Biomimetically inspired asymmetric total synthesis of (+)-19-dehydroxyl arisandilactone A

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Complex natural products are a proven and rich source of disease-modulating drugs and of efficient tools for the study of chemical biology and drug discovery. The architectures of complex natural products are generally considered to represent significant barriers to efficient chemical synthesis. Here we describe a concise and efficient asymmetric synthesis of 19-dehydroxyl arisandilactone A—which belongs to a family of architecturally unique, highly oxygenated nortriterpenoids isolated from the medicinal plant Schisandra arisanensis. This synthesis takes place by means of a homo-Michael reaction, a tandem retro-Michael/Michael reaction, and Cu-catalysed intramolecular cyclopropanation as key steps. The proposed mechanisms for the homo-Michael and tandem retro-Michael/Michael reactions are supported by density functional theory (DFT) calculation. The developed chemistry may find application for the synthesis of its other family members of Schisandraceae nortriterpenoids.

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Schisandra chinensis is also known as wu wei zi in China, which translates to five-flavour berry, a description given to it because it possesses all five basic flavours of salty, sweet, sour, spicy and bitter. Records show that for over 2,000 years five-flavour berries have been used as sedatives and tonic agents, as well as for the treatment of rheumatic lumbago and related diseases1,2.

Because S. chinensis is a traditional Chinese herbal medicine, it has been targeted in medicinal chemistry to identify lead compounds for drug discovery. There has been considerable progress in the discovery of bioactive triterpenoids from the Schisandraceae family over the past two decades. To date, over 200 nortriterpenoids have been structurally characterized1,2, and some representative structures 1-6 are shown in Fig. 1. Preliminary biological assays have indicated that some of the nortriterpenoids possess inhibitory activity toward hepatitis, tumours and HIV-1 (refs 1,2).

Natural sources of these compounds are scarce, which hampers systematic studies of their biological activities. Synthesis of these products is needed to continue biomedical research in this area, and much effort has been devoted to total synthesis of these nortriterpenoids (‘Synthetic studies on Schisandraceae triterpenoids’, see ref. 3 and related references therein). From this research, total syntheses of schindilactone A4, rubriflordilactone A3,6, schilancitrilactones B and C7 and propindilactone G8 (see Fig. 1) have been developed.

In 2010, Shen isolated (+)-arisandilactone A9 and (+)-arisandilactone C10 (1 and 2 in Fig. 1) from S. arisanensis, which is found in Taiwan. The structures of these compounds were confirmed by X-ray crystallography. Among the nortriterpenoids, arisandilactone A (1) is unique in that it has an oxa-bridged 7-9-5 tricyclic carbon core, which has not been encountered in natural products before. Because of this structural feature, arisandilactone A (1) is a challenging target for total synthesis. To the best of our knowledge, no synthesis of arisandilactone A (1) has been reported to date.

Natural products with unique and complex architectures are challenging in organic synthesis (for an excellent review, see ref. 11). In this regard, biomimetic approaches for the formation of complex natural products have proven to be effective strategies in organic synthesis12. Among the various biomimetic reactions, Michael-type reaction can be regarded as one of the most powerful reactions in the biosynthesis of natural products13. Here, we report an asymmetric total synthesis of (+)-19-dehydroxyl arisandilactone A (1a), a derivative of arisandilactone A (1), using a biomimetic synthesis involving a homo-Michael reaction and a tandem retro-Michael/Michael reaction as key steps.

Results

Retrosynthetic analysis. For the total synthesis of arisandilactone A (1), construction of its strained transannular 10-oxabicyclo[5.2.1]dec-6-en-8-one core (DE ring) bearing an oxa-bridged α,β-unsaturated ketone subunit is the most difficult task in the entire total synthesis. Thus, from a synthetic strategy point of view, this fragment should be introduced at a late stage in the total synthesis, and preferable by a biomimetic synthesis because of its high sensitivity and instability.

While conducting the model study toward the total synthesis of arisandilactone C (2), we serendipitously found that this strained bicyclic core could be constructed via an intramolecular oxahomo-Michael reaction (Fig. 2). In the event, we first synthesized aldehyde 7 and then coupled with tert-butylidimethyl((3-methyl-furan-2-yl)oxy)silane (8) via a vinylogous Mukaiyama aldol reaction (VMAR). To our surprise, product 9 was obtained in approximately 50% yield when the reaction was carried out at −78 °C in the presence of BF3·Et2O in CH2Cl2. The reaction
Arisandilactone A (5)

Figure 2 | Model study. Unified biosynthetic approach featuring homo-Michael and retro-Michael/Michael reactions for formation of the 7/9/5 tricyclic core of arisandilactone A (1).

was proposed to proceed through a typical VMAR to form intermediate B. This was followed by a homo-Michael reaction through the cleavage of its carbon–carbon bond at C13 and C16 and simultaneous formation of the five-membered F ring (see Fig. 2). The newly generated three stereogenic centres at C20, C22 and C23 in product 9 formed a syn/syn stereotriad. The arrangements of groups at the stereogenic centres at C22 and C23 were opposite to those in arisandilactone A, which has an anti/syn stereotriad. Stereoselective synthesis of the anti/syn stereotriad has proven to be challenging.

On inspection of the structure of product 9, we found that 9 could be epimerized at its C22 and C23 stereogenic centres by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) via a tandem retro-Michael/Michael reaction. This strategy has been used by Pyne and co-workers in the total synthesis of Stemona alkaloid (11S, 12R)-dihydrostefolode (C) from (11S, 12S)-dihydrostefolode (A) through intermediate B (Fig. 3). The stereochemical outcome of the DBU-initiated ring opening reaction of A can be rationalized as occurring through a deprotonation of A by DBU at the acidic γ-position of the lactone ring which would result in the anionic intermediate B, and then lead to (11S, 12R)-dihydrostefolode (C) to avoid the unfavourable steric interaction between the methoxy (C13) and methyl (C10) groups in the intermediate B (Fig. 3).

To explore the feasibility of this strategy, we treated 9 with DBU in toluene at 80 °C. As expected, the desired product 10 was obtained in 48% yield (Fig. 2), and its structure was tentatively confirmed through X-ray crystallography; however, the data were of insufficient quality to allow a definitive determination of the structure. Inspired by these results, we applied this knowledge to the total synthesis of 19-dehydroxyl arisandilactone A (1a) using the homo-Michael and the tandem retro-Michael/Michael reactions as key steps.

Figure 4 illustrates our proposed biomimetic total synthesis of 19-dehydroxyl arisandilactone A. Based on the chemistry presented above, we expected the target 1a could be produced from precursor A using the developed tandem retro-Michael/Michael reaction as a key step. The intermediate A, in turn, could be produced from B via nucleophilic attack of the silyl ether C on the aldehyde in intermediate B via a VMAR, followed by the key intramolecular homo-Michael reaction as shown above. Precursor aldehyde B could be prepared from lactone D via a series of functional group interconversions.

It is conceivable that the cis-fused 8/3-bicyclic domain in lactone D could be constructed via a Cu-catalysed intramolecular cyclopropanation of E by taking advantage of conformation control of the substrate. This reaction would generate D with three contiguous stereogenic centres at C13, C16 and C17, as well as a lactone fragment, which could serve as a handle to install the side chain. To the best of our knowledge, synthesis of a cis-fused 8/3-bicyclic ring fragment in D is unprecedented. Thus, our retrosynthetic analysis could trace back to the synthesis of the
oxa-bridged ‘tri-substituted’ cyclooctene ring in E, which could be generated from diene F using a ring-closing metathesis (RCM) reaction, a method that was utilized in our total synthesis of schindilactone A5 (3 in Fig. 1). Diene F, in turn, could be made from ketoester G by modifying the methods applied in our total synthesis of schindilactone A. Thus, (R)-(−)-carvone (H) is a logical starting material for the preparation of ketoester G.

Asymmetric synthesis of 19-dehydroxyl arisandilactone A (1a).

Our synthesis began with asymmetric construction of the fully functionalized bislactone 16 from (R)-(−)-carvone (Fig. 5). A two-step procedure for the conversion of (R)-(−)-carvone to cycloheptenone was accomplished using a Mander’s methoxycarbonylation, followed by a sequence of cyclopropanation/ring-expansion reactions20,21 to afford 11 in 68% yield. Compound 11 was hydrolysed with LiOH, and the resulting acid then underwent an AgOTf-mediated lactonisation22 to afford 12 in 66% overall yield. To install the C10 silyloxy group of 13, 12 was first exposed to TMSO(CH2)2OTMS/TMSOTf23, and the resultant ketal ester was then reacted with potassium bis(trimethylsilyl)amide in the presence of P(OMe)3 under an O2 atmosphere24, followed by reaction with triethylchlorosilane to afford 13 in 70% yield as a single diastereoisomer.

Figure 3 | Retro-Michael/Michael reaction. DBU mediated a biomimetic tandem retro-Michael/Michael reaction for the formation of (11S,12R)-dihydrostemofoline (C) from (11S,12S)-dihydrostemofoline (A) through intermediate B.

Figure 4 | Retrosynthetic analysis of 19-dehydroxyl arisandilactone A (1a). The Homo-Michael/Michael reaction were used as key steps to construct core structure of 19-dehydroxyl arisandilactone A (1a).
Figure 5 | Synthesis of compound 16. (a) (−)-carvone (1.0 eq), LiHMDS (2.1 eq), CICOOMe (1.5 eq), THF, −78 °C, 2 h, 90%; (b) Et₂Zn (2.3 eq),
CH₂C (2.3 eq), HCOOH (2.3 eq), DCM, 0 °C, 75%; (c) LiOH (2.2 eq), MeCN/H₂O (1:1), rt, 92%; (d) AgOTf (0.05 eq), ClCH₂CH₂Cl, reflux, 72%;
(e) TMSOCH₂CH₂OTMS (1.4 eq), TMSOTf (0.1 eq), DCM, −78 to −20 °C, 87%; (f) KHMD (2.0 eq), P(O)Me₃ (1.6 eq), −78 °C, THF, under a balloon filled with O₂, then TESCl (1.4 eq), 81%; (g) SeO₂ (3.0 eq), Ac₂O (1.0 eq), AcOH (0.16 eq), 4 Å MS (120% mass fraction), dioxane, 65 °C, 85%; (h) CBr₄ (1.2 eq), PPh₃ (1.2 eq), i-Pr₂NEt (0.4 eq), DCM, 0 °C, 3 h, then Pd₂(dba)₃ (0.05 eq), PivOCl (0.5 eq), PivNEt (0.8 eq), EtOH, under a balloon filled with CO, 0 °C to rt, 63%; (i) PPTS (0.1 eq), acetone/H₂O (10:1), 60 °C, 90%; (j) Pd/C (10% mass fraction), ETOAc, under balloon filled with H₂, rt, 92%; (k) Grignard reagent (3.0 eq), THF, −20 °C, 80%; (l) LiHMDS (2.0 eq), LiCl (2.0 eq), MoOCl₃ (1.5 eq), THF, −78 °C, 91%; and (m) BnBr (2.0 eq), Ag₂O (2.0 eq), DCM, rt, 97%. LiHMDS, lithium hexamethyldisilamide. KHMD, potassium hexamethyldisilylamine. MoOCl₃, oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), also referred to as Vedejs’ reagent; 4 Å MS, molecular sieves, type 4A; Pd₂(dba)₃, tris(dibenzylideneacetone)dipalladium(0); PivOCl, cesium pivolate; PPTS, pyridinium p-toluenesulfonate; TESCl, triethylsilyl chloride.
Next, we treated 13 with SeO$_2$ in the presence of AcOH$^{25}$, Ac$_2$O and 4 Å molecular sieves for an allylic oxidation. The resulting allylic alcohol was then converted to its corresponding carboxylic ester by bromination$^{26}$ and Pd-catalysed carbonylation$^{27}$ to give an ester in 63% yield in one step. After deprotection, enone 14 was obtained in 90% yield. To synthesize bislactone 16 from enone 14, we adopted the strategy developed in our total synthesis of schindilactone A$^5$. Enone 14 was sequentially subjected to a Pd-catalysed hydrogenation (92%) and Grignard reaction (80%) to give 15 in 74% yield as a single diastereoisomer. The observed diastereoselectivity could be attributed to the steric bulk of the triethylsilyloxy group in substrate 14, which allows both the hydrogenation and Grignard reactions to occur at the less-hindered face (see three-dimensional structure of 14 in Fig. 5).

To achieve facially selective α-hydroxylation, bislactone 15 was treated with LiHMDS in the presence of LiCl$^{28}$ at −78 °C in THF. The resulting enolate complex was subsequently oxidized with MoOPH$^{29}$ to afford a secondary alcohol, which was then treated with BnBr/Ag$_2$O$^{30}$ to give bislactone 16 in 88% overall yield as a single diastereoisomer. The relative stereochemistry of 16 was confirmed by X-ray crystallography (Fig. 5).

This highly stereoselective α-hydroxylation was also likely promoted by the steric effect of the triethylsilyloxy group in enolate 15a, which was generated in situ during the treatment of 15 with LiHMDS, forcing the oxidant to approach from the less-hindered face (see three-dimensional structure of 15a in Fig. 5).

We then investigated our proposed RCM reaction to construct the medium-sized ring-based tri-substituted cyclooctene in compound 18 (Fig. 6). By screening various reaction conditions (for example, catalysts, solvents, additives and reaction temperatures), we determined that the use of the second-generation Hoveyda–Grubbs catalyst (17) in toluene at 80 °C afforded the best results. Considering the potential for in situ epimerization of hemiketal during the RCM reaction$^{3,32}$, we treated bislactone 16 with vinyl magnesium bromide$^{33}$. The resulting dienes, as an epimeric mixture of hemiketals, were then subjected to a RCM reaction in the presence of catalyst 17 (ref. 34; 5 % amount-of-substance fraction) in toluene at 80 °C for 18 h. To our delight, the desired product 18 was obtained as a single diastereoisomer in an overall 79% yield for the two steps.

For stereoselective formation of the 8/3 bicyclic-ring system in 20, an efficient method was required to prepare α-diazoacetate 19 from hemiketal 18. Initial attempts to prepare 19 by esterification coupling of 18 with CICOCH$_2$NNH$_2$$^{35}$ in the presence of a base produced only a trace amount of the desired product. This could be attributed to steric hindrance at the C15 hydroxy group in 18. Consequently, we carried out a systematic study for the synthesis of 19. We found out that 19 could be effectively generated by the treatment of 18 with Ac$_2$O/Et$_3$N in the presence of DMAP followed by reaction with LiHMDS. The resulting enolate was reacted with CF$_3$CO$_2$CH$_2$CF$_3$ at −78 °C and then treated with Ts$_2$N$_2$ to afford 19 in an overall 90% yield for the three steps. We next investigated the conditions for synthesis of the rigid and highly strained intermediate 20 from 19 via the proposed intramolecular cyclopropagation reaction. To date, intramolecular cyclopropanation for the formation of an 8/3 fused bicyclic ring system has not been reported. Consequently, it was unknown whether such a rigid and highly strained intermediate could be generated. We hypothesized that strategical positioning of α-diazoacetate could be used to facilitate the cyclopropanation in a diastereoselective manner. To achieve this goal, we systematically profiled the cyclopropanation reaction with different metal catalysts, including CuSO$_4$, CuCl$_2$, bis(2,4-pentanedionato) copper(II) (Cu(acac)$_2$), CuI, Rh$_2$(OAc)$_4$ and Cu(tbs)$_2$. We found that the Cu(tbs)$_2$-catalysed cyclopropanation$^{36}$ of 19 afforded 20 in 65% yield as a single diastereoisomer. The structure of 20 was confirmed by two-dimensional NMR spectroscopy.

With lactone 20 in hand, we next investigated its transformation to aldehyde 27. As illustrated in Fig. 7, the first synthetic task was the conversion of the lactone ring in 20 to the terminal olefin in 21. Exposure of 20 to a solution of N$_2$O-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in THF at −20 °C (ref. 37) formed a Weinreb amide in 90% yield, which was reacted with methylmagnesium chloride to afford a ketone in 89% yield. This ketone then underwent Peterson olefination$^{38}$ by reaction with freshly produced (trimethylsilyl)methylmagnesium...
chloride in the presence of CeCl₃ (ref. 39) in THF at 0 °C, and the resultant mixture was worked up by the treatment with silica gel to give an olefin, which, without purification, was then subjected to a desilylation with TBAF to give 21 in 82% yield for the two steps. The structure of 21 was confirmed by X-ray crystallography.

It is worthwhile to mention that when the ketone derived from the Weinreb amide was directly reacted with a Wittig reagent derived from methyltriphenylphosphonium bromide, the expected olefination proceeded. However, epimerization occurred at C17 of the product 21.

The next task in the synthesis of aldehyde 27 was A ring formation in intermediate 24. Diol 21 was selectively protected by sequential treatment with TMS-imid. and Ac₂O/DMAP, to give 22 in an overall 93% yield for the two steps. Dieckmann-type condensation⁴ of 22 proceeded smoothly to afford product 23.

Figure 7 | Synthesis of alcohol 27. (a) MeNHOMe·HCl (5.0 eq), i-PrMgCl (10.0 eq), THF, −20 °C, 90%; (b) MeMgCl (3.0 eq), THF, 0 °C, 89%; (c) TMSCH₂MgCl (5.0 eq), CeCl₃ (5.0 eq), THF, 0 °C, then silica gel, DCM, 83%; (d) TBAF (3.0 eq), THF, 0 °C, 99%; (e) TMS-imid. (10.0 eq), DCM, 0 °C, 95%; (f) Ac₂O (15.0 eq), DMAP (1.0 eq), Et₃N (15.0 eq), PhMe, rt, 98%; (g) LiHMDS (3.0 eq), THF, −78 to −35 °C, 93% b.r.s.m.; (h) Martin’s sulfurane (1.2 eq), DCM, rt; (i) L-selectride (3.0 eq), −78 °C; (j) TBAF (5.0 eq), THF, 0 °C, 93% in three steps; (k) BMS (10.0 eq), THF, 0 °C, 0.75 h, then Na₂B₄O₇ (excess), H₂O₂ (excess), rt, 65%; (l) TPAP (1.3 eq.), DCM, 0 °C, 88%. BMS, borane-dimethylsulfide complex; b.r.s.m., based on recovered starting material; L-selectride, lithium tri-sec-butylborohydride; Martin’s sulfurane, bis[z.z-bis(trifluoromethyl) benzenemethanolato]- diphenylsulfur; TBAF, tetra-n-butylammonium fluoride; TMS-imid., 1-(trimethylsilyl)-1H-imidazole; TPAP, tetra-n-propylammonium perruthenate(VII).
Figure 8 | Total synthesis of 29. (a) 28 (3.0 eq), BF$_3$·OEt$_2$ (3.3 eq), DCM, –78 °C to –35 °C, 66%.

Figure 9 | Total synthesis of 19-dehydroxyl-arisandilactone A (1a). (a) DBU (15.0 eq), PhMe, 65 °C, 70%; (b) NiCl$_2$·6H$_2$O (1.0 eq), NaBH$_4$ (3.0 eq), MeOH, 0 °C, 62%; (c) 5% NaOMe/MeOH, rt, 73% (b.r.s.m.); (d) W-2 Raney Ni, EtOH, rt, 85%; (e) DMP (2.0 eq), NaHCO$_3$ (5.0 eq), DCM, rt, 87%. b.r.s.m., based on recovered starting material; DMP, Dess-Martin periodinane.
in 93% yield. Dehydration of the C1 hydroxyl group in 23 was achieved by treatment with Martin’s sulfurane, and the resultant \( \alpha,\beta \)-unsaturated lactone was reduced with \( \text{L-selectride} \), followed by desilylation to give 24 as a single diastereoisomer in 93% yield for three steps.

The synthesis of alcohol 26 proved challenging because 24 contained a lactone and a highly rigid three-membered ring-linked olefin. These groups are sensitive to both hydroboration and basic conditions. Thus, after extensive experimentation, we found that treatment of 24 with \( \text{BH}_3\text{SMe}_2 \) in THF at 0°C, followed by oxidation with a solution of \( \text{H}_2\text{O}_2 \) (30%) in the presence of a weak base (\( \text{Na}_2\text{B}_4\text{O}_7 \); ref. 44), product 26 could be obtained in 65% yield, together with its diastereoisomer (16% yield). The stereochemistry at C20 in 26 was confirmed by X-ray crystallography. Thus, synthesis of aldehyde 27 could be achieved in 88% yield by oxidation of substrate 26 with TPAP.

With synthesis of aldehyde 27 achieved, we attempted the proposed biomimetic synthesis of 19-dehydroxyl arisandilactone A (1a) (Fig. 8). In the event, 27 was coupled with 28 in the presence of \( \text{BF}_3 \cdot \text{Et}_2\text{O} \) in \( \text{CH}_2\text{Cl}_2 \) at −78°C, and the resultant mixture was then stirred at −35°C for 1 h, followed by workup to give product 29 in 66% yield as a single diastereoisomer. The reaction actually proceeded through a typical VMAR followed by the proposed homo-Michael reaction. The structure of 29 was confirmed by X-ray crystallography, which indicated that the stereocenters at C22 and C23 were opposite to those in the natural product.

We now move to the stage for the completion of the total synthesis. To this end, substrate 29 was treated with \( \text{DBU} \) in toluene at 65°C, as a result, product 30 was obtained in 70% yield with inversion of the stereogenic centres at C22 and C23 (Fig. 9). Thus, further treatment of 30 with \( \text{NiCl}_2 \cdot \text{6H}_2\text{O}/\text{NaBH}_4 \), the double bonds at C24 and C25 in 30 could be chemo-selectively saturated to give product 31 in 62% yield. However, X-ray crystallographic analysis of 31 indicated that its stereochemistry at C25 was opposite to that in the natural form. We, therefore, treated 31 with \( \text{NaOMe} \) in methanol to invert its stereochemistry at C25, and the resultant product was then subjected to Raney nickel-mediated debenzylation to give product 32 in 73% yield and 85% yield, respectively. The structure of 32 was confirmed by X-ray crystallography. Thus, our total synthesis of 19-dehydroxyl arisandilactone A (1a) was eventually achieved in 87% yield by oxidation of 32 with DMP. Overall, this asymmetric synthesis consists of 37 steps in its longest linear sequence from \( \text{R}(\text{R})-(-)\)-carvone.

**Computational study.** DFT calculations were carried out using the Gaussian 09 program (Gaussian Inc., Wallingford, CT, USA) to determine the diastereoselectivity for the hydroboration step to stereoselectively form 26 from 24 (see Fig. 10). The method B3LYP with 6-31G(d) basis set was used for geometry optimizations in gas phase. M06 functional with larger basis set 6-311+G(d) was used for solvation single point calculations.
in THF based on gas-phase stationary points using the continuum solvation model SMD (see Supplementary Methods for details).

As shown in Fig. 10, olefin 24 was set to relative zero for the free energy profiles. Initially, the Cossy model\textsuperscript{43} was considered to explain the diastereoselectivity. We found that the relative free energy of TS1 was 1.0 kcal mol\textsuperscript{-1} lower than that of TS2, which could be attributed to the repulsion between the borane moiety and the substituents on cyclopropane in the transition state TS2. The diastereoisomer CP1, which is the precursor of alcohol 26, is the major product generated via transition state TS1. This result is consistent with experimental observations. Moreover, we also found that rotation of an alkenyl could take place via transition state TS3 with a barrier of only 6.4 kcal mol\textsuperscript{-1}. The relative free energy of the rotational isomer CP3 was 2.7 kcal mol\textsuperscript{-1} higher than that of compound 24. This was attributed to the larger size of R\textsubscript{3} compared with R\textsubscript{2}, and the closer positioning of R\textsubscript{2} to the methyl group in CP3. However, when hydroboration takes place from CP3 via transition state TS4, the hybridization of C22 changes from sp\textsuperscript{3} to sp\textsuperscript{2}, and the size difference between the methyl and methylene groups is reduced. Therefore, the relative free energy of TS4 was only 1.0 kcal mol\textsuperscript{-1} higher than that of TS1. The DFT calculations indicated that favourable pathway for the generation of major intermediate CP1 takes place via the same transition state TS1 in both the Cossy model and our proposed reaction model. However, there are two different pathways for the generation of side intermediate CP2 including the Cossy model via transition state TS2 and our proposed model via transition state TS4, the barriers for which are closed.

We applied the same method to study the mechanism of the homo-Michael reaction. As shown in Fig. 11, complex CP4, which is formed by reaction between aldehyde 27 and silyl ether 28 with the coordination of BF\textsubscript{3} is set to the relative zero for the free-energy profiles of this reaction. With the activation of BF\textsubscript{3}, the C–O bond cleavage forms a protonated ketone intermediate CP5 via transition state TS5 with a barrier of only 9.7 kcal mol\textsuperscript{-1}. The subsequent isomerization generates intermediate CP6 with 9.7 kcal mol\textsuperscript{-1} exothermic. With the activation of BF\textsubscript{3}, Et\textsubscript{2}O, C13 and C16 is more electron-deficient. Therefore, the nucleophilic addition with hydroxyl takes place via transition state TS6 with a barrier of 13.8 kcal mol\textsuperscript{-1}. After a proton transfer, an enol intermediate CP8 is formed. The followed cyclization occurs via transition state TS7 with a barrier of 26.6 kcal mol\textsuperscript{-1}. After releasing of one molecule water coordinated BF\textsubscript{3}, product 29 is formed exothermically.

Finally, we used the same method to study the mechanism of the isomerization of 29 to 30. As shown in Fig. 12, the intramolecular electrophilic deprotonation by DBU of substrate 29, which gives intermediate CP9 endothermically, occurs via transition state TS8 with a barrier of 28.2 kcal mol\textsuperscript{-1}. Subsequently, the retro-Michael addition takes place via transition state TS9 to break the C–O bond, with the help of DBU–H\textsuperscript{+} to stabilize the formed ionic oxygen atom, to generate intermediate CP10 reversibly with a barrier of 13.3 kcal mol\textsuperscript{-1}.

In CP10 rotation of the C22–C20 single bond affords CP11 in a 2.3 kcal mol\textsuperscript{-1} exothermic step. The Michael addition takes place at the Si-face of the alkene moiety in CP11 via transition state TS10, with a barrier of 11.4 kcal mol\textsuperscript{-1}, and generates intermediate CP12 reversibly. The direct protonation of CP12 by DBU–H\textsuperscript{+} could occur via transition state TS13 or TS14.

However, 30 was not the major product because the relative free energy of TS14, which leads to the formation of CP14 was 1.0 kcal mol\textsuperscript{-1} lower than that of TS13 which leads to 30. Alternatively, we found that a single C–C bond in CP12 could rotate rapidly via transition state TS11, and isomer CP13 could...
be formed reversibly. The protonation of CP13 via transition state TS12 could also afford product 30, and the relative free energy of TS12 was 1.2 kcal mol$^{-1}$ lower than that of TS14. Moreover, the relative free energy of 30 was 2.2 kcal mol$^{-1}$ lower than that of CP14, and 2.0 kcal mol$^{-1}$ lower than that of 29. Therefore, 30 was also a thermodynamically stable product, which was observed experimentally.

**Discussion**

In conclusion, we successfully developed an asymmetric total synthesis of (+)-19-dehydroxyl arisandilactone A (1a). Construction of an oxa-bridged and moderately sized DE ring involved an unprecedented tandem VMAR and oxa-homo-Michael type reaction. Stereoselective formation of stereogenic centres at C22 and C23 of 1a were achieved by a tandem and
biomimetic retro-Michael/Michael reaction. Key steps in this total synthesis also included a RCM reaction for the diastereoselective formation of the fully functionalized eight-membered DE ring system, and an interesting Cu-catalysed intramolecular cyclopropanation that resulted in stereoselective formation of the central 8/3 cis-fused bicyclic ring system. The structure of 19-dehydroxy (+)-arisandilactone A (1a) was confirmed by X-ray crystallography of its precursor alcohol 32. Details of the reactions for the hydroboration, homo-Michael, and tandem retro-Michael/Michael reactions were determined by DFT calculations. The biological investigation of the synthesized (+)-19-dehydroxy arisandilactone A (1a), as well as the advanced intermediates in this total synthesis is currently underway in our laboratory.

Methods

General. All reactions were carried out under a nitrogen atmosphere under anhydrous conditions and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to Purification of Laboratory Chemicals (Perrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Yields refer to chromatographically and spectrally (H NMR) homogeneous materials. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China). Visualization was by ultraviolet or stained with ethanolic solution of phosphomolybdic acid and cerium sulfate, basic solution of KMnO4 and iodine vapour. If not specially mentioned, flash column chromatography was performed using anhydrous conditions and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to variations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; td, triple doublet; dq, double quartet, m, multiplet. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR spectrometer. High-resolution mass spectra were recorded on a Bruker Apex IV FTMS spectrometer using ESI (electrospray ionization) as ionization method.

For detailed experimental procedures, see Supplementary Methods. For NMR spectra of the synthesized compounds in this article, see Supplementary Figs 1–34. For the comparison of NMR spectra of the natural arisandilactone A and synthetic 19-dehydroxy arisandilactone A, see Supplementary Table 1. For ORTEP diagrams for compounds 10, 16, 21, 26, 29, 31 and 32, see Supplementary Figs 35–41. For computational calculation details, see Supplementary Methods and Supplementary Data 1. For calculation results using other methods, see Supplementary Figs 42–44.

Data availability. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1509144 for compound 10, CCDC 1508989 for compound 16, CCDC 1509314 for compound 21, CCDC 1509138 for compound 26, CCDC 1507976 for compound 29, CCDC 1507977 for compound 31, and CCDC 1507978 for compound 32. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
Y.-X.H. and Y.-L.J. contributed equally to this work. Y.-X.H., Y.-L.J., Y.Li, J.-H.C. and Z.Y. conceived the project and analysed the experimental results. Y.-X.H., Y.-L.J., Y.Li, H.-X.Y., B.-Q.T. and Z.N. performed the synthesis and characterization. S.L. and Y.Lan performed the theoretical calculations. Y.Lan and Z.Y. composed the manuscript with input from all the authors.

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