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RESEARCH ARTICLE

Novel Radical Cyclization Cascade for the Unified Synthesis of the Cedrane and Clovane Sesquiterpene Skeletons

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Abstract: Radical cyclization cascade reactions of epoxycyclohexanes possessing alkene and alkyne side chains have been achieved. Sequential 5- or 6-*exo*-*trig*/5-*exo*-*dig* reactions triggered by epoxide ring opening with Cp_2TiCl were found to provide a useful unified synthetic method for generating the carbon skeletons of clovane and cedrane, two tricyclic sesquiterpenes. The factors responsible for the development of stereoselectivity during cyclization are also discussed.

Introduction

Radical cyclization reactions[1] have attracted considerable attention as important tools in natural product synthesis because they are highly efficient and versatile. In particular, radical cyclization reactions triggered by the ring-opening of epoxides with low-valent titanium reagents[2] are useful because they are highly functional group tolerant and the stereochemistries of the cyclized products are easily predicted. This chemistry has been used to initiate radical cascade reactions and has contributed to the efficient construction of complex natural product skeletons, including steroids that especially involve the cyclization of polyenes.[3] Milestones based on this strategy include the total syntheses of sestertatin 1[4] by the Justicia and Cuerva group and formitellic acid B[5] by the Kobayashi group (Figure 1a). In contrast, polyene cyclization cascades involving multifunctional substrates tend to result in lower yields owing to side reactions, such as elimination reactions, and the formation of undesired diastereomers in each step.[4,5]

Recently, we developed radical cyclization chemistry for the stereoselective synthesis of *trans*-*anti*-tricyclic compounds (Figure 1b).[6] Using an epoxycyclohexane bearing electron-deficient cycloalkene side chain as the substrate, Cp_2TiCl reduced the epoxide moiety to generate a tertiary carboradical, that smoothly underwent addition to the cycloalkene. This reaction selectively afforded various tricyclic compounds in high yields, including nebularilactone A,[7] a drimane sesquiterpenoid. Furthermore, this reaction was used to achieve the total synthesis of kamebanin, an anti-inflammatory *ent*-kaurenoid.[8] The advantages of this method include ease of substrate preparation and stereocontrol during the reaction. We applied this synthetic method to radical cyclization cascade chemistry involving epoxycyclohexanes.

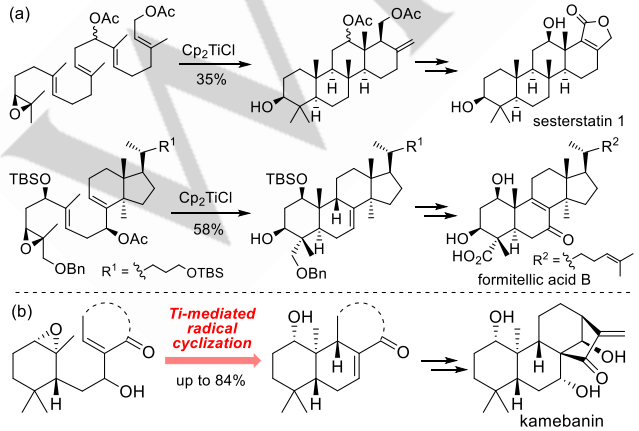


Figure 1. (a) Natural-product-synthesis milestones based on Ti^{III}-mediated polyene cyclization. (b) Our radical-cyclization-based total synthesis of kamebanin. Cp = cyclopentadienyl, TBS = *t*-butyldimethylsilyl.

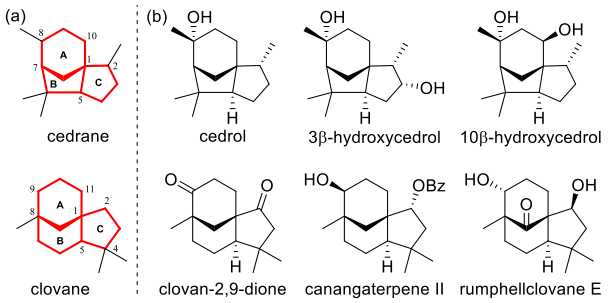
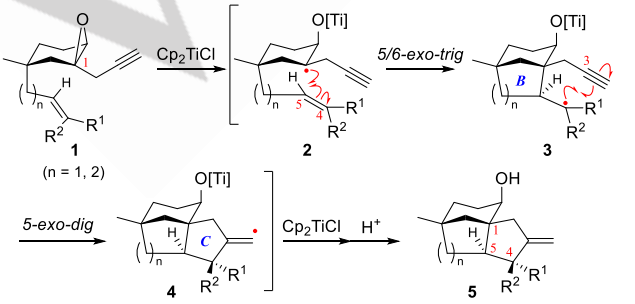


Figure 2. (a) Chemical structures of cedrane and clovane and their carbon numberings. (b) Representative natural products in the cedrane and clovane families.

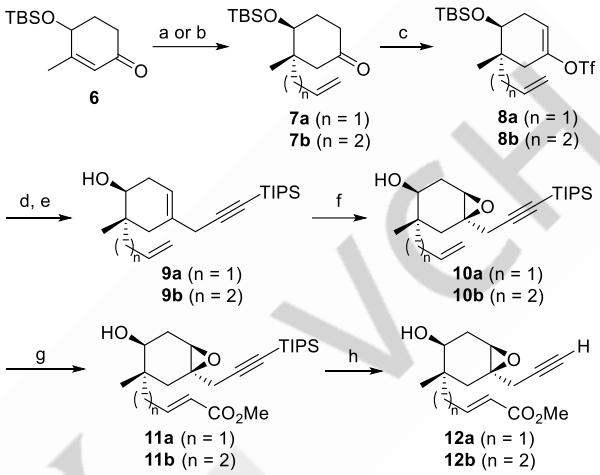
The cedrane and clovane tricyclic sesquiterpenes[9] were selected as target natural product skeletons (Figure 2). Natural compounds belonging to these families are used as fragrance ingredients[10] and generally found in cedar and clove oils; they also possess various biological properties, including antitumor, antibacterial, and anti-inflammatory activities.[11,12] The biosynthetic precursors of cedrane and clovane differ from those of bisabolene and caryophyllene oxide,[13] although coincidentally they have similar carbon frameworks. Namely, that of cedrane is tricyclo[5.3.1.$0^{1,5}$]dodecane, while that of clovane is tricyclo[6.3.1.$0^{1,5}$]undecane, differing only in the number of carbon atoms in their B-rings. These members of their respective natural product families are often supplied by biotransformation[13] or semi-synthesis;[14] therefore, the functional groups of these products are limited in their positions. Most conventional total syntheses[15,16] are based on the stepwise construction of the cedrane/clovane ring system, with the exception of a few methods reported for cedrane [15j,l,m,n,o,r] and the recent clovane synthesis reported by the group of Huang and Yang.[16m] Consequently, there is room for improvement in terms of the efficiency associated with the one-step construction of each tricyclic skeleton. Notably. owing to the attractive biological activity of rumphellclovane E,[12b] the development of synthetic methods for the clovane skeleton have recently been reported along with a series of total syntheses.[16i,k] Herein, we report the development of a unified method for the synthesis of the cedrane/clovane skeletons that involves radical cascade chemistry using low-valent titanium reagents. This study is expected to not only greatly expand the scope of radical cascade reactions in natural product synthetic chemistry, but also contribute to the development of new pharmaceuticals and flavors.

Results and Discussion

A unified method for the synthesis of the cedrane/clovane skeleton was designed as shown in Scheme 1. Reductive ring-opening of epoxycyclohexane **1**, which possesses an alkene side chain of appropriate length and a propargylic group, promoted by a low-valent titanium reagent is expected to selectively generate a tertiary carboradical at the C1 position of **2**. This carboradical then undergoes 5- or 6-*exo-trig* cyclization onto the alkene side chain to give bicyclic compound **3** through the formation of the B-ring. The resulting radical at the C4 position subsequently undergoes 5-*exo-dig* cyclization onto the propargylic side chain to construct the cedrane/clovane skeleton; subsequent quenching affords tricyclic compound **5**. The diastereoselectivity associated with the newly arising stereochemistries at the C4 and C5 positions of **5** was expected to be problematic. The stereochemistry at the C5 position depends on the conformation during the first cyclization step, while that at the C4 position depends on the *E/Z* configuration of the alkene moiety in the substrate.



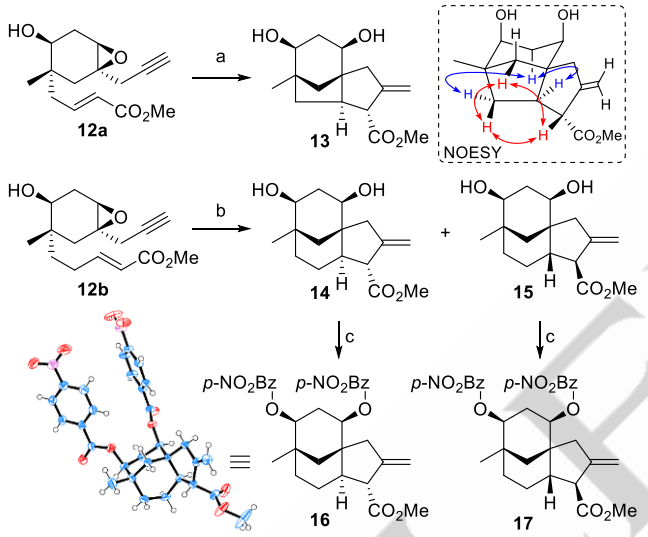
Scheme 1. Unified method for the syntheses of the cedrane and clovane skeletons.



Scheme 2. Preparing radical cyclization precursors. Reagents and conditions: (a) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, −78 to 0 °C, 81% for **7a**. (b) 3-Butenylzinc bromide, CuBr·SMe_2, TMSCl, DMA, 0 °C to rt, 91% for **7b**. (c) Comins reagent, potassium bis(trimethylsilyl)amide, THF, −78 °C, 73% for **8a**; 68% for **8b**. (d) $Pd(PPh_3)_4$, 3-triisopropylsilyl-2-propynylmagnesium bromide, Et_2O, rt. (e) 3.0 M HCl aq., MeOH, 60 °C, 51% for **9a** (2 steps); 50% for **9b** (2 steps). (f) $VO(OEt)_3$, *t*-butylhydroperoxide, CH_2Cl_2, 0 °C, 86% for **10a**; 86% for **10b**. (g) Hoveyda-Grubbs 2nd generation catalyst, methyl acrylate, 1,2-dichloroethane, reflux, 96% for **11a**; 85% for **11b**. (h) TBAF, AcOH, THF, 50 °C, 69% for **12a**; 60% for **12b**. TMS = trimethylsilyl, DMA = *N*,*N*-dimethylacetamide, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, TBAF = tetra-*n*-butylammonium fluoride.

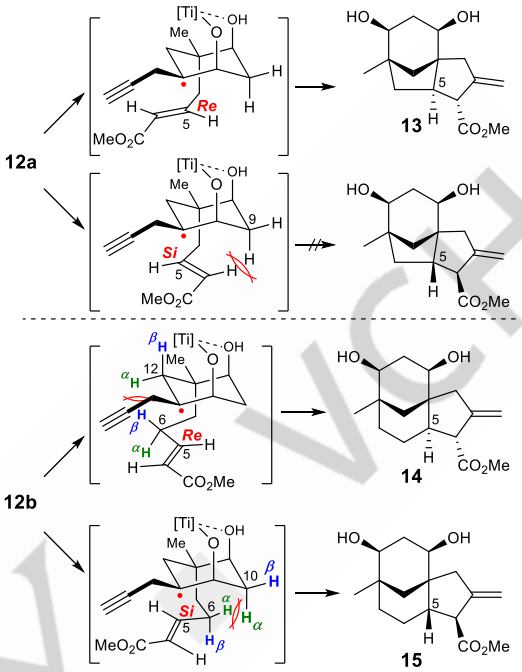
The radical cyclization precursor was prepared as in Scheme 2. Using the known 3-methyl-4-silyloxycyclohexenone **6**[17] as a starting material, each alkene side chain was stereoselectively introduced through the 1,4-addition reaction of the allylsilane[18] or homoallylzinc reagent[19] to give cyclohexanone **7a** or **7b**, respectively. Regioselective enolization with Comins reagent afforded triflate **8a/8b**. The propargyl side chain was subsequently introduced via Kumada coupling,[20] and the removal of the TBS group under acidic conditions afforded alcohol **9a/9b**. The epoxy group, the key to this synthetic method, was introduced by vanadium-catalyzed epoxidation,[21] with **10a/10b** obtained in high yield as a single diastereomer. An alcohol at the C8 position of **9a** or the C9 of **9b** was essential for controlling the stereochemistry of the epoxidation reaction.[22] The alkene cross-metathesis reaction with methyl acrylate introduced the radical-stabilizing ester group, with **11a/11b** obtained in an *E*-selective manner. Finally, removal of the TIPS group afforded the radical cyclization precursor **12a/12b**.

With precursors **12a** and **12b** in hand, we next investigated the radical cyclization cascade reactions (Scheme 3). The radical cyclization cascade involving **12a** and freshly prepared Cp_2TiCl afforded tricyclic compound **13** in 67% NMR yield as a single diastereomer. NOESY experiments revealed that the structure of **13** contains the cedrane skeleton, and that the stereochemistry at the C5 position is identical to that of observed for natural cedranes. On the other hand, radical cyclization using substrate **12b** afforded products **14** and **15** in an almost non-selective manner (**14**:**15** = 1.1:1). Diol **14** was converted into the crystalline bis(*p*-nitrobenzoate) **16**, which revealed that **14** possesses the clovane skeleton.[23] In a similar manner to **13**, the stereochemistry at the C5 position of **14** was found to be the same as that of natural clovane. In addition, X-ray crystallographic analysis of bis(*p*-nitrobenzoic acid) **17** derived from **15** confirmed that **15** is a diastereomer of **14** at both the C4 and C5 positions (see Supporting Information).



Scheme 3. Radical cyclization cascade using Cp_2TiCl. Reagents and conditions: (a) Cp_2TiCl, THF, rt, 67% (NMR yield). (b) Cp_2TiCl, THF, rt, 24% for **14**; 23% for **15**. (c) *p*-NO_2BzCl, DMAP, CH_2Cl_2, rt, 47% for **16**; 21 % for **17**. NOESY = nuclear Overhauser effect spectroscopy; DMAP = 4-dimethylaminopyridine.

We assumed that the stereoselectivities of these reactions are ascribable to facial selectivity during the first radical addition to each alkene side chain (5/6-*exo*-*trig* cyclization, Scheme 4). The transition state for addition to the *Si* face during the cyclization reaction involving **12a** is unfavorable owing to steric repulsion between the alkene side chain and the methylene group at the C9 position. Therefore, addition only proceeds at the *Re* face to yield **13**. On the other hand, the transition state for addition to the *Re* face during the reaction of **12b** (to give **14**) is destabilized by flagpole hydrogen repulsion involving the newly forming boat-type B-ring (i.e., steric repulsion between the allylic β-hydrogen at the C6 position and the α-hydrogen at the C12 position). In addition, steric repulsion exists between the α-hydrogens at the C6 and C10 positions during the addition to the *Si* face leading to compound **15**. Consequently, the energy difference between the two transition states is considered to be almost negligible. Therefore, the introduction of any α-oriented substituents at the C6 and/or C10 positions may improve the selectivity for the desired stereochemistry.



Scheme 4. Proposed transition states toward tricyclic compounds **13**–**15**.

Conclusion

We developed a unified protocol for the synthesis of the cedrane and clovane sesquiterpene skeletons via Cp_2TiCl-promoted radical cyclization cascades involving appropriate epoxycyclohexanes. We also discussed the factors responsible for the stereoselectivity at the C5 position during the radical cyclization reaction. Studies toward the syntheses of cedrane/clovane family members and their derivatives using the developed method are currently underway.

Acknowledgements

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Keywords: Cyclization • Cascade reactions • Epoxides • Radical reactions • Sesquiterpenes

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[22] Epoxidation without an OH group at the C8 or C9 position gave the corresponding epoxide with an almost 1:1 diastereomeric ratio for both substrates.

[23] Deposition numbers 2354284 (for **16**) and 2354285 (for **17**) 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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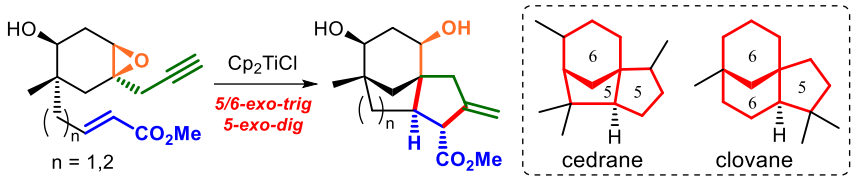

Radical cyclization cascade reactions of epoxycyclohexanes possessing alkene and alkyne side chains have been achieved. Sequential 5- or 6-*exo-trig*/5-*exo-dig* reactions triggered by epoxide ring opening with Cp_2TiCl were found to provide a useful unified synthetic method for generating the tricyclic carbon skeletons of clovane and cedrane, which are used as fragrance ingredients and show various biological activities.

Institute and/or researcher Twitter usernames: ((optional))