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Protecting-group-free synthesis of haterumadienone- and puupehenone-type marine natural products

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A divergent and expeditious access to haterumadienone- and puupehenone-type marine natural products has been achieved by using a newly developed hemiacetalization/dehydroxylation/ hydroxylation/retro-hemiacetalization tandem reaction as one of the key steps. Its applicability is showcased by the first synthesis of haterumadienone, 20-hydroxyhaterumadienone, 20-epihydroxy-haterumadienone and 20-acetoxy-haterumadienone, as well as the facile synthesis of puupehenone, puupehedione and puupehenol. The synthesis is efficient, atom- and step-economical (6 to 9 steps from commercially available starting materials), and requires no protecting groups and transition metals.

Green chemistry, which emphasizes the development of environmentally benign chemical processes and sustainable technologies, has attracted much attention over the past few decades.[1] Accordingly, the field of green chemical synthesis has made great advances, but synthesis of bioactive natural products with each step in agreement with the principle of green chemistry still remains a significant challenge to synthetic chemists. Among the strategies used for the green synthesis of natural products, atom-/step-economical[2a–d] and protecting-group-free[2e–g] syntheses and tandem reactions[3] are desirable because of their intrinsic properties of high efficiency and low waste disposal. As a proof of concept, the puupehenone-[4] and haterumadienone-type[5] marine natural products (Fig. 1) have been selected here as synthetic targets because of their promising biological activities such as antitumor,[6a–e] antiviral,[6f] antimalarial,[4b] anti-HIV,[6h] antituberculosis,[6h,i] anti-cancer[6j] and immunomodulatory.[4d] The significance and prevalence of this class of compounds have served to stimulate continual interest within the synthetic community.[7-11] Accordingly, synthetic routes to some

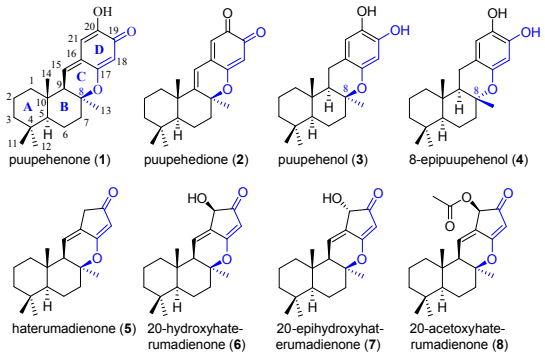
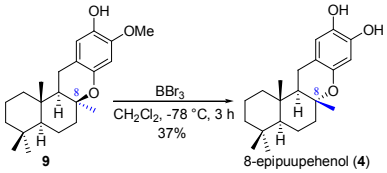


Fig. 1 Selected Haterumadienone- and Puupehenone- type marine natural products.

puupehenones have already been reported,[8-11] in which the use of protecting groups not only made the puupehenone syntheses redundant, but also lead sometimes to undesired side reactions during their removal.[7,8] As mentioned by Quideau, the deprotection of benzopyran **9** in the presence of boron tribromide (BBr_3) did not afford the desired puupehenol but 8-epipuupehenol even under mild conditions (CH_2Cl_2, -78 °C, Scheme 1) because the expected natural product is less stable than its C_8-epimer.[8] Indeed, the unnatural C_8-epimers are usually formed instead of the natural compounds.[7] To overcome this inherent problem, palladium-[9] or organoselenium-promoted[10] cycloisomerization of olefinic phenols followed by reduction have been elegantly developed for the construction of the natural unepimerized products.[8,11] These indirect modifications are helpful in reducing problems due to the undesired epimerization at the C_8 position but also increase the number of synthetic operations that must be



Scheme 1 Undesired Epimerization over Deprotection of Benzopyran **9**.

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performed. Moreover, the synthesis of haterumadienones is still blank. In this context, we wish to describe here a versatile hemiacetalization/dehydroxylation/hydroxylation/retro-hemi-acetalization tandem reaction as one of the key steps for an atom- and step-economical synthesis of haterumadienones and puupehenones without the use of protecting groups and transition metals. The tandem reaction not only avoids the undesired epimerization at the C_8 position, but also facilitates many desired transformations in only one-pot.

From a structural point of view, the main difference among these natural products resides on their D rings. We thought to develop a modular approach that allows the introduction of this structural element at the late stage of the synthesis (Fig. 2). Compounds **15** seemed to satisfy this criterion since it is potentially amenable to all of these haterumadienone- and puupehenone-type natural products. Considering dehydration, hydration,[12] retro-hemiacetalization[12] and hemiacetalization[13] processes might occur under certain acidic conditions, we envisioned that a suitable acid might facilitate the dehydration of compounds **15** to compounds **14**, hemiacetalization of hydroxy ketones **14** to hemiacetals **13**, dehydroxylation of hemiacetals **13** to compounds **12**, hydroxylation of compounds **12** to hemiacetals **11**, and retro-hemiacetalization of hemiacetals **11** to enones **5** and **5'** in a one-pot fashion. **5** could in turn be used for the synthesis of haterumadienones. On the other hand, puupehenones would be synthesized by α-hydroxylation of enone **5'** followed by redox reactions. Finally, compounds **15** were thought to be prepared by the aldol reaction of β-hydroxy aldehyde **16** and β-alkoxy enones **17**. We report herein the realization of this strategy by developing protecting-group-free synthesis of seven haterumadienone- and puupehenone-type marine natural products.

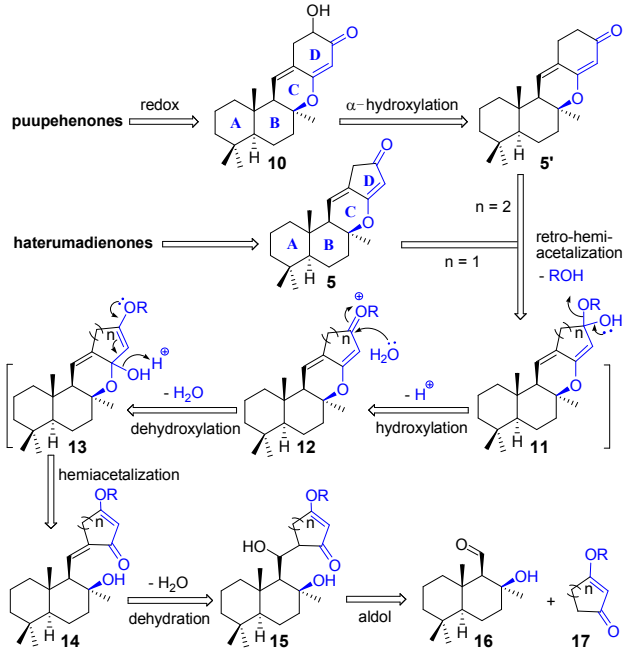
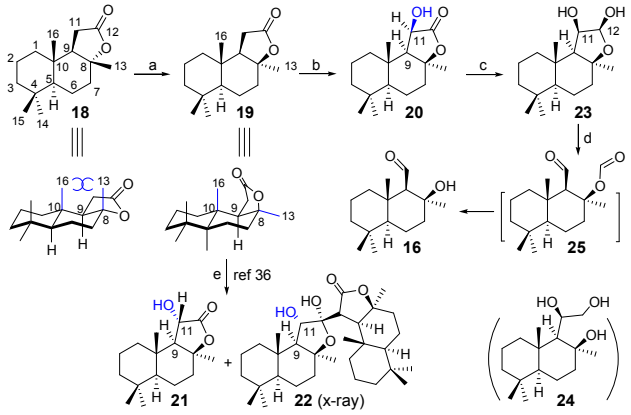


Fig. 2 Retrosynthetic Analysis.



Scheme 2 Synthesis of β-Hydroxy Aldehyde **16**. Reagents and Conditions: (a) H_2SO_4 (3.3 equiv), HCO_2H, RT, 3 h, 98%. (b) KHMDS (1.5 equiv), THF, -78 °C, 0.5 h, then $P(OMe)_3$ (1.5 equiv), O_2, -78 °C, 1 h, 77%. (c) $LiAlH_4$ (3 equiv), THF, RT, 1 h, 98%. (d) K_2CO_3 (1.5 equiv), $NaIO_4$ (2 equiv), MeOH, RT, 2 h, 89%. (e) $(DA)_2Mg$ (3 equiv), THF, RT, 0.5 h then -78 °C, 2 h, and then MoOPH (2 equiv), -78 °C to -25 °C, overnight, **21** (59%), **22** (24%). RT = room temperature, KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran, Me = methyl, $(DA)_2Mg$ = magnesium bis(diisopropylamide), MoOPH = MoO_5·pyridine·HMPA, HMPA = hexamethylphosphoramide.

As shown in Scheme 2, the synthesis commenced with commercially available and inexpensive sclareolide (**18**). Following Quideau's procedure,[11a] treatment of **18** with H_2SO_4 in HCO_2H at room temperature for 3 hours afforded 8-episclareolide **19** in 98% yield, in which the release of the 1,3-diaxial interaction between the 13- and 16-methyl groups facilitated the inversion of configuration at C_8. The lactone of **19** was *α*-hydroxylated by treatment with KHMDS at -78 °C and subsequent reaction with O_2 in the presence of $P(OMe)_3$ gave *α*-hydroxy lactone **20** in 77% yield as the sole diastereoisomer, which avoided the use of transition metal.[14] The 9,11-*cis* relative stereochemistry of **20** was deduced from the observed coupling constant between H_9/H_{11} (J = 3.6 Hz) and was confirmed by comparing its NMR data with the one of *α*-hydroxy lactone **21**.[11a] The authentic 9,11-*trans* relative stereochemistry of **21** was established by Quideau by single-crystal X-ray analysis of its dimer (**22**)[11] and was consistent with the expectation that the MoOPH would preferentially approach the enolate from the less hindered face.[15] Our and Quideau's 8-episclareolide α-hydroxylation strategies would complement each other to enrich the reaction diversity.

Subsequently, the reduction of the lactone ring of **20** using $LiAlH_4$ occurred smoothly at room temperature to afford exclusively lactol **23** in 98% yield as a single diastereomer, and no triol **24**.[11a,16] The 11,12-*cis* relative stereochemistry of **23** was tentatively established from the observed coupling constant between H_{11}/H_{12} (J = 4.2 Hz) and supported by the subsequent effective $NaIO_4$ oxidation reaction.[17] Treatment of **23** with $NaIO_4$ in the presence of K_2CO_3 at room temperature afforded the desired β-hydroxy aldehyde **16** in 89% yield. The stereospecific 8-episclareolide α-hydroxylation, highly selective lactone reduction, and *in situ* lactol-oxidation/ester-hydrolysis facilitated the synthesis of β-hydroxy aldehyde **16** with an obviously higher overall yield in comparison to the previous literature reports (i.e., 66% *versus* 10–25%).[11a,17] The synthesis

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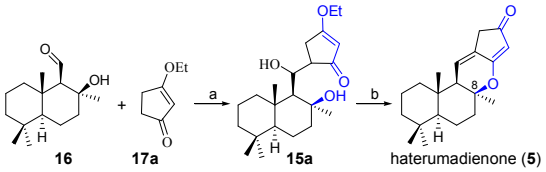
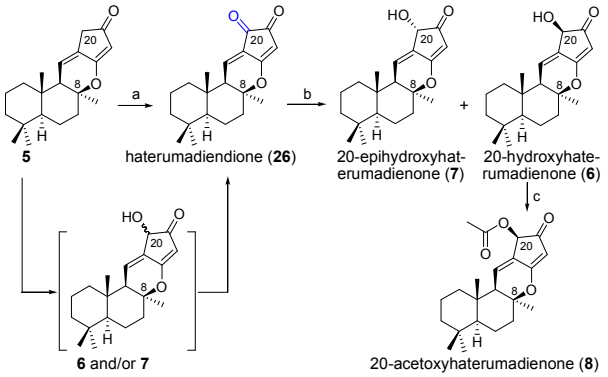


Scheme 3 Synthesis of haterumadienone (**5**). Reagents and conditions: a) **17a**, LDA, THF, −78 °C, 0.5 h, then **16**, 1 h, 75%; b) *p*TsOH, toluene, RT, 4 h, 65%. LDA = lithium diisopropylamide, *p*TsOH = *p*-toluenesulfonic acid.

of β-hydroxy aldehyde **16** is attractive from an atom-economical point of view.

With β-hydroxy aldehyde **16** in hand, the first synthesis of haterumadienone was achieved as shown in Scheme 3. Treatment of ketone **17a** with LDA in THF at -78 °C and subsequent reaction with aldehyde **16** gave aldol adduct **15a** in 75% yield. We envisaged then to achieve the dehydration/hemiacetalization/dehydroxylation/hydroxylation /retro-hemiacetalization tandem reaction mentioned in Fig. 2. After much experimentation, this tandem reaction was realized by treatment of **15a** with *p*TsOH in toluene at room temperature for 4 hours to afford the desired haterumadienone in 65% yield. The spectroscopic and spectrometric data (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$ and HRMS) of the synthetic material are identical to those of natural haterumadienone.[5] To our delight, the undesired epimerization at the C_8 position is avoided during the tandem reaction mentioned above. The concurrent installation of the C and D rings of haterumadienone in a one-pot fashion facilitated its first synthesis in 32% overall yield (only 6 steps) from the abundant feedstock chemical sclareolide, which can provide sufficient quantities for investigation of its biological and medical properties.

Encouraged by these promising results, we anticipated to synthesize the derived haterumadienone-type natural products. Treatment of **5** with KHMDS at -78 °C and subsequent reaction with O_2 in the presence of $P(OMe)_3$ did not afford the corresponding *α*-hydroxylated products (**6** and/or **7**), but haterumadiendione (**26**) was isolated in 76% yield (Scheme 4). In contrast to α-hydroxy lactone **20** (Scheme 2), the α-hydroxy enones **6**/**7** are relatively unstable because

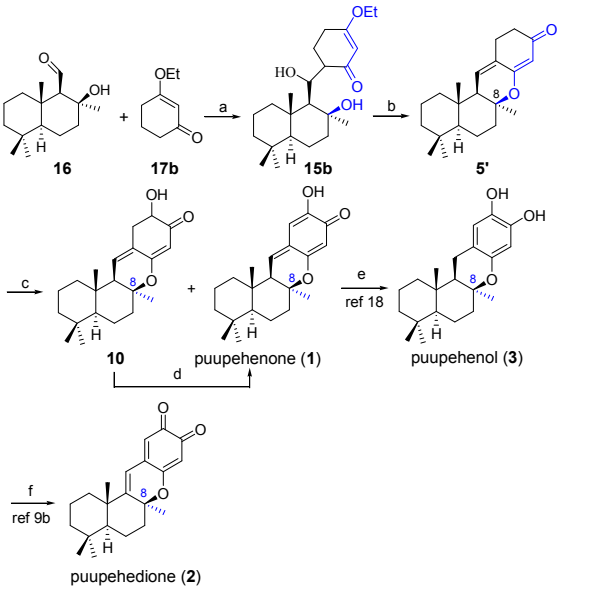


Scheme 4 Synthesis of haterumadienone-type marine natural products. Reagents and conditions: a) KHMDS, THF, −78 °C, 0.5 h, then $P(OMe)_3$, O_2, −78 °C, 1 h, 76%; b) $LiBH_4$, THF, −78 °C, 0.5 h, **6** (58%), **7** (12%); c) Ac_2O, pyridine, 0 °C, 12 h, 95%. Ac = acetyl.

the alcohols are double activated by the ketone and the C-C double bond moieties, and thereby facilitate their conversion to haterumadiendione (**26**). The facile alcohol oxidation indicated that reduction of **26** to **6**/**7** might be somewhat problematic. Indeed, a large variety of reducing agents led either to no reaction, or, under stronger conditions, to degradation. Fortunately, it was found that **26** could be reduced by $LiBH_4$ in THF at -78 °C to give 20-hydroxyhaterumadienone (**6**) and 20-epihydroxyhaterumadienone (**7**) in 58% and 12% yields, respectively. Acylation of alcohol **6** with acetic anhydride afforded 20-acetoxyhaterumadienone (**8**) in 95% yield.

Scheme 5 illustrated how the synthesis of puupehenone-type natural products **1**–**3** was completed by using the tandem reaction mentioned previously. Treatment of ketone **17b** with LDA in THF at -78 °C and subsequent reaction with aldehyde **16** gave aldol adduct **15b** in 67% yield. Hemiacetalization/dehydroxylation/hydroxylation/retro-hemi-acetalization of **15b** with consequent dehydration was achieved with HCl in MeOH at room temperature to provide enone **5'** in 92% yield without detectable epimerization. Treatment of **5'** with KHMDS at -78 °C for 0.5 hour and subsequent reaction with O_2 in the presence of $P(OMe)_3$ afforded the *α*-hydroxylated product **10** and puupehenone (**1**) in 19% and 38% yields, respectively.

The *in situ* dehydrogenation of **10** to **1** might involve processes of alcohol oxidation and ketone enolization *via* a diketone intermediate. The inherent stability associated with the large conjugated system in **1** could also facilitate the conversion of **10** to **1**. Considering that the HMDS from KHMDS might silyllate the oxygen atom of alcohol **10** and thus be disadvantageous for this dehydrogenation, a series of other



Scheme 5 Synthesis of puupehenone-type marine natural products. Reagents and Conditions: (a) **17b**, LDA, THF, -78 °C, 0.5 h, then **16**, 1 h, 67%. (b) HCl, MeOH, RT, 0.5 h, 92%. (c) KHMDS, THF, -78 °C, 0.5 h, then $P(OMe)_3$, O_2, -78 °C, 1 h, **10** (19%), **1** (38%). (d) ^{t}BuOK, ^{t}BuOH, RT, 1 h, 86%. (e) $NaBH_4$, EtOH, RT, 20 min, 92%. (f) DDQ, 1,4-dioxane, reflux, 2 h, 71%. ^{t}Bu = *tert*-butyl, DDQ= 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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bases were investigated and ^{t}BuOK was found to be relatively effective. Indeed, by treating **10** with ^{t}BuOK in *tert*-butyl alcohol at room temperature for 1 hour, puupehenone (**1**) was obtained in 86% yield. Reduction of **1** with $NaBH_4$ in EtOH at room temperature for 20 minutes afforded puupehenol (**3**) in 92% yield.[18] Besides, oxidation of **3** with DDQ in 1,4-dioxane under reflux for 2 hours provided puupehedione (**2**) in 71% yield.[9b]

Conclusions

In conclusion, we described a newly developed versatile hemiacetalization/dehydroxylation/hydroxylation/retro-hemi-acetalization tandem reaction, which is employed to the atom and step-economical synthesis of haterumadienone- and puupehenone-type marine natural products. This key tandem reaction together with stereoselective 8-episclareolide α-hydroxylation, and aerobic enone α-hydroxylation facilitated the preparation of sufficient quantities of these natural products for biological and medical studies. An additional feature of the present natural product synthesis is the design and preparation of the common intermediates 15 that can be used for the synthesis of both haterumadienones and puupehenones without the use of protecting groups. Further applications of these strategies for the green synthesis of other bioactive natural products with related heterocyclic skeletons are currently under investigation, and will be reported in due course.

Acknowledgements

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Graphical Abstract

Protecting-group-free synthesis of haterumadienone- and puupehenone-type marine natural products

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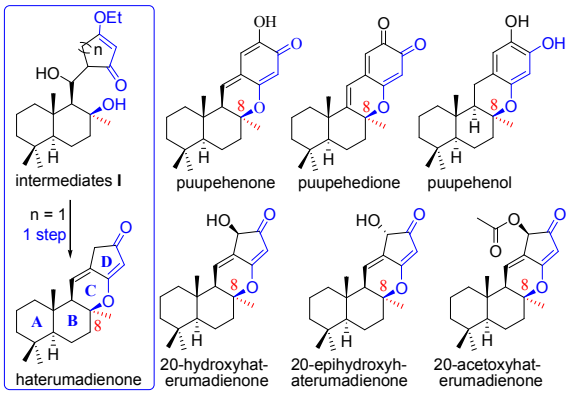

The atom- and step-economical synthesis of seven puupehenone- and haterumadienone-type marine natural products without the use of protecting groups and transition metals has been achieved from the abundant feedstock chemical sclareolide in only 6 to 9 steps. The proposed hemiacetalization/ dehydroxylation/hydroxylation/retro-hemiacetalization of intermediates **I** facilitated the construction of the labile C ring without the accident-prone epimerization at the C_8 position.