Organic LETTERS

Letter

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Total Synthesis of Panaginsene with Structural Revision

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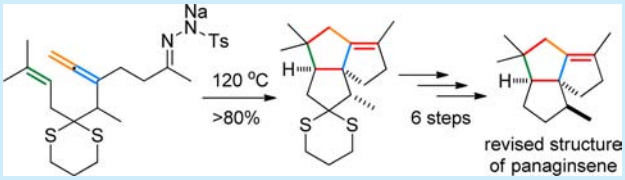
Supporting Information

ABSTRACT: A facile total synthesis of the reported structure for panaginsene through a trimethylenemethane (TMM) diyl mediated tandem cycloaddition reaction revealed that the spectroscopic data of the synthesized structure did not match with the data of the natural product. The total synthesis of the stereoisomer of the reported structure confirmed that the correct structure of panaginsene was the 11-*epi* stereoisomer of the originally proposed structure of panaginsene.



Among the hydrocarbons isolated from the roots of *Panax ginseng* C.A. Meyer,[1] a sesquiterpene hydrocarbon with an angularly fused tricyclic moiety, panaginsene **1** caught our attention, as it belongs to the senoxydane family of angularly fused triquinanes (Figure 1). The only other reported natural

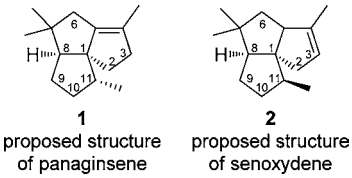
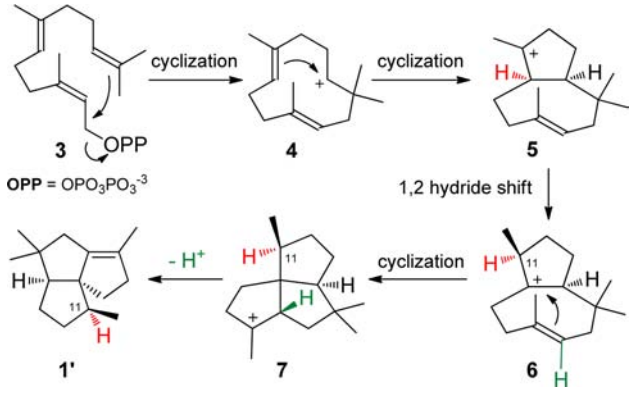


Figure 1. Proposed structures of panaginsene and senoxydene.

product with a senoxydane framework was senoxydene **2**,[2a] and its structure was proved to be incorrect through the total syntheses.[2] Although the actual structure of senoxydene is still unknown, it is noteworthy that the plausible biosynthetic route to the reported structure of senoxydene was introduced to construct its relative stereostructure. The structure of panaginsene **1** was assigned based on the NMR data, and when we adopted this biosynthetic analysis to panaginsene **1**, we could postulate that the C-11 methyl epimer of panaginsene **1**′ might also be the natural product. The stereochemistry of the methyl group at the C-11 of panaginsene might be generated through a stereospecific 1,2-hydride shift as shown in the plausible biosynthesis (Scheme 1). To confirm the structure of a senoxydane natural product, panaginsene **1**, the total synthesis of **1** was accomplished through the tandem cycloaddition reaction via trimethylenemethane (TMM) diyl.[3]

The retrosynthetic analysis of **1** (Scheme 2) suggested that angularly fused triquianane **1** could be obtained in one step stereoselectively by TMM diyl mediated intramolecular tandem [2 + 3] cycloaddition reaction[4] of the diazotized linear precursor **8**. The linear precursor **8** could readily be prepared from the propargylic bromide **9**, which would be derived from (+)-citronellal. This tandem cycloaddition reaction strategy was just right for the total synthesis of **1** since the reaction has been applied successfully to the total synthesis of various

Scheme 1. Plausible Biosynthetic Route to 1



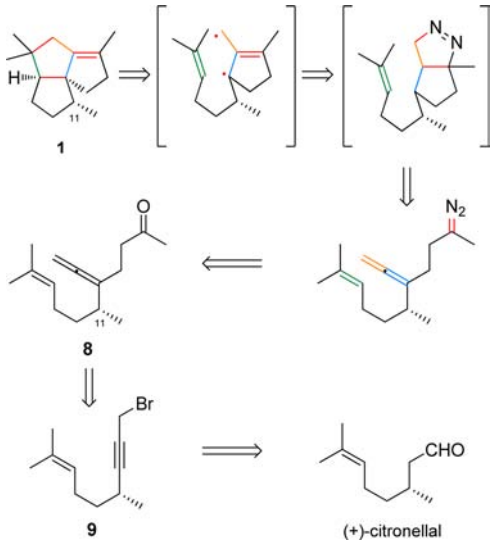
polyquinane natural products.[5] The tandem cycloaddition reaction would produce the angularly fused triquinane stereoselectively, as the C-11 carbon center should control the relative stereochemistry of the triquinane framework[4] along with the preset tetrasubstituted olefin.

The total synthesis of **1** was accomplished in 7 steps from **10** that was readily prepared from (+)-citronellal through conversion of the aldehyde of citronellal into the corresponding *gem*-dibromide[6] (Scheme 3). The *gem*-dibromide of **10** was transformed into the propargyl alcohol **11** through the two-step protocol of base treatment in refluxing petroleum ether followed by hydroxymethylation with paraformaldehyde at room temperature of the acetylide anion generated at 0 °C by the treatment of *n*-BuLi.[6a] The propargyl alcohol of **11** was converted into the allenyl precursor **8** by Cu(I)-catalyzed S_N2' reaction of the corresponding bromide **9** using Grignard reagent **12**[7] in THF at 0 °C followed by deprotection of the acetal group to the ketone using *p*-toluenesulfonic acid and aqueous formaldehyde in THF at room temperature. Finally, formation of the hydrazone **13** from the ketone of **8** using *N*-

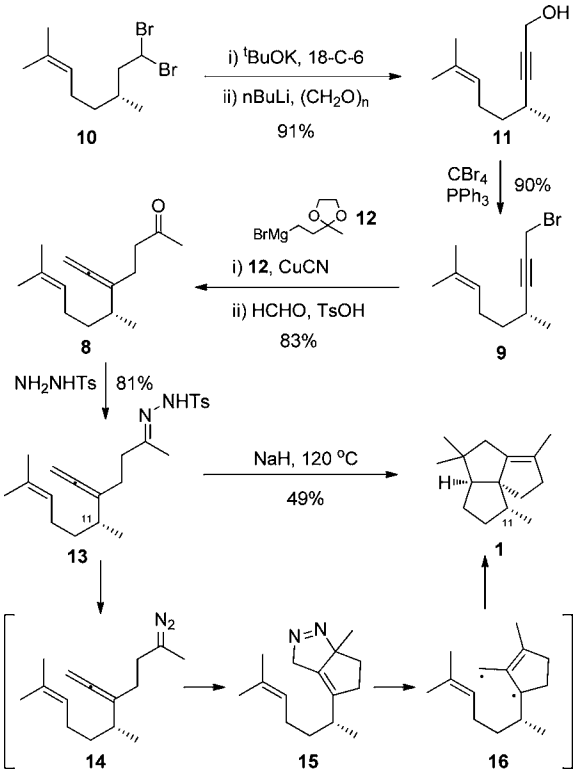
Received: March 21, 2014
Published: April 17, 2014

   dx.doi.org/10.1021/ol500849m | *Org. Lett.* 2014, 16, 2466–2469

Scheme 2. Retrosynthetic Analysis of 1



Scheme 3. Total Synthesis of 1

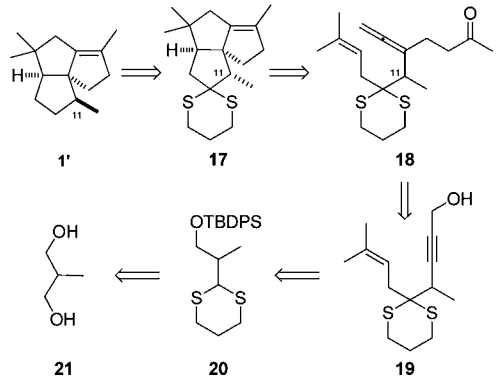


tosylhydrazide in methanol under 10 °C set the stage for the tandem cycloaddition reaction. Generation of the diazo compound **14** in refluxing toluene from the anion of **13** generated by treatment with NaH at 0 °C in toluene triggered the tandem cycloaddition reaction through TMM **16** to produce **1**.

Due to the volatile and nonpolar nature of **1** and other isomeric products, purification of the products was challenging. While there were five isomeric products other than **1** observed by the GC-MS, none of them could be purified and thus their structures could not be identified.[8] Only **1** was separated successfully in pure form using silver nitrate impregnated silica gel chromatography.[9] As we suspected, the ^{1}H and ^{13}C NMR spectroscopic data of the synthesized **1** did not match with those of the natural product. Though the NMR spectroscopic data of **1** did not match with the reported data, those data from the natural product and the synthetic one were close enough to each other to convince us that the actual structure of panaginsene might be the C-11 methyl epimer, **1′**. Therefore, we decided to synthesize **1′** to confirm the actual structure of the natural panaginsene.

Retrosynthetic analysis of **1′** indicated that an extra functionality was necessary that can epimerize the C-11 methyl stereochemistry of **17** (Scheme 4). The precursor for the

Scheme 4. Retrosynthetic Analysis of 1′

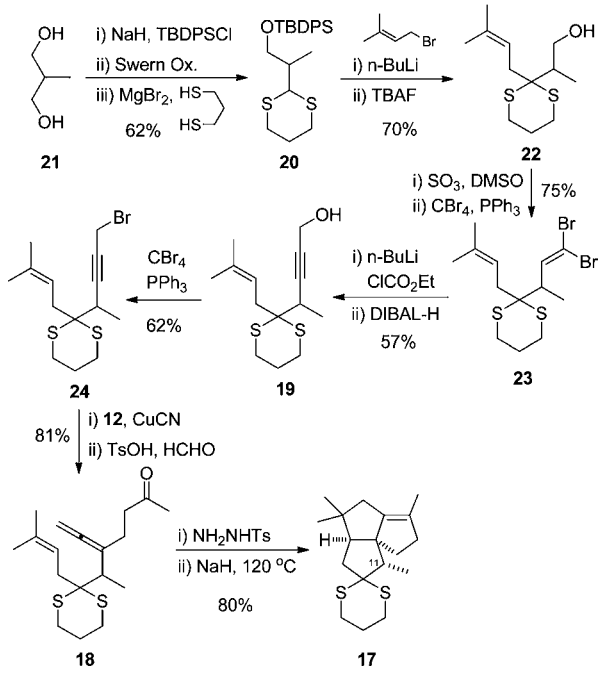


tandem cycloaddition, **18**, can be prepared from **19** in the same manner as before, and **19** could be synthesized from dithiane **20** prepared from 2-methylpropane-1,3-diol, **21**.

The total synthesis of the epimeric compound **1′** of the reported structure of panaginsene started from 2-methylpropane-1,3-diol **21**. Though enantiomerically pure protected 3-hydroxy-2-methylpropanal was available, it turned out that the absolute stereochemistry of the methyl group was lost during the dithiane formation of the aldehyde. That observation led us to use **21** as the starting material for the synthesis (Scheme 5). Monoprotection of the diol of **21** using 1 equiv of the reagents in THF followed by Swern's oxidation produced the aldehyde that was converted into dithiane **20** using propane-1,3-dithiol with magnesium bromide as a Lewis acid at 0 °C. After isoprenylation at −40 °C of the anion of **20** generated by treatment with *n*-BuLi at 0 °C, deprotection of the silyl group with tetrabutylammonium fluoride afforded the alcohol **22**. Oxidation of the alcohol of **22** that contained the dithiane functionality was most effective with Doering's reagent,[10] and subsequent treatment of the produced aldehyde with Corey−Fuchs reagent[11] produced **23**. Since direct conversion of the dibromoolefin of **23** into the propargylic alcohol **19** using the same approach as in the synthesis of **11** from **10** was not successful, **19** was synthesized in a two-step procedure of carboxylation of the acetylenic anion generated from **23** by treatment of *n*-BuLi with ethyl chloroformate at −40 °C followed by DIBAL-H reduction. The precursor for the tandem cycloaddition reaction **18** was prepared in the same manner as in the total synthesis of **1**. Tandem cycloaddition reaction of the allenyl diazo intermediate, generated from the allenyl ketone **18**, produced tricyclic compound **17** in 80% yield over two steps. To our surprise, the tandem cycloaddition proceeded much more efficiently from **18** than **13** in a selective manner. The Thorpe−Ingold effect exerted by the dithiane group must have facilitated the cycloaddition reaction toward

dx.doi.org/10.1021/ol500849m | *Org. Lett.* 2014, 16, 2466−2469

Scheme 5. Synthesis of Angularly Fused Triquinane, 17

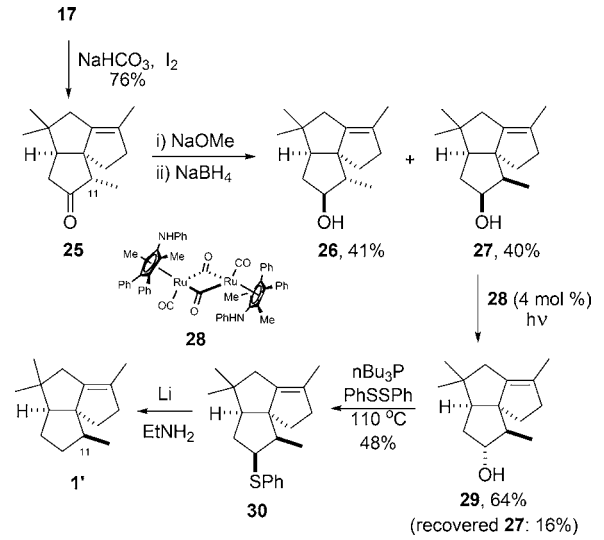


the desired triquinane structure.[12] Another surprise was that the reaction produced **17** almost stereospecifically, as the C-11 methyl epimer of **17** was not detected.

For the completion of the total synthesis of **1′**, the C-11 methyl group of **17** had to be inverted and the dithiane masked carbonyl functionality had to be removed.

Deprotection of the dithiane of **17** with iodine and sodium bicarbonate at 0 °C produced the corresponding ketone **25** (Scheme 6).[13] Base mediated epimerization of the C-11 methyl

Scheme 6. Completion of the Synthesis of 1′



group produced an inseparable mixture of **25** and its C-11 methyl epimer in a 1:1 ratio. Reduction of the epimeric mixture using $NaBH_4$ at 0 °C proceeded stereoselectively to produce a diastereomeric mixture of **26** and **27**. After the desired isomer **27** was separated, various attempted deoxygenation reactions failed to provide the reduction product.[14,15] Mitsnobu type functionalization reactions of the alcohol of **27** only produced the elimination product. Since the unexpected reactivity of the alcohol of **27** was thought to be due to the steric hindrance of the alcohol with the β-configuration, inversion of the alcohol of **27** to the more exposed α-configuration was anticipated to increase the reactivity of the alcohol and its derivatives. To drive the epimerization reaction of **27**, we adopted the reaction catalyzed by the ruthenium complex **28** developed for the dynamic kinetic resolution of racemic alcohols.[16]

When a solution of **27** in the presence of ruthenium catalyst **28** was irradiated with a fluorescent lamp, an epimerization reaction proceeded to produce a mixture of epimeric alcohols **27** and **29** with a 1:4 ratio. Fortunately, the desired alcohol **29** was thermodynamically more stable and was isolated in a 64% yield. As anticipated, Mitsunobu type sulfide formation at 110 °C to **30** was successful, though the reaction was sluggish. Finally a phenylsulfenyl group was removed by a reductive desulfurization reaction[17] in the presence of lithium in ethylamine at low temperature to form **1′**. To our delight, the spectroscopic data of **1′** were in complete agreement with the data reported for panaginsene.[18]

With both epimeric methyl isomers of panaginsene in hand, the relative stereochemistry of the C-11 stereogenic center of **1** and **1′** was firmly confirmed by $^1H-^1H$ NOE experiments (Figure 2).

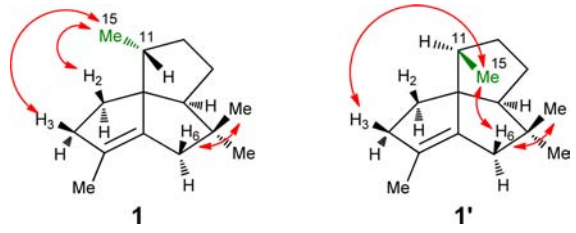


Figure 2. $^1H-^1H$ NOE experiments of **1** and **1′**.

While the W. A. König group determined the relative stereochemistry of the C-11 methyl group by $^1H-^1H$ NOE correlation of the protons of the C-15 with the proton H_3, it was observed that both protons of the C-15 of **1** and **1′** showed a correlation with the proton H_3. Furthermore, the protons of C-15 of **1′** showed a correlation with the proton H_6, though weak. On the other hand, the protons of the C-15 of **1** showed no correlation with the proton H_6. It is quite probable that the weak NOE between protons of the C-15 and the H_6 mislead the original stereochemical assignment of the natural product.

In conclusion, we have achieved the first total synthesis of the proposed structure of panaginsene **1** and the actual structure of panaginsene **1′** through the intramolecular TMM diyl-mediated tandem cycloaddition reaction with high efficiency and stereoselectivity. Through the total synthesis, we confirmed that the originally assigned structure **1** must be revised to the correct structure **1′**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (KRF-2008-314-C00198), and by a 2011-2012 basic research grant from the KAIST.

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(18) See Supporting Information.

■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 6 contained an error in the version published ASAP April 17, 2014; the correct version reposted April 21, 2014.