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

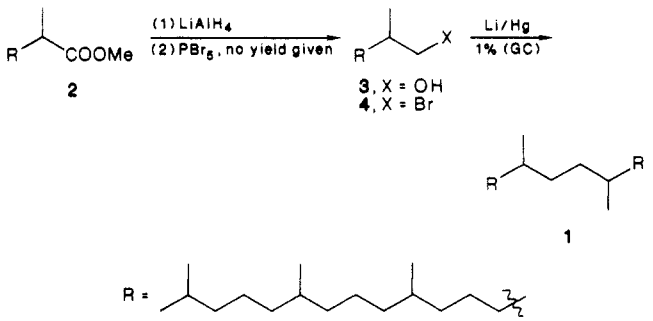
Michael E. Jung*[1] and Ching-Yang Liu

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received August 6, 1986

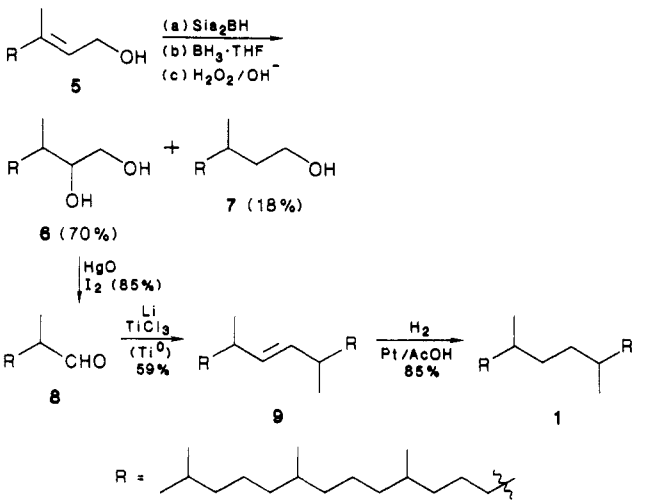
Nearly all of the biological input compounds of petroleum lose their identity in relation to their derivation source during the alteration process from organic matter to petroleum.[2] However, some classes of natural materials are stable enough to survive the harsh conditions more or less intact, and 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.[3] Today, the most widely used petroleum biomarkers are of terpene origin and are generally polycyclic polyterpenes such as modified steroids and hopane triterpenes, some tricyclic diterpenes, and linear polyterpenes.

While several saturated tail-to-tail isoprenoid hydrocarbons, e.g. lycopane,[4] squalane,[5] perhydro-β-carotene,[6] and head-to-tail isoprenoids,[7] 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.[8] They reported the synthesis of one such component, iC_{19}–iC_{19} (**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 stereochemical ambiguity. Hydroboration of phytol (**5**), followed by oxidation with basic peroxide[9] 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 rehydroborated. The amount of **7** formed was minimized by using the method of Brown,[9] 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[10] 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)[11] 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.[11] 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[8] 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.

(1) UCLA Gold Shield Faculty Awardee, 1986–1988.

(2) For general references on petroleum derivation see: (a) Tissot, B. P.; Welte, D. H. *Petroleum Formation and Occurrence*; Springer-Verlag: New York, 1978. (b) Mackinzie, A. S.; Brassell, S. C.; Eglington, G.; Maxwell, J. R. *Science (Washington, D.C.)* **1982**, *217*, 491. (c) Albrecht, P.; Ourisson, G. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 209. (d) Rullkötter, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 418.

(3) (a) Seifert, W. K.; Moldowan, J. M.; Jones, R. W. *Spectra* **1982**, *8*, 42. (b) Eglington, G.; Scott, P. M.; Besky, T.; Burlingame, A. L.; Calvin, M. *Science (Washington, D.C.)* **1964**, *145*, 263.

(4) Kimble, B. J.; Maxwell, J. R.; Philp, R. P.; Eglinton, G.; Albrecht, P.; Ensminger, A.; Arpino, P.; Ourisson, G. *Geochim. Cosmochim. Acta* **1974**, *38*, 1165.

(5) Gardner, P. M.; Whitehead, E. V. *Geochim. Cosmochim. Acta* **1972**, *36*, 259.

(6) Murphy, M. T. J.; McCormick, A.; Eglinton, G. *Science (Washington, D.C.)* **1967**, *157*, 1040.

(7) Albaiges, J.; Borbon, J.; Salagre, P. *Tetrahedron Lett.* **1978**, 595 and references therein.

(8) Moldowan, J. M.; Seifert, W. K. *Science (Washington, D.C.)* **1979**, *204*, 169.

(9) Brown, H. C.; Gavillan, R. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2906.

(10) Goosen, A.; Laue, H. A. H. *J. Chem. Soc. C* **1969**, 383.

(11) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.

0022-3263/86/1951-5446$01.50/0

Experimental Section

The IR spectra were recorded on a Perkin-Elmer 710B spectrometer. ^{1}H 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 JE&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 benzophenone ketyl immediately prior to use.

3,7,11,15-Tetramethylhexadecane-1,2-diol (6). Commercially available phytol (**5**; Aldrich) 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]

To a solution of disiamylborane (15 mL, 10.5 mmol) in tetrahydrofuran was added phytol (**5**; 3.0 g, 10.1 mmol). After the evolution of hydrogen stopped, a solution of borane (10.5 mL, 10.5 mmol) in tetrahydrofuran was added. After the mixture was stirred at 0 °C for 1.5 h, the excess hydride was decomposed 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. Column chromatography on silica gel using 1:1 ethyl acetate–*n*-hexane as eluent gave 510 mg (18%) of the primary alcohol **7** followed by 2.13 g (70%) of **6**.

6: IR (neat film) 3300, 2930, 2900, 2840, 1452, 1368, 1352, 991 cm^{-1}; 500-MHz ^{1}H NMR ($CDCl_3$) δ 3.70–3.64 (m, 1 H, CHO), 3.58–3.48 (m, 2 H, CH_2O), 3.12 (br s, 2 H, OH), 1.59–1.06 (m, 22 H, CH and CH_2), 0.92–0.84 (overlapping d, 15 H, CH_3); MS, *m/e* 314 (M^+), 296 ($M^+ - H_2O$).

7: IR (neat film) 3300, 2930, 2900, 2850; 500-MHz ^{1}H NMR ($CDCl_3$) δ 3.71–3.63 (m, 2 H, CH_2O), 1.61–1.06 (m, 23 H, CH, CH_2, and OH), 0.894 (d, 3 H, J = 6.5 Hz, CH_3), 0.867 (d, 6 H, J = 6.6 Hz, 2 CH_3), 0.845 (d, 6 H, J = 6.6 Hz, 2 CH_3); MS, *m/e* 298 (M^+), 280 ($M^+ - H_2O$).

2,6,10,14-Tetramethylpentadecanal (8). To a solution of the diol **6** (510 mg, 1.62 mmol) in 20 mL of methylene chloride was added an excess of yellow mercuric oxide–iodine reagent (prepared by the method of Goosen[10]) and the mixture stirred under a nitrogen atmosphere in the dark overnight. The mixture was extracted with ether, washed with 10% aqueous sodium thiosulfate and water, dried over magnesium sulfate, and concentrated to give 390 mg (85%) of **8** as a colorless oil. This crude aldehyde was unstable to silica gel chromatography and thus was used immediately for the next step.

8: IR (neat film) 2935, 2900, 2840, 2700, 1720, 1460, 1370 cm^{-1}; 60-MHz ^{1}H NMR ($CDCl_3$) δ 9.53 (d, 1 H, J = 2 Hz, CHO), 2.2–2.0 (m, 1 H, CHCO), 1.6–0.75 (m, 36 H).

(*E*)-2,6,10,14,17,21,25,29-Octamethyltriacont-15-ene (9). Lithium wire (134 mg, 19.3 mmol) and titanium trichloride (850 mg, 5.50 mmol) was slurried in 15 mL of dry dimethoxyethane (DME) under an argon atmosphere, and the mixture was refluxed for 1 h. After cooling to 25 °C, a solution of the crude aldehyde **8** (390 mg, 1.38 mmol) in 4 mL of DME was added. After a further 20 h at reflux, the reaction mixture was cooled to 25 °C, diluted with hexane, filtered through a small pad of Florisil on a sintered-glass filter, and evaporated to leave as a residue a black oil. Column chromatography on silica gel using *n*-hexane as eluent achieved only a partial separation, still leaving a mixture of components shown by GC to contain several monomeric (i.e., C_{19}) components. Therefore, the mixture was heated in a flask at a temperature of 100 °C (0.5 mmHg) for 1 h. The residue in the flask was then rechromatographed as before on silica gel using *n*-hexane as eluent to give 215 mg (59%) of **9** as a colorless oil.

9: 500-MHz ^{1}H NMR ($CDCl_3$) 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 0.873, 0.860, 0.850, and 0.837 for the methyl groups); MS, *m/e* 532 (M^+), 517 ($M^+ - 15$).

2,6,10,14,17,21,25,29-Octamethyltriacontane (1). A mixture of the alkene **9** (210 mg, 0.395 mmol), 10% platinum on carbon (600 mg), and 50 mL of freshly distilled acetic acid was stirred under a hydrogen atmosphere for 30 min at 25 °C. The reaction mixture was then filtered and concentrated to give a yellowish oil. Column chromatography on silica gel using *n*-hexane as eluent gave 178 mg (85%) of **1** as a colorless oil. **1**: 500-MHz ^{1}H NMR ($CDCl_3$) δ 1.54–1.51 (m, 44 H), 0.873, 0.860, 0.852, 0.833 (4 s, 30 H); MS, *m/e* 534 (M^+), 519 ($M^+ - 15$), 505, 463, 449, 448, 429, 421, 420, 407, 393, 380, 379, 378 (lower peaks match published spectrum[8]).

Acknowledgment. We thank Global Geochemistry Corp. for financial support and Dr. Christopher S. Hein of GGC for the mass spectral data.

Registry No. **1**, 70967-41-8; (*E*)-**5**, 150-86-7; (*Z*)-**5**, 5492-30-8; **6**, 30220-53-2; **7**, 645-72-7; **8**, 105373-75-9; **9**, 105373-76-0.

(12) By careful column chromatography, samples of the *E* and *Z* isomers could be isolated, with the *Z* isomer eluting from the column first. The stereochemical assignment was made by the position of the methyl resonance in the 500-MHz ^{1}H NMR spectrum of each isomer, appearing at δ 1.669 for the *E* isomer and at δ 1.736 for the *Z* isomer.[13]

(13) Sims, J. J.; Pettus, J. A., Jr. *Phytochemistry* **1976**, *15*, 1076.

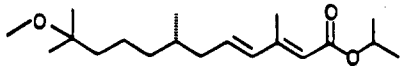
Synthesis of Radioiodinated Juvenile Hormone Analogues

Marcus F. Boehm and Glenn D. Prestwich*

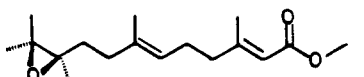
Department of Chemistry, State University of New York, Stony Brook, New York 11794-3400

Received June 16, 1986

Methoprene (**1**) is a metabolically and environmentally stable analogue of the insect juvenile hormone JH III (**2**).



1



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-labeled[2] isotopomers of methoprene have been prepared in order to study the degradation products[3] 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 enantiomerically enriched JH I and JH II labeled with tritium at high specific activity (58 Ci/mmol).[4] These and other radiolabeled juvenoids[5,6]

(1) Henrick, C. A. In *Insecticide Mode of Action*; Coats, J. R., Ed.; Academic: New York, 1982; pp 315–402.

(2) Schooley, D. A.; Bergot, B. J.; Dunham, L. L.; Siddall, J. B. *J. Agric. Food Chem.* **1975**, *23*, 293–298.

(3) Hammock, B. D.; Quistad, G. B. In *Progress in Pesticide Biochemistry*; Hutson, D. H., Roberts, T. R., Eds.; Wiley: New York, 1981; Vol. I, pp 1–81.

(4) Prestwich, G. D.; Wawrzeńczyk, C. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5290–5294.

0022-3263/86/1951-5447$01.50/0