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Nazarov Cyclization Entry to Chiral Bicyclo[5.3.0]decanoid Building Blocks and Its Application to Formal Synthesis of (−)-Englerin A

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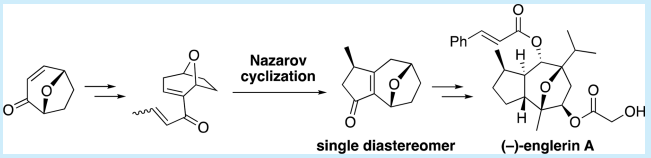
Supporting Information

ABSTRACT: A divergent entry to the chiral bicyclo[5.3.0]-decane skeletons relevant to sesqui- and higher terpenoids has been achieved. Its usefulness was demonstrated by formal synthesis of a guaiane sesquiterpenoid (−)-englerin A. The key reactions are (i) diastereoselective Nazarov cyclization for stereoselective construction of the bicyclo[5.3.0]decane skeleton, (ii) intramolecular C−H amination for tuning an oxidation state, and (iii) introduction of an alkyl group to a β-alkoxy ketone with a zinc(II) ate complex.



The bicyclo[5.3.0]decane (hydroazulene) skeleton is a prevalent structural motif found in many sesqui- and higher terpenoids,[1] serving as a versatile platform for accommodating huge arrays of structural diversity to elicit various biological activities, such as antitumor, antiviral, and antimalarial activities (Figure 1). Consequently, functionalized

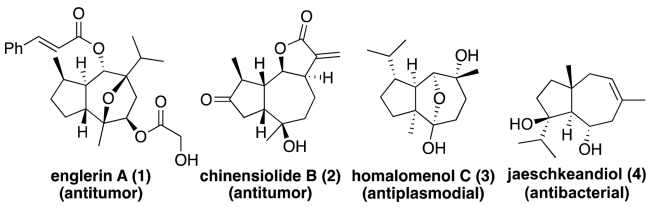
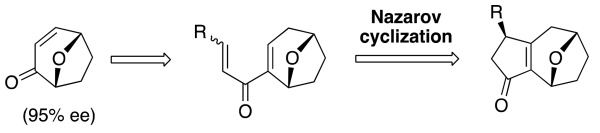


Figure 1. Examples of bicyclo[5.3.0]decane compounds (hydroazulene) in natural products.

bicyclo[5.3.0]decane derivatives have in particular continuously drawn the attention of the synthetic community in terms of the following issues; should the *cis*- or *trans*-fused ring system be targeted, what combination of substituents may be installed on the periphery, and how efficiently the enantio- and diastereoselectivity are secured.[2] Generally, target-oriented synthesis adopts a convergent strategy to pursue maximum efficiency, which does not always fit with the synthesis of the derivatives of interest. In this regard, methods that allow late-stage incorporation of diverse functionalities onto a chiral bicyclo[5.3.0]decane system will find promising use in discovery-oriented ventures in chemical biology and medicinal chemistry.[3]

We contemplated the development of bicyclo[5.3.0]decane-type building blocks stemming from a chiral cycloheptanoid building block, namely, 8-oxabicyclo[3.2.1]oct-3-en-2-one (**5**), the facile entry to which in both enantiomeric forms from 1,3-cycloheptadiene was developed previously by our group.[4] As an expedient maneuver to extend a cyclopentane ring with synthetic functionalities, Nazarov cyclization[5] of dienone **6**, which should be accessible from **5**, was expected to furnish bicyclo[5.3.0]decane scaffold **7**, where the stereoelectronic bias of **6** would impart diastereoselectivity (Scheme 1). The peculiar

Scheme 1. Nazarov Cyclization Entry to Bicyclo[5.3.0]decane Skeletons



enone juxtaposition to the oxo-bridge of **7** would provide diverse opportunities for diastereoselective functionalization around the framework. We herein report an expedient Nazarov cyclization entry to bicyclo[5.3.0]decane building blocks and its application to the formal synthesis of (−)-englerin A (**1**),[6,7] which may potentially lead to the development of antirenal cancer agents.[8]

To assess the feasibility of the concept, a panel of dienones **8a**−**8d** were prepared from **5** (see Supporting Information) and subjected to Nazarov cyclization (Table 1). After screening Lewis and Brønsted acids using (*Z*)-dienone **8a** as a model substrate, TfOH was identified as the acid of choice to give bicyclo[5.3.0]decane product **9a**, which shares a prototypical common structure with guaianoids, as a single stereoisomer in 81% yield (entry 1). The stereochemistry of the product was

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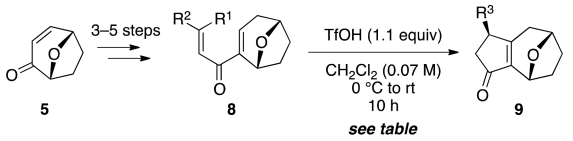
Table 1. Examination of Nazarov Cyclization

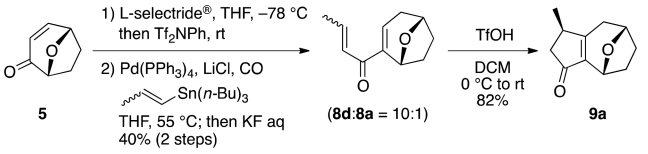


entry	substrate	product	yield (%)
1	**8a** (R^1 = Me, R^2 = H)	**9a** (R^3 = Me)	81
2	**8b** (R^1 = *i*-Pr, R^2 = H)	**9b** (R^3 = *i*-Pr)	64
3	**8c** (R^1 = H, R^2 = H)	**9c** (R^3 = H)	84
4	**8d** (R^1 = H, R^2 = Me)	**9a** (R^3 = Me)	83

determined on the basis of NOESY spectra. Carotane-related product **9b** equipped with an isopropyl substituent was obtained from **8b** in 62% yield under the same conditions (entry 2). The Nazarov cyclization of vinyl ketone **8c** afforded **9c** in 84% yield (entry 3). It was interesting to observe that (*E*)-dienone **8d** gave the same product **9a** as the (*Z*)-dienone **8a**-derived product in comparable (83%) yield (entry 4). Careful TLC analyses of the reaction mixture indicated that *Z* to *E* isomerization proceeded prior to the Nazarov cyclization under the given conditions.

Encouraged by the intriguing result, we attempted a short-step synthesis of **9a** using a readily accessible mixture of **8d** and **8a**. Thus, the enol triflate, prepared from cycloheptenone **5** via 1,4-reduction using L-selectride followed by *in situ* treatment of the corresponding enolate with Tf_2NPh, was subjected to Stille-carbonylative cross-coupling[9] to furnish a mixture of dienones **8d** and **8a** in 40% yield (Scheme 2). On treatment with TfOH in CH_2Cl_2, the mixture furnished the bicyclic enone **9a** in 82% yield as a single diastereomer.

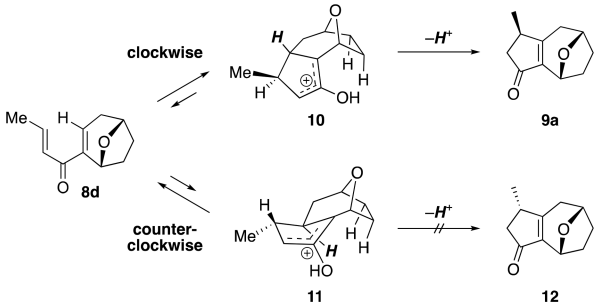
Scheme 2. Shorter-Step Synthesis of Bicyclo[5.3.0]decane 9a



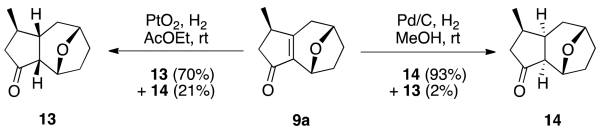
Although the reason for the perfect stereoselectivity observed in the Nazarov cyclization is unclear, examination using a molecular model indicated that the 8-oxabicyclo[3.2.1]-octenone system accommodates 4π conrotatory electrocyclization in either a clockwise or counterclockwise direction indiscriminately, which led us to assume that the deprotonation would be the critical step in this particular case where the bridgehead proton to be eliminated is better exposed at the convex face in intermediate **10** than at the concave face in intermediate **11** (Scheme 3). Calculations are underway.[10]

Having established the Nazarov cyclization entry to chiral bicyclo[5.3.0]decane footholds, we turned our attention to the use of **9a** as a chiral building block for guaiane-related sesquiterpenoids (e.g., compounds **1**–**4** in Figure 1). Thus, we searched for methods that enable the divergent installation of hydrogens onto the bridgehead alkene. It was eventually identified that Pd/C in MeOH catalyzed hydrogenation onto the enone **9a** opposite to the C4-methyl group and afforded ketone **14** in 93% yield (Scheme 4). On the other hand, PtO_2 in AcOEt was found to give diastereomer **13** selectively. The reversal of the diastereofacial selectivity may be due to the coordination of the oxo-bridge moiety onto the surface of PtO_2.

Scheme 3. Plausible Mechanism of Diastereoselective Nazarov Cyclization

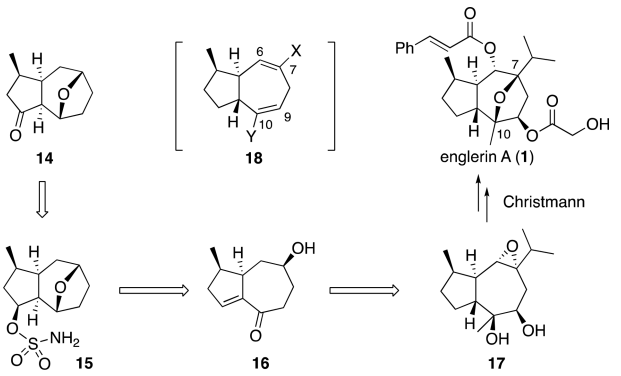


Scheme 4. Diastereodivergent Hydrogenation of 9a



At this juncture, we set (−)-englerin A (**1**) as the synthetic target to demonstrate the utility of **14**. The needed set of additional functionalities at C6, C7, C9, and C10 prompted us to propose 1,4-diene **18** as a virtual synthon (Scheme 5). **18**

Scheme 5. Synthetic Plan of (−)-Englerin A



formulated enone **16** as a feasible key intermediate, and owing to its structure, we adopted Christmann's approach[7a] relying on the intramolecular epoxide opening of **17**. To accommodate the gaps in the oxidation state between **14** and **16**, a redox-balancing sequence relying on an intramolecular C−H amination[11] was based on the seminal work by Du Bois and co-workers:[11e] sulfamate **15** was expected to undergo a Rh-catalyzed intramolecular C−H amination to furnish a cyclic sulfamate, the hydrolysis of which ultimately gives rise to enone **16** via dehydration. Although a sequence of intramolecular C−H amination of a C−H bond connected to an alkoxy group and the substitution of the resulting *N*,*O*-acetal group using an alkynyl zinc reagent were reported by Du Bois, unprecedented connection to the hydrolytic generation of a ketone via the cleavage of the N−O bond and the concomitant β-elimination of a sulfamate posed a challenge. The subsequent synthetic survey from **16** relying on conventional functional group interconversions would yield Christmann's intermediate **17**.

The synthesis commenced with diastereoselective installation of a sulfamate handhold for the projected C−H amination. On treatment with DIBAL and *n*-BuLi, tricyclic ketone **14** (95% ee) with shaping a caged structure accepted a hydride from the

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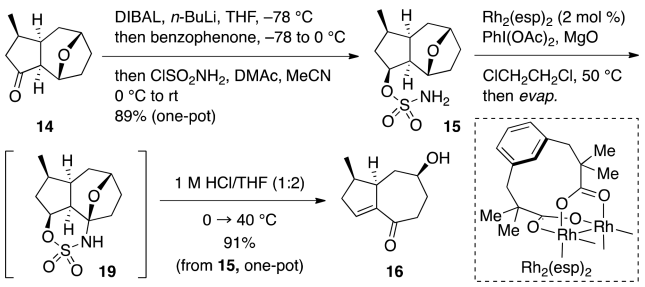
Org. Lett. XXXX, XXX, XXX−XXX

convex face to generate the corresponding alkoxide, which was trapped *in situ* with $ClSO_2NH_2$ to give sulfamate **15** in 89% yield (Scheme 6).[12] Upon exposure to typical Du Bois's C−H

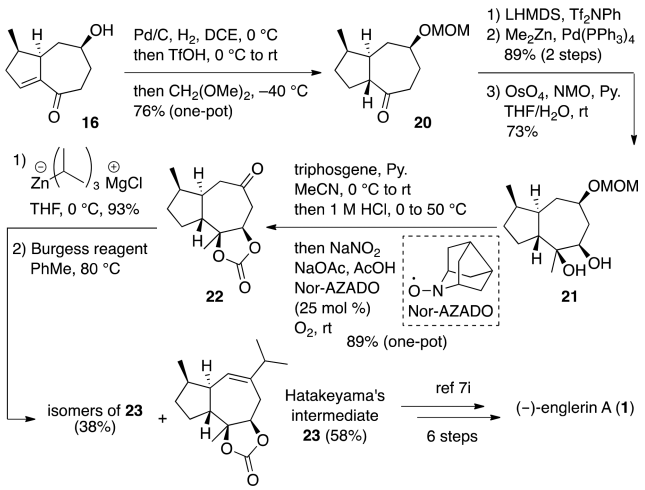
Scheme 6. Synthesis of Hydroxyenone 16



sulfamination conditions[11c−e] using $PhI(OAc)_2$ and MgO in the presence of cat. $Rh_2(esp)_2$ in warm $(CH_2Cl)_2$, sulfamate **15** underwent a smooth oxidative annulation to give **19**, and to our delight, the subsequent treatment of which in 1 M HCl in warm THF furnished enone **16** in 91% yield.

With hydroxyenone **16** obtained, effort was focused on the installation of the remaining functionalities toward the formal synthesis of (−)-englerin A, in which we settled on Hatakeyama's intermediate **23**[7i] for Christmann's approach[7a] (Scheme 7). Although our attempts in hydrogenations to

Scheme 7. Total Synthesis of (−)-Englerin A (1)



secure the *trans*-fused hydroazulene juncture were unsuccessful, we ultimately found that, after the hydrogenation without exclusion of Pd/C, a one-pot treatment of the *cis*- and *trans*-fused hydrogenated products with TfOH induced spontaneous isomerization to give *trans*-fused hydroxyenone predominantly, and the subsequent addition of dimethoxymethane[13] gave MOM ether **20** in 75% yield in a one-pot operation. The C14-methyl group of the guaiane skeleton was introduced via regioselective formation of an enol triflate and the subsequent Negishi coupling[14] to afford a trisubstituted alkene in 89% yield in two steps. Dihydroxylation of the alkene using OsO_4 proceeded diastereoselectively to give diol **21**. The sequential protection of the 1,2-diol as a carbonate, deprotection of the MOM group with aqueous HCl, and aerobic oxidation of the resulting secondary alcohol induced by Nor-AZADO−NO_x catalysis[15] was conducted in one pot to afford ketone **22** in 87% yield. Note that a conventional Dess−Martin oxidation[16] did not lead to alcohol oxidation in this particular one-pot sequence and the alcohol was recovered. The next introduction of the isopropyl group of the guaiane skeleton posed a formidable challenge. For example, addition of a Grignard reagent in the presence of $CeCl_3$ gave a complex mixture, and attempts in the formation of the corresponding enolate led to the elimination of the oxygen functional group on the *β*-position of the ketone to give the corresponding enone as a major product. After considerable experimentation, we found that a zinc(II) ate complex that was developed by Ishihara and co-workers[17] successfully induced the addition of the isopropyl group to the ketone to afford the corresponding tertiary alcohol in 93% yield as a single stereoisomer (its stereochemistry was not determined). The next regioselective dehydration also required considerable experimentation. Burgess reagent[18] provided the desired trisubstituted alkene **23** in 58% yield along with a mixture of undesired isomers in 38% yield, which can be separated from the other isomers by column chromatography. The spectral data of **23** were identical to those of Hatakeyama's intermediate[7i] in the total synthesis of (−)-englerin A. Finally, completion of the total synthesis of (−)-englerin A was achieved by a six-step sequence adopting Hatakeyama's procedure.[7i]

In conclusion, we have developed a rapid and diastereoselective entry to bicyclo[5.3.0]decane skeletons **9a−c** from readily available chiral oxa-bridged cycloheptenone **5** and have demonstrated the usefulness of **9a** for synthesis by employing it in the enantioselective formal synthesis of (−)-englerin A. The Nazarov cyclization protocol provides useful bicyclo[5.3.0]-decane-type chiral building blocks, which will prompt synthetic studies of various hydroazulene-type bioactive natural products and their analogs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02428.

Experimental procedure, ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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