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Synthetic efforts toward the bicyclo[3.2.1]octane fragment of rhodojaponin III

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ABSTRACT

Rhodojaponin III is a grayanane-type diterpenoid natural product with a novel chemical scaffold. It shows potent antinociceptive activity and may represent a new class of natural non-opioid analgesics with a novel mode of action. We explored the Au(I)-catalyzed Conia-ene cyclization and the Mn(III)-mediated radical cyclization of alkynyl ketones for the synthesis of the bicyclo[3.2.1]octane fragment of rhodojaponin III. These strategies will be applicable in the synthesis of rhodojaponin III and analogs for future biological studies.

Introduction

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Pain reduces the quality of life and imparts high health costs and economic loss to society. Current pain management heavily relies on analgesic medications. Analgesics mainly target the enzymatic cascade related to inflammatory processes (e.g., nonsteroidal anti-inflammatory drugs) or the endogenous opioid system (e.g., opioids). However, they exhibit limited efficacy, unwanted side effects, and drug abuse problems [2]. In particular, the United States is experiencing a nationwide public opioid crisis that continues to escalate. According to the US Department of Health & Human Services, more than 130 people died every day from opioid-related drug overdoses in 2016 and 2017 [3]. Therefore, to overcome this serious socioeconomic issue, the search for new antinociceptive compounds that are effective for both acute and chronic pain and do not produce tolerance or dependence is important.

Among the plants clinically used to relieve pain in China, *Rhododendron molle* G. Don (Ericaceae) is one of the most potent medicines for pain management [4,5]. It has been traditionally used as an anodyne and anesthetic. Of the natural products isolated from *Rhododendron molle*, a grayanane-type diterpenoid, rhodojaponin III (**1**, Fig. 1), showed significant antinociceptive activity in an acetic acid-induced writhing test (74% inhibition of the writhing events at 0.08 mg/kg) [6]. Rhodojaponin III (**1**) was also more potent than morphine in both acute and inflammatory pain models and 100-fold more potent than gabapentin in a diabetic neuropathic pain model. More importantly, naloxone showed no significant effect on analgesia induced by rhodojaponin III (**1**), suggesting that the endogenous opioid peptidergic system is not involved in the antinociceptive activity of **1**. Taken together, rhodojaponin III (**1**) may represent a new class of natural non-opioid analgesics. Due to the important biological activities of rhodojaponin III (**1**) and structurally related grayanane-type natural products [7], a considerable amount of effort has been made to establish an efficient synthetic approach to this class of natural products [8–10], culminating in the first total synthesis of grayanotoxin III by Matsuda, Shirahama and co-workers in 1994 [10].

We were intrigued by the great potential of rhodojaponin III (**1**) for a novel non-opioid analgesic and a chemical probe for identification of novel drug targets for pain management. Herein, we describe a stereoselective synthesis of the bicyclo[3.2.1]octane moiety of rhodojaponin III (**1**), enlisting the intramolecular radical-mediated cyclization of alkynyl ketones.

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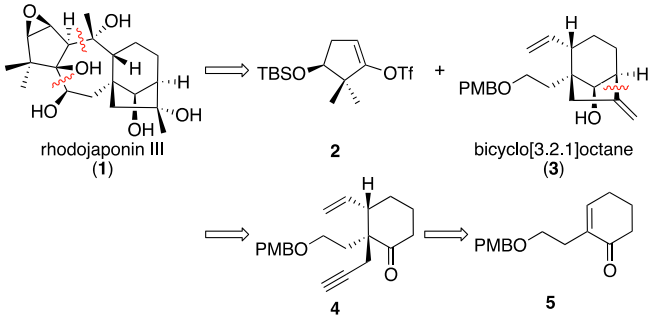


Fig 1. Structure and retrosynthesis of rhodojaponin III (**1**).

Results and discussion

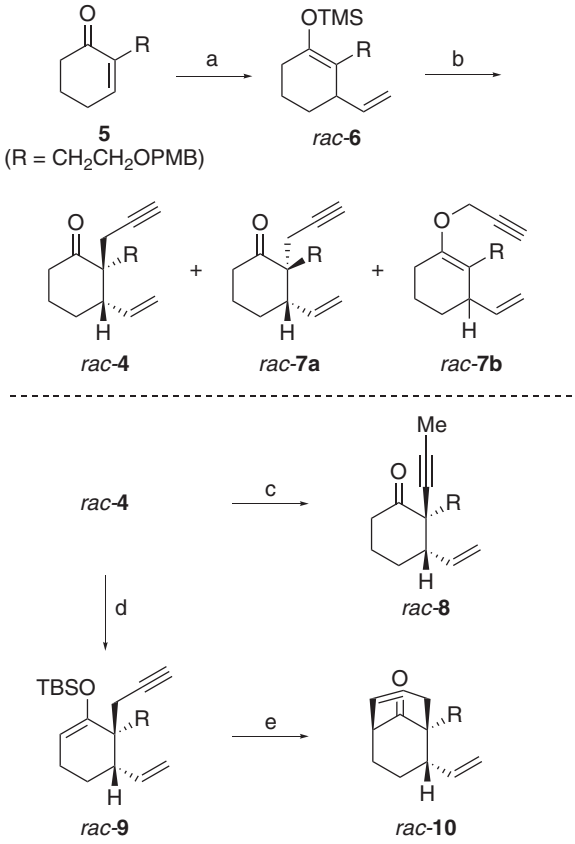
As illustrated in Fig. 1, a convergent synthesis of rhodojaponin III (**1**) could be realized by coupling bicyclo[3.2.1]octane **3** and cyclopentane **2**. Towards this goal, we embarked on a stereoselective construction of **3**. We envisioned that the stereoselective synthesis of **3** could be achieved *via* the Conia-ene-type reaction of alkynyl ketone **4** which could be prepared from α,β-unsaturated cyclic enone **5**.

There have been reports on stereoselective syntheses of structurally similar bicyclo[3.2.1]octanes. For example, the first total synthesis of principinol D by Newhouse and co-workers features a Ni-catalyzed α-vinylation reaction for the bicyclo[3.2.1]octane fragment of principinol D [11]. Ding and co-workers explored a Ti(III)-mediated reductive epoxide-opening/Beckwith–Dowd rearrangement process to efficiently assemble the bicyclo[3.2.1]octane framework of rhodomolleins XX and XXII [12]. More recently, Jia and co-workers reported the investigation of a radical-mediated cyclization of alkynyl ketones for the synthesis of the bicyclo [3.2.1]octane framework of (–)-glaucocalyxin A [13].

In order to explore the feasibility of the proposed approach to bicyclo[3.2.1]octane **3**, our synthesis began with the preparation of alkynyl ketone **4** for intramolecular cyclization. The conjugate addition of vinylmagnesium bromide in the presence of $CuBr{\cdot}SMe_2$ and TMSCl to α,β-unsaturated cyclic enone **5**, which was prepared by PMB protection of the known 2-(2-hydroxyethyl)cyclohex-2-en-1-one [14], afforded TMS enol ether **6** in 76% yield (Scheme 1) [15]. Propargylation of **6** *via* the resulting lithium enolate generated by MeLi provided the desired alkynyl ketone **4** (37%) as well as the *C*2-*epi*-diastereomer **7a** (35%) [16]. In addition to *C*-propargylation products, we also observed the formation of *O*-propargylation product **7b** (15%). X-ray crystallography was used to establish the structure and stereochemistry of the propargylation products [17].

Having prepared alkynyl ketone **4**, we turned our attention to the crucial Conia-ene-type cyclization for the construction of the bicyclo [3.2.1]octane fragment of rhodojaponin III (**1**). The intramolecular addition of enols to alkynes or alkenes represents one of the most powerful and widely employed methods for the formation of carbon–carbon bonds, known as the Conia-ene reaction [18]. Originally, Conia and co-workers studied the *thermal* intramolecular cyclization of ketones onto alkynes leading to valuable five- or six-membered carbocycles. However, high temperature is required for this reaction to occur, and many functional groups are not compatible with these restrictive reaction conditions. To overcome this shortcoming, Trauner and co-workers reported a Conia-ene cyclization of unactivated alkynes under basic conditions [19]. Unfortunately, alkynyl ketone **4** did not undergo the desired cyclization under basic conditions. Instead, **4** was isomerized to the corresponding internal alkyne **8** (Scheme 1) [20].

The Conia-ene cyclization catalyzed by transition metals has been widely employed for the formation of carbon–carbon bonds.

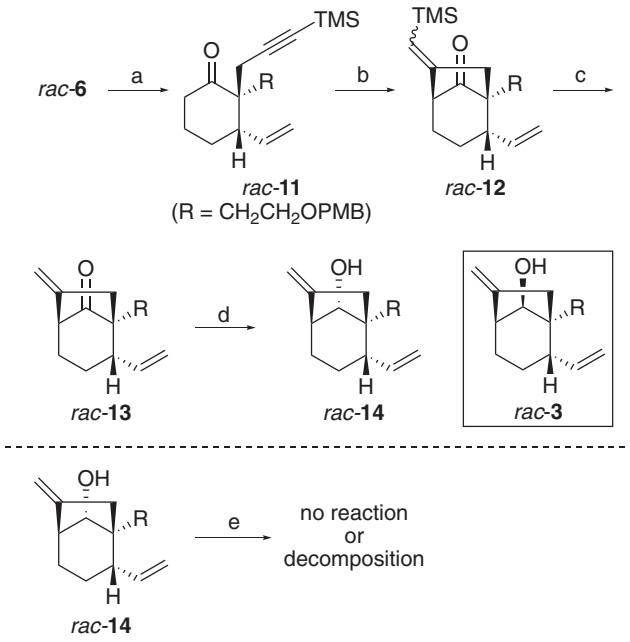


Scheme 1. Preparation and initial attempts for the Conia-ene-type cyclization of alkynyl ketone **4**. Reagents and conditions: (a) vinylmagnesium bromide, $CuBr{\cdot}SMe_2$, TMSCl, HMPA, THF, –78 °C, 3 h, 76%; (b) MeLi·LiBr, THF, 0 °C, 1 h, then, $CHCCH_2Br$, HMPA, –78 to 25 °C, 16 h, 37% (*rac*-**4**), 35% (*rac*-**7a**), 15% (*rac*-**7b**); (c) KO*t*-Bu, DMSO, 25 °C, 1.5 h, 23%; (d) Et_3N, TBSCl, NaI, MeCN, reflux, 16 h, 84%; (e) [(CyJohnPhos)Au(MeCN)]SbF_6 (0.5 equiv), acetone, 45 °C, 4 h, 58%.

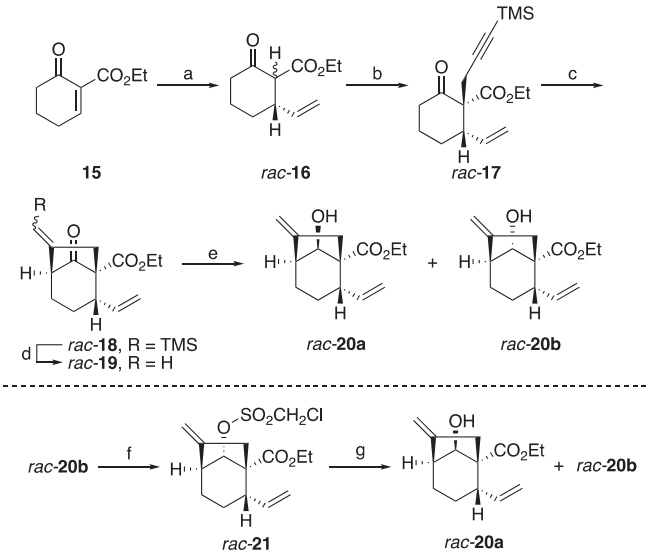
Toste and co-workers reported a catalytic Conia-ene reaction that proceeds at ambient temperatures and under neutral conditions using gold(I) complexes [21]. Carreira and co-workers adopted this catalytic version of the Conia-ene reaction towards the total synthesis of (±)-gomerone C [22]. Treatment of **4** with Et_3N, TBSCl, and NaI provided **9**, setting the stage for the Au(I) catalyzed Conia-ene reaction. However, the Au(I) catalyzed cyclization of **9** failed to provide the desired 5-*exo*-*dig* cyclization product. Instead, it resulted in the formation of the undesired 6-*endo*-*dig* cyclization product **10** [23].

Since the Conia-ene reaction failed to provide the desired 5-*exo*-*dig* cyclization product, we searched for other types of cyclization reactions. After an extensive investigation of conditions for the cyclization of alkynyl ketones, we adopted the Mn(III)-initiated cyclization method, which was originally reported by Snider and co-workers [24]. They found that the free radical cyclization of (trimethylsilyl)alkynyl ketones mediated by $Mn(OAc)_3$ provided 5-*exo*-*dig* alkenes as the major products. Gratifyingly, upon treatment of **11** with $Mn(OAc)_3$, the desired 5-*exo*-*dig* cyclization product **12** was obtained in 50% yield as an (*E*)/(*Z*) mixture (Scheme 2) [25]. Selective removal of the TMS group without the accompanying PMB deprotection was achieved by treatment of **12** with *p*-TsOH in MeCN (73%).

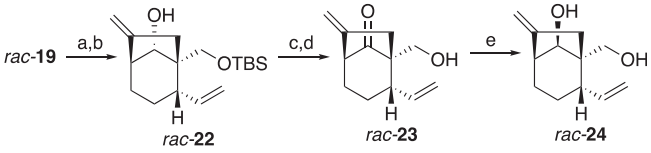
Having achieved the stereoselective construction of the bicyclo [3.2.1]octane by employing the Mn(III)-mediated radical cyclization reaction, we turned our attention to the stereoselective reduction of ketone **13** to the desired equatorial alcohol **3**. When **13** was treated with $NaBH_4$, the reduction reaction provided a single



Scheme 2. $Mn(OAc)_3$-mediated radical cyclization of alkynyl ketone **11**. Reagents and conditions: (a) MeLi·LiBr, THF, 0 °C, 1 h, then, $TMSCCCH_2Br$, HMPA, −78 to 25 °C, 16 h, 34%, d.r. = 1:1; (b) $Mn(OAc)_3$ (20 equiv), EtOH/HOAc, 100 °C, 72 h, 50%; (c) *p*-TsOH, MeCN, 0 °C, 2 h, 73%; (d) $NaBH_4$, MeOH, 0 °C, 2 h, 65%; (e) DIAD or DEAD, 4-nitrobenzoic acid, PPh_3, THF, −20 to 40 °C.



Scheme 3. $Mn(OAc)_3$-mediated free radical cyclization of alkynyl *β*-keto ester **17** and reduction of bicyclo[3.2.1]octane **19**. Reagents and conditions: (a) vinylmagnesium bromide, CuBr·SMe_2, THF, −78 °C, 1 h, 54%; (b) KO*t*-Bu, *t*-BuOH, reflux, 30 min, then, $TMSCCCH_2Br$, reflux, 1 h, 73%, d.r.>10:1; (c) $Mn(OAc)_3$ (12.5 equiv), EtOH/HOAc, 90 °C, 48 h, 43%; (d) *p*-TsOH, MeCN, 0 to 25 °C, 2 h, 69%; (e) SmI_2, PhSH, HMPA, THF, 0 °C, 5 h, *rac*-**20a**:*rac*-**20b** = 1:3; (f) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, quantitative; (g) KO_2, 18-crown-6, DMSO, 25 °C, 2 h, 5% (*rac*-**20a**), 14% (*rac*-**20b**).



Scheme 4. SmI_2-mediated reduction of *β*-hydroxy ketone **23**. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 1 h, 81%; (b) TBSCl, imidazole, CH_2Cl_2, 25 °C, 24 h, 84%; (c) PCC, CH_2Cl_2, 25 °C, 1 h, 79%; (d) 6 N HCl, THF, 0 to 25 °C, 4 h, 67%; (e) PhSH, HMPA, SmI_2, THF, 0 °C, 5 h, 78%.

stereoisomer. Careful analysis of the ^1H NMR spectral data indicated that the $NaBH_4$ reduction afforded the undesired axial alcohol **14** (see the ESI for details). Reduction of **13** under various reduction conditions such as DIBAL-H and L-Selectride did not afford the desired alcohol **3**. These results were consistent with observations made by Newhouse and co-workers during the synthesis of principinol D [11]. To obtain the desired alcohol **3**, we also attempted the Mitsunobu inversion (PPh_3, DIAD or DEAD, 4-nitrobenzoic acid) of **14**, but the reaction resulted in either recovery of **14** or decomposition.

Since no attempts with the PMB protected γ-hydroxyl ketone **13** afforded the desired equatorial alcohol, we explored *β*-keto esters or *β*-hydroxy ketones for the stereoselective reduction to give the desired alcohol. Starting from known cyclic enone **15** [26], the Cu(I)-mediated addition of vinylmagnesium bromide (54%) followed by TMS-propargylation provided TMS-alkynyl ketone **17** (73%) (Scheme 3). As expected, subjecting **17** to the Mn(III)-mediated radical cyclization reaction afforded the desired bicyclo[3.2.1]octane **18** in 43% yield as an (*E*)/(*Z*) mixture. TMS deprotection of **18** was accomplished by treatment with *p*-TsOH to give **19** (69%). We explored a wide range of reducing agents (e.g., $NaBH_4$, $MnCl_2$·$NaBH_4$, $Zn(BH_4)_2$, $Me_4NBH(OAc)_3$, NH_3·BH_3) to stereoselectively reduce the *β*-keto ester to the desired *β*-hydroxy ester, but none of these conditions gave the desired equatorial alcohol **20a**. Instead, the undesired axial alcohol **20b** was obtained, as was the case with **14** (see Scheme 2 for details). We also attempted the S_N2 inversion of **20b** to **20a**, but the S_N2 inversion reaction resulted in a limited success. When the chloromethanesulfonate **21**, prepared from **20b** and $ClCH_2SO_2Cl$, was treated with KO_2 and 18-crown-6, the S_N2 inversion reaction afforded the desired alcohol **20a** (5%) and the recovered undesired alcohol **20b** (14%).

Then, we decided to adopt Newhouse's *β*-hydroxy ketone substrate for the formation of the desired alcohol. $LiAlH_4$ reduction of keto ester **19** (81%) followed by mono TBS protection of the resulting diol gave the corresponding TBS protected alcohol **22** in 84% (Scheme 4). PCC oxidation and TBS deprotection set the stage for the SmI_2 reduction. Following Newhouse's conditions, when **23** was subjected to the SmI_2 reduction (SmI_2, PhSH, and HMPA), the reaction proceeded smoothly to give the desired equatorial alcohol **24** in 78% yield, as a single stereoisomer [11].

Having established the stereoselective route to the bicyclo[3.2.1]octane fragment of rhodojaponin III (**1**), we prepared the enantiopure *β*-vinyl cyclic ketone **16** by exploiting Helmchen's auxiliary (see the ESI for details) [27,28]. Enantiopure **16** can be converted to the enantiopure bicyclo[3.2.1]octane fragment **24** of rhodojaponin III (**1**) by following the procedure established for racemic *β*-vinyl cyclic ketone **16**.

Conclusion

Rhodojaponin III (**1**) shows great potential as a non-opioid analgesic agent for pain management. Our synthetic efforts were focused on the stereoselective synthesis of the bicyclo[3.2.1]octane fragment of rhodojaponin III (**1**). The Cu-catalyzed conjugate addition of a vinyl Grignard reagent to α,*β*-unsaturated cyclic enones followed by subsequent TMS-propargylation set the stage for the key cyclization reaction of alkynyl ketones. After an extensive search for cyclization conditions, Mn(III)-initiated radical cyclization of alkynyl ketones (**11** and **17**) provided the desired bicyclo[3.2.1]octanes (**13** and **19**, respectively). We expect that our stere-

oselective approach to the bicyclo[3.2.1]octane fragment of rhodojaponin III (**1**) in conjunction with Helmchen's chiral auxiliary will be applicable in an enantioselective total synthesis of rhodojaponin III (**1**) and related natural products. The total synthesis of rhodojaponin III (**1**) will not only allow opportunities for new, innovative, and efficacious therapies to treat pain, but also offer a new drug target to overcome the current opioid crisis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153055.

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