

Application of the Reetz Reagent, Dichlorodimethyltitanium, to Develop Sterically Congested Quaternary Centers. The Synthesis of Herbertene

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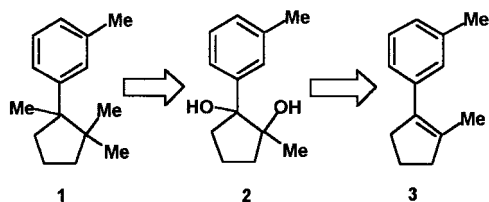
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Abstract: A general protocol for conversion of a tetrasubstituted alkene to a highly methylated hydrocarbon is tested with a concise synthesis of the natural product, herbertene. The conversion: alkene \rightarrow 1,2-diol \rightarrow 1,2-dimethylated hydrocarbon should find application in a number of synthesis designs.

Key words: herbertene, Reetz reagent, dichlorodimethyltitanium, methylation, quaternary centers

Reetz has shown that a tertiary hydroxy group can be replaced by a methyl group using dichlorodimethyltitanium.⁵ As part of our program designed to develop protocols for the rapid development of complex molecules, we envisioned a simultaneous replacement of the two adjacent hydroxy groups of a 1,2-diol with two methyl groups. An obvious test for this was found in herbertene.

Herbertene, isolated from the liverwort, *Herberta adunca*,⁶ has the structure described by **1**. Our focus is apparent in the retrosynthetic analysis (Scheme 1).

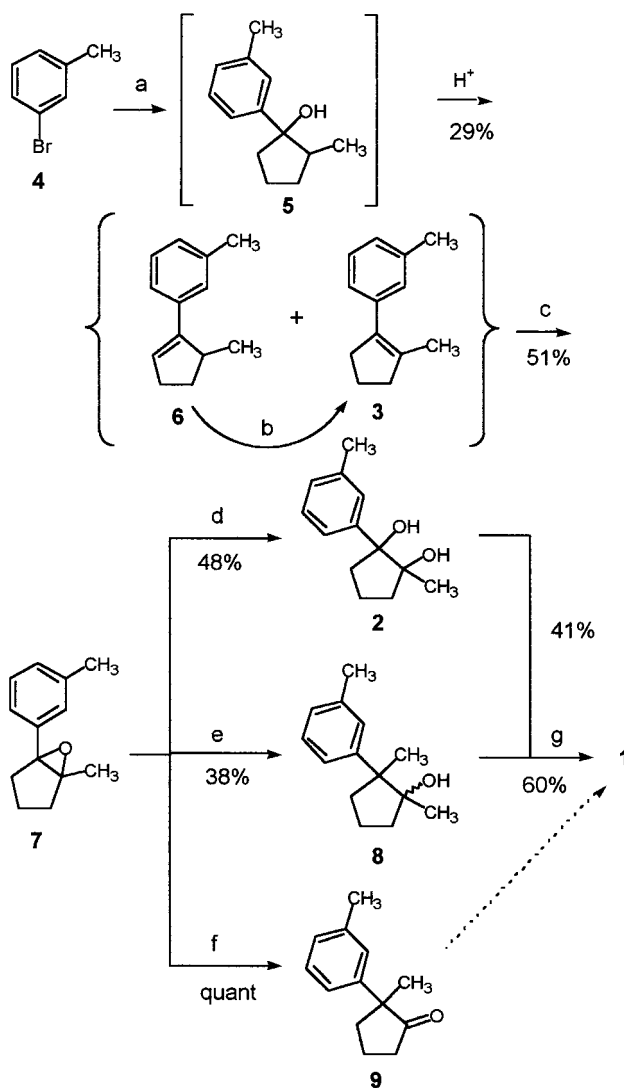


Scheme 1

While a number of syntheses for herbertene have been reported,⁷ the ability to convert the diol **2** to the title compound would provide a relatively concise route to this and other naturally occurring terpenoids.⁸ We report here two total syntheses of (\pm)-herbertene.

A summary of the synthesis of herbertene is provided in Scheme 2.

Readily available 3-bromotoluene was converted to a Grignard reagent, which when followed by addition of 2-methylcyclopentanone provided **5**. Without purification, the crude product was dehydrated with a catalytic amount of *p*-toluenesulfonic acid in toluene. The dehydration initially gave the kinetically controlled less substituted alkene, [5-methyl-1-(3-methylphenyl)cyclopentene (**6**)], as major product. However, heating the reaction mixture under reflux for 6 hours affected the isomerization to the desired **3** [ratio **3/6** 91:9].⁹ This alkene mixture was subjected to MCPBA epoxidation in dichloromethane, and the corresponding epoxide isomers were readily separated by flash column chromatography to give **7** in 51% yield.



Reagents and conditions: (a) (i) Mg, Et₂O, 22 °C, 1.5 h. (ii) 2-methylcyclopentanone, 22 °C, 3 h. (b) TsOH (cat.), toluene, 110 °C, 3 h. (c) MCPBA, CH₂Cl₂, 0 °C, 1 h. (d) HClO₄, H₂O, THF, 22 °C, 1 week. (e) AlMe₃ (5 equiv), hexane, 0 °C, 8 h. (f) pyrolysis, 200 °C. (g) Me₂TiCl₂ (10 equiv), CH₂Cl₂, 0 °C, 8 h.

Scheme 2

The diol precursor **2** was obtained in 48% yield by perchloric acid catalyzed hydrolysis¹⁰ of **7**. This product was prone to dehydration, even under conditions of mild silica gel chromatography. Other methods¹¹ of forming 1,2-diols from **6** or from **3** were of limited success. Because of the labile nature of **2**, an alternate route to **1** was devised from **8**. The homobenzylic alcohol **8** was prepared from the reaction of five equivalents of trimethylaluminum

with **7** in hexane at 0 °C under argon. Aqueous workup followed by radial thin layer chromatography gave **8** in 38% yield.

The precursors, **2** and **8**, were readily converted to **1** by reaction with excess dichlorodimethyltitanium in dichloromethane at 0 °C under an argon atmosphere. Separation of **1** from unreacted starting material was accomplished by preparative GC. Isolated yields were 41% from **2** and 60% from **8**. Herbertene was characterized by a combination of HRMS and NMR spectra (both ¹H and ¹³C). Data were in accord with those previously reported.⁴

An interesting result was noted when we attempted to isolate **7** by preparative GC. The conditions of the GC chromatograph (see experimental section) resulted in the pyrolysis of **7** to **9**. Since cuparene has been synthesized using the Reetz methylation of 2-methyl-2-(4-methylphenyl)cyclopentanone, we expect, by analogy, that **9** might also be able to undergo a similar transformation.

The unique utility of the Reetz methylation protocol to generate methylated centers from tertiary diols has been illustrated via the synthesis of (±)-herbertene. In addition, a second method for generating the title compound from epoxides has been presented. Both syntheses are characterized by a simplicity for developing vicinal methylated quaternary centers. This method should provide a synthetically useful route to a number of sesquiterpenes isolated⁷ from the class of Bryophytes known as liverworts.

Toluene and anhyd Et₂O were used as purchased from Fisher, while THF and CH₂Cl₂ were distilled from Na/benzophenone and CaH₂, respectively. Routine GC/MS analyses were performed on a Hewlett-Packard 5890 gas chromatogram coupled to a 5970 series mass selective detector using a Supelco 2-4026 15 m × 0.25 mm capillary column packed with SPBM-1 (0.25 μm). NMR spectra were recorded at 400 MHz for ¹H and 100 MHz for ¹³C on a Jeol GSX-400/54 high resolution NMR spectrometer. CDCl₃ was used as the NMR solvent unless otherwise noted. Preparative GC separations were performed on a Gow-Mac Series 350 gas chromatograph using a 8' × 0.25" 20% Carbowax 20M on Chrom-P 80/100 mesh column (injector port, oven, detector, and outlet port set to 200 °C; He flow rate = 6 mL/min). Radial TLC was performed using a Harrison Research Chromatotron fitted with a 1 mm silica gel rotor.

1-Methyl-2-(3-methylphenyl)cyclopentene (**3**):

A solution of 3-bromotoluene (10.7 g, 0.0626 mol) in Et₂O (10 mL) was added slowly to a mixture of Mg (1.53 g, 0.0630 mol) in Et₂O (25 mL) under argon. The mixture was allowed to reflux under its own heat until most of the Mg was consumed. A solution of 2-methylcyclopentanone (6.08 g, 0.062 mol) in Et₂O (10 mL) was then added slowly to the resulting Grignard solution and allowed to reflux for 3 h. The mixture was quenched with 1 M HCl, and the organic layer was then washed with water and dried (Na₂SO₄). The Et₂O was removed under reduced pressure to give a clear yellow liquid. Without purification, the crude product **5** was dissolved in toluene (40 mL), and TsOH (1.5 g) was added to this solution. The resulting solution was refluxed for 3 h, whereupon the solution turned from slightly yellow to deep purple in color. The toluene solution was then washed with sat. NaHCO₃, dried (MgSO₄), and reduced under pressure to yield a thick, purple liquid. The alkene product was collected as a clear, colorless liquid by Kugelrohr distillation (120 °C/3.2 Torr). The product (2.56 g, 29% yield) was found, by GC/MS, to consist of **3** (91%) and **6** (9%).

1,2-Epoxy-1-methyl-2-(3-methylphenyl)cyclopentane (**7**):

A solution of the alkenes **3** and **6** (2.56 g, 0.0148 mol) in CH₂Cl₂ (20 mL) was added slowly to a solution of MCPBA (4.29 g, 0.0249 mol) in CH₂Cl₂ (100 mL) at 0 °C. The reaction was allowed to warm up to r.t. overnight. The resultant milky white mixture was washed with dil NaHCO₃ (3 ×) and the organic layer was then washed with water and dried (Na₂SO₄). Removal of the solvent under reduced pressure and flash column chromatography (silica gel) gave 1.41 g (51% yield) of **7**. ¹H NMR (400 MHz): δ = 7.22–7.08 (m, 4H), 2.36 (s, 3H), 2.28–2.01 (m, 3H), 1.80–1.48 (m, 3H), 1.17 (s, 3H). ¹³C NMR (100 MHz): δ = 138.3, 138.01, 128.6, 128.5, 127.7, 124.1, 73.3, 71.0, 33.3, 32.4, 21.6, 19.0, 15.3. HRMS (EI): *m/z* calcd 188.1201, found 188.1202.

1-Methyl-2-(3-methylphenyl)cyclopentane-1,2-diol (**2**):

To THF/H₂O (1:1, 35 mL) containing **7** (0.210 g, 0.00112 mol) was added 65–85% HClO₄ (4 drops). The reaction was allowed to stir at r.t. for one week. The solvent was removed under reduced pressure and the crude product was washed with hexane to yield a white powder (110 mg) in 48% yield. ¹³C NMR (100 MHz): δ = 140.0, 136.4, 127.6, 127.5, 127.4, 126.5, 83.2, 81.9, 38.0, 35.8, 24.4, 21.0, 18.9.

1,2-Dimethyl-2-(3-methylphenyl)cyclopentan-1-ol (**8**):

To a solution of **7** (0.266 g, 0.00141 mol) in hexane (2 mL) at 0 °C was added 2 M AlMe₃ (3.5 mL, 0.00700 mol) under argon. The reaction was allowed to proceed overnight before being quenched with water. The mixture was extracted with several small portions of hexane, and the combined hexane layers were dried (Na₂SO₄) and concentrated under reduced pressure. Purification by radial chromatography using Et₂O/hexane (1:1) gave **8** (0.11 g, 38% yield) as a colorless liquid. ¹H NMR (400 MHz): δ = 7.32–6.96 (m, 4H), 2.34 (s, 3H), 2.29 (m, 1H), 1.94–1.67 (m, 3H), 1.36 (s, 3H), 1.28 (m, 2H), 0.93 (s, 3H). ¹³C NMR (100 MHz): δ = 147.4, 137.1, 127.9, 127.7, 126.3, 123.5, 82.1, 50.9, 39.0, 35.1, 25.8, 24.1, 21.9, 18.0. HRMS (EI): *m/z* calcd 204.1514, found 204.1518.

2-Methyl-2-(3-methylphenyl)cyclopentanone (**9**):

A sample of **7** (25 μL) was analyzed by preparative GC under the conditions described above. The largest fraction (*t*_R 12 min) was collected and combined with two other collections obtained in the same way. GC/MS analysis showed the product to be over 99% pure. ¹H NMR (400 MHz): δ = 7.22–7.04 (m, 4H), 2.55 (m, 1H), 2.34 (s, 3H), 2.02–1.86 (m, 5H), 1.38 (s, 3H). ¹³C NMR (100 MHz, benzene-*d*₆): δ = 218.1, 143.1, 138.2, 128.8, 128.1, 127.6, 123.6, 52.9, 37.8, 37.3, 25.6, 21.5, 18.8.

Dichlorodimethyltitanium:

The methylating reagent was prepared by adding 2 M Me₂Zn in toluene (1 equiv) to TiCl₄ (1 equiv) in CH₂Cl₂ at 0 °C under argon. The reagents are allowed to react with stirring for 10 min before addition of substrate.

(±)-Herbertene (**1**) from **2**:

A solution of **2** (0.025 g, 0.000123 mol) in CH₂Cl₂ (1 mL) was added to Me₂TiCl₂ soln (10 equiv) at 0 °C under argon. The reaction was allowed to proceed overnight, after which it was quenched by careful addition of water at 0 °C. The mixture was then extracted with several small portions of CH₂Cl₂, and the combined organic layers were dried (MgSO₄). Removal of the solvent under reduced pressure followed by preparative TLC separation gave **1** (0.010 g, 41% yield). ¹H NMR (400 MHz): δ = 7.20–7.00 (m, 4H), 2.51 (m, 1H), 2.34 (s, 3H), 1.81–1.52 (m, 5H), 1.26 (s, 3H), 1.07 (s, 3H), 0.56 (s, 3H). ¹³C NMR (100 MHz): δ = 136.7, 127.8, 127.3, 126.0, 124.1, 50.4, 44.2, 39.7, 36.7, 26.5, 24.4, 24.3, 21.8, 19.7. HRMS (EI): *m/z* calcd 202.1721, found 202.1717.

(±)-Herbertene (1) from 8:

A solution of **8** (0.524 g, 0.00256 mol) in CH₂Cl₂ (2 mL) was added to Me₂TiCl₂ soln (10 equiv) at 0°C under argon. The reaction was allowed to proceed overnight and was then quenched by careful addition of water to the mixture at 0°C. The mixture was then extracted with CH₂Cl₂, and the combined organic layers were dried (MgSO₄). Removal of the solvent under reduced pressure, followed by preparative GC separation gave **1** (0.312 g, 60% yield).

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