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A Synthetic Route to The Core Structure of (−)-Retigeranic Acid A

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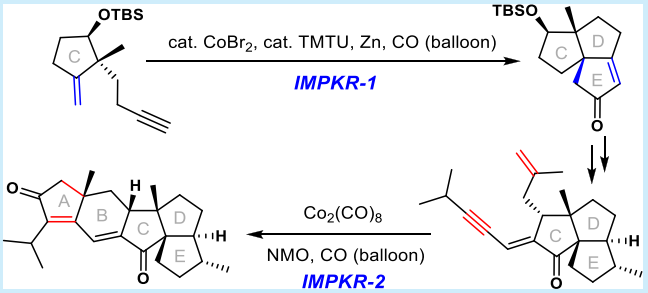
ABSTRACT: Retigeranic acid A is a uniquely structured pentacyclic sesterterpene bearing eight stereogenic centers. We report a concise route to the core structure of (−)-retigeranic acid A. The stereochemistry of its six chiral centers and three quaternary carbon centers was well-controlled. This route features two intramolecular Pauson−Khand reactions (IMPKRs): the first forged the D and E rings to deliver the triquinane subunit, and the second constructed the A and B rings and diastereoselectively installed the quaternary C_{6a} center.



Retigeranic acid A, first isolated by Seshadri in 1965 from the lichens of the *Lobaria retigera* group found in the Himalayas,[1a,b] is a structurally unique sesterterpene resulting from a remarkably intricate biosynthetic construction.[1c]

Although the biological activity of retigeranic acid A has not been determined, the significant bioactivities of its parent genus *Lobaria* and the unique structure of this molecule have captured broad attention from synthetic chemists.[2,3] Retigeranic acid A was the first isolated terpene containing an angular triquinane subunit;[4] it possesses a unique fused pentacyclic skeleton with eight stereogenic centers, including three all-carbon quaternary centers, especially the vicinal quaternary centers at the bridgehead positions (Figure 1A).

Despite formidable challenges, unremitting efforts have been devoted to accessing this molecule and have assisted the confirmation of its structure. In 1985, Corey and co-workers[5] developed a linear route to prepare the racemate of retigeranic acid using a Diels−Alder reaction, a [2 + 2] cycloaddition/ring expansion, and a ring contraction as the key steps. Shortly after that, Paquette,[6] Hudlicky,[7] and Wender[8] independently reported convergent asymmetric syntheses of retigeranic acid A using different strategies, e.g., Claisen−Schmidt condensation/1,4-addition, vinylcyclopropane−cyclopentene rearrangement, or alkene−arene *meta* photocycloaddition/Diels−Alder reaction (Figure 1B). Considering the potential biological properties and the attractive structure, developing a supplementary approach to (−)-retigeranic acid A and its analogues is highly desirable for both drug discovery and academic research.

The intramolecular Pauson−Khand[9a] reaction (IMPKR) is considered a powerful tool to construct cyclopentenone frameworks, which are useful synthetic handles for further manipulations in natural product synthesis.[9b−h] Remarkable achievements by Schore,[10a] Ishizaki,[10b−d] Kerr,[10e] Jiang,[10f] Lovely,[10g] Fox,[10h] Mukai,[10i] and our group[11] have demonstrated that when 1,1-disubstituted alkenes are employed as

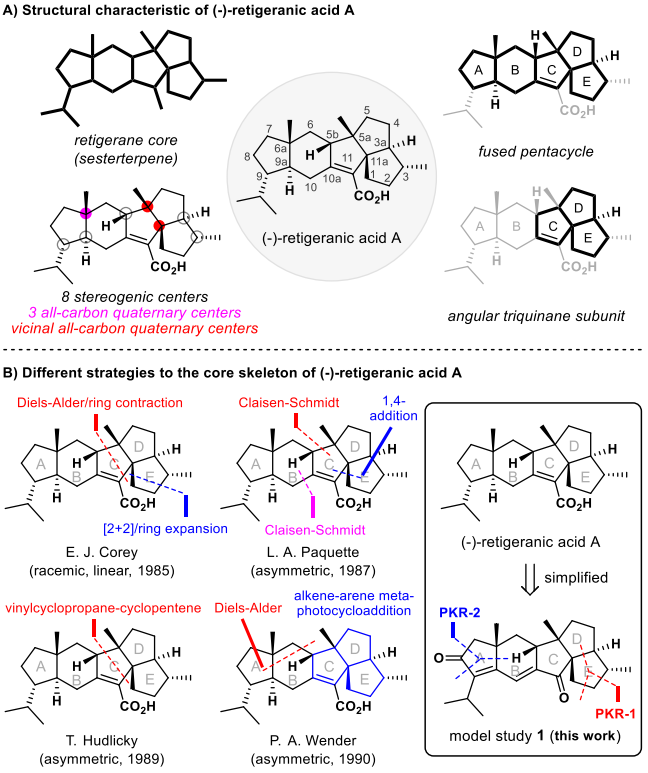


Figure 1. Structural characteristics and different strategies for the synthesis of (−)-retigeranic acid A.

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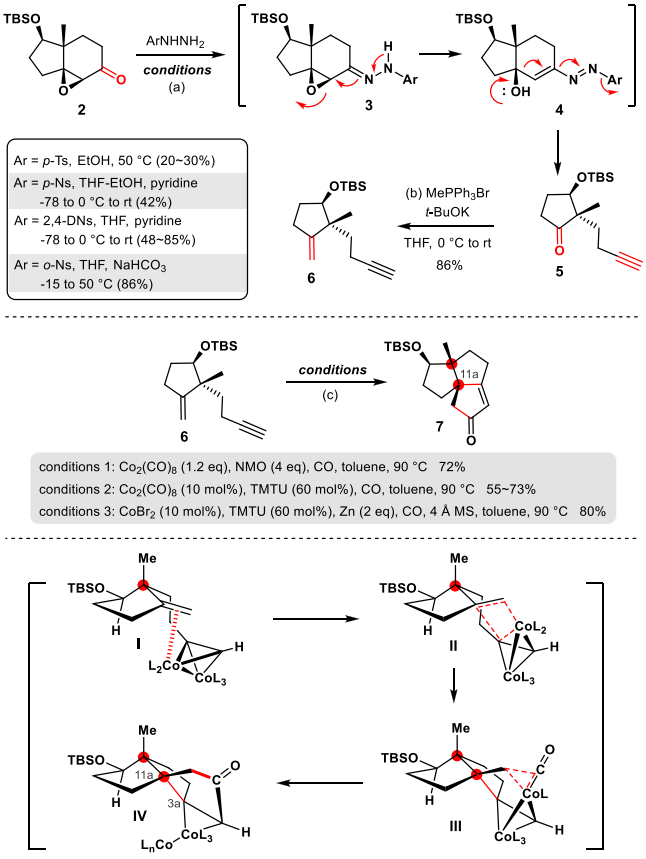
reaction partners, cyclopentenones with a quaternary carbon can be formed.

Herein we report a synthetic study toward (−)-retigeranic acid A, in which two IMPKRs were used as the key steps to forge the complex pentacyclic core structure and the bridged quaternary carbons in a diastereoselective manner.

Our study commenced with known chiral ketone compound **2**[12] (Scheme 1). Cyclic epoxy ketone hydrazone **3**, which was

Scheme 1. Evaluation of the First IMPKR[a]



[a]Reagents and conditions: (a) entry 1: *p*-TsNHNH$_2$ (1.05 equiv), EtOH, 50 °C, 1 h, 20−30%; entry 2: *p*-NsNHNH$_2$ (1.1 equiv), pyridine (1.3 equiv), THF/EtOH, −78 to 0 °C to rt, 4 h, 42%; entry 3: 2,4-DNsNHNH$_2$ (1.05 equiv), pyridine (1.3 equiv), THF, −78 to 0 °C, then rt, 18 h, 48−85%; entry 4: *o*-NsNHNH$_2$ (1.0 equiv), NaHCO$_3$ (3 equiv), THF, −15 to 50 °C, 36 h, 86%; (b) MePPh$_3$Br (1.3 equiv), *t*-BuOK (1.3 equiv), THF, 0 °C to rt, 24 h, 86%; (c) conditions 1: Co$_2$(CO)$_8$ (1.2 equiv), NMO (4.0 equiv), CO, toluene, 90 °C, 8 h, 72%; conditions 2: Co$_2$(CO)$_8$ (10 mol %), TMTU (60 mol %), CO, toluene, 90 °C, 48 h, 55−73%; conditions 3: CoBr$_2$ (10 mol %), TMTU (60 mol %), Zn (2 equiv), 4 Å MS, CO, toluene, 90 °C, 18 h, 80%. TBS = *tert*-butyldimethylsilyl, *p*-Ts = *p*-toluenesulfonyl, *p*-Ns = *p*-nitrobenzenesulfonyl, 2,4-DNs = 2,4-dinitrobenzenesulfonyl, *o*-Ns = *o*-nitrobenzenesulfonyl, NMO = 4-methylmorpholine *N*-oxide, TMTU = tetramethylthiourea, MS = molecular sieves.

prepared in situ from the condensation of ketone **2** and the aromatic sulfonylhydrazide, could undergo an Eschenmoser−Tanabe fragmentation[13] to deliver acyclic alkynone **5**. Preliminary investigation by variation of the sulfonylhydrazide,[14] solvent, and base showed that a yield of 86% could be obtained when the reaction was carried out with *o*-nitrobenzenesulfonylhydrazide[15] and sodium bicarbonate in THF. A Wittig olefination of ynone **5** produced enyne compound **6**.

We then tested different conditions for the first IMPKR. Treatment of enyne **6** with stoichiometric Co$_2$(CO)$_8$ and NMO under a CO atmosphere resulted in the formation of fused tricyclic compound **7** in 72% yield as a single diastereomer. However, Co$_2$(CO)$_8$ is expensive, and this reaction required high-quality NMO. The use of hygroscopic NMO dramatically decreased the efficiency of the reaction.

We therefore explored alternative ways to prepare this key intermediate. Initially, we tested the annulation reaction using a catalytic amount of Co$_2$(CO)$_8$ and TMTU under a CO atmosphere,[11a] but the product yield was affected by the quality of the Co$_2$(CO)$_8$, and the yield of **7** was inconsistent, ranging from 55 to 73%. We finally found out that product **7** could be obtained in 80% yield by treatment of air- and moisture-stable CoBr$_2$ with zinc dust (2.0 equiv) in the presence of TMTU.[11b] It is noteworthy that the stereochemistry at the C$_{11a}$ position matched that of (−)-retigeranic acid A. A conformational analysis **I** → **IV** showed that the enyne−cobalt complex got close to the alkene moiety from below and eventually forged the C$_{3a}$−C$_{11a}$ bond with excellent diastereoselectivity.

1,4-Reduction of conjugated carbonyl compound **7** with copper hydride using lithium tri-*tert*-butoxyaluminum hydride (LTBA)[16] as the hydrogen source followed by trapping of the resultant enolate anion with iodomethane afforded ketone **8** in 90% yield with excellent diastereoselectivity (Scheme 2). Reduction of the ketone into an alcohol and subsequent removal of the hydroxyl group through a Barton−McCombie radical deoxygenation[17] delivered silyl ether **10**.

The subsequent desilylation/oxidation sequence[18] transformed **10** into ketone compound **11**. Conversion of the ketone into an enol silyl ether followed by a visible-light-promoted organocatalytic aerobic oxidation developed by our group[19] generated cyclopentenone **12** in 70% yield over two steps. A Grignard reaction of **12** using 2-methylallylmagnesium chloride gave allylic alcohol **13**, and its structure was established by X-ray crystallographic analysis. Pyridinium dichromate (PDC)-mediated oxidative rearrangement[20] of allylic alcohol **13** afforded enone **14** in 86% yield over two steps. The next step was a selective reduction of the enone into a ketone in the presence of the terminal alkene moiety, which proved to be difficult because the terminal alkene was easily reduced under many reductive conditions. Eventually, this was realized by treatment of enone **14** with Li/NH$_3$(l) at −78 °C, and ketone **15** was obtained as an inseparable mixture of diastereoisomers in a ratio of 4:1 and a combined yield of 80%. Subsequent installation of the alkyne moiety at the α-position of the ketone was achieved through a three-step reaction sequence, specifically, aldol addition, activation of the resultant alcohol with methanesulfonyl chloride, and base-promoted β-elimination of the newly generated mesylate, delivering enyne **16** in 78% yield.

Enyne compound **16** was an inseparable mixture of diastereoisomers. After a Luche reduction, allylic alcohol **17** was isolated as the major isomer in 70% yield, but the stereochemistry at C$_{5b}$ could not be identified (Scheme 3). Subjecting **17** to IMPKR conditions successfully produced a fused pentacyclic compound in a highly diastereoselective manner. However, this proved to be C$_{5b}$,C$_{6a}$-bis-*epi*-**1** after a careful analysis of the ^{1}H−^{1}H NOESY spectra, meaning that the stereochemistry at C$_{5b}$ of the major diastereoisomer in the mixed enyne **16** was the opposite of that in (−)-retigeranic acid A.

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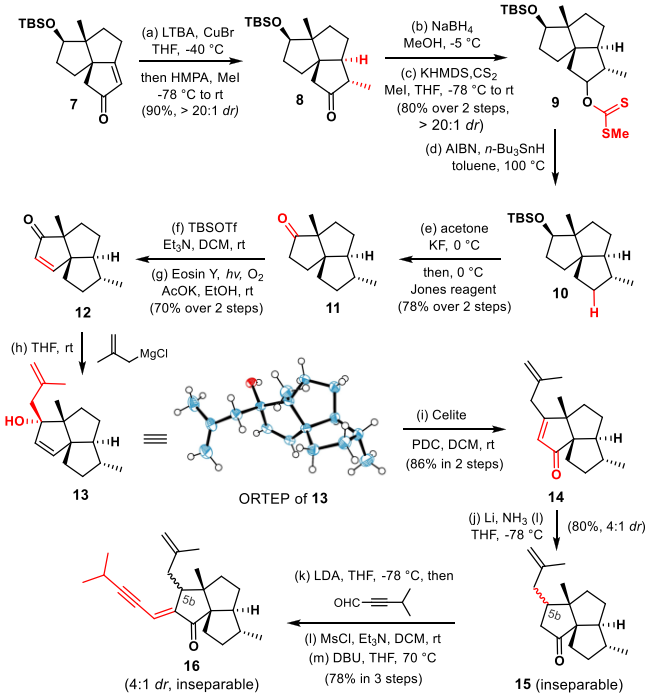
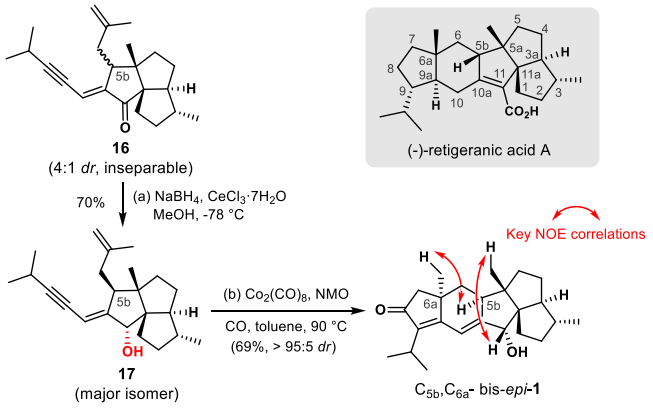
Scheme 2. Synthesis of the Enyne Precursor for the Second IMPKR[a]



[a]Reagents and conditions: (a) CuBr (2.0 equiv), LTBA (1.5 equiv), THF, −40 °C, 2 h, then −78 °C, HMPA (9.0 equiv), MeI (9.0 equiv), −78 °C to rt, 24 h, 92%; (b) $NaBH_4$ (1.1 equiv), MeOH, −5 °C, 2 h; (c) KHMDS (1.2 equiv), CS_2 (1,2 equiv), THF, −78 °C to rt, 2 h, then MeI (2.4 equiv), 0 °C to rt, 2 h, 89% over two steps; (d) AIBN (0.1 equiv), n-Bu_3SnH (2.0 equiv), toluene, 100 °C, 8 h; (e) acetone, KF (8.0 equiv), Jones reagent (5.0 equiv, 2.5 M in 4 M H_2SO_4), 0 °C, 12 h, 78% over two steps; (f) TBSOTf (1.5 equiv), Et_3N (3 equiv), DCM, 0 °C to rt, 8 h; (g) Eosin Y (0.05 equiv), AcOK (1.2 equiv), EtOH, O_2, hv, 8 h, 70% over two steps; (h) 2-methylallylmagnesium chloride (1.5 equiv), THF, 12 h; (i) PDC (3.0 equiv), Celite (1.5 g per mmol of **15**), DCM, 12 h, 86% over two steps; (j) Li (20.0 equiv), NH_3 (1 mL per mmol of Li), THF, −78 °C, 5 h, 80%, 4:1 dr; (k) LDA (1.5 equiv), THF, −78 °C, 2 h, then 4-methylpent-2-ynal (3 equiv), −78 °C; (l) MsCl (2 equiv), Et_3N (4 equiv), DCM, 4 h; (m) DBU (4 equiv), THF, 70 °C, 78% over three steps, 4:1 dr. LTBA = lithium tri-*tert*-butoxyaluminum hydride, HMPA = hexamethylphosphoramide, KHMDS = potassium bis(trimethylsilyl)amide, AIBN = 2,2′-azobis(2-methylpropionitrile), Tf = trifluoromethanesulfonyl, PDC = pyridinium dichromate, LDA = lithium diisopropylamide, MsCl = methanesulfonyl chloride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

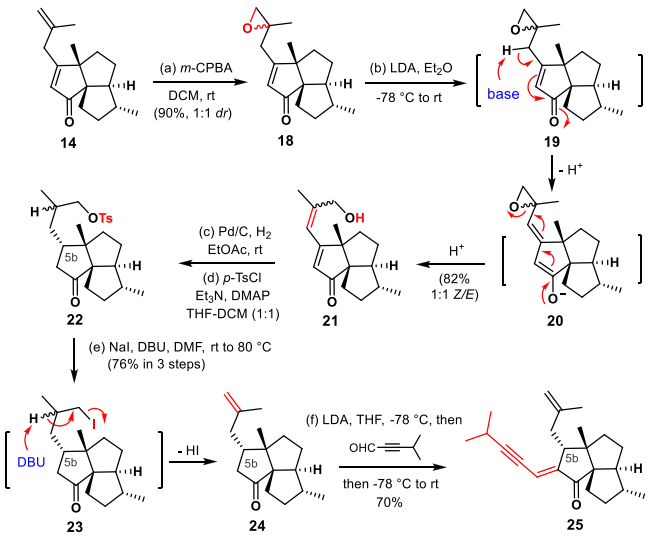
To access the enyne precursor of the IMPKR with the correct stereochemistry at C_{5b}, an alternative route was developed. As shown in Scheme 4, selective epoxidation of the terminal olefin in enone **14** with 3-chloroperoxybenzoic acid (*m*-CPBA) afforded **18** in 90% yield with 1:1 dr. Treatment of epoxide **18** with LDA resulted in the formation of conjugated ketone **21** with a 1:1 *Z*/*E* ratio.[21] This reaction was proposed to proceed through deprotonation at the γ-position of the α,β-unsaturated ketone to form conjugated enolate anion intermediate **20**, which then underwent ring opening of its epoxide to generate **21**. Hydrogenation of the carbon−carbon double bonds followed by activation of the hydroxyl group with *p*-toluenesulfonyl chloride delivered ketone **22**. To our delight, the stereochemistry at C_{5b} of **22** was well-controlled and matched that of (−)-retigeranic acid A. Regeneration of the alkene moiety was then achieved by treatment of **22** with NaI and DBU, which went through replacement of *p*-toluenesulfonate with the iodine anion and base-promoted H−I elimination of intermediate **23**.[22] The formed alkene **24** underwent an aldol condensation with 4-methylpent-2-ynal in the presence of LDA as the base to afford enyne compound **25** in 70% yield with the correct stereochemistry at C_{5b}.

Scheme 3. Preliminary Evaluation of the Second IMPKR Using the C_{5b}-*epi*-Enyne Precursor[a]



[a]Reagents and conditions: (a) $NaBH_4$ (1.1 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), MeOH, −78 °C, 3 h, 70%; (b) $Co_2(CO)_8$ (1.2 equiv), NMO (4.0 equiv), CO, toluene, 90 °C, 8 h, 69%.

Scheme 4. Synthesis of the Enyne Precursor with Correct Stereochemistry at C_{5b} for the Second IMPKR[a]



[a]Reagents and conditions: (a) *m*-CPBA (2.0 equiv), DCM, rt, overnight, 90%; (b) LDA (2.6 equiv), Et_2O, −78 °C to rt, 2 h, 82%; (c) Pd/C (20 wt %), H_2 (5−8 MPa), EtOAc, 4 h; (d) *p*-TsCl (3.0 equiv), DMAP (3.0 equiv), Et_3N (3.0 equiv), THF/DCM (1:1), overnight; (e) NaI (5.0 equiv), DBU (3.0 equiv), DMF, rt to 80 °C, 6 h, 76% over three steps; (f) LDA (1.5 equiv), THF, −78 °C, 1 h, then 4-methylpent-2-ynal (4.0 equiv), −78 °C to rt, 2 h, 70%. *m*-CPBA = 3-chloroperoxybenzoic acid, DMAP = 4-dimethylaminopyridine.

With enyne **25** in hand, we investigated the second IMPKR (Scheme 5). Two representative sets of conditions were tested.

The IMPKR performed with stoichiometric $Co_2(CO)_8$ and NMO under a CO atmosphere delivered the desired pentacyclic compound **1** with the correct stereochemistry at

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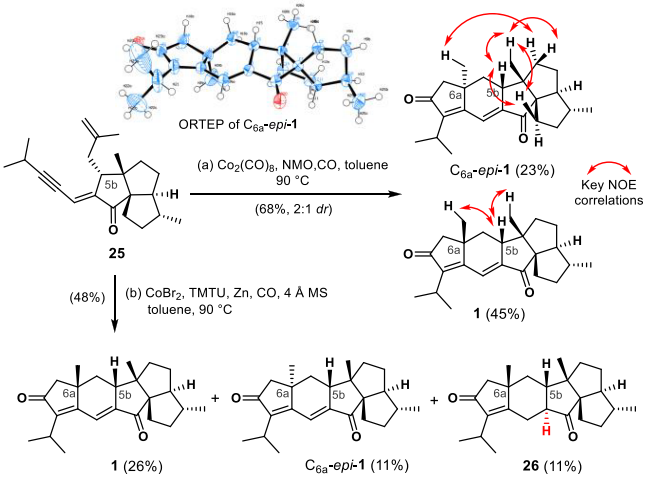
Scheme 5. Evaluation of the Second IMPKR[a]



[a]Reagents and conditions: (a) $Co_2(CO)_8$ (1.2 equiv), NMO (4.0 equiv), CO, toluene, 90 °C, 18 h, 68%; (b) $CoBr_2$ (20 mol %), TMTU (120 mol %), Zn (2 equiv), 4 Å MS, CO, toluene, 90 °C, 36 h, 48%.

both C_{5b} and C_{6a} in 45% yield. The C_{6a} epimer of **1** was generated as a minor product (23%). The structure of C_{6a}-*epi*-**1** was further confirmed by X-ray crystallographic analysis, while the stereochemistry of C_{6a} quaternary center of **1** was defined through $^1H-^1H$ NOESY spectral analysis.

Treatment of enyne **25** with alternative conditions[11b] using $CoBr_2$ (20 mol %), TMTU (1.2 equiv), and zinc dust (2 equiv) under a CO atmosphere, which proved to be the best choice for the first IMPKR, gave inferior yields of both **1** (26%) and C_{6a}-*epi*-**1** (11%). During this reaction, an unexpected reduction product **26** featuring a *trans*-fused [6,5] ring system was obtained in 11% yield, which was probably generated through further reduction of **1** with a small amount of in situ-formed [CoH] species.[23]

In summary, the core structure of (−)-retigeranic acid A has been synthesized with six well-defined stereogenic centers, all of which matched with those of the target molecule. This synthetic route features two IMPKRs. The application of the first IMPKR forged the D and E rings to afford the triquinane subunit in a highly diastereoselective manner, while the second one constructed the A and B rings and efficiently installed the C_{6a} quaternary center with the correct stereochemistry. Additionally, the Eschenmoser−Tanabe fragmentation, the configuration inversion at C_{5b}, and the diastereoselective 1,4-reduction/methylation sequence are also crucial to the success of this route. Further studies toward the total synthesis of retigeranic acids are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01633.

Experimental details and characterization data; Tables S1 and S2; Figures S1 and S2; copies of ^1H and ^{13}C NMR spectra; copies and assignments of COSY, HSQC, HMBC, and NOESY spectra; crystallographic data for compound **13** and C_{6a}-*epi*-**1** (PDF)

Accession Codes

CCDC 2074440 and 2074441 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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