Total Synthesis and Structure Revision of (+)-Lancilactone C

Hidetaka Kuroiwa, Soichiro Suzuki, Kazuhiro Irie, and Chihiro Tsukano*

Graduate School of Agriculture, Kyoto University, Kitashirakawa-Oiwakecho, Sakyo-ku, Kyoto 606-8502, Japan

ABSTRACT: Lancilactone C is a tricyclic triterpenoid that inhibits human immunodeficiency virus (HIV) replication in H9 lymphocytes with no cytotoxicity. Its tricyclic skeleton comprises *trans*-dimethylbicyclo[4.3.0]nonane and 7-isopropylenecyclohepta-1,3,5-triene. The latter unique structure, in which all carbon atoms are sp^2 hybridized, is not found in other triterpenoids and needs to be verified synthetically. Herein, we have accomplished the first total synthesis of lancilactone C (proposed structure) by developing a new domino [4+3] cycloaddition reaction involving oxidation, Diels–Alder reaction, elimination, and electrocyclization. We have also revised the structure based on the total synthesis of lancilactone C according to its plausible biosynthetic pathway.

Lancilactone C was isolated from the stems and roots of *Kadsura lancilimba*, which have been traditionally used in Chinese folk medicine, along with lancilactones A, B, and kadsulactone A while searching for potential anti-HIV agents (Figure 1).[1] Its structure, including relative stereochemistry, was determined using high-resolution mass spectroscopy and extensive nuclear magnetic resonance (NMR) analyses, including 2D NMR (HETCOR, COSY, and NOESY). Although the structure of lancilactones A-C contains a common *trans*-dimethylbicyclo[4.3.0]nonane linked to unsaturated lactone, the oxidation state of the unsaturated seven-membered ring differs from each other. Lancilactone C is notable for its unique 7-isopropylenecyclohepta-1,3,5-triene structure, which entirely comprises sp^2 hybridized carbon atoms. This unique structure is not found in other triterpenoids and requires synthetic verification. Among lancilactones, only lancilactone C inhibited HIV replication in H9 lymphocytes, with a half-maximum effective concentration (EC_{50}) of 1.4 μg/mL, while it did not show cytotoxicity even at a concentration of 100 μg/mL.[1] To the best of our knowledge, so far, the total synthesis and synthetic studies of lancilactone C have not been reported. Additionally, the total synthesis of the 9,10-cleaved cycloartane-type triterpenoids,[2] to which lancilactones belong, has never been achieved. Given its unique structure and biological activities, we have embarked on a total synthesis of lancilactone C.

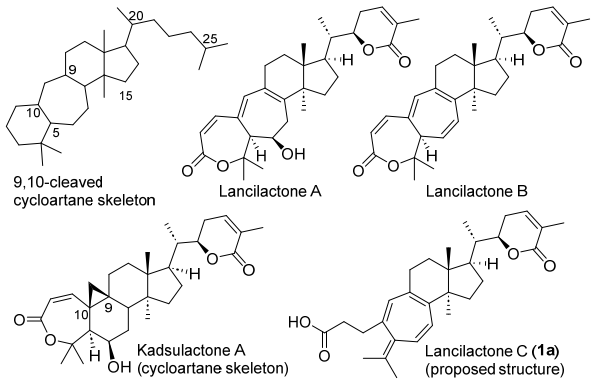
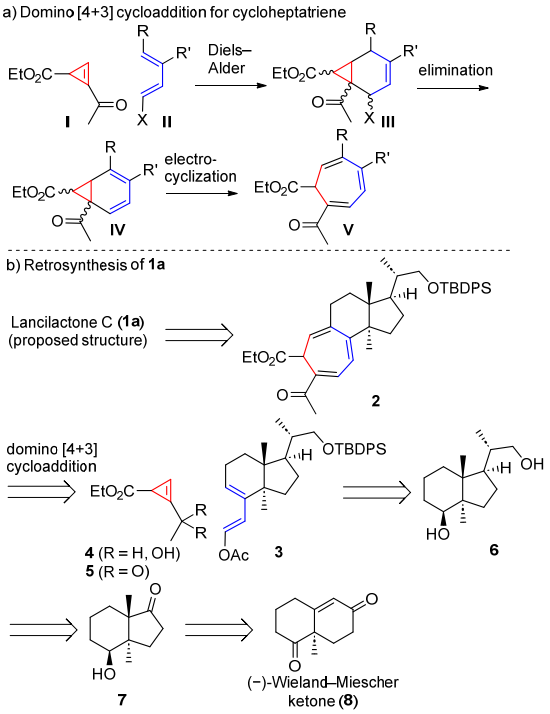


Figure 1. Lancilactones and kadsulactone A.

To construct the unique cycloheptatriene ring system comprising the tricyclic skeleton **1a**, we designed a new domino reaction which involves the Diels–Alder reaction between dienophile **I** and diene **II** to form compound **III**, followed by the elimination of a leaving group and the electrocyclization of the resulting bicyclo[4.1.0]heptadiene **IV** to give 1,3,5-cycloheptatriene **V** (Scheme 1a). This domino [4+3] cycloaddition reaction affords the direct construction of **2**, which is a synthetic precursor of **1a**, using diene **3** bearing an acetoxy group as a leaving group and alcohol **4**, which is oxidized to form dienophile **5** during this reaction.

Scheme 1. a) Synthetic strategy for cycloheptatriene and b) Retrosynthesis of lancilactone C (proposed structure).

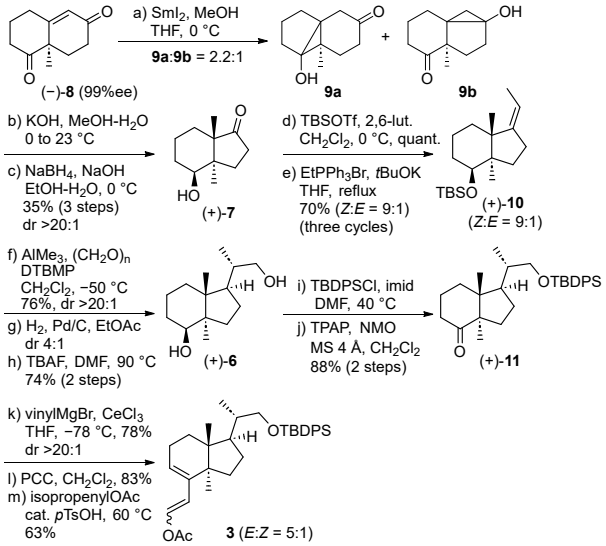


In previous total syntheses, the bicyclo[4.1.0]heptadiene skeleton related to **IV** has been constructed via intramolecular cyclopropanation of the benzene ring.[3] However, the proposed novel approach features a regioselective intermolecular reaction in one pot. While cyclopropene **5** having carbonyl substituents may be unstable, it can be used in the Diels–Alder reaction by oxidizing the corresponding alcohol in situ.[4] Controlling the diastereoselectivity in the proposed reaction using dienes having leaving groups and establishing this reaction as a domino reaction involving elimination and electrocyclization are necessary. Diene **3** can be derived from compound **6**, which can be accessed via a diastereoselective ene reaction using bicyclo[4.3.0]nonane **7** having a contiguous quaternary carbon at the angular position. Compound **7** can be synthesized using (−)-Wieland–Miescher ketone (**8**) via intramolecular cyclopropanation and ring cleavage.

Herein, we have successfully developed the domino [4+3] cycloaddition reaction involving a cyclopropene, which enabled us to accomplish the first total synthesis of the proposed structure of lancilactone C. This total synthesis revealed a structural misassignment of the proposed **1a**. Consequently, a revised structure **1b** was synthesized to unveil the true structure of lancilactone C (Figure 2).

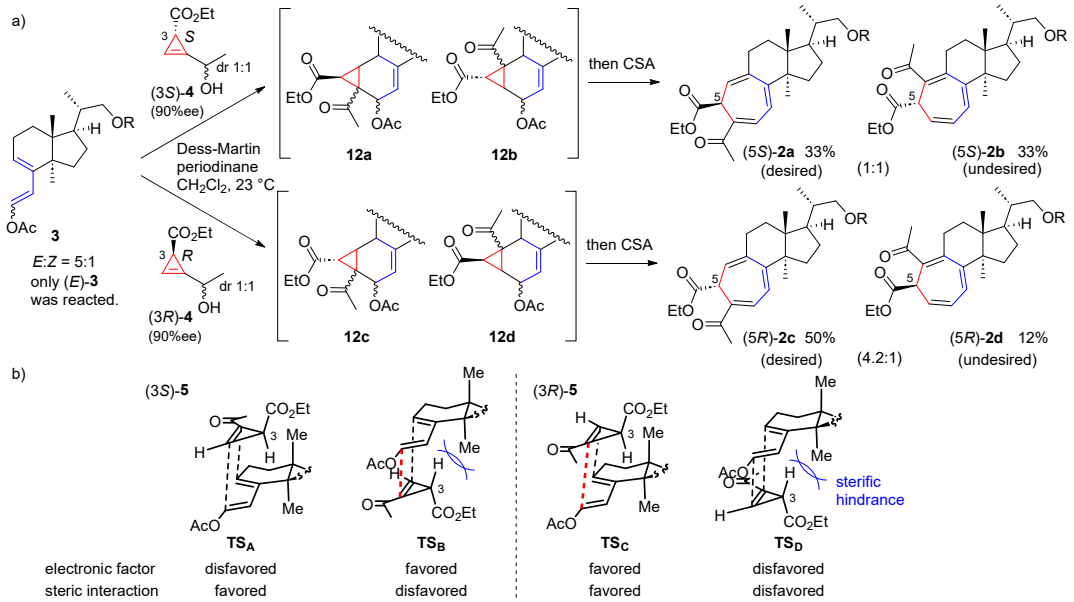
The synthesis started from constructing *trans*-dimethylbicyclo[4.3.0]nonane from (−)-Wieland–Miescher ketone (**8**), prepared from commercially available 1,3-cyclohexadione using a chiral organocatalyst (Scheme 2).[5] In 1977, Reusch reported the synthesis of *trans*-dimethylbicyclo[4.3.0]nonane under Birch conditions using liquid ammonia.[6] Since then, no alternative method has been investigated; we initially examined modified conditions using SmI_2.[7] After screening reaction conditions, it was found that intramolecular cyclopropanation with SmI_2 in the presence of methanol as an additive at 0 °C gave a mixture of cyclopropanols **9a** and **9b**. Treatment of the mixture under basic conditions without separation resulted in cleavage of a cyclopropane ring to construct dimethylbicyclo[4.3.0]nonane. Interestingly, both **9a** and **9b** could be converted to the same skeleton (see SI for details).[6b] After a regioselective and stereoselective reduction, the resultant ketoalcohol **7** was converted to trisubstituted olefin **10** (*Z*:*E* = 9:1) via silylation and Wittig reaction with ethyltriphenylphosphonium bromide and *t*BuOK. Although the Wittig reaction did not complete under these screened conditions, the recovered starting material was recycled three times to convert into **10** with a total yield of 70%. Using trimethylaluminum, paraformaldehyde,[8] and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), a stereoselective ene reaction of trisubstituted olefin **10** was conducted to form homoallyl alcohol, which was hydrogenated to give the desired diastereomer as a major product (dr = 4:1). After removing the TBS group, the minor isomers were separated to isolate a single diastereomer **6** in 56% overall yield from **10**. The diastereomer **6** was subjected to a silylation followed by an oxidation of the secondary alcohol to give ketone **11**. Treating **11** with vinylmagnesium bromide in the presence of anhydrous cerium chloride[9] followed by pyridinium chlorochromate (PCC) oxidation produced an α,β-unsaturated aldehyde. Acetoxydiene **3** was synthesized by treating the α,β-unsaturated aldehyde with isopropenyl acetate under acidic conditions.

Scheme 2. Synthesis of diene 3.



After synthesizing diene **3**, we investigated the Diels–Alder reaction involving diastereomers (3*S*)- and (3*R*)-**4**,[10] which are precursors of the unstable dienophiles **5** (Scheme 3a). We aimed to utilize the stereocenter of cyclopropene **5** to control the regioselectivity and stereoselectivity of the Diels–Alder reaction. Treatment of (3*S*)-**4** with Dess-Martin periodinane in the presence of diene **3** afforded the Diels–Alder adducts **12a** and **12b**. At this stage, **12a** and **12b** comprised eight diastereomers, which were difficult to separate using silica gel column chromatography. However, acid treatment of the mixture of **12a** and **12b** resulted in the elimination of the acetoxy group followed by electrocyclization, yielding cycloheptatriene **2a** and **2b** in the form of a 1:1 mixture.[11] Moreover, this reaction was conducted in one pot without isolating the Diels–Alder adducts **12a** and **12b**. The stereochemistry of C3 on the cyclopropene ring had a substantial effect on the selectivity of the reaction center in this reaction. In the case of the reaction using (3*R*)-**4**, the selectivity was improved to 4.2:1 in comparison to the reaction with (3*S*)-**4**, yielding the desired product **2c** and its diastereomer **2d** in 50% and 12% yield, respectively.[11] The Diels–Alder reaction involving cyclopropene was reported to exhibit endo–anti selectivity,[4,12] and the selectivity origins from the steric repulsion between the substituents (i.e., H and CO_2Et) on C3 of a cyclopropene and a dienophile, or C–H/π interaction between hydrogen on the cyclopropene and diene.[13] Herein, we assumed that the two transition states (**TS**s) among the eight possible **TS**s in each of (3*S*)-**5** and (3*R*)-**5** could be favorable in terms of the endo–anti selectivity, in which the diene approaches the cyclopropene from the substituent hydrogen side on C3 (Scheme 3b and Figure S1 in SI).[14] In the case of (*3S*)-**5**, $\mathbf{TS_B}$ was less favorable than $\mathbf{TS_A}$ in terms of the steric interaction owing to the repulsion between the hydrogen on C3 of cyclopropene and the methyl group at the angular position. However, owing to the substitution of the acetoxy and carbonyl groups, the electronic factor was more favored in $\mathbf{TS_B}$ than in $\mathbf{TS_A}$, in which the two factors did not agree with each other. On the other hand, for (*3R*)-**5**, the transition state of $\mathbf{TS_C}$ was sterically less repulsive to the methyl group on the angular position and electronically favorable than that of $\mathbf{TS_D}$. Hence, $\mathbf{TS_C}$ was favored for matching electronic

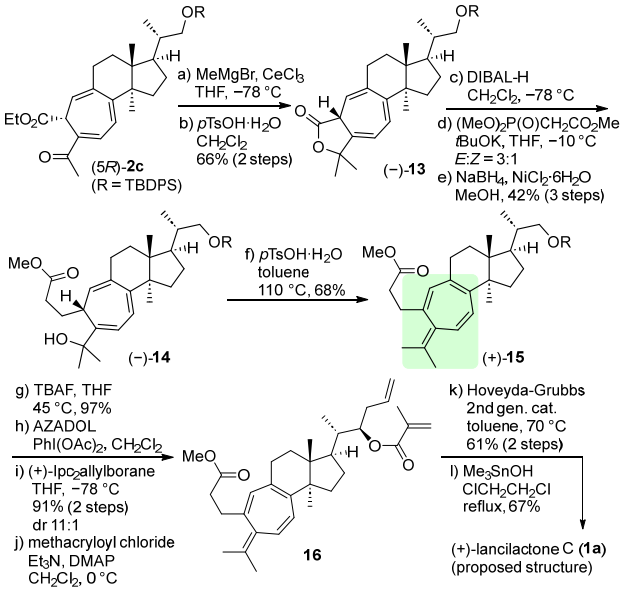
Scheme 3. a) Construction of cycloheptatriene via the Diels–Alder reaction and 6π-electrocyclization and b) endo–anti transition states of Diels–Alder reaction of 3 involving (3*S*)-5 or (3*R*)-5.



and steric factors, and 4.2:1 selectivity was observed for (*3R*)-**5**, whereas no selectivity was observed for (*3S*)-**5**.

After successfully constructing the tricyclic skeleton **2c**, we investigated the construction of 7-isopropylenecyclohepta-1,3,5-triene (Scheme 4). After treating compound **2c** with methylmagnesium bromide in the presence of anhydrous cerium chloride,[9] lactonization under acidic conditions afforded **13**. Using diisobutylaluminium hydride (DIBAL–H), compound **13** was reduced to a lactol, followed by the Horner–Wadsworth–Emmons reaction and 1,4-reduction with $NaBH_4$ and $NiCl_2$ to give ester **14**.[15] The desired 7-isopropylenecyclohepta-1,3,5-triene **15** was constructed via dehydration under acidic conditions without any double bond isomers. In the final stage of the total synthesis, the lactone ring on the side chain was introduced as follows. After removing the *tert*-butyldiphenlysilyl (TBDPS) group of **15**, the resulting alcohol was oxidized to an aldehyde using 2-azaadamantane 2-ol (AZADOL).[16] The resultant aldehyde was treated with (+)-Ipc$_2$allylborane[17] to give a homoallylic alcohol, which was acylated using methacryloyl chloride to afford compound **16**. The ring-closing metathesis (RCM) of **16** with a Hoveyda–Grubbs second-generation catalyst[18] and selective hydrolysis of methyl ester[19] resulted in the first asymmetric total synthesis of lancilactone C (**1a**, the proposed structure). Although its spectral data supported the structure of **1a**, the NMR spectrum of the synthetic **1a** did not match with the reported NMR spectra for lancilactone C,[1] suggesting a structural revision.

Scheme 4. Total synthesis of (+)-Lancilactone C (1a, proposed structure).



After reinvestigating the ^{1}H NMR data of lancilactone C,[20] we noticed that both chemical shifts and coupling patterns of the hydrogens (H_b and H_c) assigned onto the seven-membered ring of **1a** differed significantly between the data of synthetic **1a** and isolated sample (Figure 2). In the case of the reported data from the isolation group, it was more reasonable to assign these two hydrogens to the aromatic ring and 2-methyl-1-propenyl group, respectively. Although there are several possibilities for the position of the substituents on the benzene ring, the structure of **1b** was the most reasonable considering its biosynthesis from lancilactone B. The isolation group pro-

posed that a 7-isopropylenecyclohepta-1,3,5-triene ring was formed upon the ring-opening of the lactone ring on lancilactone B (path a). However, we have proposed that the triene structure of the seven-membered ring forms a six-membered ring via a 6π-electrocyclization followed by a ring-opening of the lactone and cyclopropane rings with rearomatization to produce **1b** (path b). Therefore, we investigated the synthesis of the revised structure **1b** from ketone **11** (Scheme 5). After introducing the diene moiety via the triflatation of **11** and subsequent Suzuki–Miyaura coupling with boronic ester **17** in the presence of $Pd(PPh_3)_4$, the cyclization precursor **19** was synthesized by treatment with acid anhydride **18**, prepared from propiolic acid. The intramolecular Diels–Alder reaction of **19** proceeded smoothly at 110 °C in toluene, and the resulting 1,4-diene was oxidized using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to form the benzene ring. The lactone ring of **20** was carefully reduced with DIBAL–H to lactol, followed by the Wittig reaction with a stable ylide to afford α,β-unsaturated ester **21**. 1,4-Reduction, oxidation, and Wittig reaction introduced a trisubstituted olefin, followed by removing the TBDPS group and oxidation to afford aldehyde **23**. Similar to synthesizing the proposed structure **1a**, the lactone ring on the side chain was constructed via RCM, and finally, the *t*Bu group was removed under acidic conditions to synthesize the revised structure of lancilactone C (**1b**). The ^1H and ^{13}C NMR spectral data for **1b** completely agreed with those for the reported data in the literature.[1] These results indicate that the structure of lancilactone C is **1b**.

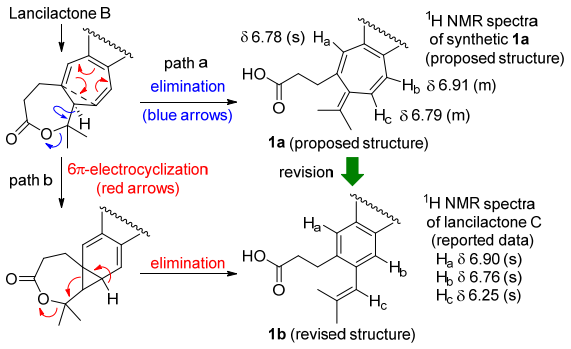
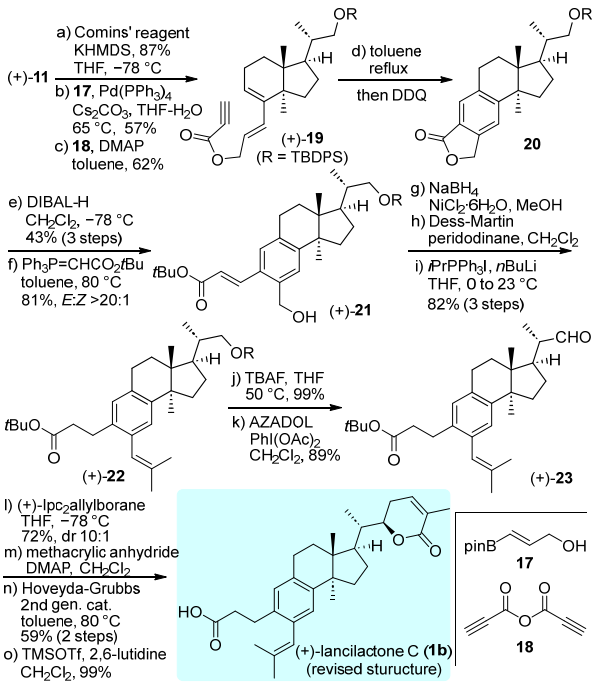


Figure 2. The revision of the structure of lancilactone C and the proposed biosynthetic path for **1b** (revised structure).

In summary, we have successfully achieved the asymmetric total synthesis of lancilactone C (**1a**) based on a domino [4+3] cycloaddition reaction, which involves the Diels–Alder reaction of diene **3** and cyclopropene **4**, elimination, and electrocyclization to construct the cycloheptatriene structure. Furthermore, by comparing NMR spectra of synthetic **1a** with the reported data and considering the plausible biosynthesis including 6π-electrocyclization, the proposed structure **1a** was revised to **1b**. The revision was supported by comparing the spectra data of synthetic **1b** with the reported data. The proposed domino [4+3] cycloaddition reaction can be extended to synthesize other analogs with an unsaturated seven-membered ring of the 9,10-cleaved cycloartane-type triterpenoids and multisubstituted cycloheptanes. We are currently investigating these possibilities and evaluating the anti-HIV activity of the synthetic compounds for revealing the structure–activity relationships.

Scheme 5. Total synthesis of Lancilactone C (1b, revised structure).



ASSOCIATED CONTENT

Supporting Information.

Supporting Information is available free of charge at http://pubs.acs.org.

- Additional experimental details, experimental procedures, spectroscopic data, and ^1H, ^{13}C and 2D NMR spectra.

AUTHOR INFORMATION

Corresponding Author

* E-mail: tsukano.chihiro.2w@kyoto-u.ac.jp

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Chen, D. F.; Zhang, S. X.; Wang, H. K.; Zhang, S. Y.; Sun, Q. Z.; Cosentino, L. M.; Lee, K. H. Novel Anti-HIV Lancilactone C and Related Triterpenes from *Kadsura lancilimba*. *J. Nat. Prod.* **1999**, *62* (1), 94–97. DOI: 10.1021/np980291d

(2) Selected reviews of triterpenoids, see: (a) Kuo, R. Y.; Qian, K.; Morris-Natschke, S. L.; Lee, K. H. Plant-derived Triterpenoids and Analogues as Antitumor and Anti-HIV Agents. *Nat. Prod. Rep.* **2009**, *26*, 1321–1344. DOI: 10.1039/B810774M (b) Hill, R. A.; Connolly, J. D. Triterpenoids. *Nat. Prod. Rep.* **2017**, *34*, 90–122. DOI: 10.1039/C6NP00094K (c) Hill, R. A.; Connolly, J. D. Triterpenoids. *Nat. Prod. Rep.* **2018**, *35*, 1294–1329. DOI: 10.1039/C8NP00029H (d) Hill, R. A.; Connolly, J. D. Triterpenoids. *Nat. Prod. Rep.* **2020**, *37*, 962-998. DOI: 10.1039/C9NP00067D

(3) Selected examples, see: (a) Kennedy, M.; McKervey, M. A. Pseudoguaianolides from Intramolecular Cycloadditions of Aryl Diazoketones: Synthesis of (±)-Confertin and an Approach to the Synthesis of (±)-Damsin. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2565–2574. DOI: 10.1039/P19910002565 (b) King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids: The Preparation of Gibberellins (±)-GA_{103} and (±)-GA_{73} *J. Am. Chem. Soc.* **1997**, *119* (16), 3828–3829. DOI: 10.1021/ja963935h (c) Levin, S.; Nani, R. R.; Reisman, S. E. Enantioselective Total Synthesis of (+)-Salvileucalin B. *J. Am. Chem. Soc.* **2011**, *133* (4), 774–776. DOI: 10.1021/ja110192b (d) Fu, C.; Zhang, Y.; Xuan, J.; Zhu, C.; Wang, B.; Ding, H. Diastereoselective Total Synthesis of Salvileucalin C. *Org. Lett.* **2014**, *16* (12), 3376–3379. DOI: 10.1021/ol501423t (e) Zhang, Q.; Yang, Z.; Wang, Q.; Liu, S.; Zhou, T.; Zhao, Y.; Zhang, M. Asymmetric Total Synthesis of Hetidine-Type C_{20}-Diterpenoid Alkaloids: (+)-Talassimidine and (+)-Talassamine. *J. Am. Chem. Soc.* **2021**, *143* (18), 7088–7095. DOI: 10.1021/jacs.1c01865

(4) Fisher, L. A.; Smith, N. J.; Fox, J. M. Chiral Cyclopropenyl Ketones: Reactive and Selective Diels–Alder Dienophiles. *J. Org. Chem.* **2013**, *78* (7), 3342–3348. DOI: 10.1021/jo302683t

(5) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J.; Viozquez, S.; Guillena, G.; Najera, C. Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues. *Adv. Synth. Catal.* **2009**, *351* (14-15), 2482–2490. DOI: 10.1002/adsc.200900321

(6) (a) Reusch, W.; Grimm, K.; Karoglan, J. E.; Martin, J.; Subrahamanian, K. P.; Toong, Y.-C.; Venkataramani, P. S.; Yordy, J. D.; Zoutendam P. Preparation of Fused-ring Cyclopropanol Derivatives by Reductive Cyclization of Bicyclic Enediones Related to the Wieland-Miescher Ketone. *J. Am. Chem. Soc.* **1977,** *99* (6), 1953–1958. DOI: 10.1021/ja00448a044 (b) Reusch, W.; Grimm, K.; Karoglan, J. E.; Martin, J.; Subrahamanian, K. P.; Venkataramani, P. S.; Yordy, J. D. Transformations of Cyclopropanol Intermediates. 3. Ring-opening Reactions of 6-methyl-5-hydroxytricyclo[4.4.0.01,5]decan-9-one. *J. Am. Chem. Soc.* **1977,** *99* (6), 1958–1964. DOI: 10.1021/ja00448a045

(7) (a) Namy, J. L.; Girard, P.; Kagan, H. B. A New Preparation of Some Divalent Lanthanide Iodides and their Usefulness in Organic Synthesis. *Nouv. J. Chim.* **1977**, *1* (1), 5–7. For reviews of SmI_2-mediated reactions, see: (b) Molander, G. A.; Harris, C. R. Sequencing Reactions with Samarium(II) Iodide. *Chem. Rev.* **1996**, *96* (1), 307–338. DOI: 10.1021/cr950019y (c) Gopalaiah, K.; Kagan, H. B. Use of Samarium Diiodide in the Field of Asymmetric Synthesis. *New J. Chem.* **2008**, 32, 607–637. DOI: 10.1039/B718330P (d) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. Samarium Diiodide-Mediated Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2009**, *48* (39), 7140–7165. DOI: 10.1002/anie.200902151 (e) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. Cross-Coupling Reactions Using Samarium(II) Iodide. *Chem. Rev.* **2014**, *114* (11), 5959–6039. DOI: 10.1021/cr400685r

(8) Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskokovic, M. R. Stereoselective Introduction of Steroid Side Chains at C (17) and C (20). *Helv. Chim. Acta.* **1981**, *64* (5), 1682–1687. DOI: 10.1002/hlca.19810640546

(9) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. Reactions of carbonyl compounds with Grignard reagents in the presence of cerium chloride. *J. Am. Chem. Soc.* **1989**, *111* (12), 4392–4398. DOI: 10.1021/ja00194a037

(10) (a) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. A New Chiral Rh(II) Catalyst for Enantioselective [2 + 1]-Cycloaddition. Mechanistic Implications and Applications. *J. Am. Chem. Soc.* **2004**, *126* (29), 8916–8918. DOI: 10.1021/ja047064k (b) Lou, Y.; Remarchuk, T. P.; Corey, E. J. Catalysis of Enantioselective [2+1]-Cycloaddition Reactions of Ethyl Diazoacetate and Terminal Acetylenes Using Mixed-Ligand Complexes of the Series $Rh_2(RCO_2)_n$ (L^*_{4-n}). Stereochemical Heuristics for Ligand Exchange and Catalyst Synthesis. *J. Am. Chem. Soc.* **2005**, *127* (41), 14223–14230. DOI: 10.1021/ja052254w

(11) Due to use of 90%ee of cyclopropenes (3*S*)- and (3*R*)-**4**, trace amount of other diastereomers were observed, but they were not isolated.

(12) Wiberg, K. B.; Bartley, W. J. Cyclopropene. V. Some Reactions of Cyclopropene. *J. Am. Chem. Soc.* **1960**, *82* (24), 6375–6380. DOI: 10.1021/ja01509a045

(13) (a) Xidos, J. D.; Gosse, T. L.; Burke, E. D.; Poirier, R. A.; Burnell, D. J. Endo−Exo and Facial Stereoselectivity in the Diels−Alder Reactions of 3-Substituted Cyclopropenes with Butadiene. *J. Am. Chem. Soc.* **2001**, *123* (23), 5482–5488. DOI: 10.1021/ja0030919 (b) Levandowski, B. J.; Houk, K. N. Hyperconjugative, Secondary Orbital, Electrostatic, and Steric Effects on the Reactivities and *Endo* and *Exo* Stereoselectivities of Cyclopropene Diels–Alder Reactions. *J. Am. Chem. Soc.* **2016**, *138* (51), 16731–16736. DOI: 10.1021/jacs.6b10463 (c) García, J. I.; Mayoral, J. A.; Salvatella, L. Do Secondary Orbital Interactions Really Exist? *Acc. Chem. Res.* **2000**, *33* (10), 658–664. DOI: 10.1021/ar0000152

(14) All eight transition states, including $\mathbf{TS_A}$-$\mathbf{TS_D}$ in Scheme 3b, are shown in Figure S1 of Supporting Information.

(15) Satoh, D.; Hashimoto, T. Preparation of Card-17 (20)-enolides from Carda-16, 20 (22)-dienolide. *Chem. Pharm. Bull.* **1975**, *24* (8), 1950–1953. DOI: 10.1248/cpb.24.1950

(16) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. 2-Azaadamantane *N*-Oxyl (AZADO) and 1-Me-AZADO: Highly Efficient Organocatalysts for Oxidation of Alcohols. *J. Am. Chem. Soc*. **2006**, *128* (26), 8412–8413. DOI: 10.1021/ja0620336

(17) (a) Brown, H. C.; Jadhav, P. K. Asymmetric carbon-carbon bond formation via *B*-allyldiisopinocampheylborane. Simple Synthesis of Secondary Homoallylic Alcohols with Excellent Enantiomeric Purities. *J. Am. Chem. Soc*. **1983**, *105* (7), 2092–2093. DOI: 10.1021/ja00345a085 (b) Matsuya, Y.; Yamakawa, Y.; Tohda, C.; Teshigawara, Y.; Yamada, M.; Nemoto, H. Synthesis of Sominone and Its Derivatives Based on an RCM Strategy: Discovery of A Novel Anti-Alzheimer's Disease Medicine Candidate "Denosomin". *Org. Lett.* **2009**, *11* (17), 3970–3973. DOI: 10.1021/ol901553w

(18) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc*. **2000**, *122* (34), 8168–8179. DOI: 10.1021/ja001179g

(19) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide. *Angew. Chem. Int. Ed.* **2005**, *44* (9), 1378–1382. DOI: 10.1002/anie.200462207

(20) See SI for comparison of NMR spectra.