Efficient Synthesis of a Head-to-Head Isoprenoid Geochemical Biomarker from Phytol

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Nearly all of the biological input compounds of petroleum lose their identity in relation to their derivation source during the alteration process from organic matter to petroleum. However, some classes of natural materials are stable enough to survive the harsh conditions more or less intact, and the compounds of these classes can therefore serve as chemical fossils or biomarkers. These biomarkers may contain certain information concerning the biological input source and the conditions of alteration or diagenesis. Today, the most widely used petroleum biomarkers are of terpene origin and are generally polycyclic hydrocarbons such as modified steroids and hopane triterpenes, some tricyclic diterpenes, and linear terpenes.

While several saturated tail-to-tail isoprenoid hydrocarbons, e.g., lycopene, squalene, perhydro-β-carotene, and head-to-head isoprenoids, have been identified in petroleum samples for years, it was only in 1979 that Moldowan and Seifert reported the discovery of head-to-head-linked isoprenoid hydrocarbons in crude oil. They reported the synthesis of one such component, iC19-iC19 (1), in a three-step route from methyl pristanate (2) via pristanol (3) and the corresponding bromide 4. The low yield of this route (the last step proceeds in only 1% as determined by GC) coupled with the unavailability of methyl pristanate (not commercially available) indicates that a new route must be found for the preparation of usable amounts of this geochemical biomarker. Since a need for this compound existed within the petroleum geochemistry community, we decided to prepare it by a different, more efficient route. We now report a four-step synthesis of 1 from commercially available phytol (5).

The commercial sample of phytol (5) was shown to be a mixture of E and Z isomers about the olefinic double bond by high-field proton NMR but was used in this state since the next step, hydroboration, would remove this stereochimical ambiguity. Hydroboration of phytol (5), followed by oxidation with basic peroxide produced a mixture of the desired 1,2-diol (6) (as a mixture of stereoisomers) and the simple primary alcohol 7. This byproduct 7 is formed by elimination of the β-borinato organoborane to give the terminal alkene which is then hydroborated. The amount of 7 formed was minimized by using the method of Brown, namely treating the allylic alcohol with 1 equiv of disiamylborane followed by 1 equiv of borane in THF. In this way we were able to isolate after chromatography a 70% yield of 6 along with 18% of 7. Several methods for the oxidative cleavage of 6 were examined before deciding on the following procedure. Treatment of 6 with an excess of the yellow mercuric oxide–iodine reagent in the dark overnight followed by normal workup produced the aldehyde 8 as a colorless oil in an 85% crude yield. This material was somewhat unstable to chromatography and was therefore not purified but rather used directly in the next step. A titanium metal induced pinacol reaction and elimination (McMurry coupling) applied to 8 gave the desired olefin 9 in 59% yield. The somewhat low yield is probably due in part to impurities present in the crude aldehyde. The overall yield of purified 9 from 6 is 50%. The isolated olefin 9 is mainly one isomer by GC and high-field proton NMR. We assume it to be the E isomer on the basis of steric hindrance in the formation of the Z isomer and by analogy to similar cases in the literature. Finally catalytic hydrogenation of 9 on Pt/C in acetic acid at atmospheric pressure produced the desired hydrocarbon 1 in 85% yield, thus ending a four-step synthesis of 1 from phytol 5 in an overall yield of 30%. The mass spectrum of 1 matches that published by Moldowan and Seifert for the lower mass region of the spectrum and additionally shows a molecular ion at m/e 534 with a significant M+ - 15 peak.

We believe that the above route represents a significant improvement over the former synthesis and makes the geochemically important compound 1 much more readily available.
Experimental Section

The IR spectra were recorded on a Perkin-Elmer 710B spectrometer. 1H NMR spectra were recorded at 500 or 60 MHz on a Bruker AM-500 or a Varian T-60 spectrometer, respectively, using tetramethylsilane as an internal standard. GLC analyses were carried out on a Varian 3700 gas chromatograph on a 30-m J&W DB-5 (0.25-µm phase thickness) fused capillary column with the column temperature at 200 °C for 1 min, followed by a rise of 12 °C/min to 310 °C, at which the temperature was held for 30 min. The mass spectra were taken on a Finnigan 4000 mass spectrometer. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium benzenophenone ketyl immediately prior to use.

To a solution of disiamylborane (15 mL, 10.5 mmol) in tetrahydrofuran was added phytol (5; Aldrich) by the cautious addition of water. The oxidation was carried out by adding 4 mL of 3 N sodium hydroxide, followed by dropwise addition of 1.5 mL of 30% hydrogen peroxide. The solution was then saturated with potassium carbonate, and the layers separated. The organic layer was dried over magnesium sulfate and evaporated to leave as a residue a black oil. Column chromatography on silica gel using 1:1 ethyl acetate-n-hexane as eluent gave 178 mg (85%) of 1 as a colorless oil. 1H NMR spectrum of each isomer, appearing as a doublet, was used to determine the chemical shifts of the other isomers. The precise assignment was made by the position of the methyl resonance in the 500-MHz 1H NMR spectrum of each isomer, appearing at δ 1.689 for the E isomer and δ 1.798 for the Z isomer.

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Synthesis of Radiolabeled Juvenile Hormone Analogues

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Methoprene (1) is a metabolically and environmentally stable analogue of the insect juvenile hormone JH III (2). It was developed by Zoecon for fly and mosquito control, and it was the first insect growth regulator (IGR) to be registered for use in pest control.1 Recently, it has become an important ingredient in home-use flea control products. Tritium-2 and carbon-14-labeled2 isotopomers of methoprene have been prepared in order to study the degradation products in target organisms, nontarget organisms, and the ecosystem. Despite the economic importance of this IGR, little is known of its mode of action on a molecular level. In order to determine the macromolecular binding sites for such a potent hormone analogue, high specific activity juvenoids are required. We recently described the preparation of radiomembranically enriched JH I and JH II labeled with tritium at high specific activity (58 Ci/mm).4 These and other radiolabeled juvenoids5


9: 500-MHz 1H NMR (CDCl3) δ 5.18 (m, 2 H, CH), 2.04 (m, 2 H, =CCH), 1.54-0.83 (m, 72 H, includes four distinct peaks at 0.975, 0.860, 0.850, and 0.837 for the methyl groups); MS, m/e 532 (M+) 517 (M+ - 15).

2,6,10,14-Tetramethylpentadecan-2-diol (6). Commercially available phytol (5) was purified by column chromatography on silica gel to give the pure mixture of E and Z isomers that were used in the hydroboration step.12