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# Introduction of an Isopropyl Group at the Gamma Position of a Hydrindenone Derivative

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# INTRODUCTION OF AN ISOPROPYL GROUP AT THE GAMMA POSITION OF A HYDRINDENONE DERIVATIVE

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**Abstract**: The oxy hydrindenone derivative **6b** was converted stereoselectively into the corresponding γ-isopropyl derivative **10** by a five-step sequence.

Hydrindenones such as **1**, which may be prepared by Robinson annulation of 2-methyl-5-isopropylcyclopentanone, are useful intermediates for the synthesis of sesquiterpenes (Scheme 1).[1] For example, upon conversion to the corresponding cross-conjugated cyclohexadienones (**2**) and irradiation in glacial acetic acid the 5/6-fused acetoxy enones **3a** and **3b**, which have been converted into racemic oplopanone (**4**)[1a] and racemic α-cadinol (**5**),[1b] respectively, were obtained.

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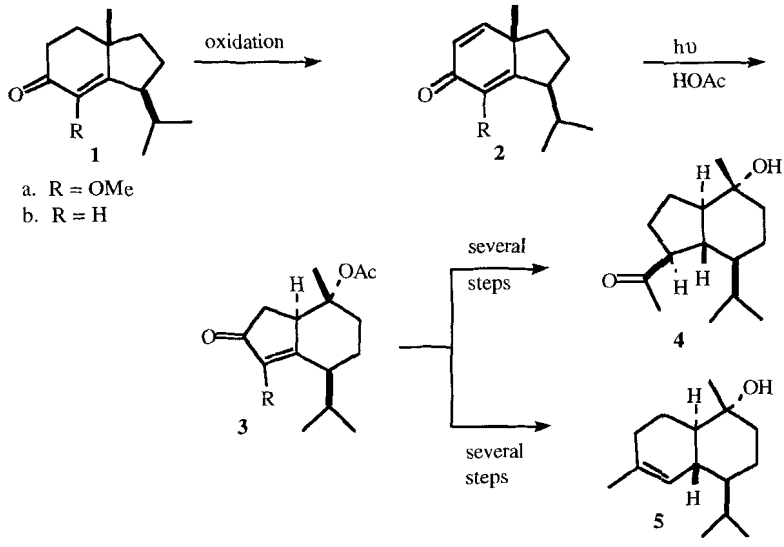
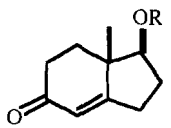


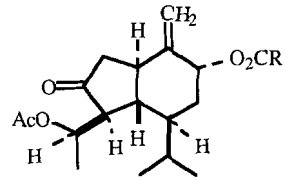

**Scheme 1**

The hydroxy hydrindenone **6a** is readily available in optically active form from the S-(-)-proline-catalyzed aldol condensation of the Michael adduct of methyl vinyl ketone and 2-methyl-1,3-cyclopentandione followed by selective reduction of the carbonyl group in the five-membered ring.[2] It appeared that the introduction of an isopropyl group at the γ-position of a hydroxyl-protected derivative of **6a** would provide a hydrindenone which would be readily convertible into a highly oxygenated oplopane derivative such as notonipetrone (**7a**),[3a] petasipaline A (**7b**),[3b] or tussilagone (**7c**)[3c,d] via a route similar to that shown in Scheme 1. The feasibility of using oxy hydrindenones in this type of photochemical approach has been previously demonstrated by

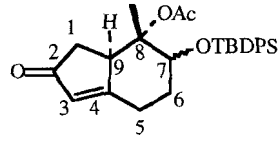
the preparation of the 5/6-fused acetoxy ketones **8a** and **8b**, analogous to **3**, from the t-butyl-diphenylsilyl (TBDPS) derivative of **6a**, i.e., **6b**,[4a] and the corresponding a siloxy enone **9**, respectively.[4b] We now wish to report the conversion of **6b** into γ-isopropylated enone **10**.



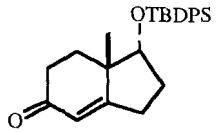

**6a**. R = H
**b**. R = TBDPS



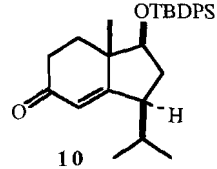

**7a**. R = isobutyl
**b**. R = Me
**c**. R = E-2-methyl-1-butenyl




**8a**. 7β-isomer
**b**. 7α-isomer

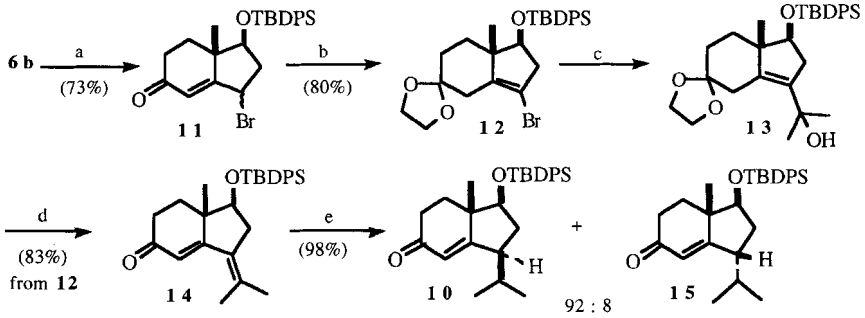



**9**




**10**

As shown in Scheme 2, enone **6b** was subjected to allylic bromination with NBS in the presence of a catalytic amount of benzoyl peroxide to give the γ-bromo enone **11** as a mixture of γ-bromo diastereomers in 73% yield. The α,γ-dibromo derivative of **6b** was also produced in *ca.* 12% yield in this reaction. Ketalization of **11** led to migration of the α,β double bond to the β,γ-position to form the vinyl bromide **12** in 80% yield. Treatment of **12** with 2.1 equiv of t-BuLi in THF at -78 °C gave the corresponding vinyllithium derivative which was reacted by anhydrous acetone to yield the crude tertiary alcohol **13**. Treatment of **13** with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone led to deketalization, migration of the β,γ-double bond into the α,β-position, and dehydration of the tertiary alcohol to give the linearly




**Scheme 2**

a) NBS, cat. amt. $(PhCO_2-)_2$, $CCl_4$, reflux, 1.0 h; b) $(CH_2OH)_2$, PTSA, PhH, reflux, 7.0 h; c) 1. *t*-BuLi, (2.1 equiv), THF, -78° C, 30 min, 2. $CH_3COCH_3$, -78° C, 3.0 h; d) PPTS, $CH_3COCH_3$-$H_2O$, reflux, 18.0 h; e) Pd/C, $C_6H_{10}$, $CH_3CH_2OH$, reflux, 12.0 h.

conjugated dienone **14** in 83% overall yield from the bromo ketal **12**. Selective reduction of the γ,δ-double bond of **14** was accomplished by transfer hydrogenation using palladium-on-carbon and excess cyclohexene in ethyl alcohol at reflux.[5] Examination of a model of **14** indicated that hydrogenation of the γ,δ-double bond would occur preferentially from the α face of the molecule to give the β-isopropyl enone **10**. In fact, the reduction occurred with good stereoselectivity to give a 92:8 mixture of **10** and the corresponding α-isomer **15** in 98% yield. The nonequivalent methyl groups of the isopropyl group of **10** exhibited doublets at δ 0.84 and 0.90 in the $^1H$ NMR spectrum which were in similar locations to those reported for the 1-deoxy enones **1a** and **1b**.[1b] The doublets for the corresponding methyl groups in enone

**15** occurred at δ 0.76 and 0.30. These absorptions were at significantly higher field than those reported for the diastereomer of **1b** which has an α isopropyl group .[1b] Apparently, in enone **15** this group experiences a significant amount of shielding by the α,β-double bond and/or by the phenyl groups of the TBDPS group.

Enone **10** was thermodynamically unstable and underwent epimerization of the isopropyl group to give a *ca.* 1:1 mixture of enones **10** and **15** on standing for several days. Further studies on the use of dienone **10** for the photochemical synthesis of oplopane sesquiterpenes such as **7** are in progress.

## EXPERIMENTAL

**(1(S),7a(S))-(tert-Butyldiphenylsiloxy)-3-Bromo-7-methyl-7,7a-dihydro -5(6H)-indanone (11).** To a mixture of 3.46 g (8.56 mmol) of enone **6b** in 85 mL of $CCl_4$ was added 1.83 g (9.42 mmol) N-bromosuccinimide (NBS) and 17 mg of benzoyl peroxide. The mixture was shielded from light with aluminum foil and heated at reflux for 90 min. The reaction mixture was cooled, the precipitate of succinimide was filtered off, and the filtrate was concentrated under reduced pressure to give a crude oil. Purification of the residue by flash column chromotography (20% ether in hexane) gave a first fraction containing 0.6 g (14%) of the 3,4-dibromo derivative of **6b**, which was homogeneous by TLC analysis, Rf = 0.67 (25% ether in hexane): $^1H$ NMR (360 MHz) δ 1.09 (S, 9 H), 1.45 (m, 1 H) 1.94 (m, 1 H), 2.64 (m, 4 H), 3.69 (d of d, J = 7.7, 10 Hz, 1 H), 4.56 (t, J = 8.0 Hz, 1 H), 7.43 (m, 6 H),

7.63 (m, 4 H); IR ($CDCl_3$) 3910, 3850, 1690, 1540, 1240, 1210, 1140, 1105, 1000, 975, 700 cm-1; HRMS m/z calcd for $C_{22}H_{21}O_2SiBr$ (M - $C_4H_9$ (tert-butyl)): 504.9657, obsd: 504.9697; and a second fraction containing 2.96 g (78%) of an inseparable mixture of 2α- and 3β-monobromo ketones **11** in 1.5:1 ratio as determined by $^1H$ NMR spectroscopy. The mixture showed one spot on TLC analysis, Rf = 0.47 (25% ether in hexane): $^1H$ NMR (360 MHz) δ 1.09 (s, 5.4 H), 1.10 (s, 3.6 H), 1.11 (s, 1.8 H), 1.23 (s, 1.20 H), 1.96 - 2.55 (m, 6 H), 3.67 (d of d, J = 7.5, 10 Hz, 0.6 H), 4.15 (d of d, J = 7, 10 Hz, 0.4 H), 4.51 (d of d, J = 1.5, 7 Hz, 0.6 H), 4.92 (d, J = 9.5 Hz, 0.4 H), 5.97 (s, 0.6 H), 6.03 (s, 0.4 H), 7.45 (m, 6 H), 7.66 (m, 4 H); $^{13}C$ NMR (360 MHz) d 16.60, 17.32, 19.31, 26.96, 33.11, 33.29, 33.83, 34.57, 34.69, 35.00, 39.79, 41.84, 42.40, 44.44, 44.96, 45.80, 46.21, 78.81, 79.70, 126.78, 127.29, 127.80, 130.11, 130.24, 132.98, 133.49, 134.80, 135.86, 171.41, 172.31, 199.05, 199.59; IR ($CHCl_3$) 3940, 3850, 1670, 1480, 1440, 1400, 1100, 650 cm-1; HRMS m/z calcd for $C_{22}H_{22}0_2SiBr$ (M - $C_4H_9$ (tert-butyl)): 427.0552, Obsd: 427.0557. Further elution gave 0.27 g of the starting material **6b**.

**Preparation of the Bromo Ketal 12.** To a solution of 2.96 g (6.13 mmol) of **11** in 30 mL dry benzene was added 0.062 g (0.32 mmol), of *p*-toluenesulfonic acid and 0.86 mL (15.33 mmol) of anhydrous ethylene glycol. The solution was heated at reflux for 7.0 h with azeotropic removal of water using a Dean-Stark trap. The solvent was removed *in vacuo* to give a crude oil. Purification of this material by flash column chromotography (20% ether in hexane) gave 2.54 g (77%) of bromo ketal **12**, which was homogeneous by TLC analysis, Rf = 0.65

(20% ether in hexane): $^1$H NMR (360 MHz) δ 1.21 (s, 9 H), 1.23 (s, 3 H), 1.33 (m, 1 H), 1.62 (m, 2 H), 3.89 (m, 4 H), 4.12 (t, J = 7.5 Hz, 1 H), 7.34 (m, 6 H), 7.63 (m, 4 H); $^{13}$C NMR δ 16.10, 19.35, 27.00, 31.12, 35.07, 35.48, 46.18, 48.49, 64.39, 64.44, 81.13, 108.84, 111.22, 127.64, 129.79, 134.79, 135.87, 142.32; IR ($CHCl_3$) 3970, 3960, 3870, 1490, 1410, 1150, 1130 cm-1; HRMS m/z calcd for $C_{24}H_{26}O_3SiBr$ (M - $C_4H_9$ (tert-butyl)): 471.0814, obsd: 471.0842.

**Preparation of the Hydroxy Ketal 13.** To a solution of 3.61g (6.9 mmol) of bromo ketal **12** containing a few crystals of α,α'- bipyridyl in 65 mL THF cooled to -78 °C under nitrogen, was added 8.6 mL (14.5 mmol) of t-BuLi (1.7 M in hexane) dropwise with stirring over a period of 10 min. The solution was stirred for 30 min at -78 °C and quenched with 5.1 mL (69 mmol) acetone (freshly distilled over $P_2O_5$) and the reaction mixture was stirred at -78 °C for 3 h. The reaction mixture was allowed to warm to room temperature and quenched by addition of 5 mL of cold saturated aqueous $NH_4Cl$. The solvent was then removed under reduced pressure, the residue was dissolved in 20 mL ether and the solution was washed twice with brine (25 mL), dried and filtered. The solvent was removed *in vacuo* to give 3.29 g of crude product, the bulk of which was used in the next step without further purification. An analytical sample of pure hydroxy ketal **13** was obtained by preparative thin layer chromatography (25% ethyl acetate in hexane). It was homogeneous by TLC analysis, Rf = 0.2 (25% ethyl acetate in hexane); $^1$H NMR (200 MHz), δ 1.10 (s, 9 H), 1.12 (s, 3 H), 1.19 (s, 3 H), 1.20 (s, 3 H), 1.69 (m, 3 H), 2.20 (m, 4 H), 3.21 (d of d, J = 12.0 and 1.0 Hz, 1 H), 3.80 - 4.05 (m, 5

H), 7.40 (m, 4 H), 7.69 (m, 6 H); IR ($CDCl_3$) 3600, 3480, 3980, 3920, 3890, 1640, 1590, 1460, 1380, 1360, 1200 cm-1; HRMS m/z calcd for $C_{31}H_{42}SiO_4$ (M+): 506.2852, Obsd: 506.2868.

**Preparation of the Linear Dienone 14.** A solution of 3.75 g of the crude hydroxy ketal **13** and 0.375 g (1.5 mmol) of PPTS was dissolved in 80 mL of a 10:1 acetone/water mixture. The resulting solution was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. To the crude residue was added 10 mL brine and the mixture was extracted with three 20-mL portions of ether. The combined organic layers were dried and filtered. Removal of the solvent *in vacuo* gave 3.29 g of an oil. Purification of the product by flash column chromotography (30% ether in hexane) gave 2.53 g (83%) of the pure linear dienone **14**, which was homogeneous by TLC analysis, Rf = 0.39 (30% ether in hexane); $^1H$ NMR δ, 1.10 (s, 9 H), 1.23 (s, 3 H), 1.48 (m, 1 H), 1.68 (s, 3 H), 1.90 (s, 3 H), 2.00 (m, 1 H), 2.31 (m, 3 H), 2.49 (m, 1 H), 3.82 (t, J = 8.8 Hz, 1 H), 5.91 (s, 1 H), 7.41 (m, 6 H), 7.68 (m, 4 H); $^{13}C$ NMR (360 MHz) δ 15.18, 19.35, 23.00, 24.73, 27.02, 29.67, 33.08, 34.32, 37.59, 46.84, 79.55, 121.81, 127.56, 129.77, 135.88, 141.00, 167.52, 200.39; IR ($CDCl_3$) 3010, 2910, 2860, 1659, 1642, 1586, 1420, 1220, 1110, 900 cm-1; HRMS m/z calcd for $C_{25}H_{27}O_2Si$ (M+ $C_4H_9$ (tert-butyl)): 387.1780, obsd: 387.1755.

**(1(S),3(R),7a(S))-1-(tert-Butyldiphenylsiloxy)-3β-isopropyl-7a-methyl-7,7a-dihydro-5(6H)-indanone (10).** To a

stirred solution of 0.88 g (1.99 mmol) of the linear dienone **14** in 17 mL (0.168 mmol) cyclohexene and 80 mL of ethanol was added 0.36 g of 10% palladium-on-carbon. The reaction mixture was stirred at reflux temperature under nitrogen for 12 h. The mixture was allowed to cool to room temperature, the catalyst was removed by filtration, and the solvent removed *in vacuo* to give the isopropyl enone **10** as a crude oil. Purification of this material by flash column chromatography (25% ether in hexane) gave 0.87 g (98%) of a sample containing 92% of the enone **10** with the 3-isopropyl group β and approximately 8% of the C-3α epimer **15** according to $^1$H NMR analysis: $^1$H NMR (360 MHz) δ 0.30 (d, J = 6.8 Hz, 0.24 H), 0.76 (d, J = 6.8 Hz, 0.24 H), 0.84 (d, J = 6.6 Hz, 2.76 H), 0.90 (d, J = 6.6 Hz, 2.76 H), 1.09 (s, 9 H), 1.23 (s, 2.76 H), 1.24 (s, 0.24 H), 1.42 (m, 1 H), 1.74 (m, 3 H), 1.94 (m, 1 H), 2.27 (m, 2 H), 2.50 (m, 1 H), 3.60 (d of d, J = 6.9, 10.4 Hz, 0.08 H), 3.73 (d of d, J = 6.9, 10.4 Hz, 0.92 H), 5.70 (s, 0.08 H), 5.73 (s, 0.92 H), 7.41 (m, 6 H), 7.67 (m, 4 H); $^{13}$C NMR (360 MHz) δ 16.20, 19.34, 21.30, 26.55, 27.01, 31.75, 33.23, 33.40, 35.16, 46.20, 46.38, 80.32, 123.93, 127.65, 129.59, 129.87, 135.86, 135.90, 177.04, 199.59; IR ($CHCl_3$) 3060, 2960, 2920, 2860, 1660, 1460, 1425, 1380, 1110 cm-1; HRMS m/z calcd for $C_{25}H_{29}O_2Si$ (M - $C_4H_9$ (tert-butyl)): 389.1937, obsd: 389.1930.

Upon standing for several days at room temperature, epimerization occurred at C-3 to give a *ca.* 1:1 mixture of the 3β- and 3α-isopropyl derivatives **10** and **15** which showed the expected $^1$H NMR and IR spectral properties and $[\alpha]_D^{20}$ - 18° (c = 0.12 M in $CHCl_3$).

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