Organic LETTERS

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# Synthesis of the Tricyclic Ring Structure of Daphnanes via Intramolecular [4 + 3] Cycloaddition/$SmI_2$-Pinacol Coupling

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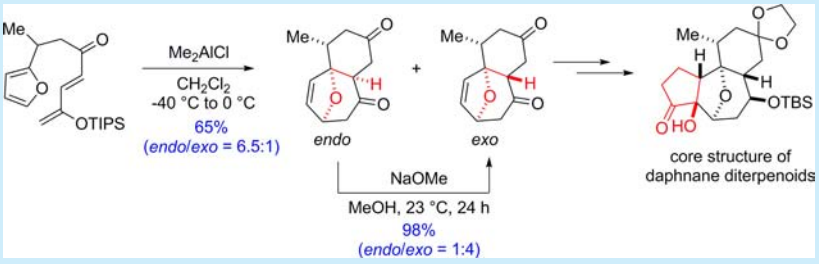
Supporting Information




**ABSTRACT:** A synthetic approach toward the tricyclic 5,7,6-membered ring structure of daphnane-family natural products is described. An intramolecular [4 + 3] cycloaddition reaction of furan with an oxypentadienyl cation constructed the oxa-bridged bicyclic structure in a stereoselective fashion. Structural analysis revealed that the desired *exo* isomer was predominantly acquired through epimerization. Finally, formation of the five-membered ring was achieved through $SmI_2$-mediated pinacol coupling.

Daphnane diterpenoids, mainly found in *Thymelaeaceae* and *Euphorbiaceae*, share a common characteristic 5−7−6 tricyclic ring system with highly oxygenated functional groups.[1] To date, more than 100 daphnane diterpenoids have been isolated from nature showing a wide range of biological activities including skin irritant, anti-HIV, cytotoxic, antileukemic, and neurotrophic effects.[2] For example, resiniferatoxin (**1**) exhibits an analgesic effect through activation of transient receptor potential vanilloid 1 (TRPV1), which induces desensitization of nociceptive neurons (Figure 1).[3] Kirkinine

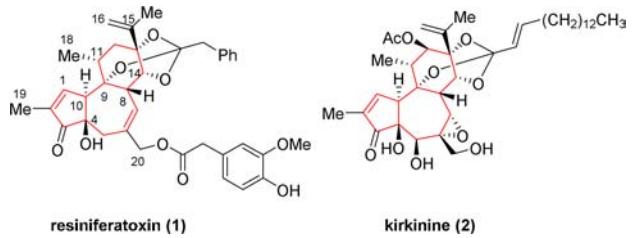



**Figure 1.** Representative daphnane-family natural products.

(**2**) functions as a potent neurotrophin that promotes neuronal survival.[4] Because of their structural complexity and promising biological activities, the daphnane-family natural products have become attractive synthetic targets to organic chemists. A number of synthetic approaches toward the core ring structures of this family have been reported,[5] and the only total syntheses of resiniferatoxin and yuanhuapin were completed by Wender and co-workers.[6] Despite these synthetic efforts, an efficient and amenable synthetic route to the common structure of the daphnanes is still necessary because the investigation of them as potential therapeutic candidates is challenging for drug discovery.[7] Herein, we describe our synthetic approach to the tricyclic ring system of the daphnane family using a stereocontrolled intramolecular [4 + 3] cycloaddition followed by a $SmI_2$-mediated pinacol coupling.

The [4 + 3] cycloaddition reaction is an efficient strategy for the construction of seven-membered ring structures. In particular, cycloaddition of furan with allyl cations provides stereochemically defined oxabicylic cycloadducts, which can be further transformed into useful carbon scaffolds for the syntheses of various synthetic targets.[8] Recently, Harmata and co-workers reported that an intermolecular [4 + 3] cycloaddition of furan with 4-silyloxypentadienals produced oxabicycles with high selectivity.[9] Inspired by this study, we envisioned that an intramolecular version of this synthetic method could be applied to the synthesis of the 7,6-membered carbon framework of daphnanes. As depicted in Scheme 1, acyl substitution of **7** with **8** would give furyl 4-silyloxydienone **6**, which could be converted to oxabicycle **5** via the intramolecular [4 + 3] cycloaddition. To the best of our knowledge, utilization of an oxypentadienyl cation for such an *intramolecular* [4 + 3] cycloaddition of furan has not been explored. In this event, we proposed that **5a/b** could be obtained through either a *compact-exo-TS* (**A**) or a *compact-endo-TS* (**B**).[10] Although a W-

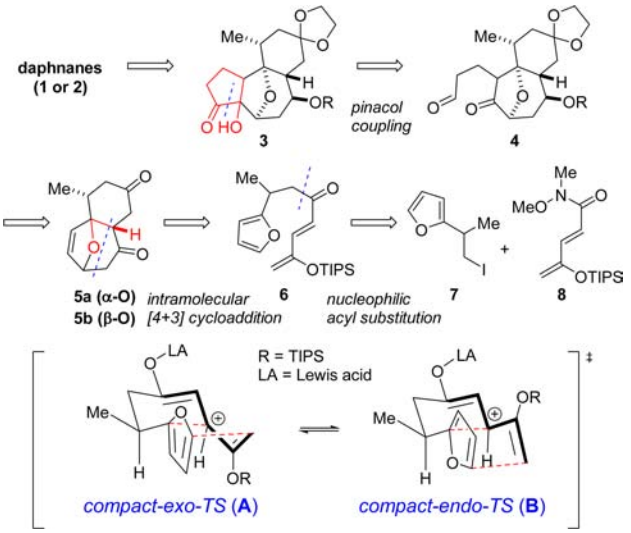
**Received:** April 12, 2015
**Published:** May 21, 2015





DOI: 10.1021/acs.orglett.5b01054
*Org. Lett.* 2015, 17, 2672−2675

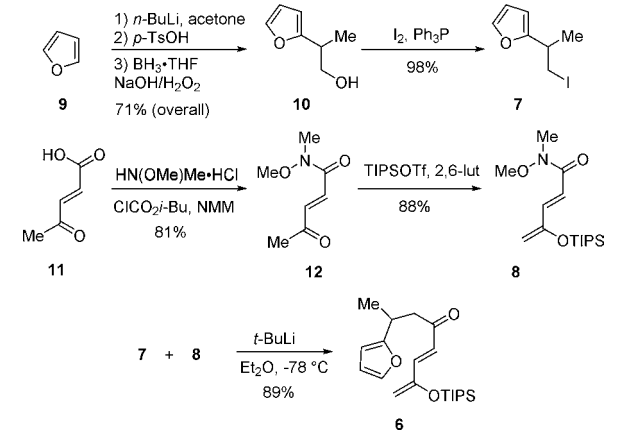
**Scheme 1. Our Retrosynthetic Analysis**




type shape in transition state **B** would generally be favored over a sickle shape in transition state **A**, the stereoselectivity would be controlled by the equatorial methyl group in a chairlike conformation, in which $A^{1,3}$ strain between the furan C−H and the methyl group in configuration **A** could be minimized. At the final stage, selective protection of cycloadduct **5** followed by three-carbon installation would provide compound **4**, which would be cyclized through pinacol coupling to generate the five-membered ring with a quaternary hydroxyl group.

Our work commenced with the preparation of furyl 4-silyloxydienone **6** as shown in Scheme 2. Starting from furan **9**,

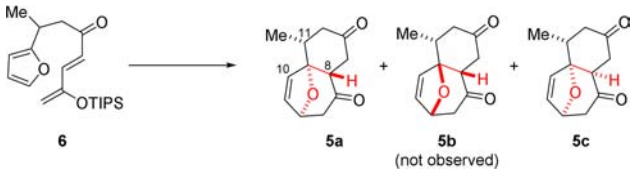
**Scheme 2. Synthesis of Furyl 4-Silyloxydienone 6**




addition of lithiated furan to acetone, elimination of the resulting alcohol with TsOH, and subsequent hydroboration/oxidation produced alcohol **10**[11] in 71% yield over three steps, which underwent a substitution reaction to afford iodide **7** in excellent yield. Amide **8** was prepared from readily available 4-oxopent-2-enoic acid **11**[12] in two steps: conversion of the acid to the Weinreb amide[13] and formation of the silyl enol ether. Finally, the lithium anion of **7**, generated via treatment with *t*-BuLi at −78 °C, was reacted with amide **8** to give desired dienone **6** in 89% yield.

Next, we investigated the intramolecular [4 + 3] cycloaddition of **6** under various reaction conditions (Table 1). Initially, mild Lewis acids such as $ZnCl_2$, $InCl_3$, $In(OTf)_3$, and

**Table 1. Intramolecular [4 + 3] Cycloaddition of 6 Using Various Lewis Acids**




| entry | reagents | solvent | *t* (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | $ZnCl_2$ | $CH_2Cl_2$ | −78 to rt | 24 | NR[a] |
| 2 | $InCl_3$ | $CH_2Cl_2$ | −78 to −10 | 6 | −[b] |
| 3 | $In(OTf)_3$ | $CH_2Cl_2$ | −78 to −20 | 6 | −[b] |
| 4 | $Sc(OTf)_3$ | $CH_2Cl_2$ | −78 to 0 | 6 | −[b] |
| 5 | TMSOTf | $CH_2Cl_2$ | −78 to 0 | 4 | −[b] |
| 6 | TFA/piperidine | $CH_2Cl_2$ | −78 to rt | 24 | −[b] |
| 7 | $TiCl_4$ | $CH_2Cl_2$ | −78 | 0.1 | 5[c] |
| 8 | $SnCl_4$ | $CH_2Cl_2$ | −78 | 0.1 | 13 (1:3.2)[d] |
| 9 | $Me_2AlCl$ | $CH_2Cl_2$ | −40 to 0 | 1 | 64 (1:6.5)[d] |
| 10 | $Me_2AlCl$ | THF | −20 to rt | 24 | NR[a] |
| 11 | $Me_2AlCl$ | toluene | −20 to rt | 2 | −[b] |
| 12 | $Me_2AlCl$ | $CH_3NO_2$ | −78 to rt | 24 | 13 (1:1.7)[d] |

[a]No reaction. Starting material **6** remained. [b]Starting material **6** decomposed. [c]The diastereomeric ratio was not determined. [d]The ratio of **5a** and **5c**.

$Sc(OTf)_3$ were used; however, the desired products were not observed (entries 1−4). The cyclization reactions in the presence of organic catalysts such as TMSOTf and trifluoroacetic acid led to decomposition of the starting materials (entries 5 and 6). We obtained cycloadduct **5** in very low yields when we used $TiCl_4$ and $SnCl_4$ as Lewis acids (entries 7 and 8). Finally, we found that **6** could be rapidly transformed to a 1:6.5 mixture of two cycloadducts **5** in 64% yield when the reaction of **6** with $Me_2AlCl$ in $CH_2Cl_2$ was performed at −40 °C, which was allowed to warm to 0 °C (entry 9). Further optimization by changing the solvents did not improve the yield of this reaction (entries 10−12).

At this moment, we attempted to elucidate the structures of the two isomers of **5** using NOE experiments. The minor isomer showed NOE enhancement between the protons at the $C_8$, $C_{10}$, and $C_{11}$ positions, which indicates that the angular proton ($C_8$) is *cis* to the $C_{11}$ proton and *trans* to the bridged oxygen. Thus, this compound proved to be **5a** as suggested in Scheme 1. In the case of the major isomer, however, we could not observe an NOE correlation between the $C_{11}$ proton and the angular proton ($C_8$). Instead, substantial NOE interaction between the methyl group ($C_{11}$) and the angular proton ($C_8$) was detected. This result suggests that the second isomer corresponds to **5c** (not **5b**), in which the $C_{11}$ methyl group is located at the axial position. The predicted structures of **5a** and **5c**, resulting from the NOE analysis, were clearly established by X-ray crystallographic analysis as shown in Figure 2. Considering this structural determination, we suggested that the predominant formation of **5c** could be explained by revised transition state **B′** (Figure 3), in which the $C_{11}$ methyl group occupies the axial position in the chairlike conformation, minimizing the $A^{1,3}$ strain between the furan and the methyl group without changing the preferential W-shape configuration.

Although we obtained **5c** as the major diastereomer in this crucial cycloaddition, we speculated that **5c** could be converted to **5a** under equilibrium conditions because **5c** experiences



DOI: 10.1021/acs.orglett.5b01054
*Org. Lett.* 2015, 17, 2672−2675

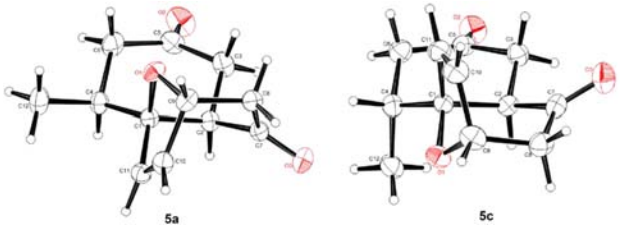



**Figure 2.** X-ray crystal structures of **5a** and **5c**.

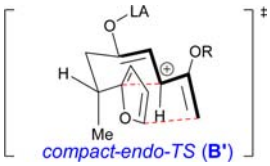
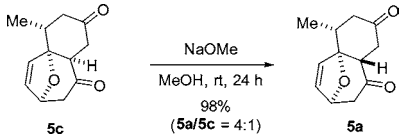



**Figure 3.** Proposed transition state for the formation of **5c**.

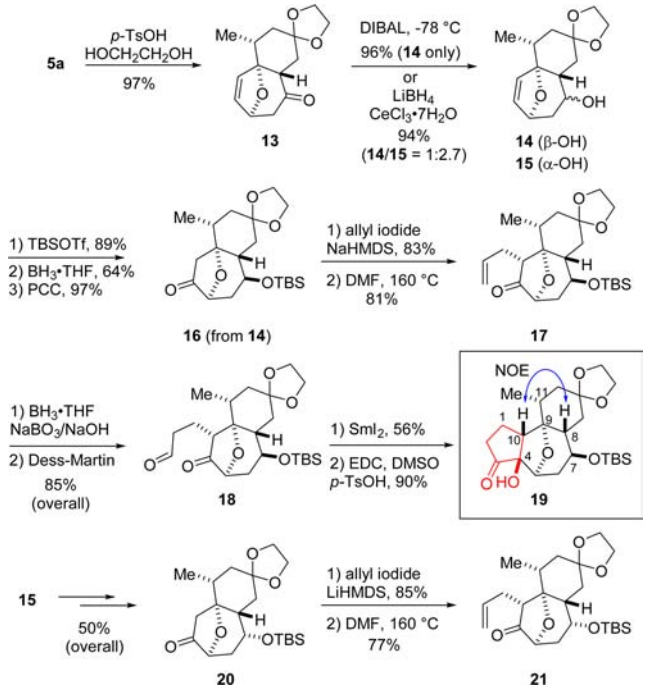
unfavorable 1,3-diaxial interactions due to not only the axial methyl group but also the axial olefinic C−H at the ring junction. Furthermore, isomer **5a** is predicted to be 1.15 kcal/mol more stable than isomer **5c** based on the DFT calculation of ground state conformations.[14] As anticipated, treatment of **5c** with NaOMe in MeOH for 24 h produced a 4:1 mixture of **5a** and **5c**, which was easily separated (Scheme 3). Therefore, desired compound **5a** is the thermodynamically more stable isomer, which is readily accessible via the cycloaddition/isomerization process.

**Scheme 3. Epimerization of 5c to 5a**




With cycloadduct **5a** in hand, we turned our attention to the formation of the five-membered ring (Scheme 4). In order to introduce the three-carbon unit into the alkene moiety of **5a**, the two ketones should be differentiated using different protecting groups. Thus, diketone **5a** was selectively protected as monoacetal **13**. The remaining ketone on the seven-membered ring of **13** was reduced with DIBAL to afford *β*-alcohol **14** in 96% yield as a single diastereomer. Alternatively, we attempted to obtain *α*-alcohol **15** to explore the steric effect of the silyloxy substituent in an *α*-allylation step (*vide infra*). The best yield (94%) and selectivity (**14**/**15** = 1:2.7) in the synthesis of **15** was achieved when **13** was treated with $LiBH_4$ in the presence of $CeCl_3{\cdot}H_2O$. TBS protection of **14** followed by hydroboration/oxidation and PCC oxidation gave ketone **16**. Then, *α*-allylation of **16** unexpectedly resulted in formation of the *O*-allylated product, which was subjected to Claisen rearrangement in DMF at 160 °C to provide the desired C-allylated product **17**. At this moment, we could not determine the stereochemistry of the allyl group in **17**, but tentatively assumed that it was *syn* to the bridged oxygen. Treatment of **17** with borane produced a 1,5-diol intermediate, which was oxidized with Dess-Martin periodinane to afford 1,5-dicarbonyl compound **18**. Direct annulation of **18** to **19** through benzoin condensation using thiazolium as a catalyst[15] did not give any desired product. However, $SmI_2$-mediated pinacol coupling of **18** successfully produced the corresponding diol as a single

**Scheme 4. Construction of the Five-Membered Ring**




diastereomer, which was subsequently converted to **19** under Pfitzner−Moffatt oxidation conditions.[16] The relative configuration was unambiguously confirmed by NOE experiments, which showed significant NOE correlations between protons at $C_8$, $C_{10}$, and $C_{11}$. We also attempted direct allylation at the $C_{10}$ position by utilizing *α*-alcohol **15** as a substrate, in which the $C_{10}$ reaction site would be sterically less hindered. Toward this end, we prepared ketone **20** through the same reaction sequence, which was treated with allyl iodide and LiHMDS. Unfortunately, we obtained the corresponding *O*-allylated product again, which was converted to **21** via Claisen rearrangement. The stereochemistry of the allyl group in **21** appeared to be the same as that in **17**, which was confirmed by NOE analysis of the corresponding tricyclic compound, the $C_7$-epimer of **19** (see the Supporting Information for details).

In conclusion, we have reported a synthetic approach to oxa-bridged tricycle **19**, which is a highly functionalized core structure of the daphnane-family natural products. The key features of this synthetic route include (1) rapid synthesis of the 7,6-membered ring system using the intramolecular [4 + 3] cycloaddition of furan with oxypentadienyl cation followed by the epimerization based on the structural analysis of corresponding cycloadducts **5a** and **5c** and (2) formation of the five-membered ring via $SmI_2$-mediated pinacol coupling. This study demonstrates that the intramolecular [4 + 3] cycloaddition reactions of conformationally well-defined carbon scaffolds can be applied to the construction of a complex oxa-bridged polycyclic system in a stereoselective manner. Further syntheses of daphnane terpenoids using this approach are currently in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Detailed experimental procedures, copies of all spectral data, and X-ray crystallographic data. The Supporting Information is



DOI: 10.1021/acs.orglett.5b01054
*Org. Lett.* 2015, 17, 2672−2675

available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01054.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This research was supported by the Korea Institute of Science and Technology (KIST-2E25473, 2E25240, 2E25580) and the National Research Foundation of Korea (NRF-2013R1A1A2005550 and NRF-2014M3C1A3054141) funded by the Ministry of Science, ICT and Future Planning.

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DOI: 10.1021/acs.orglett.5b01054
*Org. Lett.* 2015, 17, 2672−2675