Total synthesis of C_{37} alken-2-one temperature geomarkers

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ABSTRACT

The total synthesis of the natural (8*E*,15*E*,22*E*)-heptatriaconta-8,15,22-trien-2-one and (15*E*,22*E*)-hepta-triaconta-15,22-dien-2-one is reported. Our synthesis involved a modular and convergent approach, based on the copper-catalyzed addition of Grignard reagents to allylic olefins. The obtention of these methyl ketones is an important asset for the use of these compounds as analytical patterns with application in Earth sciences.

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Introduction

During the last decades, the use of the C_{37} tri- and di-unsaturated alken-2-ones **1** and **2**, (Scheme 1) has shown to be an important reference tool in organic geochemistry. Both ketones are usually found in marine sediments and are produced by the *Hapto-phyte* algae type, to which belong the coccolithophores *Emiliania huxleyi* [1,2] and *Gephyrocapsa oceanica* [3]. Due to the preferential synthesis of the mentioned unsaturated compounds by *Hapto-phyceae* in correspondence to the water temperature [4,5] in which this algae grows, an estimation of the water temperature on the geologic timescale can be determined, by simply knowing the relative composition of **1** and **2**.

Typically, there is a linear correlation with the average annual sea surface temperature (SST) in the world ocean and the alkenone unsaturation indices [6–8]. Aside from the reconstruction of pale-otemperatures [9,10], it is also noteworthy their use as proxies for estimating the variability of current systems by using the SST profile [11], its applications as a biomarker for marine organisms [12], the estimation of the paleo-partial pressure of carbon dioxide [13] and the growth rate of alkenone producers [14].

Although the important applications of these *E* alkenones (Scheme 1) as reference temperature markers in paleogeochemistry projects none of them are commercial available, which makes necessary their synthetic approach. In order to reach this goal, literature was examined and few publications [15,16] reported the

synthesis of these interesting products. The synthesis of these two compounds (and other related natural products) were first reported by Rechka et al. [15] in 1988 based in the conversion of an aldehyde to an *E*-alkene by means of a geminal dichromium reagent, prepared by direct reduction of a *gem*-diiodoalkane with chromium (II) chloride [17], although no experimental details were provided and in our hands it was not possible to reproduce. There is no other report until 2020 when Berton et al. [16] describes a successive cascade of Wittig reactions that yield mostly the unwanted *Z*-isomers of both compounds requiring a late-stage of photoisomerization and crystallization steps to obtain the target compounds. Alternatively to the Berton strategy, our approach takes advantage of the use of metal hydride reductions [18,19] which affords *E*-isomers avoiding complex mixtures of isomers that requires of photochemical UV apparatus and additional step of crystallization to obtain the pure isomer. Furthermore, in comparison to the methodology reported by Rechka that uses chromium, this is a more environmentally friendly route.

Results and discussion

The synthetic approach designed to obtain compounds **1** and **2** (Scheme 1), involved the coupling of Grignard reagents with allylic compounds, and the preparation of 3 key compounds (Scheme 1): bromide **3** and the Grignard reagents **4** and **5**, which can be synthesized from a common intermediate, the alcohol **6**. As depicted in Scheme 1, the synthesis of bromide **3** and alcohol **6** involved additional reduction and coupling steps from commercially available materials.
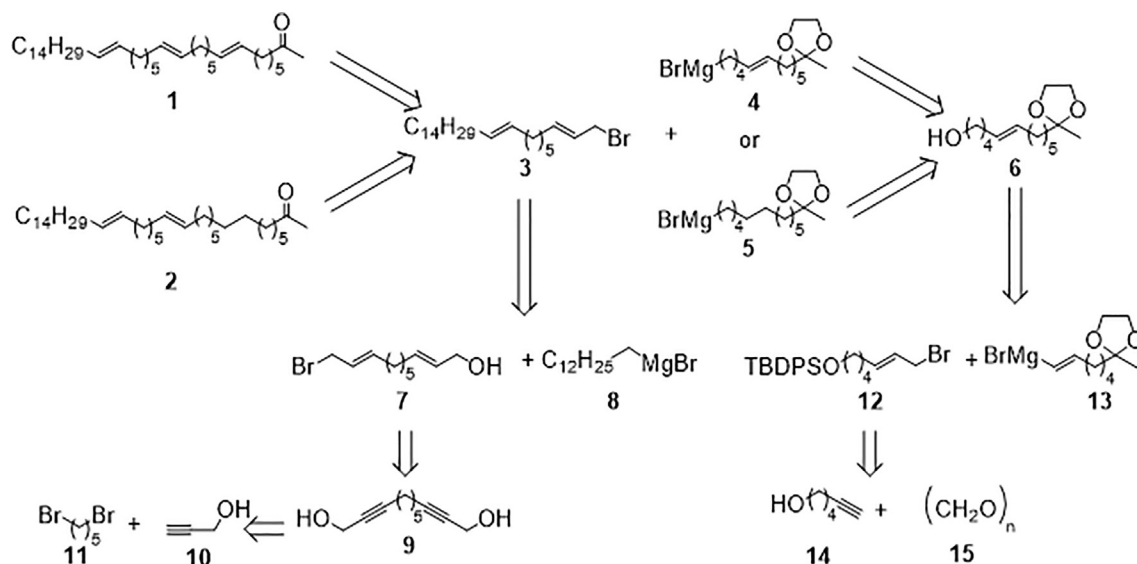
Scheme 1. Retrosynthetic route designed to prepare the target compounds **1** and **2**.

The synthesis of the key compounds **3**, **4** and **5** was carried out as illustrated in the following schemes (Schemes 2–5).

The synthesis of the bromide **3** (Scheme 2), started from commercially available 1,5-dibromopentane (**11**) that was reacted with propargyl alcohol by using *n*-BuLi as a base in the presence of hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF). This afforded diol **9** in a 92% yield, which was reduced with LiAlH₄ to give the symmetric (*E,E*)-dienediol **16** quantitatively. In this case, the proximal alcohol is essential for the reaction to proceed through a *trans*-selective hydrometallation of the triple bond releasing the *E*-alkene on protolytic work-up. After monobromination, a coupling with tridecylmagnesium bromide **8** in the presence of dilithium tetrachlorocuprate (II) (Li₂CuCl₄) as a catalyst, provided alcohol **17** which was obtained as a mixture of α and γ additions to the bromide. The desired α-adduct is easily separated by a silver ion column chromatography [20]. Finally, alcohol **17** was converted into a mesylate group, which due to its high reactivity was displaced in-situ by the bromide anion present in the reaction mixture, giving bromide **3**, one of the key intermediates for the synthesis of the target ketones **1** and **2**.

On the other hand, the synthesis of the Grignard reagents **4** and **5** started with the alcohol protection of the commercially available hexynol **14** with *tert*-butyldiphenylchlorosilane (TBDPSCl) and imidazole in DMF to afford product **18** in a 98% yield (Scheme 3). This was subsequently reacted with *p*-formaldehyde in the presence of

n-BuLi to give the alcohol **19**, which was reduced with Red-Al® in order to give the desired *E*-olefin **20** in a moderate yield but preserving the protecting group. After that, allylic alcohol **20** was treated with MsBr and DIPEA giving the allylic bromide **12**, which was reacted with freshly prepared organomagnesium compound **13** (Scheme 4) and the *t*-butyldimethylsilyl ether group was later cleaved to obtain the corresponding alcohol **6** accompanied by the product resulting from the γ-coupling that can be easily removed by silica column chromatography coated with AgNO₃ [20] to obtain de pure alcohol **6** in a 35% yield (two steps).

Regarding the synthetic route designed to obtain the organomagnesium **13** (Scheme 4), it started with the protection of the ketone group of commercial ethyl 5-oxohexanoate (**21**), giving access to acetal **22** in a 90% yield. In the next stage, the ethyl ester functionality was reduced with DIBAH in high yield to afford alcohol **23**, which was reacted with MsCl/NEt₃ TEA in CH₂Cl₂ to give intermediate **24**, which was converted into the bromide **25**, precursor of Grignard reagent **13**.

Alcohol **6** was obtained as depicted in Scheme 3 and converted to mesylate **26** in a 94% yield (Scheme 5). Afterwards, this product was reacted with LiBr in THF to give **27** quantitatively, which was reacted with magnesium to obtain the first key Grignard reagent **4**. On the other hand, compound **6** was transformed in the alcohol **28** (Scheme 5) by Pd-catalyzed hydrogenation that was mesylated to
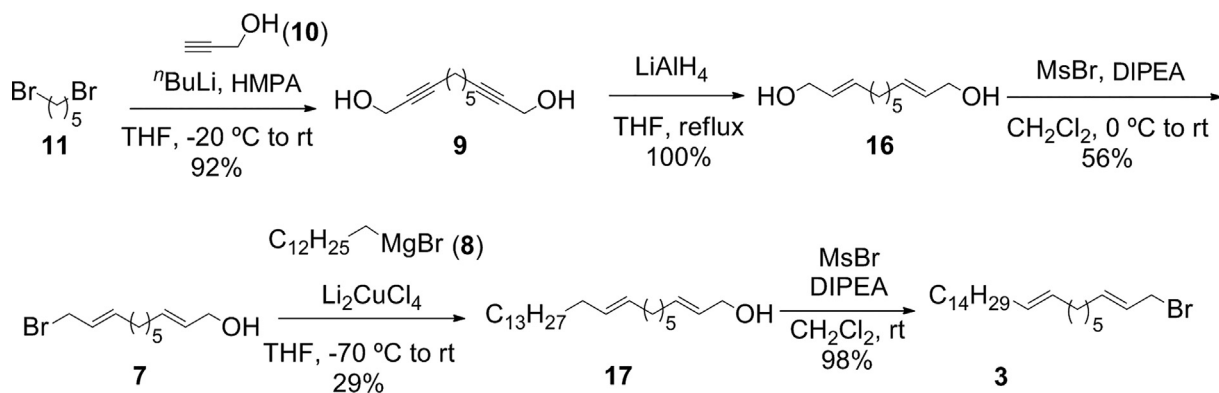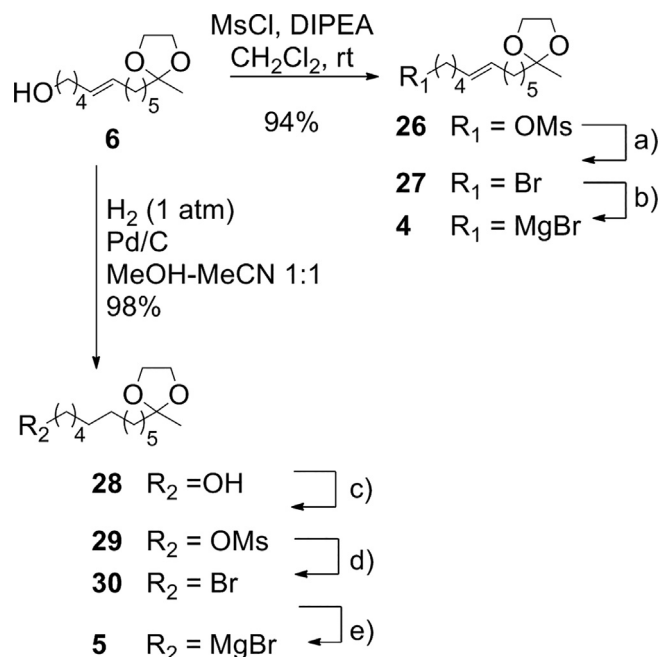

Scheme 2. Synthesis of compound **3**.
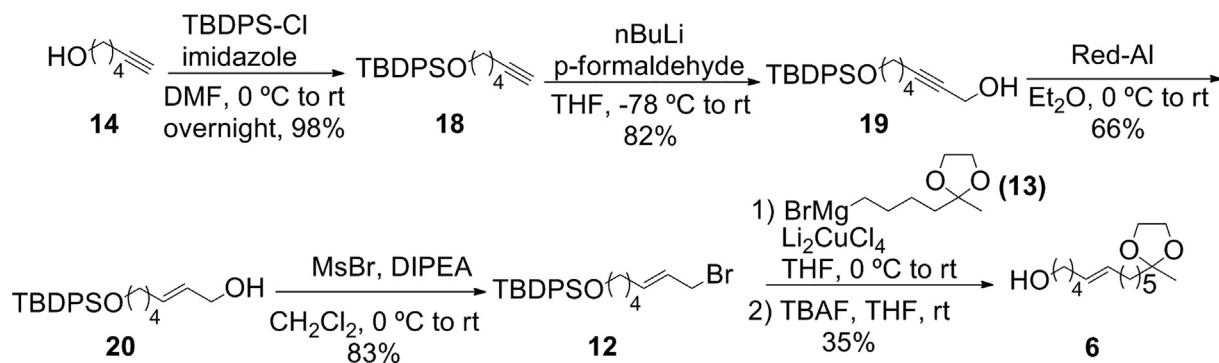
Scheme 3. Synthesis of the key compound **6**.
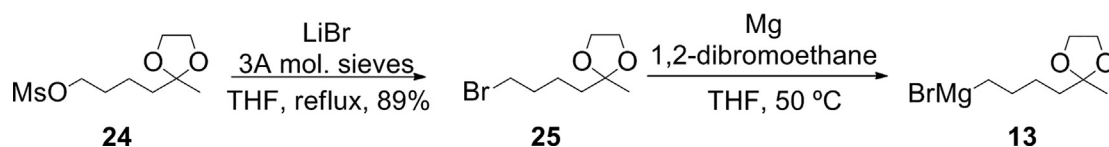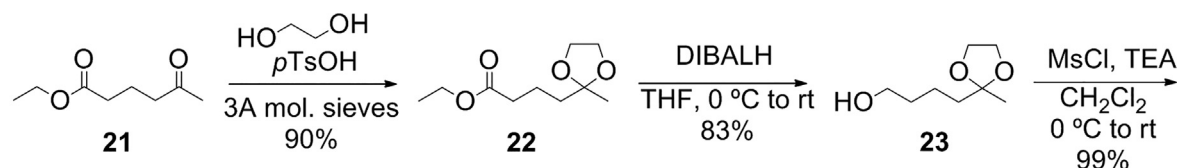
Scheme 4. Synthesis of Grignard reagent **13**.

Scheme 5. Synthesis of the Grignard reagent **4** and **5**. a) LiBr, 3A mol. sieves, THF, reflux, 85%; b) Mg, 1,2-dibromoethane, THF, 50 °C; c) MsCl, DIPEA, CH2Cl2, 0 °C to rt, 94%; d) LiVr, 3A mol. sieves, THF, reflux, 74%; e) Mg, 1,2-dibromoethane, THF, 50 °C.

compound **29** and followed by LiBr reaction to give **30**. This bromide was used to prepare the second key Grignard reagent **5**.

As depicted in Scheme 6, the unsaturated straight-chain bromide **3** was separately reacted with freshly prepared Grignard reagents **4** and **5**, again as a simple mixture of the two regioisomers α and γ. Later on, the acetal group was cleaved in the presence of Amberlyst-15 in acetone and the targeted C37 alken-2-ones of interest **1** and **2** were isolated after purification by column chromatography on SiO$_2$ coated with AgNO$_3$ [20] in 29% and 7% yields, respectively, accomplishing the synthetic objectives of this work.

Conclusion

We have developed a convergent total synthesis of (8*E*,15*E*,22*E*)-heptatriaconta-8,15,22-trien-2-one (**1**) and (15*E*,22*E*)-heptatriaconta-15,22-dien-2-one (**2**) in 23% (5 steps) and 5% yields (6 steps), respectively, starting from alcohol material **6**. Here, the key reactions are the copper-catalyzed coupling of Grignard reagents to allylic halides and the stereoselective reduction of propargyl alcohols to *E*-alk-2-en-1-ols with high isomeric purities. This synthesis provides a new strategy to obtain these long-chain unsaturated ketones, with relevant applications in paleoclimatic, paleoceanographic or geochemical studies.

Data availability

Data will be made available on request.

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.
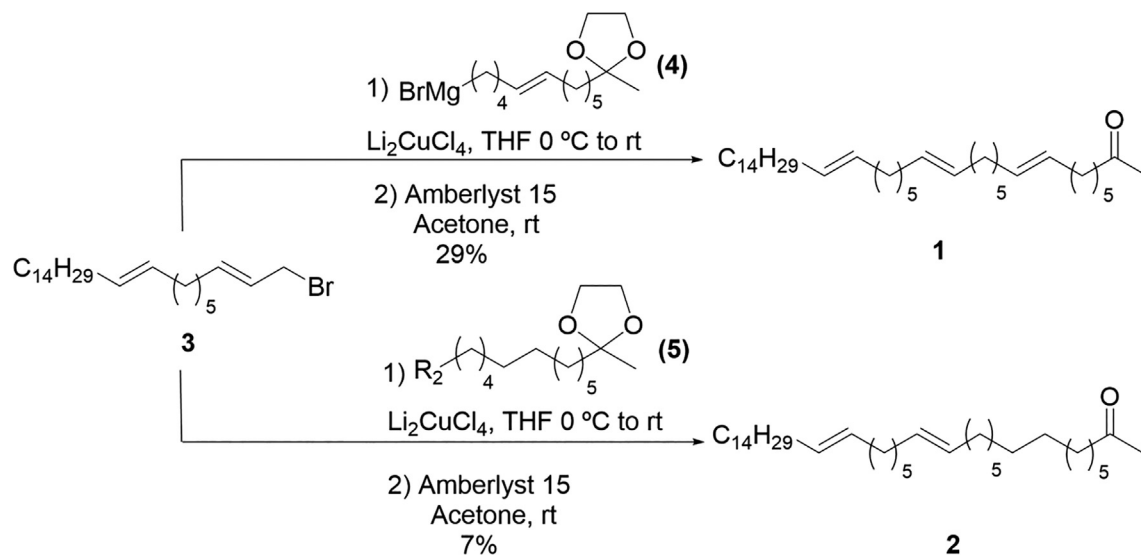
Scheme 6. Addition reactions of Grignard reagents **4** and **5** to bromide **3** to get triene **1** and diene **2**.

Acknowledgments

Appendix A. Supplementary data

Supplementary data (containing experimental procedures and characterization data for all new compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154571.

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