Asymmetric Total Synthesis of Shagenes A and B

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Abstract: We report the first total synthesis of shagenes A and B, which are tricyclic terpenoids containing a *cis*-substituted cyclopropane, via ring-closing metathesis of an enamide and Ir-catalyzed double-bond isomerization of an alkylidenecyclopropane. Chemo- and diastereoselectivity in the distorted *cis*-substituted structures were controlled by the alkylidenecyclopropane reactivity and using the ketone functionality as a remote directing group for the Ir catalyst, respectively. The total synthesis suggested the absolute configuration of shagenes.

Leishmaniasis, a neglected tropical disease, is a parasitic infection that is prevalent in tropical areas and presents a public health problem.[1] The development of pharmaceuticals against this disease is important to help affected regions overcome poverty issues. Baker and coworkers searched for natural products that exhibited strong toxicity against *Leishmania donovani*, a protozoan that causes leishmaniasis. In 2014, they isolated tricyclic terpenoids shagenes A (**1**) and B (**2**) from a soft coral in the Scotia Sea, located between South America and Antarctica (Figure 1).[2] The structure and relative stereochemistry of these compounds have been determined by high-resolution MS and extensive NMR spectroscopy studies, but their absolute configuration has yet to be determined. These compounds are characterized by a novel tricyclic skeleton with a 3/6/5-membered ring system, six or seven contiguous chiral centers, and a *cis*-substituted cyclopropane. Shagene A exhibits strong toxicity against *L. donovani* (IC_{50} = 5 μM) and shows no toxicity towards mammalian cells, while shagene B has no activity against *L. donovani*.[2] These results indicate that the methoxy group at C8 is important for the activity against *L. donovani*. Owing to its biological activity and high selectivity, the shagene skeleton is expected to be a novel lead for drug development. Despite the importance of shagenes, their total synthesis has yet to be reported. Therefore, we initiated synthetic studies to establish an efficient synthetic route to shagenes. Herein, we report the first enantioselective total synthesis of shagenes A and B, and the investigation of their absolute configuration.

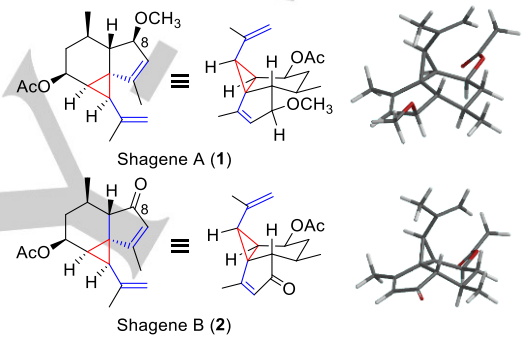
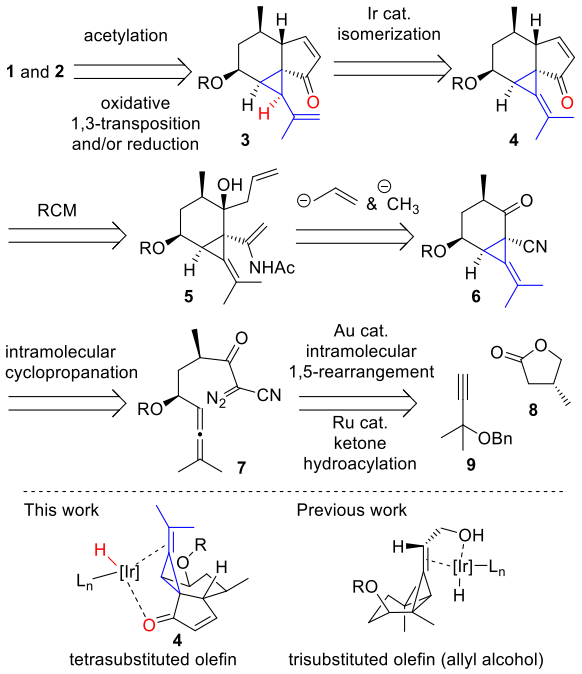


Figure 1. Shagenes A and B. The structures of **1** and **2** were calculated by Spartan 18 at the ωB97X-D/6-31G* level of theory.

As stereoselective synthesis of the congested *cis*-substituted cyclopropane found in the complex cyclic system of shagenes is challenging, a synthetic strategy for its construction was needed.[3,4] To access shagenes A (**1**) and B (**2**), compound **3** was designed as a common intermediate, which would be readily converted to **1** and **2** by oxidative 1,3-transposition of a tertiary allyl alcohol, reduction, and protecting group manipulation (Scheme 1). The sterically congested *cis*-substituted cyclopropane structure of **3** was expected to be unstable because it contains a vinyl substituent. Therefore, the construction of *cis*-substituted cyclopropane **3** was envisaged through late-stage synthesis from intermediate **4** by Ir-catalyzed double-bond isomerization of the alkylidenecyclopropane to release strain. Although the isomerization of alkylidenecyclopropanes containing an allyl alcohol has been reported previously,[4,5] whether a tetrasubstituted olefin can be isomerized to a 1,1-disubstituted olefin with stereochemical control is unclear. Employing the ketone functionality of **4** as a remote directing group to control the diastereoselectivity is also challenging, as there is no precedent.[6] The tricyclic skeleton of **4**, containing the alkylidenecyclopropane moiety, would be constructed by Rh-catalyzed diastereoselective intramolecular cyclopropanation[7] of α-diazo-β-ketonitrile **7** and ring-closing metathesis (RCM) of enamide **5**.[8] If the nitrile group, which is essential for cyclopropanation, were converted to an enamide

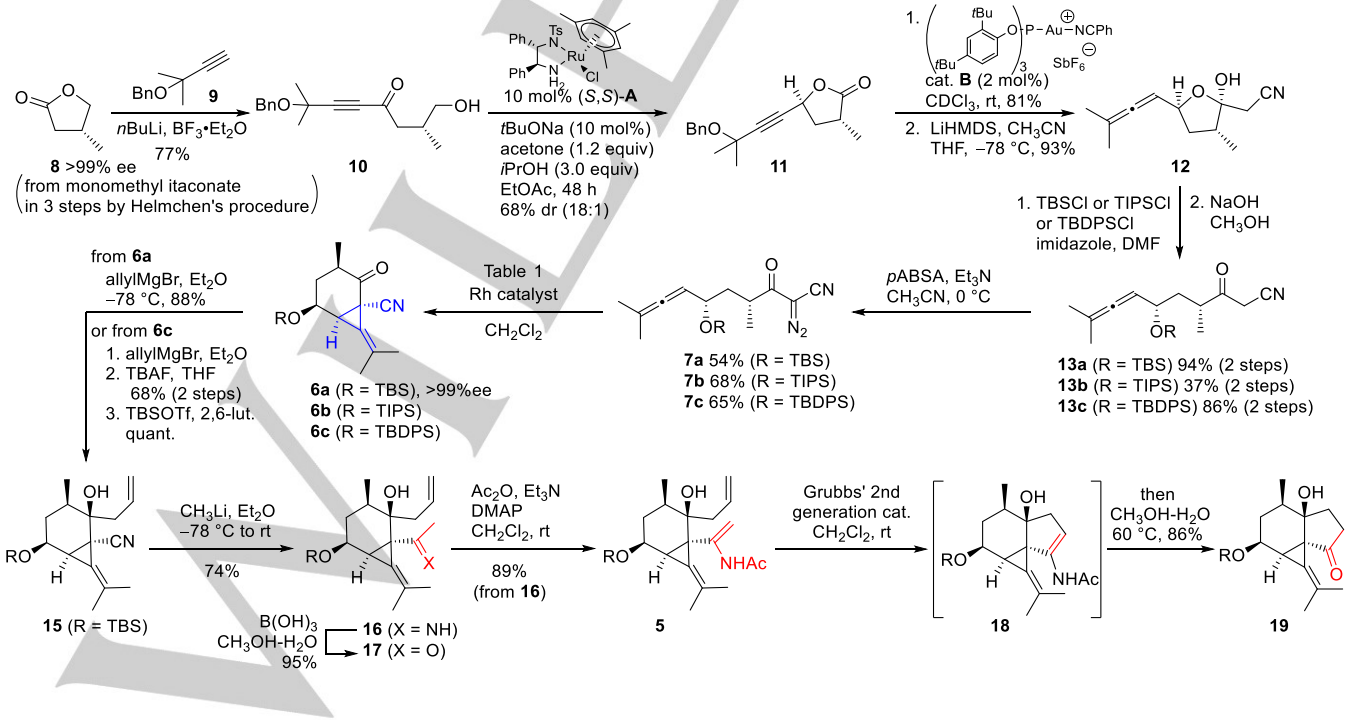
directly, a synthetic route to the cyclopentanone skeleton would be newly established. Compound **7** could be accessed from known chiral lactone **8** and benzyl-protected propargyl alcohol derivative **9** via introduction of a trisubstituted allene by Au-catalyzed intramolecular 1,5-rearrangement[9] and Ru-catalyzed ketone hydroacylation.[10]



Scheme 1. Retrosynthesis of shagenes A and B.

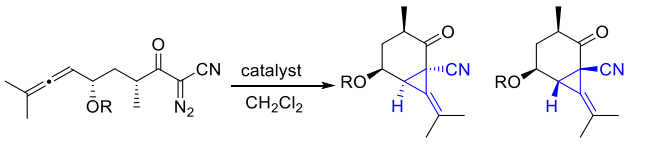
First, several α-diazo-β-ketonitriles **7a–c** were prepared to investigate the diastereoselective intramolecular cyclopropanation. (*R*)-4-Methyldihydrofuran-2(*3H*)-one **8**, prepared from monomethyl itaconate in three steps by Helmchen's procedure (>99% ee),[11] was coupled with alkyne **9** in the presence of $BF_3{\cdot}OEt_2$ to give ketoalcohol **10** (Scheme 2). Diastereoselective ketone hydroacylation of ketoalcohol **10** using chiral Ru catalyst **A**, following Dong's procedure,[10] gave lactone **11** in 68% yield with high selectivity (18:1). Treatment of lactone **11** with gold catalyst **B** produced an allene via a 1,5-hydride shift of the propargyl benzyl ether and fragmentation.[9] Nucleophilic addition of deprotonated acetonitrile to the resultant allene afforded compound **12** containing an inseparable ring-opened isomer. Treatment of compound **12** with *tert*-butyldimethylsilyl (TBS) chloride resulted in silylation of the alcohol along with conversion of the ketonitrile to a silyl enol ether. Selective deprotection of the silyl enol ether gave compound **13a** in 94% yield over two steps. Diazo transfer using *p*-acetamidobenzenesulfonyl azide[12] gave cyclization precursor **7a** in 54% yield. Other cyclization precursors protected by triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups (**7b** and **7c**) were synthesized from **12** by the same method as **7a**.[13] This synthetic route was robust and α-diazo-β-ketonitriles **7a** and **c** were prepared on a gram-scale.

Next, we investigated the intramolecular cyclopropanation of diazoketonitriles **7a–c** containing allene using Cu and Rh catalysts. In the case of **7a** with $Cu(hfacac)_2$, the reaction did not proceed, and starting material **7a** was recovered (Table 1, entry 1). The use of 1 mol% of $Rh_2(OAc)_4$ was not sufficient to complete the reaction. The reaction with 5 mol% catalyst proceeded completely to give compound **6a**[14] as a major product along with **14a** in 54% total yield with 1.6:1 diastereoselectivity (entry 2).



Scheme 2. Construction of 3/6/5 tricyclic ring system of shagenes.

Table 1. Intramolecular cyclopropanation of allenes.



7a (R = TBS) **6a** (R = TBS) **14a** (R = TBS)
7b (R = TIPS) **6b** (R = TIPS) **14b** (R = TIPS)
7c (R = TBDPS) **6c** (R = TBDPS) **14c** (R = TBDPS)

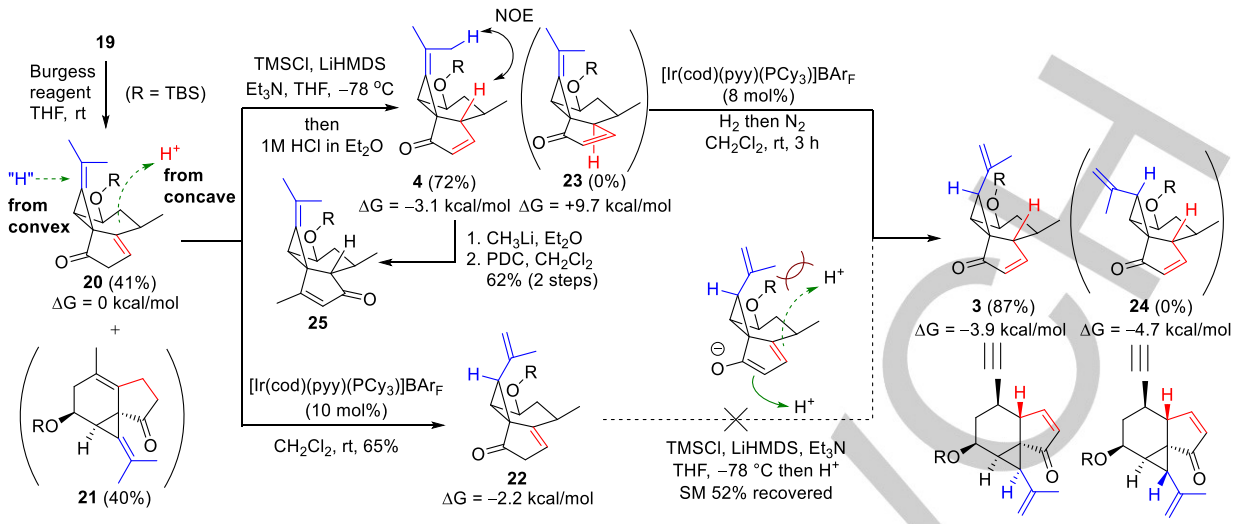
Entry	Substrate (R)	Catalyst	Yield[a]	dr (**6**:**14**)
1	**7a** (TBS)	$Cu(hfacac)_2$	NR[b]	NA[c]
2	**7a** (TBS)	$Rh_2(OAc)_4$	54%	1.6:1
3	**7a** (TBS)	$Rh_2(pfb)_4$	60%	1:1.8
4	**7a** (TBS)	$Rh_2(cap)_4$	13%	20:1
5	**7a** (TBS)	$Rh_2(esp)_2$	73%	3.4:1
6	**7b** (TIPS)	$Rh_2(esp)_2$	50%	6:1
7	**7c** (TBDPS)	$Rh_2(esp)_2$	63%	16:1
8[d]	**7c** (TBDPS)	$Rh_2(esp)_2$	77%	13:1

[a] Isolated yield. [b] NR, no reaction. [c] NA, not applicable. [d] One-gram scale. Abbreviations: TBS, *tert*-butyldimethylsilyl; TIPS, triisopropylsilyl; TBDPS, *tert*-butyldiphenylsilyl; hfacac, hexafluoroacetylacetonato; pfb, perfluorobutyrate; cap, caprolactamate; esp, α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid.

Both diastereomers were separated by silica gel column chromatography, and their stereochemistry was determined by X-ray crystallography (Figure S1).[15] The reaction with $Rh_2(pfb)_4$[16] (1 mol%) gave desired products **6a** and **14a** in 60% yield, albeit with low diastereoselectivity (1:1.8, entry 3). $Rh_2(cap)_4$[16] did not fully consume starting material **7a**, although high diastereoselectivity (20:1) was observed (entry 4). When 1 mol% of $Rh_2(esp)_2$[17] was employed, desired product **6a** was obtained in 73% yield with 3.4:1 diastereoselectivity (entry 5). Therefore, we investigated improving the diastereoselectivity using the steric effect of siloxy groups. When bulkier silyl groups, such as TIPS and TBDPS groups, were introduced, higher diastereoselectivity was observed (entries 6 and 7). When **7c** with a TBDPS group was treated with $Rh_2(esp)_2$, desired product **6c** was obtained in 63% yield with 16:1 diastereoselectivity (entry 7). These conditions could be applied to the gram-scale synthesis of **6c** (entry 8).

We then turned our attention to construction of the five-membered ring. Treatment of compound **6a** with allyl magnesium bromide gave **15** in 88% yield. Subsequent nucleophilic addition using CH_3Li gave imine **16**, which was sufficiently stable to be isolated by silica gel column chromatography (Scheme 2). The structure of imine **16** was confirmed by derivatization to ketone **17**. For compound **6c**, after introducing the allyl group, a protecting group manipulation was essential for subsequent nucleophilic addition to the nitrile group to decrease steric bulkiness around the alkylidenecyclopropane. After **16** was converted to enamide **5** by acetylation, RCM of the enamide and terminal olefin using Grubbs' second generation catalyst proceeded smoothly to give compound **18**, which was unstable and readily hydrolyzed to give corresponding ketone **19**. Therefore, the nitrile group was efficiently employed to construct the cyclic ketone in the complex tricyclic ring system.

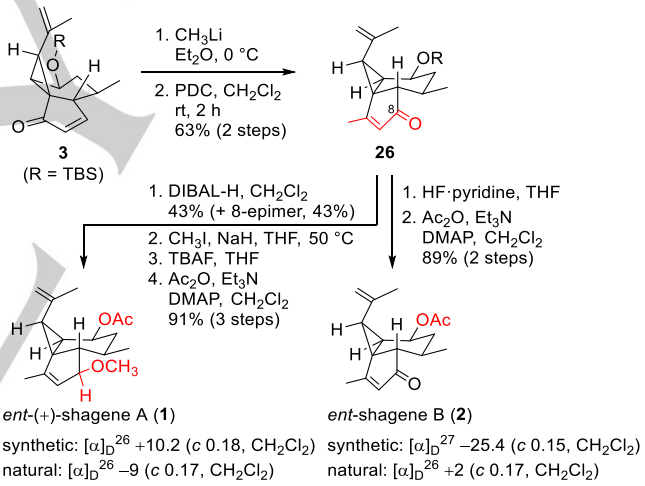
Next, construction of the congested *cis*-substituted cyclopropane was attempted. After dehydration of the tertiary alcohol to give compound **20** and its isomer **21**,[18] stereoselective isomerization of the two different double bonds in **20** was investigated (Scheme 3). The introduction of hydrogen atoms from the convex and concave side of the molecule was necessary to isomerize the alkylidenecyclopropane and trisubstituted olefin, respectively (shown in blue and red). After extensive investigation, isomerization of the trisubstituted olefin was attempted before the *cis*-substituted structure was constructed. Treatment of compound **20** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or lithium diisopropylamide (LDA) did not achieve double-bond isomerization, but formation of a silyl enol ether at −78 °C followed by treatment with 1 M HCl in ether gave desired enone **4** in 72% yield. Compound **4** was then treated with Crabtree-type catalyst $[Ir(cod)(pyr)(PCy_3)]BAr_F$.[19] Alkylidenecyclopropane isomerization proceeded to give congested *cis*-substituted cyclopropane **3** in 87% yield with excellent diastereoselectivity. In contrast, although compound **20** smoothly reacted with the Crabtree-type catalyst to give desired *cis*-substituted cyclopropane **22** in 65% yield with excellent selectivity, stereoselective isomerization of trisubstituted olefin **22** was difficult owing to the steric bulkiness of its isopropenyl group. Notably, no ring-opening of the vinylcyclopropane (VCP) in **3** and **22** was observed during these optimizations. Pioneering studies by Wender reported that the cleavage of VCPs proceeds in the presence of metal catalysts.[20–22] However, as our double-bond isomerization proceeded at room temperature and the product was a non-activated VCP, ring-opening did not occur. Density functional theory calculations were also performed to estimate the thermodynamic stabilities of several diastereomers from the two isomerizations. In the first reaction, product **4** was 12.8 kcal/mol more stable than its diastereomer **23**. Interestingly, for double-bond isomerization, *cis*-substituted structure **3** was 0.8 kcal/mol more stable than alkylidenecyclopropane **4**, but 0.8 kcal/mol less stable than *trans*-substituted structure **24**. These results indicated that formation of the *cis*-substituted cyclopropane was driven by the elimination of strain in the alkylidenecyclopropane; however, the reaction proceeded kinetically. In this reaction, a ketone on the five-membered ring likely functions as a remote directing group for the Ir catalyst, as shown in the bottom of Scheme 1. Indeed, double-bond isomerization of compound **25**, in which no ketone participated in the reaction, did not occur using the Crabtree-type catalyst.



Scheme 3. Stereoselectivity of diastereoselective double-bond isomerization and relative thermodynamic stabilities of intermediates calculated by Spartan 18 at the ωB97X-D/6-31G* level of theory.

Having successfully constructed tricyclic skeleton **3** containing the *cis*-substituted cyclopropane, we turned our attention to completing the total synthesis. Treatment of compound **3** with CH_3Li was followed by oxidative 1,3-transposition of the resultant allyl alcohol into enone **26** using pyridinium dichromate (PDC) (Scheme 4). Unexpectedly, the 1,2-reduction of enone **26** was problematic, with the desired product only obtained by treatment with DIBAL-H, along with its 8-epimer. When using $NaBH_4/CeCl_3$, $Al(OiPr)_3$, K-Selectride, and L-Selectride, decomposition was observed owing to product instability, which readily produced allyl and cyclopropylcarbinyl cations. After methylation, removal of the TBS group followed by acetylation completed the first total synthesis of shagene A (**1**). The first total synthesis of shagene B (**2**) was also achieved using a similar protecting group manipulation. Analytical data for synthetic **1** and **2** obtained by HRMS and ^1H and ^{13}C NMR spectroscopy were completely consistent with reported data.[2] Our synthetic shagene A had an optical rotation of similar magnitude and opposite sign to that reported for the natural product. These results suggested that the absolute configuration of natural shagene A is (1*S*,1a*S*,2*R*,4*S*,4a*R*,7a*S*).[23]

In summary, we have accomplished the first total synthesis of shagenes A and B in 21 and 19 steps from known chiral lactone **8**, respectively. The key steps of the total synthesis were Ir-catalyzed isomerization of the tetrasubstituted olefin to the terminal olefin by eliminating the strain of the alkylidenecyclopropane, and diastereoselective fabrication of the distorted *cis*-substituted structure using the ketone functionality as a remote directing group. This study also provides a new strategy for the synthesis of cyclic ketones through RCM of enamides. Other important steps included the diastereoselective synthesis of an alkylidenecyclopropane using a Rh catalyst, allene formation by intramolecular 1,5-rearrangement using a Au catalyst, and ketone hydroacylation using a Ru catalyst. We are currently investigating the synthesis of natural enantiomers and the development of analogs toxic to *Leishmania* parasites using the synthetic strategy developed herein.



Scheme 4. Total synthesis of shagenes A and B.

Acknowledgements

We are grateful to Prof. B. J. Baker for providing ^1H and ^{13}C NMR spectra, optical rotation (solvent and concentration) data and information for shagenes A and B. We would like to thank Prof. T. Taniguchi (Hokkaido University) for theoretical calculations of CD spectra of shagene A and B. This work was supported by JSPS KAKENHI (Grant Nos. JP17H05051 and JP21H02131, CT).

Conflict of Interest

The authors declare no competing financial interests.

Keywords: total synthesis • shagene • allenes • iridium • Leishmaniasis

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[13] In the case of the TIPS group, **12** was recovered in 35% yield in addition to **13b** (37% yield) in this two-step conversion.

[14] Enantiomeric excess of **6a** was >99% ee. Also, see Supporting Information.

[15] Deposition numbers CCDC2087733 (for **6a**) and CCDC2087734 (for **14a**) contain the supplementary crystallographic data for this paper. Also see Supporting Information

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[18] Use of the Burgess reagent gave better results, although various conditions were attempted including Martin's sulfurane and MsCl, to convert **19** into **20**. In the case of Martin's sulfurane, no reaction occurred. Treatment with MsCl and Et_3N gave undesired product **21** as a major compound (45%) together with a small amount of desired product **20** (7%). Conversion of byproduct **21** to **3** was not attempted owing to instability.

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[23] The originally reported optical rotation for natural products was revised due to a calculation error (by personal communication with Prof. Baker). Although the optical rotation of synthetic shagene B was larger magnitude than that of the natural product, it is expected to have the same absolute configuration as shagene A. CD spectra of synthetic shagenes A and B were also measured, see Supporting Information.

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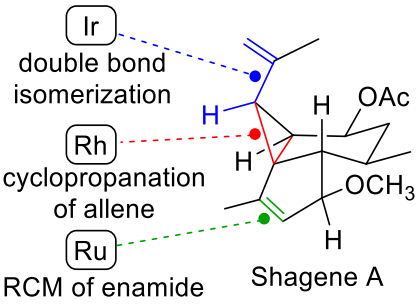

Shagene A, which exhibits strong toxicity against *Leishmania donovani*, a protozoan that causes leishmaniasis, contains an intriguing strained structure that includes a multisubstituted cyclopropane. This study reports the first total synthesis of shagenes A and B via Ru-catalyzed ring-closing metathesis of an enamide and Ir-catalyzed double-bond isomerization of an alkylidenecyclopropane. The total synthesis suggested the absolute configuration of shagenes.

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