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Communication

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Enantioselective Total Synthesis of Cotylenin A

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ABSTRACT: A convergent enantioselective total synthesis of cotylenin A is described. The A-ring fragment, prepared via the catalytic asymmetric intramolecular cyclopropanation developed in our laboratory, and the C-ring fragment, prepared from a known chiral compound via a modified acyl radical cyclization, were successfully assembled by the Utimoto coupling reaction. The formidable carbocyclic eight-membered ring of cotylenin A was efficiently constructed by a palladium-mediated cyclization. All the hydroxy groups in the scaffold were stereoselectively introduced and a modified reducing reagent, $Me_4NBH(O_2C^iPr)_3$, has been developed. The sugar moiety fragment was prepared via three consecutive carbon-oxygen bond-forming reactions, and the glycosylation was accomplished using Wan's protocol.

Cotylenin A (Figure 1) was initially isolated as a plant growth regulator;[1] however, biological studies later revealed that it induces the differentiation of murine and human myeloid leukemia cells and the apoptosis of a wide range of human cancer cell lines by combined treatment with interferon-α.[2] The crystal structure of cotylenin A in a complex with 14-3-3 protein and a phosphopeptide of H^+-ATPase (QSYpTV-COOH) has been reported[3] to confirm that cotylenin A binds to inhibitory 14-3-3 interaction sites of C-RAF, pSer233, and pSer259 but not the activating interaction site, pSer621. Moreover, the combined treatment of cotylenin A with an anti-epidermal growth factor receptor antibody is reported to synergistically suppress tumor growth in vitro and in vivo, which provides a novel pharmacologic strategy for treatment of RAS mutant cancers.[4]

Because of the promising bioactivity as an anti-cancer agent and the unique mechanism of action, cotylenin A has attracted considerable attention from the scientific community in the past decades. However, *Cladosporium* sp. 501-7W, the producer of cotylenin A, has lost its ability to proliferate during preservation on a slant,[5] thus hampering further biological studies. Hence, a steady supply of cotylenin A is desired.

Total synthesis is a potential method for providing cotylenin A and for the discovery of biologically important derivatives that are difficult to prepare from natural resources. However, despite the elucidation of its absolute structure by X-ray crystallographic analysis in 1998, the total synthesis of cotylenin A has not yet been reported,[6,7] and only one total synthesis of its aglycone, cotylenol, has been reported by Kato and co-workers thus far.[8]

The fused 5-8-5 carbocyclic ring system of cotylenin A includes a formidable all-carbon quaternary stereogenic center, an acid-sensitive chiral allylic tertiary alcohol, a stereotetrad including a *trans*-1,2-diol, and a four-substituted alkene with an isopropyl group. Moreover, cotylenin A bears a structurally unique glucose-fused trioxabicyclo[2.2.1]heptane with methyl and epoxyethyl groups, so that these structural features make cotylenin A a distinguished member among the fusicoccan diterpenoids.

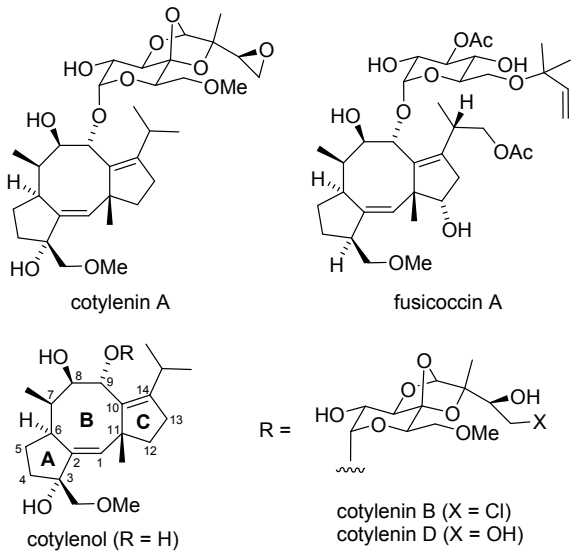
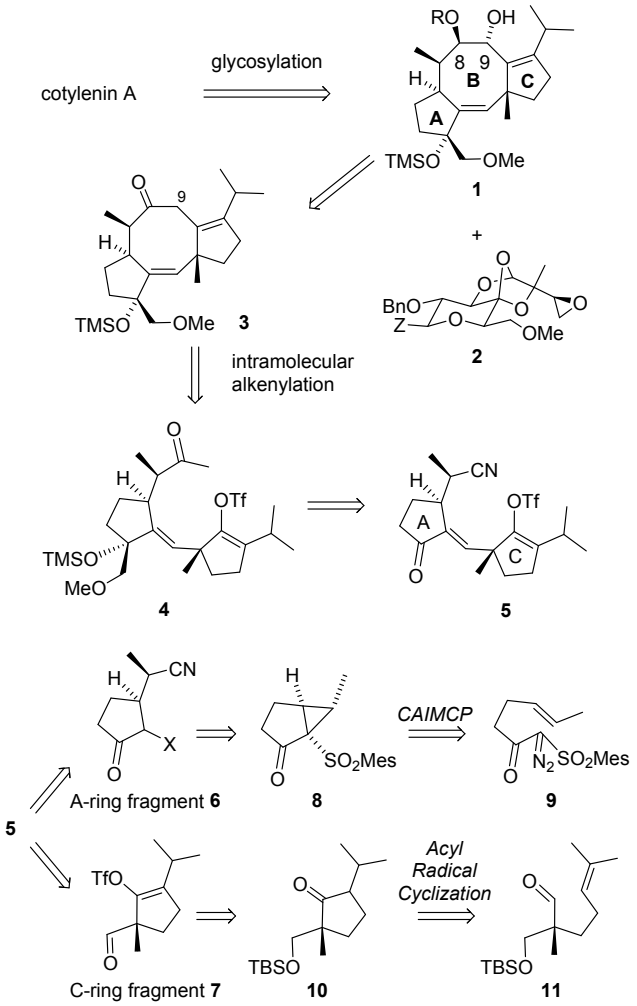


Figure 1. Structures of cotylenin A, B, and D, cotylenol, and fusicoccin A.

The intriguing biological activity and mechanism of action, dearth of supply, and unique structural features make cotylenin A an attractive synthetic target. Hence, the total synthesis of cotylenin A was initiated, and the successful results are reported herein.

Scheme 1 shows our retrosynthetic analysis of cotylenin A. Cotylenin A could be synthesized via the glycosylation of cotylenol derivative **1** and sugar moiety fragment **2**. The C8-C9 *trans*-1,2-diol of **1** could be formed by the stereoselective C9 hydroxy-directed reduction of the α-hydroxyketone, which could be prepared by stereoselective C9 hydroxylation of **3**. The palladium-catalyzed alkenylation of methyl ketone **4** was selected to construct the formidable eight-membered carbocyclic B-ring because we previously reported that the palladium-catalyzed intramolecular alkenylation of a methyl ketone successfully formed the eight-membered carbocyclic ring of taxol in 97% yield.[9]

Scheme 1. Retrosynthetic Analysis of Cotylenin A



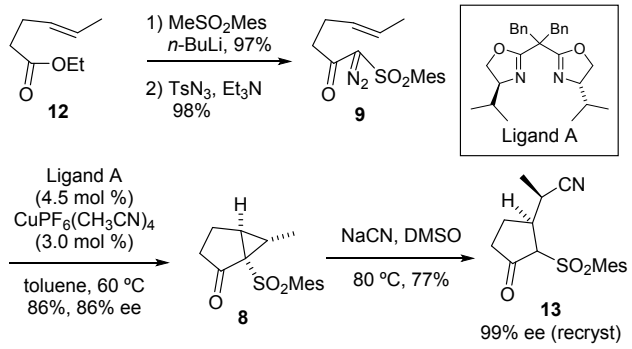
Compound **4** could be derived from **5**, which would be prepared by assembling the A-ring fragment **6** and the C-ring fragment **7**. A-ring fragment **6** was planned to prepare via the stereoselective reaction of sodium cyanide with cyclopropane **8**, which would be formed by the catalytic asymmetric intramolecular cyclopropanation (CAIMCP)[10] of **9** developed by us. The C-ring fragment **7** could be prepared from ketone **10** via the acyl radical cyclization[11] of a known chiral aldehyde **11**.[12]

In the forward synthesis of the A-ring fragment (Scheme 2), compound **9**, which was prepared from compound **12**, was subjected to the CAIMCP to afford cyclopropane **8** in 86% yield with 86% ee. The reaction of **8** with sodium cyanide afforded β-keto sulfone **13**, the absolute structure of which was confirmed by X-ray crystallographic analysis.[13]

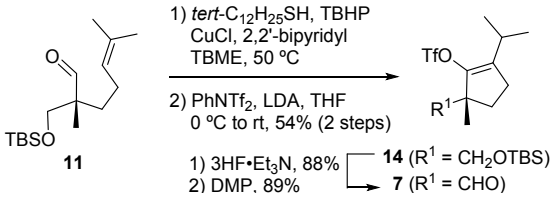
The C-ring fragment **7** was synthesized from aldehyde **11** (Scheme 3). Thus, **11** was subjected to acyl radical cyclization under the modified conditions,[14] and subsequent formation of enol triflate **14**, removal of the TBS group, and Dess-Martin oxidation furnished **7**.

Having prepared **13** and **7**, their coupling reaction was attempted. Interestingly, although the desulfonation of **13** with SmI_2 proceeded, the subsequent aldol reaction with **7** did not take place. Extensive survey of the reaction conditions, including the use of additives and other reagents such as lithium naphthalenide and LiDBB, did not change the results.

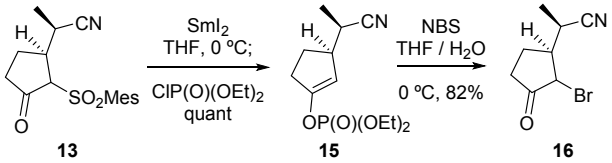
Scheme 2. CAIMCP of 9 and Preparation of 13



Scheme 3. Preparation of 7 via Acyl Radical Cyclization



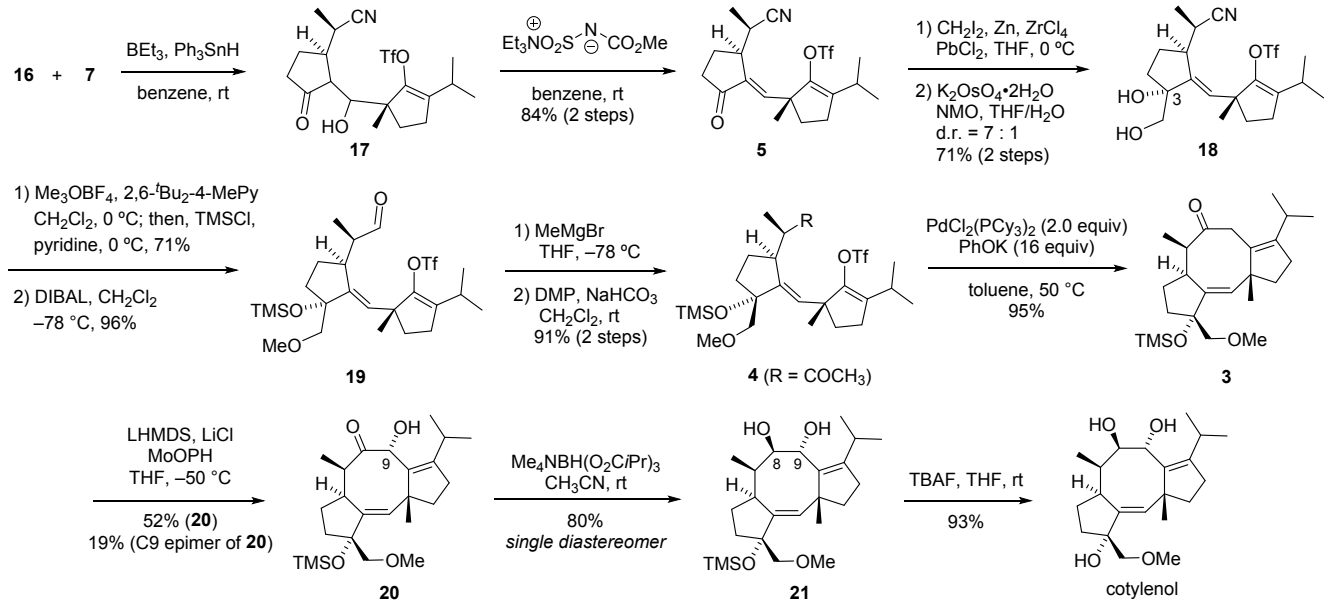
Scheme 4. Preparation of 16



It has been reported that the Utimoto coupling reaction[15,16] proceeds even when the reacting aldehyde is sterically hindered. Hence, to examine assembly of the A- and C-ring fragments by the Utimoto coupling reaction, **13** was converted to α-bromo ketone **16** (Scheme 4). The enolate generated from **13** using SmI_2 or lithium naphthalenide was again unsuitable for the preparation of **16**, but reacted with acetic anhydride[17] to afford the corresponding enol acetate in 20-30% yield. This result encouraged us to use chloro diethylphosphate as a trapping reagent to improve the yield of enol phosphate **15** (quant), which was converted to **16** (82%).

The Utimoto coupling reaction of **16** and **7** successfully afforded **17** as the sole product in 92% yield (Scheme 5). The dehydration of **17** with the Burgess reagent stereoselectively afforded enone **5**, but the following Wittig methylenation resulted in recovery of the starting material owing to the formation of the enolate of **5**. However, Takai reaction[18] of **5** gratifyingly afforded the desired *exo*-methylene compound, which was subjected to dihydroxylation to stereoselectively afford the desired **18** in 46% yield (2 steps). The yield was further improved to 71% (2 steps) when the methylenation was carried out using $ZrCl_4$.[19] The primary hydroxy group of **18** was selectively methylated with the Meerwein reagent, and the acid-labile tertiary hydroxyl group was protected as a TMS ether by a one-flask operation. Subsequent conversion to methyl ketone **4** using organometallic reagents such as methyl lithium and methyl magnesium bromide induced reaction with the enol triflate in the C-ring moiety. Hence, the nitrile was converted to **20** by DIBAL-H reduction, and subsequent methylation and oxidation afforded **4**.

Scheme 5. Enantioselective Total Synthesis of Cotylenol



We have reported that the palladium-catalyzed intramolecular alkenylation of methyl ketones effectively affords carbocyclic eight-membered rings.[9,20] Therefore, we carried out the reaction of **4** under the same reaction conditions as those used in the total synthesis of taxol ($Pd(PPh_3)_4$ (30 mol %), PhOK (3.0 equiv), toluene, 100 °C).[9] However, interestingly, no reaction occurred. The reaction was attempted under several conditions that were effective for the alkenylation in the previous studies,[9,20] but the desired product was not formed. The difference between **4** and previous substrates is that **4** is an enol triflate and not an alkenyl halide. Hence, electron-rich tricyclohexylphosphine was used to enhance the oxidative addition of palladium to enol triflate **4**. The reaction with 50 mol % of $PdCl_2(PCy_3)_2$ at 100 °C dramatically afforded the product **3**; however, epimerization of the C7 position took place.[21] Reduction of the temperature to 50 °C prevented the epimerization, but two equivalents of $PdCl_2(PCy_3)_2$ were required to access 95% yield of **3**. It should be noted that the enol triflate group was able to survive through 10 steps (from **14** to **4**) though it is hindered by the adjacent all-carbon quaternary center and isopropyl group.

We next explored the C9 hydroxylation using a variety of reagents and found that the use of MoOPH/LHMDS in the presence of LiCl[22] as an additive improved the yield and diastereoselectivity. The subsequent stereoselective reduction of α-hydroxy ketone **20** to *trans*-1,2-diol **21** was first conducted using $NaBH(OAc)_3$ or $Me_4NBH(OAc)_3$.[23] However, low reproducibility in the yield and stereoselectivity was problem.[24] After several attempts, the reaction with $Me_4NBH(O_2C^iPr)_3$,[25] which was newly developed in this synthesis, was found to afford **21** as the single isomer. Finally, treatment of **21** with TBAF afforded cotylenol. All the spectroscopic data of the synthesized product were identical to those reported for naturally occurring cotylenol.[26]

We next addressed the preparation of the sugar moiety fragment of cotylenin A (Scheme 6).The sugar moiety features the trioxabicyclo[2.2.1]heptane scaffold, which consists of α-hydroxy aldehyde bearing an epoxyethyl group **22** and glucose-derived α-hydroxy ketone **23**.[27] Hence, the reaction of **22** and **23** seemingly afforded **24**, but reactive **22** easily dimerized prior to the reaction with **23** under the given conditions, and desired product **24** was not formed. The reaction of dimethyl acetal **22'** with **23** did not afford the desired product either, too. Hence, the rational design of an alternative fragment instead of **22** was required to construct the bis-acetal moiety in the trioxabicyclo[2.2.1]heptane scaffold.

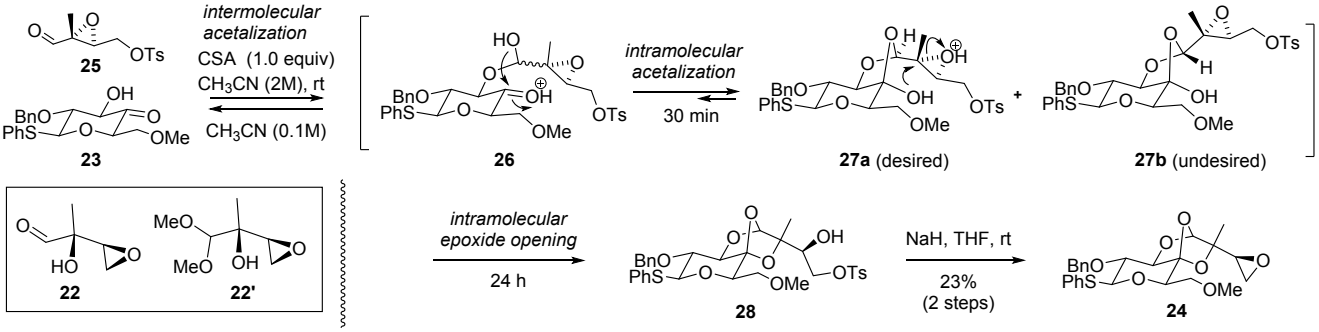
After several attempts, finally, epoxy aldehyde **25**[28] was designed as the alternative fragment for **22** because it was envisioned that the reaction of **23** and **25** under acidic conditions would afford hemiacetal **26**, and the generated hydroxy group of the hemiacetal could successively react with the ketone in the glucose unit to form new hemi-acetals **27a** and **27b**. And finally, the resultant hydroxy group could react with the epoxide to form compound **28**. The reaction of **23** and **25** should form two diastereomers **27a** and **27b**, and **27a** could afford hemi-acetal **28**, while another diastereomer **27b** could isomerize to the reacting diastereomer **27a** via **26** under equilibrium conditions.

As hoped, the envisioned consecutive transformations were realized. The reaction of **23** and **25** afforded **28** in the presence of CSA in acetonitrile at room temperature. The concentration of the starting material (2 M) was found to be important for the effective formation of **27a** and **27b**. Hemi-acetals **27a** and **27b** were unstable to isolate and easily decomposed to give a mixture of **23** and **25**. Indeed, **27a** and **27b** could not be detected by TLC analysis, but their formation as a mixture of diastereomers (1:1) was confirmed by ^{1}H-NMR. The reaction of **23** and **25** to **27a** and **27b** reached equilibrium after 30 min and interestingly, after the formation of **27a** and **27b** in the 2 M solution, dilution of the reaction mixture to 0.1 M with acetonitrile shifted the equilibrium to the starting materials **23** and **25**, resulting in the disappearance of **27a** and **27b**.

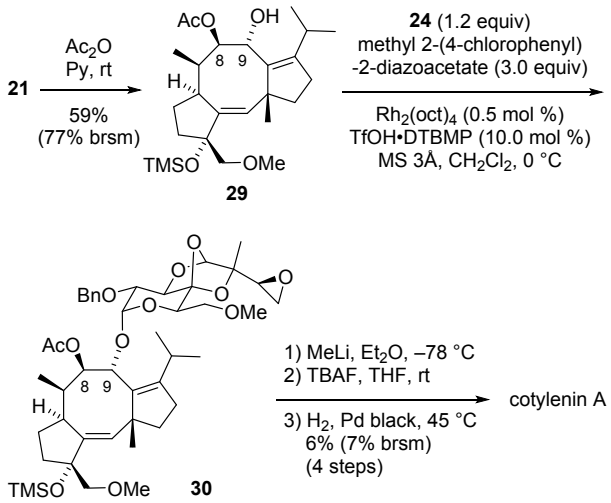
The intramolecular reaction of the hydroxy group in **27a** with the epoxide proceeded slowly, and compound **28** was formed after 24 h after the initiation of the reaction. Hemi-acetal **27b**, which did not afford the bis-acetal owing to the stereochemical restriction, remained intact because the

reaction after 48 h did not change the yield. These results could be attributed to the slow interconversion between **27a** and **27b**.

Scheme 6. Preparation of 24 via Acetalizations and Epoxide-Opening Cascade



Scheme 7. Enantioselective Total Synthesis of Cotylenin A



Compound **28** was not fully purified by silica-gel column chromatography, and contained a small amount of inseparable impurities. Hence, it was treated as is with sodium hydride to afford epoxide **24** in 23% yield (from **23** and **25**). The yield of **24** could be improved by further optimization of the reaction conditions.

Having succeeded in the preparation of the sugar moiety fragment **24**, compound **29**, prepared in 59% yield (77% brsm) by the reaction of **21** and Ac_2O, was subjected to the glycosylation with **24** (Scheme 7). Glycosylations using common reagents such as Tf_2O or MeOTf for the activation of thioglycoside resulted in decomposition of **24**, and Crich's conditions[29] afforded **30** but unfortunately, the yield was low.

After several attempts, we finally found that rhodium-catalyzed sulfonium ylide formation and subsequent Brønsted-acid catalyzed glycosylation, recently reported by Wan's group,[30] afforded **30** in moderate yield.[31] The C8 acetate of **30** resisted hydrolysis but was successfully removed by the reaction with methyllithium at low temperature and finally, removal of the TMS and benzyl groups afforded cotylenin A. The spectroscopic data of the synthesized product were identical to those of naturally occurring cotylenin A,[1,32] indicating that the enantioselective total synthesis of cotylenin A has been accomplished.

In conclusion, a convergent enantioselective total synthesis of cotylenin A was successfully achieved by 25 longest linear steps from geraniol. The A-ring fragment, prepared via the catalytic asymmetric intramolecular cyclopropanation developed in our laboratory, and the C-ring fragment, prepared from a known chiral compound via a modified acyl radical cyclization, were effectively assembled by the Utimoto coupling reaction. A palladium-mediated cyclization was crucial for the efficient construction of the carbocyclic eight-membered ring of cotylenin A. All the hydroxy groups in the scaffold were stereoselectively introduced and a modified reducing reagent, $Me_4NBH(O_2C^iPr)_3$, has been developed. The sugar moiety fragment was successfully prepared via three consecutive carbon-oxygen bond-forming reactions. The glycosylation was accomplished using Wan's protocol. Studies are underway to optimize the reaction conditions of the low-yielding steps to supply an adequate amount of cotylenin A for biological studies.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge at https://pubs.acs.org/doi/XX.XXXX/jacs.XXXXXX.

Experimental details, characterization of new compounds, HPLC DATA, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interests.

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(13) CCDC 1983382 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.1983382.

(14) The acyl radical cyclization of **11** under the conditions described in ref. 11 and subsequent enol triflate formation afforded **14** in 40% yield. Application of the modified conditions to other substrates will be reported elsewhere.

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(21) A mixture of **3** and its C7 epimer **3a** (dr = 1.8:1) was obtained in 87% yield. See Supporting Information.

(22) It was reported that the reaction without LiCl afforded **20** and its C9 epimer in the reduced yield and stereoselectivity.[8]

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(24) The reduction of **20** with $NaBH(OAc)_3$ was reported to afford **21** and its C8 epimer of **21** in the reduced yield and stereoselectivity.[8]

(25) $Me_4NBH(O_2C^iPr)_3$ is easily prepared by commercially available Me_4NBH_4 and $^iPrCO_2H$. The high stereoselectivity and reproducibility which were realized using $Me_4NBH(O_2C^iPr)_3$ would be attributed to the bulky lipophilic ligand (O_2C^iPr) which could work favorably in the transition state and also improve solubility of the reagent.

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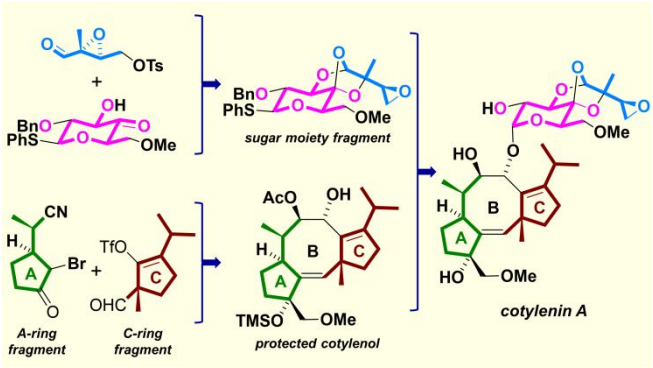
(31) Because compound **30** was inseparable from a small amount of impurities, which were finally removed at the last step of this synthesis, subsequent three steps were carried out using materials including the impurities.

(32) To the best of our knowledge, specific rotation of cotylenin A has not been reported thus far.


OTs
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C-ring fragment
AcO
OH
B
TMSO
protected cotylenol
HO
cotylenin A