Reactivity of (3-Methylpentadienyl)iron(1+) Cation: Late-stage Introduction of a (3-Methyl-2Z,4-pentadien-1-yl) Side Chain

Subhabrata Chaudhury, Shukun Li, and William A. Donaldson*

Department of Chemistry, Marquette University, P. O. Box 1881, Milwaukee, WI 53201-1881 USA

Abstract: The 3-methyl-2Z,4-pentadien-1-yl sidechain is found in various sesquiterpenes and diterpenes. A route for the late stage introduction of this functionality was developed which relies on nucleophilic attack on the (3-methylpentadienyl)iron(1+) cation, followed by oxidative decomplexation. This methodology was applied to the synthesis of the proposed structure of heteroscyphic acid A methyl ester. Realization of this synthesis led to a correction of the proposed structure.

Keywords: Organoiron complexes; Alkylation; Diene ligands; Terpenoids

Introduction

The 3-methyl-2Z,4-pentadienyl sidechain is a functionality appearing in a number of naturally occurring sesquiterpenes and diterpenes. For example, (+)-striatene (1, Figure 1), and the labdane diterpenes (+)-solidagol (2) and (-)-ent-3β-acetoxylabda-8(17),12Z,14-trien-2α-ol (3) were isolated from the liverwort Pychanthus striatus, from Canadian golden rod (Solidago canadensis) and from the ornamental plant Plectranthus fruticosus respectively. Similarly, the clerodane diterpene (+)-caseargrewiin E (4), isolated from a Thai shrubby tree, exhibited cytotoxic activity against KB, BC1 and NCI-H187 cancer cell lines in the range 0.15-0.91 μg/mL range. In spite of these and other examples, only a single synthesis of a terpene containing this functionality has been reported. Audran and co-workers reported the synthesis of 1 which involved enolate alkylation with 5Z-bromo-3-methylpent-3-en-1-yne, followed by hydrozirconation (Scheme 1). It should be noted that attempts at reduction of the 5 using H2 and a poisoned catalyst were unsuccessful.

As part of our interest in the application of organoiron complexes to organic synthesis, we have examined the reactivity the (3-methylpentadienyl)Fe(CO)3PPh3+ cation (6, Scheme 2) with nucleophiles as a means for late-stage introduction of the 3-methyl-2Z,4-pentadienyl sidechain.

Figure 1. Sesquiterpenes and diterpenes possessing a 3-methyl-2Z,4-pentadienyl sidechain.
Scheme 1. Synthesis of the (3-methyl-2Z,4-pentadien-1-yl) side chain of (+)-striatene (ref. 5).

Heteroscyphic acids A, B and C, isolated from cultured cells of *Heteroscyphus planus*, were assigned the proposed structures 7a, 7b, and 7c (Figure 2) containing a 3-methyl-2Z,4-pentadienyl sidechain on the basis of their spectroscopic data. We have previously utilized the (3-methylpentadienyl)Fe⁺ cation 6 to prepare the methyl ester of the 8-desmethyl-analog (8) of 7a. Comparison of the NMR spectral data for 8 with that reported for heteroscyphic acid A led to the conclusion that the structures of the heteroscyphic acids were more consistent with a 3-methyl-2E, 4-pentadienyl sidechain. We herein report the full experimental details for these studies.

Figure 2. (3-Methylpentadienyl)Fe⁺ cation as a synthon for 3-methyl-2Z,4-pentadien-1-yl and the “proposed” structures for heteroscyphic acids A, B and C.

Scheme 2. Synthesis of octahydronaphthalene synthons (heteroscyphic atom numbering).

Results and Discussion

Alkylation of the dianion of methylacetoacetate with the known bromide 9 gave the acyclic β-ketoester 10 (Scheme 2). Oxidative cyclization of 10, according to the literature procedure, gave a chromatographically separable mixture of trans-decalone (±)-11 along with minor amounts of the cis-isomer (±)-12. Separation of these two isomers was facilitated by the fact that 12 exists almost entirely in its enol tautomer. Compounds 11 and 12 were characterized by comparison to the literature data for the corresponding ethyl esters. Acid catalyzed
isomerization of the exocyclic olefin of 11 gave the endocyclic isomer (±)-13. The structural assignment of 13 was based on its NMR spectral data. In particular signals at δ 140.1 and 122.2 ppm in the 13C NMR spectrum and at δ 5.29 (1H, m) and 1.65 ppm (3H, d, J = 1.5 Hz) in the 1H NMR spectrum are characteristic of the C-3 and C-4 olefinic carbons and their associated proton and methyl group respectively.

Attempted olefination of 13 with the ylide generated from the reaction of butyl lithium with methyltriphenyolphosphonium bromide in THF gave recovered starting material; presumably due to deprotonation of the acidic β-ketooester in polar solvents. Alternatively, addition of the salt-free ylide generated from trimethylphosphonium bromide with sodium amide in toluene 17 to 13 gave (±)-14 in moderate yield. The structural assignment of 14 was based on its NMR spectral data. In particular, signals at δ 146.2 and 107.9 ppm in the 13C NMR spectrum and at δ 4.80 (1H, br s) and 4.49 ppm (1H, br s) in the 1H NMR spectrum are characteristic of the exocyclic olefinic carbons and the attached protons.

β-Ketoester 13 was converted into its methoxymethyl vinyl ether (±)-15 by treatment with LDA followed by reaction with MOMCl. O-alkylation (as compared to C-alkylation) was evident by the presence of two olefinic peaks in the 13C NMR spectrum of 15 at δ 151.1 and 116.3 ppm. Treatment of 15 with Li/NH3 gave (±)-16 via reduction of the enoate of 15, followed by elimination of CH3OH anion and reduction of the resultant enolate 13. The ester substituent in 16 was assigned to occupy an axial orientation on the basis of its 1H NMR spectral data. In particular, the signal for H-9 (δ 2.57-2.49 ppm) of 16 did not evidence any large couplings, and thus pointed to an equatorial orientation for H-9.

With octahydronaphthalene synthons 13, 14, and 16 successfully prepared, attention was turned to installation of the 3-methyl-2Z,4-pentadien-1-yl sidechain. Toward this end, the sodium salt of 13, generated by reaction with sodium hydride, was reacted with (3-methylpentadienyl)iron(1+) cation 6 to afford a mixture of diastereomeric complexes 17/17’ (Scheme 3). While the mixture of 17/17’ gave a satisfactory combustion analysis, interpretation of the NMR spectra was complicated due to signal overlap of the diastereomers as well as 31P coupling. Nonetheless, oxidative decomplexation of this mixture gave a single product (±)-18. In a similar fashion, the lithium salt of 14 or 16 (generated by reaction with LDA) with 6, gave a mixture of isomeric complexes 19/19’ or 20/20’ respectively; decomplexation of each mixture gave a single product (±)-21 or (±)-8.

The structural assignments for 18, 21 and 8 were based on their NMR spectral data. For products 18 and 21, the pentadienyl sidechain was assigned the β-orientation, while for 8 the sidechain was assigned the α-orientation. In particular, for 18 the singlet for Me-19 appears at δ 1.03 ppm while for 8 this singlet appears at δ 0.84 ppm. The upfield chemical shift for this signal of 8 is consistent with an axial ester group at C-9 14. In addition, there is an NOE interaction observed between Me-19 and one of the H-12 protons of 18, while a NOESY interaction was observed between the Me-19 and the methyl ester of 8. For 21 the upfield chemical shifts of the H-17 olefinic methylene protons (δ 4.78 and 5.00 ppm) may be attributed to the anisotropic effect of the neighboring ester substituent in an α-orientation. Notably, these orientations are consistent with the known 15 stereoselectivity for alkylation on the α-face of other bicyclo[4.4.0]decane β-ketoesters while alkylation of the exocyclic enolate derived from a bicyclo[4.4.0]decane 2-carboxylate generally proceeds on the β-face 16. In addition, the 3-methyl-2,4-pentadienyl side chain for 18, 21 and 8 were all assigned the Z-configuration. In particular, the signals for H-14 appear at ca. δ 6.8-6.7 ppm while signals for the C-14, C-15 and the dienyl methyl C-16 appear at ca. δ 135, 114 and 20 ppm respectively. These chemical shifts are characteristic of a 3-methyl-2Z,4-pentadienyl group 25. This was found to be in sharp contrast to the chemical shifts reported 9 for H14 (δ 6.37 ppm) C14, C15 and the dienyl methyl C16 (δ 141.7, 111.1 and 12.1 ppm) of the sidechain of heteroscyphic acid methyl ester. In fact, these chemical shifts are more consistent with those reported 17 for diterpenes which possess a 3-methyl-2E,4-pentadienyl sidechain.
Conclusion

The ability to rapidly introduce a 3-methyl-2Z, 4-pentadienyl sidechain was demonstrated by the synthesis of 8, a nor-diterpene related to the proposed structure of heteroscyphic acid A, as well as 18 and 21. While this synthetic exercise revealed that the sidechains of the heteroscyphic acids more likely possess the E-stereochemistry, this methodology might be applied to the synthesis of compounds such as 1-4.

Acknowledgements

This work was supported by the National Science Foundation (CHE-0415771). Mass spectrometry was provided by the Washington University Mass Specrometry Resource, an NIH Research Resource.

Experimental Section


1H and proton-decoupled 13C NMR spectra were recorded at 300 MHz and 75 MHz respectively. Proton and carbon assignments refer to heteroscyphic acid skeleton numbering. High-resolution mass spectra were obtained from the Washington University Resource for Biomedical and Bioorganic mass spectrometry. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Anhydrous CH2Cl2 and anhydrous DMF were purchased from Aldrich Chemical Company. Compounds 69 and 910 were prepared by literature procedures.

Methyl 6-methyl-3-oxo-6,11-dodecadienoate (10). To a flame-dried round-bottom flask, NaH (60% dispersion in mineral oil, 2.53 g, 63.3 mmol) was suspended in dry THF (165 mL) under N2. The suspension was cooled in an ice bath and methyl acetoacetate (6.81 g, 58.7 mmol) was added slowly (CAUTION: hydrogen gas is evolved during the addition). The mixture was stirred for 10 min, and then a solution of n-butyl lithium in THF (2.5 M, 25.3 mL, 63.3 mmol) was added. During this addition, the solution became a bright orange in color. After stirring at 0 °C for 10 min, a solution of 1-bromo-2-methyl-2,7-octadiene (5.96 g, 29.4 mmol) in THF (15 mL) was added. The ice bath was removed and the solution stirred at room temperature for 30 min. A solution of 3 M HCl (50 mL) was added followed by ether (50 mL). The mixture was separated and the aqueous layer was extracted several time with ether. The combined organic layers were dried (MgSO4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO2, hexanes-ethyl-acetate = 8:1 → 5:1 gradient) to afford 10 (5.21 g, 75%) as a pale yellow oil;

IR (neat) 3076, 2927, 1750, 1717, 1637, 911 cm−1.

1H NMR (CDCl3): δ = 5.80 (1H, dtd, J = 16.9, 6.8, 3.3 Hz, H-11), 5.13 (1H, br t, J = 7.7 Hz, H-7), 4.97 (2H, m, =CH2), 3.74 (3H, s, OMe), 3.46 (2H, s, H-2), 2.64 (2H, br t, J = 7.5 Hz), 2.27 (2H, br t, J = 7.8 Hz), 2.04-1.78 (4H, m), 1.59 (3H, s, Me-6), 1.41 (2H, pent, J = 7.3 Hz).

13C NMR (CDCl3): δ = 202.5 (C-3), 167.7 (C-1), 138.9 (C-10), 133.3 (C-6), 125.4 (C-7), 114.6 (C-11), 52.6 (OMe), 49.2, 42.0, 33.6, 33.4, 29.2, 27.6, 16.4 (Me-6).


Decahydro-4a-methyl-5-methylene-2-oxo-1-naphthalencarboxylic acid methyl ester (11). To a degassed solution of 10 (3.31 g, 13.9 mmol) dissolved in glacial acetic acid (35 mL) was added solid Mn(OAc)3 (1.75 g, 6.53 mmol), followed by solid Cu(OAc)2 (0.590 g, 3.24 mmol). The reaction mixture was stirred under N2 for 7 h at room temperature and then filtered through a bed of celite. The filter bed was washed several times with ether,
the combined ethereal extracts were washed with saturated NaHCO3, followed by water, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO2, hexanes-ethyl acetate = 8:1 → 5:1 gradient) to afford (±)-11 (1.45 g, 44%) as a colorless oil, followed by a variable but minor amount of the cis-isomer (10).

**11: IR** (neat) 3086, 1715, 1635 cm⁻¹.

**1H NMR** (CDCl3): δ = 4.74 (1H, br s, =CH2), 4.65 (1H, br s, =CH2), 3.75 (3H, s, OMe), 3.27 (1H, d, J = 12.9 Hz, H-9), 2.55-2.47 (2H, m), 2.40-2.32 (1H, m), 2.05-1.76 (6H, m), 1.45-1.37 (2H, m), 1.22 (3H, s, Me-19).

**13C NMR** (CDCl3): δ = 205.6 (C-8), 170.3 (CO2R), 155.0 (C-4), 106.3 (=CH2), 60.3 (C-9), 52.3 (OMe), 47.7, 38.1, 38.0, 36.1, 32.7, 27.6, 27.4, 17.5 (Me-19).

**FAB-HRMS** m/z 237.1485 (calcd for C14H21O3 [M+H]+ m/z 237.1491).

1,2,3,4,4a,7,8,8a-Octahydro-4a,5-dimethyl-2-oxo-1-naphthalenecarboxylic acid methyl ester (13). To a solution of 11 (200 mg, 0.847 mmol) in benzene (10 mL) was added p-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol). The mixture was heated at reflux for 2 d under N2. The mixture was cooled to room temperature and then a few drops of triethylamine were added to neutralize the acid. The mixture was filtered through a pad of celite, the filter bed washed with ether, and the combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography (SiO2, hexanes-ethyl acetate = 8:1) to afford (±)-13 (708 mg, 84%) as a colorless oil;

**IR** (neat) 1746, 1712 cm⁻¹.

**1H NMR** (CDCl3): δ = 5.29 (1H, br s, H-3), 3.74 (3H, s, OMe), 3.29 (1H, d, J = 13.5 Hz, H-9), 2.50-2.42 (2H, m), 2.19 (1H, td, J = 13.2, 2.7 Hz, H-10), 2.10-1.97 (3H, m), 1.65 (3H, d, J = 1.5 Hz, Me-18), 1.60-1.30 (3H, m), 1.16 (3H, s, Me-19).

**13C NMR** (CDCl3): δ = 206.0 (C-8), 170.5 (CO2R), 140.1 (C-4), 122.2 (C-3), 60.0 (C-9), 52.2 (OMe), 45.2, 37.9, 36.4, 35.3, 25.7, 23.8, 18.8 (Me-18), 17.7 (Me-19).

**FAB-HRMS** m/z 237.1485 (calcd for C14H21O3 [M+H]+ m/z 237.1491).

1,2,3,4,4a,7,8,8a-Octahydro-4a,5-dimethyl-2-methylene-1-naphthalenecarboxylic acid methyl ester (14). To a suspension of NaNH2 (637 mg, 16.3 mmol) in dry toluene (41 mL) under N2, was added methyltriphenylphosphonium bromide (4.48 g, 12.5 mmol), and the mixture was heated at reflux for 3 h. During this time formation of the ylde was detected by change of the solution to a bright orange color. The warm solution was transferred by a cannula to a solution of 13 (593 mg, 2.51 mmol) in toluene (6 mL) under N2. The reaction mixture was stirred at room temperature for 6 h and then filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in hexanes to induce the precipitation of triphenylphosphine oxide and then filtered again. The filtrate was washed with water, dried (MgSO4) and concentrated. The residue was purified by column chromatography (SiO2, hexanes-ethyl acetate = 8:1) to afford (±)-14 (382 mg, 66%) as a colorless oil.

**IR** (neat) 2937, 1740, 1645, 891 cm⁻¹.

**1H NMR** (CDCl3): δ = 5.27-5.22 (1H, narrow m, H-3), 4.80 (1H, br s, =CH2), 4.49 (1H, br s, =CH2), 3.75 (3H, s, OMe), 3.09 (1H, d, J = 12.5 Hz, H-9), 2.36-2.29 (2H, m), 2.10-1.96 (2H, m), 1.82 (1H, td, J = 12.3, 3.1 Hz, H-10), 1.62 (3H, br s, Me-18), 1.55-1.20 (4H, m), 1.06 (3H, s, Me-19).

**13C NMR** (CDCl3): δ = 174.1 (CO2R), 146.2 (C-8), 141.7 (C-4), 121.1 (C-3), 107.9 (=CH2), 52.0 (OMe), 51.6, 45.7, 37.0, 36.7, 31.4, 25.9, 23.2, 18.8, 18.2.

**FAB-HRMS** m/z 234.1615 (calcd for C14H21O3 [M+] m/z 234.1620).

3,4,4a,7,8,8a-Hexahydro-2-(methoxymethyl)-4a,5-dimethyl-1-naphthalenecarboxylic acid methyl ester (15). To a suspension of NaH (40 mg, 1.0 mmol) in HMPA (3 mL) at 0 °C under N2 was added a solution of 13 (200 mg, 0.847 mmol) in HMPA (3 mL). The reaction mixture was warmed to room temperature over a 2 h period. To this solution was added chloromethyl methyl ether (82 mg, 1.0 mmol) and the reaction mixture was stirred for an additional 3 h. The resulting mixture was poured into a separatory funnel containing ice-water, saturated NaHCO3 (10 mL) and ether (15 mL). The layers were separated, and the aqueous layer was extracted several times with ether. The combined organic layers were dried (MgSO4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO2, hexanes-ethyl acetate = 10:1) to afford (±)-15 (150 mg, 64%) as a colorless solid; mp 65-68 °C;

**IR** (neat) 2949, 2830, 1725, 1680 cm⁻¹.

**1H NMR** (CDCl3): δ = 5.23 (1H, br s, H-3), 4.91 (1H, d, J = 6.9 Hz, OCH2OMe), 4.85 (1H, d, J = 6.9 Hz, OCH2OMe), 3.73 (3H, s, CO2Me), 3.42 (3H, s, OCH2OMe), 2.57-2.49 (1H, m), 2.39-2.30 (2H, m), 2.10-2.02 (2H, m), 1.97-1.88 (1H, m), 1.64 (3H, br s, Me-18), 1.56-1.40 (3H, m), 0.98 (3H, s, Me-19).

**13C NMR** (CDCl3): δ = 169.5 (CO2R), 151.1 (C-8), 141.4 (C-4), 121.2 (C-3), 116.3 (C-9), 93.2 (OCH2OMe), 56.5 (OCH2OMe), 51.6 (CO2Me), 41.7, 35.9, 31.8, 25.7, 22.8, 21.4, 18.9, 18.2.

**Anal. Caled.** For C14H21O4: C, 68.55; H, 8.63. Found: C, 68.69; H, 8.46.

1,2,3,4,4a,7,8,8a-Octahydro-4a,5-dimethyl-1-naphthalenecarboxylic acid methyl ester (16). To a dispersion of lithium metal (80 mg, 12 mmol) in liquid NH3 at -78 °C under N2 was added a solution of 15 (460 mg, 1.64 mmol) in ether (8 mL). The reaction mixture was stirred at -78 °C for 15 min, and then quenched by addition of solid NH4Cl (2.46 g) in one portion. The mixture was stirred for
an additional 30 min at -78 °C and then slowly warmed to room temperature. Additional ether (30 mL) was added, and the mixture was filtered through a pad of filter-aid. The inorganic salts were washed several times with ether and the combined ethereal layers were concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexanes-ethyl acetate = 10:1) to afford (±)-16 (240 mg, 66%) as a colorless oil.

IR (neat) 1728 cm⁻¹.

¹H NMR (CDCl₃): δ = 5.23 (1H, m, H-3), 3.66 (3H, s, OMe), 2.53 (1H, br t, J = 4.8 Hz, H-9), 2.21-2.12 (1H, m), 2.06-1.85 (4H, m), 1.80-1.72 (2H, m), 1.66-1.61 (1H, m), 1.57 (3H, d, J = 1.8 Hz, Me-18), 1.44-1.30 (2H, m), 1.13 (1H, dt, J = 13.2, 4.1 Hz), 0.86 (3H, s, Me-19);

¹³C NMR (CDCl₃): δ = 176.2 (CO₂R), 143.0 (C-4), 121.2 (C-3), 51.3 (OMe), 46.1, 43.3, 38.3, 36.8, 28.6, 27.0, 25.5, 19.3, 18.2, 17.5.

EI-HRMS m/z 222.1619 (calcd for C₁₄H₂₀O₂ [M+H⁺] m/z 222.1620).

1,2,3,4,4a,7,8,8a-Octahydro-4a,5-dimethyl-1-(3-methyl-2Z,4-pentadien-1-yl)-2-oxo-1-naphthalene carbonyl acid methyl ester (18). To a solution of NaH (25 mg, 0.64 mmol) in dry THF (10 mL) at 0 °C under N₂, was added a solution of 13 (150 mg, 0.635 mmol) in THF (10 mL). The mixture was stirred for 30 min, and then solid cation 6 (381 mg, 0.635 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h and then 30 min at room temperature. The reaction mixture was poured into saturated NaCl solution (15 mL), and extracted several times with ethyl acetate. The combined extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexanes-ethyl acetate = 8:1) to afford a mixture of diastereomeric diene-iron complexes 17/17⁺ (325 mg, 75%) as a yellow solid. mp (decomposes) 89-100 °C.

The ¹H and ¹³C NMR spectra for this product were too complex for complete interpretation due to the presence of diastereomers.

¹H NMR (partial, CDCl₃): δ = 7.56-7.30 (m, 15H, PPh₃), 5.26-5.05 (m, 3H), 4.24-4.07 (br m, 1H), 3.64 and 3.61 (2 x s, 3H).

Anal. calcd. for C₂₀H₂₄O₂PFe: C, 69.57; H, 6.27. Found: C, 69.42; H, 6.40.

To a solution of the 17/17⁺ (110 mg, 0.159 mmol) in methanol (10 mL) was added solid ceric ammonium nitrate [CAN] (220 mg, 0.401 mmol) in two portions. Monitoring of the reaction by TLC indicated that complete disappearance of 17/17⁺ in 30 min. Water (15 mL) was added and the reaction mixture was extracted several times with ether. The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexanes-ethyl acetate = 10:1) to afford (±)-18 (50 mg, 99%) as a colorless oil.

IR (neat) 2950, 1713, 1435, 1217 cm⁻¹.

¹H NMR (CDCl₃): δ = 6.82 (1H, dd, J = 17.3, 10.7 Hz, H-14), 5.30-5.18 (3H total, br m & d, J = 16.6 Hz, H-3, H12 and H-15), 5.12 (1H, d, J = 10.9 Hz, H-15a), 3.66 (3H, s, OMe), 2.83 (1H, dd, J = 14.7, 6.5 Hz, H-11), 2.62 (1H, dd, J = 14.4, 9.1 Hz, H-11), 2.47 (1H, ddd, J = 15.5, 4.7, 2.3 Hz, H-7a), 2.10-1.96 (1H, m), 1.90-1.78 (2H, m), 1.72 (3H, s, Me-16), 1.65-1.63 (1H, m), 1.54 (3H, s, Me-18), 1.43 (1H, dt, J = 16.5, 4.9 Hz), 1.08-1.04 (2H, m), 1.03 (3H, s, Me-19);

¹³C NMR (CDCl₃): δ = 208.0 (C-8), 173.9 (CO₂Me), 141.2 (C-4), 135.1 (C-14), 133.3, 125.1, 122.4 (C-3), 114.6 (C-15), 61.8 (C-9), 52.3 (OMe), 50.0, 38.1, 37.7, 36.4, 31.0, 27.2, 21.1, 20.5 (Me-16), 18.6, 17.5.

FAB-HRMS m/z 323.2182 (calcd for C₂₀H₂₄O₂Li (M+Li⁺) m/z 323.2199).

1,2,3,4,4a,7,8,8a-Octahydro-4a,5-dimethyl-1-(3-methyl-2Z,4-pentadien-1-yl)-2-methylene-1-naphthalene carbonyl acid methyl ester (21). To a solution of 14 (100 mg, 0.427 mmol) in dry THF (10 mL) at 0 °C under N₂, was added a solution of lithium diisopropylamine in THF (1.8 M, 0.3 mL, 0.5 mmol). The mixture was stirred for 1 h at 0 °C, and then solid cation 6 (0.31 g, 0.54 mmol) was added in one portion. The reaction mixture was stirred for 3 h and then worked up in a fashion similar to that for 17/17⁺. Purification of the residue by column chromatography (SiO₂, hexanes-ethyl acetate = 20:1) gave a diastereomeric mixture of diene-iron complexes 19/19⁺ (70 mg, 30%) as a yellow oil.

The ¹H and ¹³C NMR spectra for this product were too complex for complete interpretation due to the presence of diastereomers.

¹H NMR (partial, CDCl₃): δ = 7.56-7.32 (m, 15H, PPh₃), 5.26-5.05 (m, 3H), 4.21-4.10 (br m, 1H), 3.64 and 3.61 (2 x s, 3H).

¹³C NMR (partial, CDCl₃, diastereometric signals reported as pairs: δ = 176.6 and 175.8 (CO₂Me), 149.7, 146.9, 142.9 and 142.6 (C3), 136.3 (d, J₉H = 37.5 Hz), 133.3 (d, J₉H = 10.2 Hz), 129.8, 128.3 (d, J₉H = 8.7 Hz), 121.7 and 121.2, 112.0 and 111.1, 103.1 and 102.3, 94.1 and 93.45.

Anal. calcd. for C₂₀H₂₄O₂PFe₂H₂O: C, 69.70; H, 6.70. Found: C, 69.77; H, 6.95.

Decomplexation of the mixture of 19/19⁺ (70 mg, 0.16 mmol) in methanol (10 mL) with CAN (112 mg, 0.204 mmol) was carried out in a fashion similar to the decomplexation of 17/17⁺. Purification of the residue by column chromatography (SiO₂, hexanes-ethyl acetate = 10:1) gave (±)-21 (22 mg, 70%) as a colorless oil.

IR (neat) 2963, 1718, 1436, 1265 cm⁻¹.

¹H NMR (CDCl₃): δ = 6.82 (1H, dd, J = 17.4, 10.9 Hz, H-14), 5.34 (1H, t, J = 6.5 Hz, H-12), 5.28-5.20 (2H, m, H-3 and H-15), 5.13 (1H, d, J = 10.6 Hz, H-15a), 5.00 (1H, s, H-17a), 4.78 (1H, s, H-17b).
3.65 (3H, s, OMe), 2.86-2.63 (3H, m), 2.34-2.25 (1H, m), 2.02-1.78 (8H, m), 1.57 (3H, br s, Me-18), 1.30-1.20 (2H, m), 0.95 (3H, s, Me-19).

1D C NMR (CDCl₃): δ = 176.4 (CO₂R), 148.8 (C-8), 142.7 (C-4), 133.9, 133.7, 125.6, 121.7 (C-3), 114.5 (C-15), 110.6 (C-17), 53.7, 50.6, 38.9, 38.4, 32.4, 31.6, 29.9, 27.5, 20.8, 20.2 (Me-16), 18.4, 17.8.

FAB-HRMS m/z 314.2240 (calcd for C₁₁H₁₃O₂ [M+H⁺] m/z 314.2246).

References


5 - For other examples of diterpenes containing a 3-methyl-2Z,4-pentadien-1-yl side chain see:


16 - (a) T. Ling, C. Chowdhury, B. Kramer, B. G. Vong, M. Palladino and E. A. Theodorakis,