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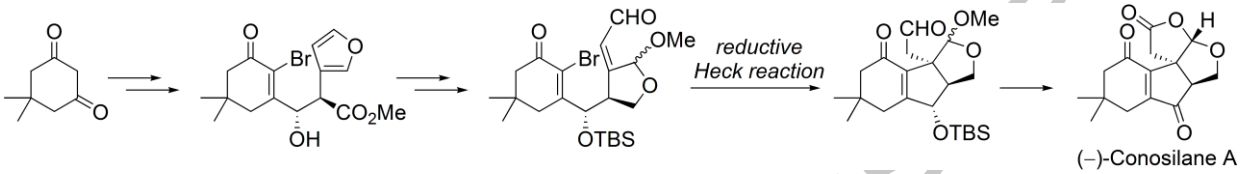

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Synthesis of both enantiomers of conosilane A

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ABSTRACT

Conosilane A, an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 isolated from *Conocybe siliginea*, is a tremulane sesquiterpene with highly oxygenated tetracyclic ring system. In this study, we report the synthesis of both enantiomers of conosilane A. The key steps of this synthesis involve asymmetric aldol reaction, furan-ring oxidation followed by transacetalization and intramolecular reductive Heck-type cyclization.

Introduction

The mushroom *Conocybe siliginea* is known as a rich source of bioactive tremulane-type sesquiterpenes.[1] Some of these compounds have vasodilating activity and inhibitory activity against 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes reduction of cortisone to cortisol. In 2012, Yang *et al.* isolated conosilane A (**1**)[2] from the culture broth of *Conocybe siliginea* as a novel tremulane sesquiterpene with highly oxygenated tetracyclic ring system (Fig. 1). This compound has moderate inhibitory activity against enzyme 11β-HSD1. Although racemic synthesis of **1** has been achieved by Yuan *et al.* in 2018,[3] asymmetric synthesis of **1** has not yet been reported. In this study, we report the synthesis of both enantiomers of conosilane A from commercially available dimedone.

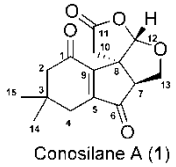
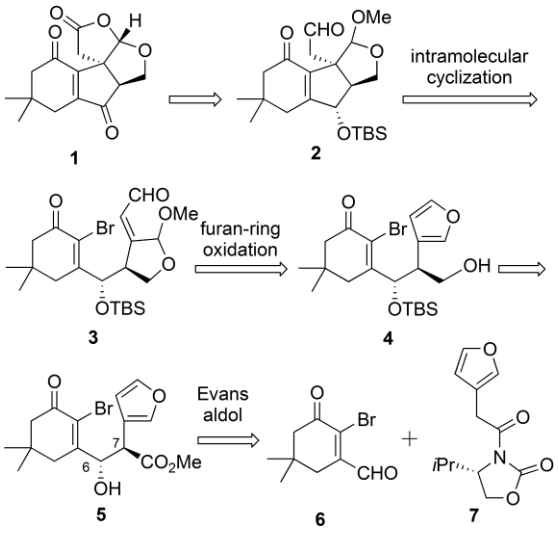


Figure 1. Structure of conosilane A (**1**).

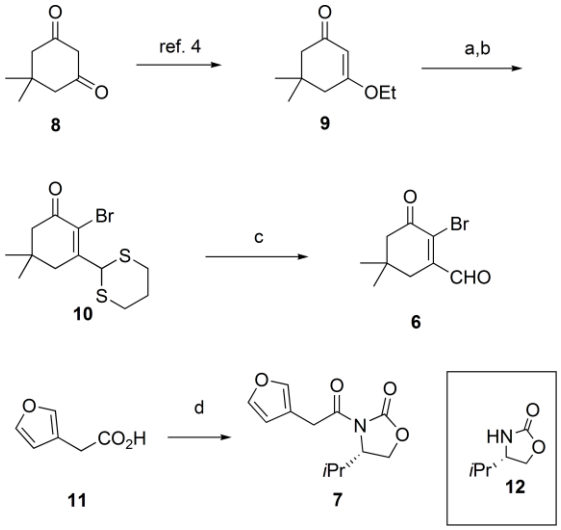
Results and discussion

Our synthetic strategy is shown in Scheme 1. The target compound **1** would be prepared from **2** via lactone formation. Construction of C8 quaternary stereocenter of **2** could be achieved stereoselectively by intramolecular cyclization of **3**. The right segment of **3** would be synthesized by furan-ring oxidation followed by transacetalization of **4**, which would be obtained from β-hydroxyester **5**. Formation of the C6–C7 carbon bond in **5** should be accomplished by asymmetric aldol reaction of aldehyde **6** with oxazolidinone **7**.



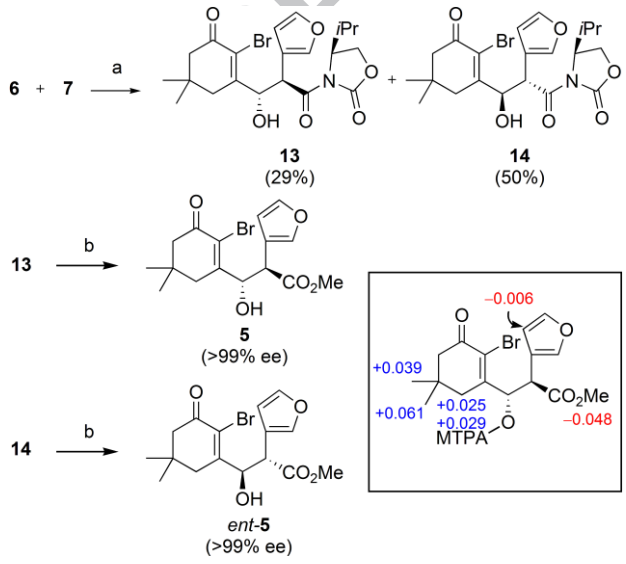
Scheme 1. Synthetic strategy for conosilane A.

Synthesis of aldehyde **6** and oxazolidinone **7** is shown in Scheme 2. We started the synthesis of **1** from commercially available dimedone (**8**), which was converted to the known enol ether **9** (93%) according to the reported procedure.[4] After α-bromination of **9** (77%), the resulting enone was treated with 2-lithio-1,3-dithiane to give compound **10**.[5] In this reaction, addition of a catalytic amount of $Mg(OTf)_2$ (20 mol%) drastically improved the yield of **10** up to 88%, whereas the yield was less than 30% without $Mg(OTf)_2$. Aldehyde **6** was prepared by removal of dithioacetal of **10** on multigram scale (97%). On the other hand, oxazolidinone **7** was prepared from the known acid **11** in 80% yield.[6]



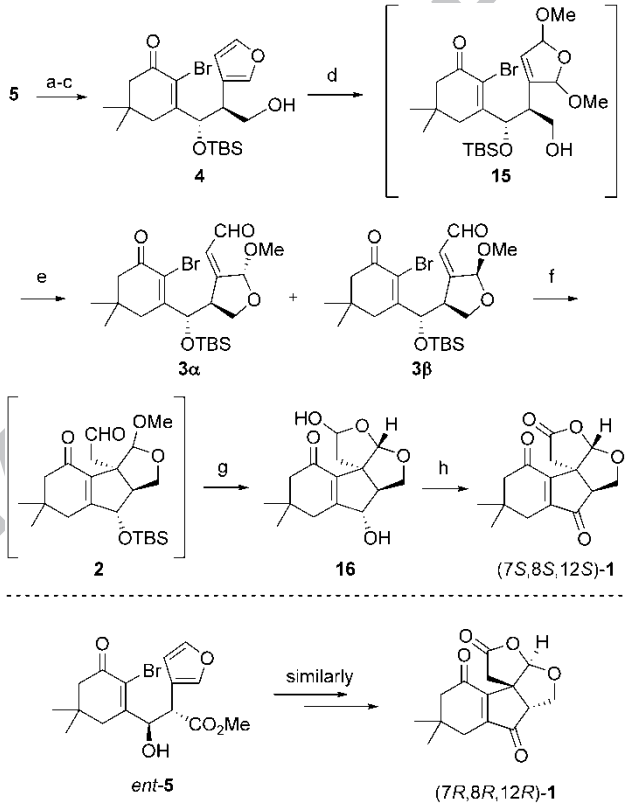
Scheme 2. Synthesis of the intermediates **6** and **7**. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C, 2 h, then Et_3N, CH_2Cl_2, 1 h, 77%; (b) 1,3-dithiane, *n*-BuLi, $Mg(OTf)_2$ (20 mol%), Et_2O, 0 °C, 2 h, 88%; (c) HIO_4•$2H_2O$, THF/Et_2O, 0 °C to rt, 30 min, 97%; (d) $(COCl)_2$, cat. DMF, CH_2Cl_2, reflux, 1.5 h, then **12**, *n*-BuLi, Et_2O, −78 °C to rt, 1 h, 80%.

With two units **6** and **7** in hand, aldol reaction between **6** and **7** was investigated (Scheme 3). In our early-phased studies, we found that the *anti*-type aldol adduct was preferable to the *syn*-adduct for the key intramolecular cyclization (**3**→**2**). This might be due to the steric hindrance caused by the C6 substituent. Thus, Mg-mediated asymmetric *anti*-aldol conditions reported by Evans *et al.*[7] were applied. However, in this reaction, the diastereoselectivity was not observed, whereas the *anti*-selectivity was perfect. The resulting diastereomeric mixture of **13** and **14** was separated by column chromatography to afford **13** (29%) and **14** (50%), respectively. This result was not expected but allowed us to synthesize both enantiomers of **1** from **13** and **14**. The removal of chiral auxiliary of **13** and **14** was performed by treatment with NaOMe to give **5** (91%) and *ent*-**5** (73%), respectively. The enantiomeric exesses of both enantiomers were estimated to be >99% ee by HPLC analysis. The absolute configuration of **5** was determined by the modified Mosher's method.[8]



Scheme 3. Synthesis of **5** and *ent*-**5**. Reagents and conditions: (a) $MgBr_2$•OEt_2, Et_3N, TMSCl, EtOAc, rt, 24 h; TFA, MeOH, rt, 1 h; (b) NaOMe, MeOH, 0 °C, 5 min, 91% for **5**, 73% for *ent*-**5**.

The synthesis of (7*S*,8*S*,12*S*)-**1** is shown in Scheme 4. Both ketone and hydroxy group of **5** were protected by treatment with TBSOTf/Et_3N. Reduction of the ester with DIBAL followed by acidic hydrolysis of silyl enol ether afforded **4** in good yield (78% from **5**). The mild oxidation of furan-ring in **4** was successfully performed by treatment with NBS in MeOH at 0 °C to give **15**, which was directly transacetalized under acidic conditions to furnish the key intermediate **3** in almost quantitative yield. Although compound **3** was an anomeric mixture (**3α**:**3β** = 2:1), this mixture was used for the next step without purification.[9]



Scheme 4. Synthesis of (7*S*,8*S*,12*S*)- and (7*R*,8*R*,12*R*)-**1**. Reagents and conditions: (a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, overnight; (b) DIBAL, CH_2Cl_2, −78 °C, 3 h (c) dil. HCl, THF, rt, 5 h, 78% for three steps; (d) NBS, MeOH, 0 °C, 15 min; (e) *p*-TsOH•H_2O, MeCN, rt, 10 min, 95% in two steps, **3α**:**3β** = 2:1; (f) $Ni(COD)_2$, $Mg(OTf)_2$, MeCN, rt, overnight; (g) 3 M HCl, THF, rt, overnight, 59% in two steps; (h) PDC, MS 4A, CH_2Cl_2, rt, 24 h, 97%.

With the key intermediate **3** in hand, we examined the intramolecular cyclization. Initially, radical conditions (*n*-Bu_3SnH/AIBN in refluxing toluene) was applied, but the yield of the desired product **2** was low (< 30%). It was likely that the substrate **3** would be unstable under rather harsh conditions. Because the milder conditions would be suitable for this reaction, we then investigated transition metal-mediated reductive Heck-type cyclization. Pd-mediated conditions were initially attempted, but the desired **2** was obtained in lower yield (ca. 15%) by treatment with a catalytic amount of $Pd(PPh_3)_4$. After screening several conditions, the use of a stoichiometric amount of $Ni(COD)_2$ in MeCN[10] led to a significant improvement in yield (57%). Remarkably, in this reaction, **2** was obtained as a single isomer with α-OMe group, even though the substrate was an anomeric mixture (**3α**/**β**). The orientation of anomeric OMe group in **3** was considered crucial for the cyclization, and this kinetic separation should be due to steric hindrance caused by the β-oriented OMe group in **3β**. Therefore, addition of a Lewis acid for the activation of the unreactive **3β** was attempted. We examined various mild Lewis acids, e.g., $Zn(OTf)_2$, $Sc(OTf)_3$,

$Mg(OTf)_2$, $Al(OTf)_3$, and eventually found that the addition of $Mg(OTf)_2$ gave the best result (66%). The cyclized product **2** was immediately treated with 3M HCl in THF to remove protective groups, affording a diastereomeric mixture of tetracyclic hemiacetal **16** (59% in two steps, dr = 4:1). Finally, the synthesis of (7*S*,8*S*,12*S*)-**1** was accomplished by PDC oxidation of **16**. ^{1}H and ^{13}C NMR data of the synthetic **1** agreed with those of the natural product. Specific rotation of the synthetic (7*S*,8*S*,12*S*)-**1** {$[\alpha]_D^{26}$ −66.3 (*c* 0.33, MeOH)} also agreed with that of the natural product {$[\alpha]_D^{19}$ −52.4 (*c* 0.25, MeOH)}. Similarly, starting from *ent*-**5**, we also synthesized (7*R*,8*R*,12*R*)-**1**, {$[\alpha]_D^{26}$ +59.8 (*c* 0.38, MeOH)}.

Conclusion

In conclusion, we have achieved the synthesis of both enantiomers of conosilane A (**1**) from commercially available dimedone (**8**). Highlights of our synthesis include *anti*-selective aldol reaction, furan-ring oxidation and stereoselective intramolecular cyclization. Although the desired diastereoselectivity was not observed in the aldol reaction, the resulting diastereomeric mixture was chromatographically separable, which provided access to both enantiomers of **1**. The key intramolecular reductive Heck-type cyclization was successfully performed by treatment with a stoichiometric amount of $Ni(COD)_2$. In particular, the addition of $Mg(OTf)_2$ was found to be effective for this reaction. The overall yields of (7*S*,8*S*,12*S*)-**1** and (7*R*,8*R*,12*R*)-**1** were 6.8% and 9.8% in 14 steps, respectively.

Supplementary Data

References and Notes

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Highlights :

Synthesis of both enantiomers of conosilane A was achieved.
Conosilane A is an unprecedented sesquiterpene isolated from *Conocybe siliginea*.
Its highly oxygenated tetracyclic ring system was constructed stereoselectively.