Diastereoselective Synthesis of *trans*-*anti*-Hydrophenanthrenes via Ti-mediated Radical Cyclization and Total Synthesis of Kamebanin

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**Abstract:** *Ent*-kaurenes consist of an ABC-ring based on a *trans*-*anti*-hydrophenanthrene skeleton and a D ring with an exomethylene. Highly oxygen-functionalized *ent*-kauren-15-ones have promising anti-inflammatory pharmacological activity. In this study, we developed a novel diastereoselective synthesis of *trans*-*anti*-hydrophenanthrenes via a Ti-mediated reductive radical cyclization. We also demonstrated the applicability of this method by developing the first total synthesis of (±)-kamebanin (longest linear sequence; 17 steps, overall yield; 6.5%). Furthermore, this synthesis provided a formal semi-pinacol rearrangement for the construction of the quaternary carbon at C8 and a novel Thorpe-Ziegler type reaction for the construction of the D ring.

Introduction

Plants of the genus *Isodon* have been used as herbal medicine since ancient times owing to its active ingredient *ent*-kaurene diterpenes (Figure 1a).[1] Thus far, more than 600 natural *ent*-kaurenes that have different degrees of oxidation, positions of the oxygen functional groups, *seco*-structures, and glycosides have been isolated from this genus. *Ent*-kaurenes have been extensively studied in medicinal chemistry, and most of them demonstrate antibacterial and antitumor activities. *Ent*-kauren-15-ones such as oridonin, xindongnin A, and kamebakaurin (Figure 1b) inhibit the NF-kB transcription activity.[2] Therefore, structure-activity relationship studies[3] and mechanism elucidation studies[4] on the NF-kB inhibitory activity of *ent*-kauren-15-ones have been widely conducted to identify potential drug candidates for diseases related to NF-kB. Consequently, several total syntheses of *ent*-kauren-15-ones[5] have been reported during the last decade.

However, special attention must be paid to the commonly functionalized positions during the total synthesis of the bioactive, highly oxidized *ent*-kauren-15-ones. Analysis of *ent*-kaurenoids with registered pharmacological activities (1635 compounds) using SciFndern[6] revealed that almost all the compounds are *O*-functionalized at the C7, C14, and C15 methylene groups and half the compounds at the C1 and C6 methylene groups (Figure 1c). Therefore, for easy access to bioactive, highly oxidized *ent*- kauren-15-ones, a new synthetic strategy dedicated to the oxygen functionalization of these positions is required. Ideally, the carbon skeleton should be assembled from oxygen-functionalized, easy-to-prepare substrates rather than introducing oxygen-functional groups into the molecule after constructing the carbon skeleton. In this study, we developed a convergent method for the diastereoselective construction of *trans*-*anti*-hydrophenanthrene skeleton, which is the ABC-ring of *ent*-kaurenes, via Ti-mediated radical cyclization. Moreover, we developed the first total synthesis of (±)-kamebanin,[2a,2b,7] 1a,7a,14b-trihydroxy-*ent*-kauren-15-one, via a formal semi-pinacol rearrangement of a cyanomethylene moiety and a novel Thorpe-Ziegler-type reaction of g-ketonitrile to form the D-ring moiety of *ent*-kaurenes.

**Figure 1.** (a) Chemical structure of *ent*-kaurene. (b) Representative bioactive highly oxidized *ent*-kauren-15-ones. (c) Analysis of the oxygen functionalization position of the pharmacologically active *ent*-kaurenes by SciFindern.

Results and Discussion

Scheme 1a shows our retrosynthesis of highly oxidized *ent*-kauren-15-ones. Owing to the lability of the conjugate *exo*-enone moiety, D-ring formation from **1** should be executed in the last stage of the total synthesis. Therefore, the *trans*-*anti*-hydrophenanthrene **2**, which possesses oxygen functional groups in each ring, would be the most probable intermediate. Generally, *trans*-*anti*-hydrophenanthrenes are synthesized by cationic or radical polyene cyclization[8] in moderate to good yields (Scheme 1b). However, only a few examples[9] of radical polyene cyclization with multi-functionalized substrates that afforded polycyclic compounds in moderate yield have been reported. These yields could be attributed to the side reactions of the cationic or radical monocyclic intermediates (i.e., a C–O bond formation of a carbocation or elimination of oxy radicals). We envisioned that the Ti-mediated radical cyclization reaction[10] of cyclohexane epoxide **4** would afford *trans*-*anti*-hydrophenanthrene **2** via radical intermediate **3** in a diastereoselective manner, similar to the polyene cyclization. B-ring formation would proceed in a 6-*endo* rather than 5-*exo* cyclization mode, giving a C8 radical that would be stabilized by the C14 ketone. Radical termination at C8 with radicalophile **X** could be expected to introduce a bridgehead substituent for D-ring formation. Epoxide **4** can be easily prepared from A-ring moiety **5**[11] and cyclohexenone derivative **6** in a convergent manner. Functionalized cyclohexanes are commercially available, which is advantageous over the previous methods that used geranyl/farnesyl derivatives which require functionalization.

**Scheme 1.** (a) Retrosynthetic analysis of highly oxidized *ent*-kauren-15-ones. (b) Possible side reactions in the polyene cyclization reaction.

Scheme 2 shows a typical example of hydrophenanthrene synthesis via Ti-mediated radical cyclization. The precursor **11a** was prepared from commercial 2,4,4-trimethylcyclohex-2-en-1-one (**7**) by a five-step sequence (DIBAL reduction, Eschenmoser–Claisen rearrangement, epoxidation with *m*CPBA,[11b] reduction with Schwartz reagent,[12] and the addition of organolithium **10a**). The treatment of **11a** with the stoichiometric amount of Cp2TiCl prepared from Cp2TiCl2 and activated Zn in THF predominantly afforded enone **12a** in 76% yield, owing to the elimination of the C7 hydroxy group.[13] The X-ray crystallographic analysis of **12a** revealed the desired *trans*-*anti*-tricyclic skeleton.[14] However, the desired b-hydroxyketone **13a** was not observed, whereas a trace amount of C9-epimer **14a** was observed.

**Scheme 2.** Synthesis of hydrophenanthrene **12a** via Ti-mediated radical cyclization of **11a** DIBAL = diisobutylaluminium hydride; *m*CPBA = 3-chloroperbenzoic acid.

Next, the substrate scope of Ti-mediated radical cyclization was investigated (Table 1a). The cyclization reactions of silyl ether **11b** and acetate **11c** furnished **12a** via elimination, along with a substantial amount of C9 epimer **14a**. The radical cyclization of C7 methylene substrate **11d** afforded the desired *trans*-*anti*-ketone **12d** selectively in 83% yield, whereas that of 7-oxo substrate **11e** afforded cyclobutanol **15e** via 1,2-addition, which is consistent with that in a previous report[11c]. The radical cyclization using 7-oxo-14-dioxolane **11f** resulted in a mixture of *trans*-*anti*- and *cis*-*anti*-diketones (**12f**:**16f** = 1:1.4) in their enol forms in 51% yield. The alcohol **12g** was obtained from allyl acetate **11g** in 35% yield, which is consistent with that reported by Kobayashi *et al*.[9a] This suggests that the electron-withdrawing group at C14 plays a significant role in the radical cyclization and that only sp3 carbons with less bulky substituents are allowed at the C7 position.

Subsequently, the substrate scope of various cyclic carbonyl compounds that form the C-ring in cyclization (Table 1b) was explored to demonstrate its applicability in the synthesis of terpenoids other than *ent*-kaurenes. The use of 13- and 12-dimethyl substrates afforded *trans*-*anti*-enones **12h** and **12i** in

**Figure 2.** Substrate scope of (a) C7 and C14 functional groups and (b) C-ring forming cyclic carbonyl compounds in Ti-mediated radical cyclization.a

a Isolated yield. b After the completion of the reaction, the reaction mixture was treated with 1 M aq. NaOH for 30 min at room temperature. c After the completion of the reaction, the reaction mixture was treated with 1 M aq. HCl for 30 min at room temperature.

84% and 74% yields, whereas the reaction with the 11-dimethyl substrate afforded none of the desired products owing to steric hindrance. In an attempt to construct successive quaternary carbons, we used a 9-methyl substrate that afforded the desired **12k** in poor yield (16%). This was ascribed to the preferential 1,2-addition to the ketone, affording dehydroabietane **17k** in 50% yield. We also studied Ti-mediated radical cyclizations other than cyclohexenones. The use of a six-membered lactone successfully afforded tricyclic lactone **12l** in 69% yield. The reaction of a cyclopentenone derivative furnished *trans*-*anti*-tricyclic ketones **12m** and **12m’** in 41% and 26% yields, respectively. The same results were obtained when 5-membered lactones were used, affording *trans*-*anti*-tricyclic lactones **12n** and **12n’**. Lactone **12n** is a natural product, nebularilactone A,[15] a drimane sesquiterpenoid isolated from the fungus *Lepista nebularis*, and **12l** and **12n’** are 1- and 7-hydroxy derivatives of the corresponding terpenoids,[16,17] respectively. However, attempts to capture the putative intermediate, carboradical at the C8 position, with radicalophiles have been unsuccessful.

To demonstrate the applicability of this synthetic method, we developed the total synthesis of (±)-kamebanin.[7] First, we investigated the construction of the C8 quaternary carbon center in the *ent*-kaurene skeleton for which we used our recently developed formal semi-pinacol rearrangement reaction.[18] Diastereoselective 1,2-addition of α-cyanocarbanion to the enone moiety of the MOM-protected **12a** and subsequent vanadium-catalyzed diastereoselective epoxidation afforded **18** in high yield (97%). The formal semi-pinacol rearrangement of the cyanomethyl group proceeded via the sequential treatment of **18** with Me3Al and LiNEt2, which afforded β-hydroxy ketone **20**. The mechanism of the formal semi-pinacol rearrangement reaction is as follows: The C14 tertiary alcohol is masked as an aluminium alkoxide and reacts with LiNEt2 to afford an a-cyanocarbanion, which attacks the neighboring epoxide to form cyclopropane **19**. The ring-opening reaction of the cyclopropanol occurs during workup to complete the formal rearrangement.

Then, the resulting secondary alcohol was protected, and treated with **20** in the presence of KHMDS/TIPSOTf to produce enol ether **21** in 26% yield, along with tetracyclic compound **22** in 63% yield. We postulated that TIPSOTf activates the nitrile of **21** as a Lewis acid to generate the tetracyclic **22** in one step via a Thorpe-Ziegler-type reaction.[19] Therefore, the three-step conversion from **21** to **22** using the intramolecular Mukaiyama aldol reaction[20] is unnecessary. Wittig reaction of diketone **22** afforded *exo*-methylene **23**, which was subjected to diastereoselective reduction of the C14 ketone. All the standard conditions such as metal hydride reduction, Birch reduction, and SmI2 reduction failed to afford the desired 14b-alcohol **24**. According to the total synthesis of Glaucocalyxin A reported by Jia *et al*.,[5g,21] Birch reduction without a proton source afforded the desired alcohol **24** as a major isomer in 58% yield. The best result of the one-electron reduction was obtained when an excess of Ca metal in MeOH[22] was used, where the desired 14b-alcohol **24** was obtained in 66% yield (dr = 2.6:1). Finally, allylic oxidation with SeO2, Dess–Martin oxidation, and removal of MOM groups completed the total synthesis of (±)-kamebanin (17 steps from **7** with an overall yield of 6.5%). All spectral data were consistent with those of the natural kamebanin.[7]

**Scheme 3.** Total synthesis of (±)-kamebanin. MOM = methoxymethyl; DIPEA = *N*,*N*-diisopropylethylamine; acac = acetylacetonate; TBHP = *t*-butyl hydroperoxide; HMPA = hexamethylphosphoric triamide; KHMDS = potassium bis(trimethylsilyl)amide; TIPS = triisopropylsilyl; LDA = lithium diisopropylamide.

Conclusion

We have achieved the diastereoselective construction of *trans*-*anti* hydrophenanthrenes, i.e., ABC-ring of *ent*-kaurene

diterpenoids, via a Ti-mediated radical cyclization. We demonstrated that this synthetic method is applicable to the total synthesis of the natural products; (±)-nebularilactone A and (±)-kamebanin. This synthetic method also enables a convergent and efficient approach to highly functionalized skeletons of bioactive natural products such as steroids and diterpene alkaloids. In the total synthesis of (±)-kamebanin, we have accomplished the selective construction of the C7 and C8 stereochemistry via a formal semi-pinacol rearrangement and the D-ring construction of the *ent*-kaurene skeleton via a novel Thorpe-Ziegler-type reaction of g-ketonitrile. Synthetic studies of other pharmacologically active *ent*-kauren-15-ones based on this method are currently underway.

Experimental Section

**General procedure for the Ti-mediated radical cyclization:** A solution of Cp2TiCl (0.30 M, THF) was prepared from Cp2TiCl2 and Zn in THF (2.0 mL). The deep green solution of Cp2TiCl (3.0 equiv.) was slowly added to a solution of epoxide (1 equiv.) in THF (0.10 M) over 10 min at room temperature. After the mixture was stirred for 10-30 min, the reaction was quenched with 1 M solution of HCl. The organic layer was separated, and the aqueous layer was extracted with Et2O. The combined organic layers were washed with saturated aqueous NaHCO3 solution, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc as an eluent) to afford a product.

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**Keywords:** Diastereoselectivity • *ent*-Kaurenes • Natural product • Radical cyclization • Total synthesis

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[14] Deposition Numbers 2215373 (**12a**), 2215375 (**12d**), 2215376 (**15e**), 2215377 (**16f**), 2215381 (**12k**), 2215378 (**12l**), 2215379 (**12m’**), 2215380 (**12n’**), 2215382 (**18**), 2215383 (**20**), and 2215385 (kamebanin) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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[18] Details of the formal semi-pinacol rearrangement will be reported in near future.

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A diastereoselective synthesis of the functionalized *trans*-*anti*-hydrophenanthrenes via Ti-mediated reductive radical cyclization has been developed. This method enabled the convergent total synthesis of nebularilactone A and the first total synthesis of kamebanin via a novel formal semi-pinacol rearrangement reaction and an unprecedented Thorpe-Ziegler-type D-ring formation reaction.

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