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Asymmetric Total Synthesis of (+)-Waihoensene

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Asymmetric Total Synthesis of (+)-Waihoensene

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Supporting Information Placeholder

ABSTRACT: The asymmetric total synthesis of (+)waihoensene, which has a cis-fused [6,5,5,5] tetracyclic core bearing an angular triguinane, a *cis*-fused six-membered ring, and four contiguous quaternary carbon atoms, was achieved through a sequence of chemical reactions in a stereochemically well-defined manner. The total synthesis features: 1) Cucatalyzed asymmetric conjugated 1,4-addition; 2) diastereoselective Conia-ene reaction; 3) diastereoselective intramolecular Pauson-Khand reaction; 4) Ni-catalyzed diastereoselective conjugated 1,4-addition; and 5) radicalinitiated intramolecular hydrogen atom transfer (HAT). experiments and density functional Control theory calculations support the proposed HAT process.

Polyquinanes constitute an important class of carbocyclic frameworks containing fused 5-membered rings (Figure 1) and are found in various natural products, such as terpenoids and steroids.¹ In 1997, Weavers and co-workers isolated (+)-waihoensene (1) from the New Zealand podocarp, *Podocarpus totara var waihoensis*.² Structurally, 1 contains a highly congested and *cis*-fused tetracyclic core decorated with six contiguous stereogenic centers, among them four are contiguous all-carbon quaternary carbon atoms (C3a, C5a, C9a and C11a). Thus, 1 was widely regarded as a challenging target for total synthesis.³

Given its structural complexity, **1** has been a focus of the synthetic community for many years.⁴ In 2017, Lee and co-workers published an impressive synthesis of (\pm) -waihoensene for the first time in 18 steps, featuring a tandem [2+3] cycloaddition to construct the BCD tricyclic ring with two contiguous quaternary stereogenic centers⁵ (Figure 1a).

We recently became interested in the total synthesis of complex natural products bearing all-carbon quaternary stereogenic centers,⁶ and the total synthesis of **1** was a particular challenge involving such a structure.⁷ Herein, we report our recent contribution for the asymmetric total synthesis of **1** in 15 steps with 3.8% overall yield. The cornerstone of our plan is the recognition of structural and stereochemical relationships between substrates **D**, **E** and **F** and their corresponding products **E**, **F** and **G**, which allowed us to construct the key intermediates **E**, **F** and **G** in a highly diastereoselective manner.

As shown in Figure 1b, the initial chiral quaternary stereogenic center at C5a in diyne **D** could be installed via a Cu-catalyzed

asymmetric conjugate addition⁸ of enone **C**. From inspection of the favorable transition state **TS**_{**D**-E} and the 3D structure of enyne **E** (see **E**' in Figure 1b), two of the three requisite quaternary stereogenic centers at C9a and C3a in the core of angular triquinane⁹ **F** could be constructed diastereoselectively by a sequence of Conia-ene type reaction¹⁰ of diyne **D** and intramolecular Pauson-Khand reaction¹¹ of enyne **E**. According to the results reported in Lee's total synthesis of waihoensene (1),⁵ one of the four requisites quaternary stereogenic centers at C11a in intermediate **G** could be build up via a cuprate-mediated conjugated addition reaction. Thus, the asymmetric total synthesis of (+)-waihoensene (1) could be accomplished upon diastereoselective saturation of its C9–C15 double bond in **G**.



Figure 1: Total synthesis of (+)-waihoensene (1).

The total synthesis began with developing an asymmetric approach for enantioselective synthesis of diyne 7. Initially, we developed a six-step approach to prepare 7 in a racemic form (see

SI for details). We then decided to adopt Alexakis' strategy¹² for the asymmetric synthesis of 7 (Scheme 1). Enone **2** was reacted with the Grignard reagent to afford **3**.^{8c} and then the C5a stereogenic center in **4** was installed from **3** in a 61% overall yield, using the method of Alexadis¹². Allylation of enone **4** via Sakurai reaction,¹³ and subsequent ozonolysis¹⁴ of olefin **5** afforded aldehyde **6** in a 58% yield over the two steps. Chiral diyne **7** was then obtained in 72% yield by reaction of aldehyde **6** with Ohira-Bestmann reagent,¹⁵ accompanied by *in situ* TMS-desilylation.

Scheme 1. Asymmetric synthesis of diyne 7.



^aReagents and conditions: (a) Grignard (2.0 equiv), THF, 0 °C to RT, 12 h, 98%; (b) CuTc (5 mol%), L (10 mol%), Me₃Al (2.0 equiv), Et₂O, -30 °C, overnight; then "BuOCH₂NEt₂ (2.5 equiv), RT, 3 h; (c) mCPBA (1.5 equiv), DCM, RT, 1 h, 61% for 2 steps, 91% *ee*; (d) Allyltrimethylsilane (1.5 equiv), BF₃•Et₂O (1.1 equiv), DCM, -78 °C to RT, 30 min, 89%; (e) O₃ (1 atm.), DCM, -78 °C, 5 min, then PPh₃ (1.0 equiv), RT, overnight, 65%; (f) Ohira-Bestmann reagent (1.3 equiv), K₂CO₃ (2.3 equiv), MeOH, 0 °C to RT, 3 h, 72%. CuTc = Copper(I) thiophene-2-carboxylate; mCPBA = 3-chloroperoxybenzoic acid; Ohira-Bestmann reagent = dimethyl (acetyldiazomethyl)phosphonate; DCM = dichloromethane; THF = tetrahydrofuran.

With a streamlined synthesis of diyne 7 in hand, we turned our attention to the synthesis of diketone 10 bearing the four contiguous quaternary stereogenic centers (Scheme 2). The sequence began with preparation of envne 8, which was diastereoselectively prepared in 83% yield as a single diastereomer via a Conia-ene type cyclization by treatment of 7 with a catalytic amount of 'BuOK.10f We envisaged that the envne 8, which has Thorpe-Ingold assistance,¹⁶ could be a good substrate for the proposed Pauson-Khand (PK) reaction to form the 6-5-5-5 tetracyclic compound 9 bearing an angular triquinane core with three contiguous quaternary chiral centers. To this end, we initially profiled several typical PK reaction conditions, such as Co₂(CO)₈-mediated PK¹⁷ reaction in the presence of trimethylamine N-oxide (TMANO),¹⁸ methyl morpholine N-oxide (NMO)¹⁹ and tetramethyl thiourea (TMTU),²⁰ as well as other transition metal-catalyzed PK reaction, such as PdCl₂/TMTU,²¹ and [Rh(CO)₂Cl]₂.²² However, in most cases, the desired product 9 was only isolated in 22-38% yield (see SI for details). We later found out that 9 could be obtained in 59% yield in 93% ee when the reaction was carried out in the presence of N-oxide $(N_2O)^{23}$ in dichloroethane (DCE) at 80 °C for 20 h. The structure of enone 9 was unambiguously confirmed by X-ray crystallo-graphic analysis. Finally, a Ni-catalyzed methylation²⁴ of 9 lead to the formation of diketone **10** in 81% yield as a single diastereoisomer.

After the diastereoselective installation of the angular triquinane motif, the remaining challenge was regio- and diastereo-selective methylation at the C-3 and C-9 positions. As indicated by Snyder,^{7b} due to its lower steric hindrance, the C2 ketone group in **10** could be selectively protected as its corresponding mono-ketal in **11**, which could then undergo a Wittig reaction to afford **12** bearing an exocyclic olefin. To prove this theory, treatment of **10** with 2-ethyl-2-methyl-1,3-dioxolane in the presence of a catalytic amount of TsOH led to **11** in 91% yield, which then underwent a Wittig reaction, followed by deketalization to give ketone **12** in 69% yield in two steps.

However, the diastereoselective hydrogenation of the exocyclic olefin in **12** was found to be extremely difficult, and commonly used transition metal catalysts (such as Pd/C, PtO_2 ,²⁵ Rh(PPh)₃Cl²⁶) afforded the product bearing the opposite stereochemistry of C9 in **13**, as the inherent concave-face of the *exo*-cyclic double bond in **12** is more sterically hindered than its convex-face. As a result, the catalyst would approach the double bond from its convex-face, leading to the product bearing the incorrect stereochemistry.

Recently, hydrogen atom transfer (HAT) reactions have emerged as a powerful method for complex natural product total synthesis.²⁷ We conjectured that the newly formed C9 carbon radical in **13a**, derived from a radical-mediated reductive reaction from **12**, could abstract a proton through an intramolecular HAT from the C3, due to the close proximity (2.4 Å) of C3 and C9 and their position next to the C2 carbonyl group. As a result, the diastereoselective saturation of the C9–C15 double bond might be achieved (scheme 2).

Scheme 2. Total synthesis of (+)-waihoensene (1).



^aReagents and conditions: (a) 'BuOK (0.5 equiv), DMSO, RT, 4 h, 83%. (b) $Co_2(CO)_8$, N_2O (1 atm), DCE, 80 °C, 22h, 59%, 93% *ee*; (c) Ni(acac)_2 (10 mol%), LiBr (3.0 equiv), Me_2Zn (5.0 equiv), Et_2O, 0 °C to RT, 48 h, 81%; (d) 2-ethyl-2-methyl-3-dioxolane (5.0 equiv), PTSA•H₂O (5 mol%), Et₂O, RT, 1 h, 91% (brsm 99%); (e) Ph₃P⁺MeBr (5.0 quiv), 'BuOK (4.9 equiv), toluene, reflux, 1 h; then 15 (1.0 equiv), toluene, reflux, 19 h, 78% (brsm 90%); (f) HCl(1 M, 2.6 equiv), THF, RT, overnight, 89%. (g) Fe(acac)₃ (0.2 equiv), PhSiH₃ (1.0 equiv), EtOH, 60 °C, 75%. (h) lithium bis(trimethylsilyl)amide (5.0 equiv), 'BuOK (4.9 equiv), toluene, reflux, 1 h; then 19 (1.0 equiv), MeI (8.5 equiv), toluene, reflux, 1 h; then 19 (1.0 equiv), BuOK (4.9 equiv), toluene, reflux, 1 h; then 19 (1.0 equiv), BuOK (4.9 equiv), toluene, reflux, 1 h; then 19 (1.0 equiv), BuOK (4.9 equiv), toluene, reflux, 1 h; 90%. Ni(acac)₂ = bis(2,4-pentanediono)nickel; PTSA•H₂O = *p*-toluenesulfonic acid monohydrate; DMSO = dimethyl sulfoxide; DCE = dichloroethane.

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With this chemistry in mind, we first applied Shenvi's protocol for the treatment of **12** with catalyst $Mn(dpm)_3$ in the presence of PhSiH₃ and TBHP.²⁸ As expected, **13** was obtained in 67% yield as the major isomer, together with a 10% yield of its diastereoisomer. We then tested Baran's conditions²⁹ by using Fe(acac)₃ as a catalyst in the presence of PhSiH₃. To our delight, **13** was obtained in 75% yield as a single diastereoisomer, demonstrating the power of the HAT reaction.

To complete the total synthesis of (+)-waihoensene, we adopted Lee's protocol⁵ to install the final methyl group. Ketone **13** was treated with LiHMDS, and the resultant enolate was reacted with methyl iodide to give **14** in 90% yield. Upon further treatment of **14** with methylene triphenylphosphonium ylide in refluxing toluene, product **1** was obtained in 90% yield on a 100 mg scale. The ¹H and ¹³C NMR spectra and specific rotation of the synthesized waihoensene (**1**) were in agreement with those reported in the literature^{2,5} ([α]23 D = +49.33, c = 0.15 in CHCl₃; lit. [α]22 D = +43.9, c = 0.09 in CHCl₃), establishing the absolute stereochemistry of (+)-waihoensene (**1**) for the first time.

With regard to the critical role of HAT in our total synthesis, we then carried deuterium experiments and control experiment (scheme 3). Accordingly, when 12 was treated with a catalytic amount of Fe(acac)₃ in the presence of PhSiD₃ (1.0 equiv.) in EtOH at 60 °C for 1 h, deuterated ketone 15 was obtained in 75% yield as a single diastereoisomer. When the same reaction was carried out in the presence of deuterated ethanol (CD₃CD₂OD) at 60 °C for 1 h, product 16 was obtained in 75% yield and deuterium atoms were found in both C3 (29% D) and C1 (17% D) (D/H \approx 1/3 in total) by NMR spectroscopic analysis. This indicated that both [1,4] and [1,5]-HAT processes by abstractions of protons from both C1 and C3 carbons could occur in this radical-based reduction (when we treated 13 with condition b in scheme 3, no deuterium atoms were found in the product, see SI for details). We also envisaged that the ketal 17, in which the protons at C1 and C3 position are less activated compared with ketone 12, would afford different results. Indeed, when 17 was subjected to the identical conditions listed in Scheme 3b. 13-iso bearing the opposite stereochemistry at C9 was obtained in 70% yield, together with a 9% yield of 13.

Scheme 3. Deuterium labeling studies and control experiment.

a. Deuterium labeling studies a) Fe(acac)₃ (0.2 equiv.) PhSiD₃ (1.0 equiv.) EtOH, 60 °C (75%) b) Fe(acac)₃ (0.2 equiv.) PhSiH₃ (1.0 equiv.) CD₃CD₂OD, 60 °C (75%) 12 b. Control experiment c) Fe(acac)₃ PhSiH₃ d) HCI (79%, 2 steps) 13 (9%) 13-iso (70%) (dr = 7.7 : 1)

Based on the deuterium and control experiments, two difference reaction pathways might account for the observed results, which are associated with the chair-like conformation **13a** and boat-like conformation **13b** (Figure 2). Our mechanistic analysis suggested that HAT processes proceeded through the chair-like transition state **13a** (see SI for details).

In order to acquire a further appreciation for the observed chemistry for the formation of **15** and **16** in Scheme 3, we carried out a density functional theory (DFT) experiment to account for the excellent diastereoselectivity (Figure 2). For the chair-like conformation **13a**, the small difference in the activation energy between 1,4-HAT via a 5-membered transition state **TS1** (the most favored transition state, $\Delta\Delta G^{f} = 0$, for details, see SI) and 1,5-HAT via a 6-membered transition state **TS4** ($\Delta\Delta G^{f} = 1.2$ kcal/mol) accounts for the results of deuterium labeling studies (scheme 3a). For the boat-like conformation **13b**, the energy barriers of both the 1,4-HAT transition state **TS2** ($\Delta\Delta G^{f} = 17.5$ kcal/mol) and 1,5-HAT transition state **TS3** ($\Delta\Delta G^{f} = 24.1$ kcal/mol) are much higher than that via **TS1** and **TS4**, which indicates that **TS2** and **TS3** are not favorable for the formation of **13** from **12**.



Figure 2. Diastereoselective determined transition state calculation in B3LYP-D3/6-31G**//B3LYP-D3/6-311++G** level in EtOH (SMD solvation model).

To account for the formation of **13**-*iso* as the major product from **17** (Scheme 3b), we also carried out a DFT experiment, which indicates that due to the protection of the ketone group in **12**, the resultant ketal **17** might proceed via both an intramolecular HAT reaction and an intermolecular hydrogen-abstraction reaction to afford products **13** and **13**-*iso* (see SI for details).

In summary, the asymmetric total synthesis of (+)-waihoensene has been achieved for the first time in 15 steps and 3.8% overall yield. The key step in this total synthesis was identification of the Fe(acac)₃/PhSiH₃-mediated intramolecular HAT reaction, which enabled the diastereoselective saturation of the exo-cyclic double bond of C9–C15 in 12 via both [1,4]- and [1,5]-HAT processes. The total synthesis also features an enantioselective construction of the angular triquinane core bearing four contagious quaternary stereogenic centers via key steps: 1) a Cu-catalyzed asymmetric conjugate addition; 2) a Conia-ene type reaction; 3) a Co-mediated intramolecular PK reaction; and 4) a Ni-catalyzed alkylation. Application of this synthetic strategy to the total synthesis of other complex natural products is currently underway in our laboratories, and will be reported in due course.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterizations (PDF); X-ray diffraction of compound 9 (CIF), 11 (CIF).

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Notes

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The authors declare no competing financial interest.

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