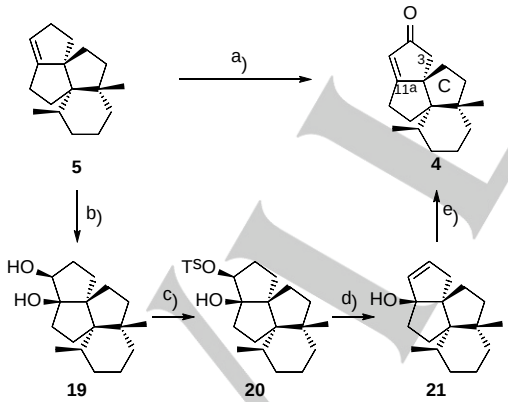


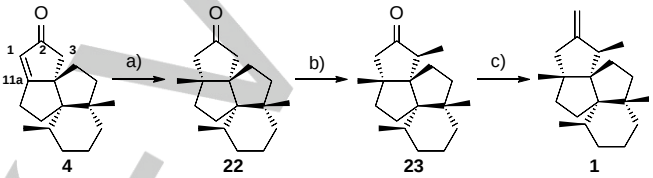
Scheme 5. Possible products from transition states of TMM diyls.

Successful construction of the tetracyclic structure for waihoensene along with three contiguous quaternary centers set up the final stage of the synthesis that required introduction of one methyl group for the last quaternary center, stereoselective introduction of a methyl group, and regioselective introduction of a methylene group. For those reactions, conversion of **5** into the enone **4**, had to be preceded. First, we tried allylic oxidation of **5** with PDC and TBHP in benzene, the oxidation condition used in the synthesis of crinipellin A.[5k] The oxidation reaction was quite daunting as the desired product **4** was obtained along with other oxidation products in low yield (<22%) and was separated only after the formation of **22**. We attempted several other allylic oxidation conditions[14] but the outcome was not any better. Alternatively, we were able to obtain **4** through 4-step sequence (Scheme 5). Dihydroxylation using OsO_4 followed by the selective tosylation of the secondary alcohol of **19** produced **20** selectively. Then, **20** was converted to the allylic alcohol **21** by elimination reaction with DBU in DMF at 115 °C, and subsequent oxidative rearrangement produced **4**.



Scheme 6. Reagents and conditions: a) PDC, celite, TBHP, DCM, 0 °C; b) OsO_4, NMO, acetone, water, 0 °C to r.t.; c) TsCl, DMAP, DCM, r.t., 39% for 2 steps; d) DBU, DMF, 115 °C, 50%; e) PDC, DCM, r.t., 68%. PDC = pyridinium dichromate, TBHP = 1,1-dimethylethyl hydroperoxide, NMO = N-methylmorpholine N-oxide, DMAP = N,N-dimethylpyridin-4-amine, DBU = 1,8-diazabicycloundec-7-ene, DMF = N,N-dimethylformamide.

With the enone **4** in hand, overcoming the rigidity and steric congestion of **4** for introduction of two methyl groups and a methylene group was crucial for the successful completion of the total synthesis. The first step in the original plan, introduction of the methyl group at the **C-3** of **4** using standard enolate alkylation procedures or Noyori's protocol[15] for alkylation with dimethylzinc as the catalyst did not yield any product, presumably due to the rigidity of the ring skeleton and the steric hindrance between the **H-3** and the C-ring of **4**. We decided to compromise the original plan by reversing the sequence of methylations. The methyl group at the ring junction (**C-11a**) was introduced first in a hope that alteration of the carbonyl conformation would allow the enolate alkylation reaction to proceed in the second step, even though reversed methylation sequence could pose a regioselectivity issue during the second methylation step at the **C-3**.



Scheme 7. Reagents and conditions: a) CuCN, MeLi, BF_3·Et_2O, THF, -78 °C to -55 °C, 65%; b) LiHMDS, MeI, THF, -78 °C to r.t., 75%(81% brsm); c) Cp_2TiMe_2(Petasis reagent), toluene, r.t. to 70 °C, 32%. LiHMDS = lithium bis(trimethylsilyl)amide.

Methylation at **C-11a** of **4** with ordinary cuprate($LiCu(CH_3)_2$) again failed to yield the product because of the steric hindrance imposed by the C-ring. Gratifyingly, treatment of the enone with higher order cuprate in presence of boron trifluoride etherate delivered the methyl group to produce the desired product **22** (Scheme 6).[16] Fortuitously, **22** was obtained as a solid form and single-crystal X-ray diffraction of crystalized **22** established the relative stereochemistry and the atom connectivity of the congested tetracyclic structure (Figure 2). Careful analysis of the crystal structure[17] indicated that bases and electrophiles couldn't approach from α-face of **22** due to steric hindrance by the **C-15** of **22** and the concave feature of the structure, therefore methylation from β-face should be preferable. Analysis of the dihedral angles in the X-ray crystal structure also revealed that the **H-3a** of **22** was pseudo-axial while **H-1a** was pseudo equatorial. Thus the regioselective enolate formation toward the **C-3** position would be possible, and we were convinced that the desired compound **23** would be formed selectively among possible regio- and stereo-isomeric products from the enolate methylation of **22**.

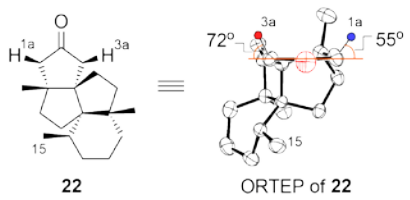


Figure 2. ORTEP of **22**.

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As anticipated, a typical alkylation condition of a ketone enolate using LiHMDS and iodomethane afforded the desired methylated product **23** without any other isomers. The final introduction of methylene group using regular Wittig type olefination reaction did not proceed at all due to the steric congestion of **23** and methylation with MeMgBr followed by dehydration produced undesired olefin isomers including **3**. Finally, the target natural product **1** was obtained by methylenation of **23** using the Petasis reagent.[18] Comparison of the spectroscopic data of the final product **1** and the reported data for waihoensene confirmed the structural integrity of both compounds.

In summary, the first total synthesis of the complex diterpene waihoensene was completed in 18 steps starting from **9**. The key transformation was intramolecular TMM diyl mediated tandem cycloaddition reaction which served to establish the tetracyclic core structure of waihoensene with three contiguous quaternary carbon centres at once. Since enantiomerically pure ketoester **9** is known in the literature,[19] the current total synthesis could be easily extended to the asymmetric total synthesis of waihoensene and would confirm the absolute stereochemistry of waihoensene as well as laurenene.

Keywords: natural product • tandem cycloaddition reaction • Trimethylenemethane diyl • total synthesis • waihoensene

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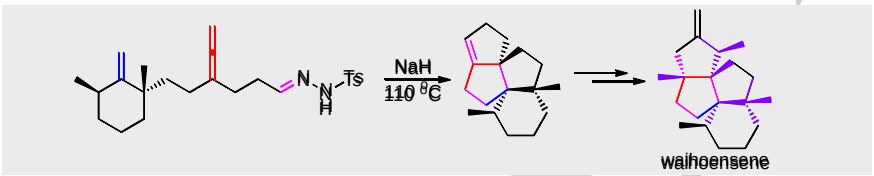

*Dr. Hongsoo Lee, Dr. Taek Kang and Prof. Dr. Hee-Yoon Lee**

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Total Synthesis of (±)-Waihoensene

Total synthesis of waihoensene, a tetracyclic diterpene natural product with four contiguous quaternary carbon centres was achieved through the tandem cycloaddition reaction of an allenyl diazo substrate via trimethylenemethane (TMM) intermediate.