Tetrahedron Letters 54 (2013) 347–350

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of the core framework of the proposed structure of sargafuran

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ARTICLE INFO

Article history:
Received 11 October 2012
Revised 7 November 2012
Accepted 12 November 2012
Available online 23 November 2012

Keywords:
Sargafuran
Cyclopentadienol
Furan
Synthesis
Natural products

ABSTRACT

Synthesis of 2-homoprenyl-1-methyl-3-(5-methylfuran-2-yl)cyclopenta-2,4-dien-1-ol, the core framework of the proposed structure of the brown alga derived natural product sargafuran, was achieved in six steps from the commercially available 5-methylfurfural via the Piancatelli rearrangement of furylcarbinol. The concise synthetic route to the 1,2,3-trisubstituted cyclopentadienol is established. However, the ^{1}H and ^{13}C NMR spectral data of the synthetic analog of sargafuran suggest that the originally proposed structure of sargafuran must be incorrect. In addition, the structure of the natural sargafuran is also discussed.

Members of the brown algae genus *Sargassum* have been shown to produce diverse meroterpenoids, such as sargatriol (**1**),[1,2] sargaquinoic acid (**2**),[3,4] sargahydroquinoic acid (**3**),[4,5] and sargachromenol (**4**).[3,4,6] Some of these compounds exhibit antioxidant,[7] antiviral[7], or antitumor[8] activities. In 2009, Kamei and colleagues isolated sargafuran from *Sideroxylon macrocarpum* as an anti-*Propionibacterium acnes* compound, whose cytotoxicity against human normal dermal fibroblast cells was reported to be remarkably low.[9] Thus, sargafuran is thought to be a potent lead compound to develop new anti-*P. acnes* materials and new skin care cosmetics that control acne. The structure of sargafuran was estimated to be **5** by spectroscopic analyses, including IR, ^{1}H, and ^{13}C NMR spectra (Fig. 1). The reported structure includes a unique 2-alkyl-3-furyl-1-methylcyclopenta-2,4-dien-1-ol moiety and a C_{16} side chain, presumably derived from three isoprene-units and an additional methylene group. Our interest in sargafuran's distinguishing structural features and significant biological activity led us to its synthesis. To the best of our knowledge, several useful synthetic methods leading to cyclopentadienols have been reported.[10,11] However, none of these methods were thought to be effective for the synthesis of compound **5** because of its particular 1,2,3-trisubstituted pattern.

Before starting the synthesis of sargafuran, we attempted the synthesis of the simplified analog **6** to establish the general synthetic route for 1,2,3-trisubstituted-cyclopenta-2,4-dien-1-ol, a core framework of the reported structure of sargafuran. Our synthetic plan for **6** is illustrated in Scheme 1. The cyclopentadienol

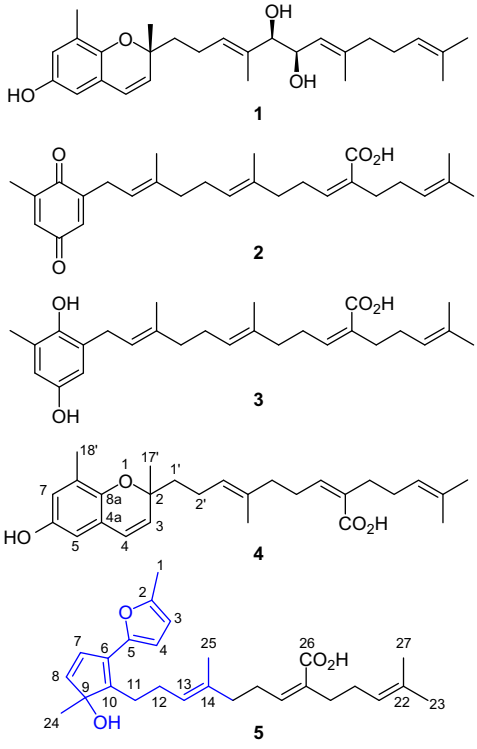

Figure 1. Structures of brown algae derived meroterpenoids **1** to **4** and reported structure of sargafuran **5**.

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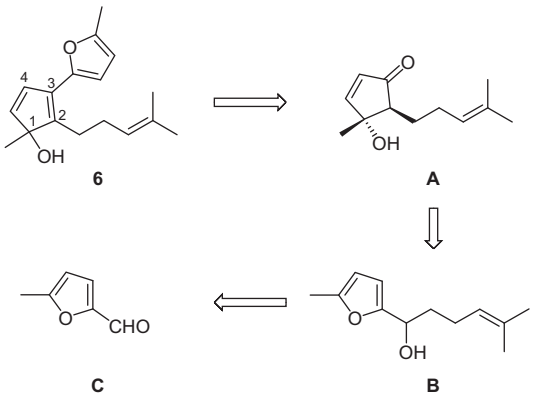
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.052



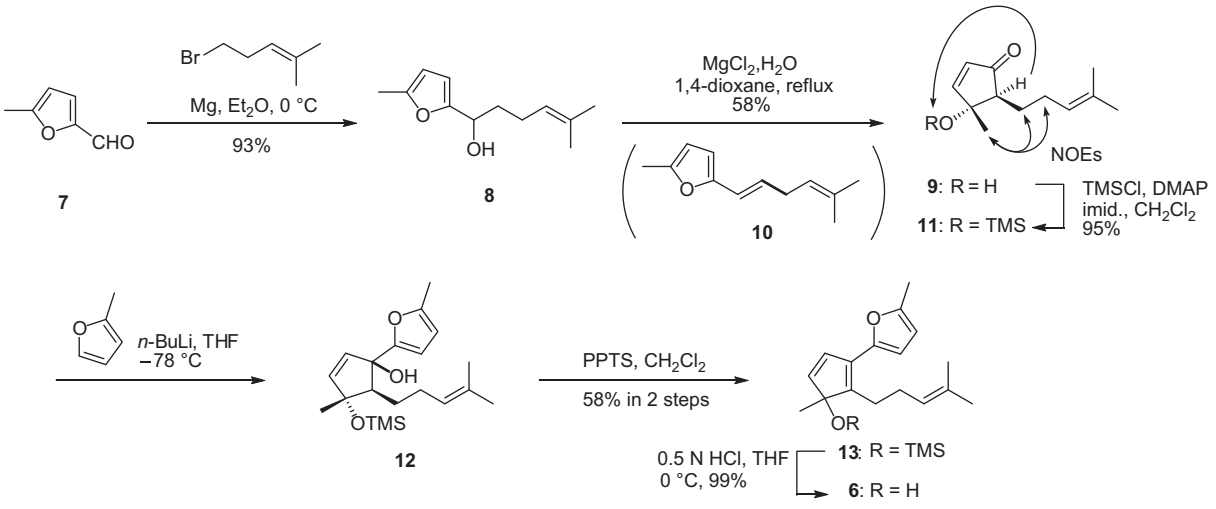
Scheme 1. Retrosynthetic analysis of compound **6**.

moiety is thought to be relatively unstable, thus it would be constructed at a later stage of the synthesis. Furylcyclopentadiene **6** would be prepared from cyclopentenone **A** by installation of the methylfuryl group followed by dehydration of one of the two tertiary hydroxy groups. Therefore the structure of compound **A** is a two substituted hydroxycyclopentenone, it would be prepared by the Piancatelli rearrangement[12–17] of furylcarbinol **B**. General mechanistic outline of the Piancatelli rearrangement includes protic or Lewis acids catalyzed dehydration, ring opening of furylcarbinol to give the enedione intermediate, followed by the 4π electrocyclization to give hydroxycyclopentenone derivatives. Corresponding furylcarbinol **B** could be accessible from 5-methylfurfural **C** by the addition of an appropriate organometallic reagent.

The synthesis of model compound **6** is shown in Scheme 2. To prepare unit **B**, 5-methylfurfural (**7**) was reacted with homoprenylmagnesium bromide in THF to give the adduct **8** (=**B**) in good yield (93%). The corresponding furylcarbinol **8** was subjected to a furan ring opening and a subsequent annulation to cyclopentenone via the Piancatelli rearrangement.[12–17] Unfortunately, the treatment of **8** with several reported conditions yielded only a small amount of the desired enone **9**, producing instead the dehydrated product **10** as the major product along with unidentified degradation products (yields of **9**: polyphosphoric acid, MeCN, H_2O, trace or $ZnCl_2$, 1,4-dioxane or acetone, H_2O, up to 34%). On the other hand, using magnesium(II) chloride as a Lewis acid gave the desired **9**[18] as a single diastereomer in moderate yield (58%). The relative stereochemistry of enone **9** was confirmed to be *trans*[12] relationship between the methyl group and the side chain by NOE experiments after conversion into the corresponding TMS ether **11**. We first attempted to install a furyl group by the sp^2–sp^2 cross coupling reaction of the enol triflate derived from **11**. However, the corresponding enol triflate of **11** could not be prepared under various conditions (KHMDS or LHMDS, Tf_2O or $PhNTf_2$, Comins reagent). Alternatively, the installation of the furyl group was achieved by the addition of 5-methylfuryllithium to the enone **11** to give the adduct **12**.[19] The conversion of **12** into **6** required only dehydration and desilylation, but this procedure presented a challenge. Treatment with various protic acids (PPTS, MeOH or HCl, CH_2Cl_2) yielded only trace amounts of the dehydrated product(s) **13** and/or **6** with poor reproducibility. A stepwise dehydration and deprotection were necessary to avoid such problems. First, compound **12** was dehydrated by treatment with PPTS in CH_2Cl_2. Finally, the TMS group of **13** was successfully removed by treatment with diluted HCl in THF to yield **6**, a model compound of the proposed structure of sargafuran (**5**). The structure of **6** was confirmed by IR and by the ^1H, ^{13}C, NOE, HMQC, and HMBC NMR spectra of compounds **6** and **13**.[20,21] These data clearly indicated that methyl, methylfuryl, homoprenyl, and hydroxy groups correctly substituted cyclopentadiene moiety. However, the synthetic material **6** is a relatively unstable compound,[22] to obtain accurate 2D NMR spectra, using relatively stable analog **13** instead of **6** is more suitable. Furthermore, NMR data of the core framework of these two compounds are quite similar (cf. Supplementary data).

Our target material **6** in hand, the NMR data of synthetic **6** and natural sargafuran[9] were compared (Table 1). Remarkably, there were significant differences between these compounds in ^1H and ^{13}C NMR spectra, even though the only structural difference between compounds **5** and **6** was in the side chain at C-10. For the ^1H NMR spectral data of the natural product, a coupling constant of H-7/H-8 was reported to be 10.0 Hz, which is much larger than the standard value for the olefinic protons of cyclopentenes (4.0–5.9 Hz).[23–26] On the other hand, synthetic material **6** shows a typical 5.8 Hz coupling constant. The finding about the instability of compound **6** also indicates that compound **5** is unsuitable for isolation from the natural material, especially in the reported isolation protocol of sargafuran.[9] These facts clearly reveal that the structure of reported sargafuran must be improperly assigned.

Here, the correct structure of the natural sargafuran will be discussed. Interestingly, the ^1H and ^{13}C NMR spectral data of sargafuran are identical to those of sargachromenol (**4**), a well-known



Scheme 2. Synthesis of cyclopentadienol **6**.