J. Braz. Chem. Soc., Vol. 8, No. 3, 275-283, 1997.
Printed in Brazil.

0103 – 5053 $6.00 + 0.00

Article

Synthesis of a Bicyclo[6.3.0]undecene Skeleton Characteristic of Some Cyclooctanoids by an Intramolecular Reductive Coupling of Carbonyls Promoted by Low-Valent Titanium

***Edson Luiz da Silva Lima*[a], *and Carlos Roque Duarte Correia*[b]**

[a]*Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco H, Ilha do Fundão 21941-950 Rio de Janeiro - RJ, Brazil*

[b]*Instituto de Química da Universidade Estadual de Campinas 134081-970 Campinas - São Paulo, Brazil*

Received: September 1, 1995

A síntese do esqueleto biciclo[6.3.0]undeceno, característico de um grande número de ciclooctanóides naturais é descrita neste trabalho. A metodologia aplicada na construção do sistema ciclooctanóide está baseada na reação intramolecular de acoplamento redutivo de dialdeídos promovida por titânio em baixa valência (reação de McMurry). O dialdeído 15, precursor do sistema bicíclico [6.3.0]undeceno, foi preparado em 5 etapas com um rendimento global de 40% a partir da 2-metóxicarbonil-ciclopentanona como material de partida. O uso de C_8K-$TiCl_3$ como agente alternativo para efetuar o acoplamento redutivo intramolecular do dialdeído **15** também foi investigado. O acoplamento redutivo do dialdeído **15** para gerar o anel ciclooctânico ocorreu em baixos rendimentos (~10%) apesar de diversas alterações nas condições de reação visando melhorar sua eficiência.

The synthesis of a bicyclo[6.3.0]undecene skeleton characteristic of a number of cyclooctanoid natural products is described. The methodology applied relies on an intramolecular reductive coupling of a dialdehyde promoted by low valent titanium to construct the key eight-membered ring. The use of C_8K-$TiCl_3$ as an alternative process to the classical coupling developed by McMurry is presented. The dialdehyde **15**, precursor of the bicyclo[6.3.0]undecene system, was constructed in a concise manner from 2-carbomethoxy-cyclopentanone in 5 steps with an overall yield of 40%. The key carbonyl coupling of dialdehyde **15** to produce the eight-membered ring proceeded in low yields (~10%) despite several attempts to increase its efficiency.

Keywords: *cyclooctanoids, carbonyl coupling, low-valent titanium*

Introduction

Naturally occurring cyclooctanoid compounds bearing an eight-membered ring fused to a five-membered ring form a growing family of natural products that has been attracting much attention from the chemical community over the last fifteen years[1]. Examples of these cyclooctanoids are illustrated in the Figure below: i) the sesquiterpenes dactylol **1**[2], and asteriscanolide **2**[3]; ii) the diterpenes pleuromutilin **3**, possessing antibiotic activity[4], and the fusicoccin H **4** exhibiting phytohormone activity[5]; iii) the sesterterpenoids, such as variecolin **5** with antihypertensive properties[6]; and iv) the lignans represented by steganacin **6** possessing antileukemic activity[7].

The presence of a carbocyclic eight-membered ring as the main structural feature of these compounds has posed a significant synthetic challenge since these are considered to be the most difficult medium-sized rings to prepare[8]. It

• Present address: Fundação Oswaldo Cruz-Farmanguinhos. Manguinhos, Rio de Janeiro, 21041-250 RJ. This work was taken in part from the Ph.D. thesis of Edson Luiz da Silva Lima, Universidade Federal do Rio de Janeiro, 1992.

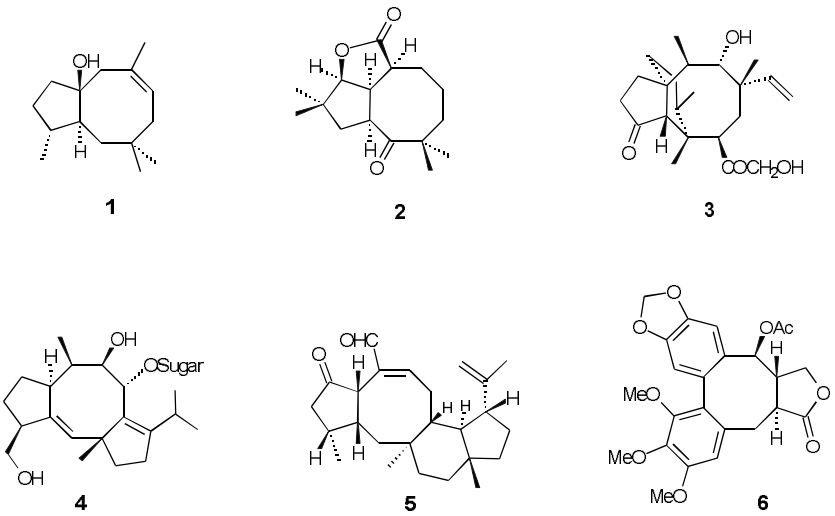


Figure 1. Examples of naturally occurring cyclooctanoids.

was the synthetic challenge in the construction of an eight-membered ring in conjunction with the interesting biological activities of several of these cyclooctanoids that prompted the numerous synthetic studies described in the literature[1].

Among the several methodologies now available to prepare an eight-membered ring the reductive coupling of carbonyls promoted by low-valent titanium (McMurry reaction) appears to be one of the most promising[9]. Remarkably, applications of this methodology in the construction of more densely functionalized intermediates are few[10].

Considering the strategic effectiveness of the McMurry transformation we decided some time ago to apply this transformation as the key step in the construction of cyclooctanoid compounds. Our initial target was the structurally irregular cyclooctanoid dactylol[2]. The envisioned synthetic strategy is depicted in Scheme 1.

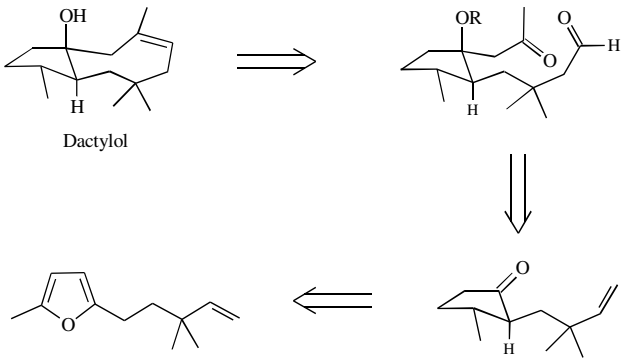
Although the carbonyl coupling represented in Scheme 1 appears direct, the potential lability of the β-hydroxy ketone moiety could prove troublesome in the reductive coupling process. This perception prompted us to initiate our studies more cautiously by first investigating the McMurry transformation on a model substrate. Thus, the preparation of the bicyclo[6.3.0]undecene **9** was conceived as shown in Scheme 2 where dialdehyde **8** is the substrate that undergoes an intramolecular McMurry reductive coupling.

The work presented in this paper describes our results concerning the implementation of this preliminary study.

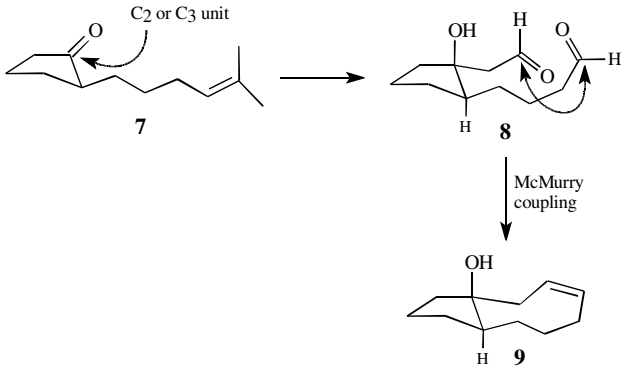
Experimental

General

Nuclear magnetic resonance spectra (NMR) were recorded as solutions in the indicated solvents on Gemini 200 MHz or Varian 60 MHz spectrometers. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane or $CDCl_3$ as internal standard. Coupling constants are reported in hertz (Hz). The infrared spectra were recorded on a Perkin-Elmer 783 spectrometer. The mass spectra were obtained from an VG Autospec Instrument, and the data are reported as m/z (abundance). All solvents used were reagent grade and were distilled prior to use. DME used in the carbonyl coupling experiments was distilled from potassium metal under Ar, followed by deoxygenation with a steady flow of Ar under ultrasound



Scheme 1. Retrosynthetic analysis for dactylol.



Scheme 2. Strategy for the construction of bicyclo[6.3.0]undecene.

for 0.5 h. Unless indicated otherwise, all reagents used were at least reagent grade and used as received. $MgCl_2$(Aldrich) was treated with thionyl chloride for 10 h, rotary evaporated (heating bath at 60-70 °C), and kept under N_2. The Zn-Cu alloy and the C_8K were prepared according to literature procedures and kept under N_2.[11] 2-Carbomethoxycy-clopentanone, 6-methylhept-5-ene-2-one and $TiCl_3$ were purchased from Aldrich Co. $TiCl_3$ is a pyrophoric solid. Unless otherwise noted, all reactions were carried out under a dry nitrogen atmosphere using oven or flame-dried glassware. Capillary gas chromatography (GC) analyses were performed on a Varian 1400 chromatograph equipped with a flame ionization detector and OV-101 column (25 m x 0.32 mm) or on a HP 5890 gas chromatograph interfaced to the above mass spectrometer. Flash chromatography was performed as previously described[12] on E. Merck silica gel 60 (230-400 mesh). All reactions were monitored by thin layer chromatography (TLC) or capillary GC. All compounds submitted to spectroscopic analyses were shown to be homogeneous by TLC.

*Alkenyl-keto ester **11***

To a suspension of K_2CO_3 (9.1 g, 66 mmol) in acetone (20 mL), was added a solution of 2-carbomethoxy-cyclopentanone (2.3 g, 16.5 mmol) in acetone (13 mL). After 15 min the bromide **10** (4.9 g, 27.9 mmol) was added. The resulting mixture was stirred under reflux for 60 h, after which it was partitioned between water (30 mL) and CH_2Cl_2 (3 x 30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated in vacuum. Distillation of the residue at low pressure (0.3 mmHg/ 112-116 °C) afforded 3.1 g (78%) of **11** as a colorless oil. **IR** (film): ν = 2960, 2860, 1750, 1730, 1410, 1380, 1240, 1160, 840 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 1.18-2.60 (m, 12H), 1.58 (s, 3H), 1.65 (s, 3H), 3.72 (s, 3H), 5.06 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, APT): δ = 214.7 (C), 171.2 (C), 131.7 (C), 123.6 (CH), 63.5 (C), 52.2 (CH_3), 37.7 (CH_2), 33.4 (CH_2), 32.4 (CH_2), 27.9 (CH_2), 25.4 (CH_3), 19.3 (CH_2), 17.4 (CH_3). **MS** (70 eV): m/z (%) = 238 (M^+, 4), 207 (17), 178 (10), 161 (59), 150 (54), 142 (60), 96 (51), 82 (100), 67 (58), 55 (51).

*Cyclopentanone **7***

To a solution of KCN (2.27 g, 35.0 mmol) in DMSO (14 mL) was added a solution of the keto ester **11** (2.08 g, 8.74 mmol) in DMSO (15 mL). The mixture turned from colorless to pale brown. The flask was placed into a pre-heated oil bath at 150 °C. After 2 h the mixture was cooled to room temperature; then diluted with water (40 mL) (exothermic!), and extracted with hexane (4 x 40 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuum to give 1.19 g (76%) of the cyclopentanone **7** in pure enough form to be used directly in the next step. **IR** (film): ν = 2960, 2920, 2850, 1730, 1450, 1420, 1380, 1160, 830 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 1.15-2.38 (m, 13H), 1.58 (s, 3H), 1.68 (d, J = 1.2 Hz, 3H), 5.04-5.16 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, APT): δ = 221.2 (C), 131.2 (C), 124.0 (CH), 48.8 (CH), 37.8 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.7 (CH_2), 27.5 (CH_2) 25.4 (CH_3), 20.4 (CH_2), 17.3 (CH_3). **MS** (70 eV): m/z (%) = 180 ($M^{+\bullet}$, 81), 97 (57), 84 (100), 69 (51), 55 (46).

*Cyclopentanol **12***

To a 300 mL flask containing dry $MgCl_2$ (8.1 g, 86 mmol) under argon was added THF (65 mL) followed by small pieces of freshly cut potassium (4.4 g, 115 mmol). The heterogeneous mixture was stirred under a gentle reflux until a dark suspension is formed. Abrupt heating should be avoided at this stage since it may lead to intense foam formation resulting in projection of the reaction medium. After 2 h the heating bath was removed and the resulting suspension was stirred at room temperature for 0.5 h. Allyl bromide (2.5 mL, 29 mmol) was then added in such a rate to avoid the reflux of THF. After an additional 0.5 h the reaction mixture was cooled to -10 °C. A solution of **7** (1.2 g, 7.1 mmol) in THF (12 mL) was added over 1 h with the aid of a syringe-pump. After 0.5 h the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (~30 mL). The cooling bath was removed and upon warming to room temperature a 5% aqueous HCl solution was added until the pH = 8. The mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic phase was washed with brine (80 mL), dried (Na_2SO_4) and concentrated in vacuum. Flash-chromatography of the residue (5.0 x 9.0 cm, EtOAc/Hexane 5%) afforded 1.2 g (77%) of the tertiary alcohol **12** as a colorless oil in a 3:1 diastereomeric ratio. **IR** (film): ν = 3460, 3080, 2920, 2860, 1640, 1445, 1350, 1080, 990, 910 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 1.15-2.08 (m, 14H), 1.60 (s, 3H), 1.68 (s, 3H), 2.08-2.23 (dd, J=13.6 Hz and 7.1 Hz, 1H), 2.32-2.47 (dd, J = 13.6 Hz and J= 7.7 Hz, 1H), 5.04-5.21 (m, 3H), 5.76-6.02 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ = 17.5 (CH_3), 20.9 (CH_2), 25.6 (CH_3), 28.2 (CH_2), 28.8 (CH_2), 29.9 (CH), 38.8 (CH_2), 44.0 (CH_2), 47.8 (CH), 118.0 (CH_2), 124.6 (CH), 131.2 (C), 134.4 (CH). **MS** (70 eV): m/z (%) = 204 (19), 181 (4), 163 (34), 125 (2), 97 (28), 82 (100), 69 (47).

*MEM-ether **13***

To a solution of the alcohol **12** (473 mg, 2.1 mmol) and DMAP (26 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) was added diisopropylethyl amine (1.2 mL, 6.3 mmol) dropwise, followed by addition of MEM-Cl (796 mg, 6.3 mmol). The mixture was stirred at room temperature during 14 h. It was

then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NH_4Cl, 5% aqueous $NaHCO_3$ and brine (10 mL each). The organic phase was dried (Na_2SO_4) and concentrated in vacuum. Flash-chromatography of the residue (2.0 x 10 cm, hexane-EtOAc/hexane 5%) afforded 607 mg (92%) of the MEM-ether **13** as a pale yellow oil. **IR** (film): ν = 3070, 2960, 2850, 2820, 1640, 1450, 1360, 1340, 1200, 1160, 1100, 1080, 920, 845 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 1.10-2.20 (m, 13 H), 1.62 (s, 3 H), 1.70 (s, 3 H), 2.25-2.55 (ddd, J=7.5 Hz, 7.6 Hz, and 13.8 Hz, 2 H), 3.38 (s, 3 H), 3.50-3.75 (m, 4 H), 4.72-4.85 (m, 2H), 4.95-5.20 (m, 2 H), 5.65-6.02 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, DEPT): δ = 17.4 (CH_3), 20.6 (CH_2), 25.4 (CH_3), 27.7 (CH_2), 28.3 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 33.1 (CH_2), 40.2 (CH_2), 47.1 (CH), 58.7 (CH_3), 66.6 (CH_2), 71.6 (CH_2), 87.2 (C), 90.0 (CH_2), 117.2 (CH_2), 124.7 (CH), 131.0 (C), 134.4 (CH). **MS** (70 eV): m/z (%) = 234 (3), 204 (17), 193 (16), 163 (6), 89 (86), 82 (64), 69 (26), 59 (100).

*TBS-ether **14***

To a cold (0 °C) solution of the alcohol **12** (222 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added triethyl amine (270 μL, 2 mmol) followed by *t*-butyldimethylsilyl triflate (340 μL, 1.5 mmol). After 0.5 h the cooling bath was removed and the mixture was stirred at room temperature for an additional hour. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (3.0 mL). The mixture was diluted with CH_2Cl_2 (5.0 mL) and washed with saturated aqueous NH_4Cl and brine (5 mL each). The organic phase was dried (Na_2SO_4) and concentrated in vacuum. Flash-chromatography (1.0 x 5.0 cm, hexane) afforded 309 mg (92%) of the TBS-ether **14** as a colorless oil. **IR** (film): ν = 3080, 2960, 2930, 2860, 1645, 1475, 1465, 1390, 1380, 1360, 1260, 1060, 915, 840, 775 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 0.08 (s, 6H), 0.88 (s, 9H), 1.00-2.30 (m, 12H), 1.58 (s, 3H), 1.68 (s, 3H), 2.36 (d, J = 7.3 Hz, 1H), 4.97-5.19 (m, 3H), 5.64-6.02 (m, 3H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, APT): δ = -2.5 (CH_3), -2.0 (CH_3), 17.5 (CH_3), 20.0 (C), 20.9, (CH_2), 25.8 (3 CH_3), 28.1 (CH_2), 28.3 (CH_2), 28.6 (CH_2), 29.6 (CH_3), 29.7 (CH_2), 37.4 (CH_2), 43.3 (CH_2), 46.9 (CH), 84.6 (C), 117.1 (CH_2), 124.9 (CH), 131.9 (C), 134.9 (CH). **MS** (70 eV): m/z (%) = 336 ($M^{+\bullet}$, 1), 321 (2), 295 (44), 280 (17), 279 (69), 267 (5), 204 (3), 180 (2), 163 (26), 147 (55), 74 (94), 73 (100).

*General procedure for the ozonolysis of **13** and **14***

A 0.25 M solution of the protected diene in CH_2Cl_2 at -78 °C was treated with a diluted stream of ozone in oxygen. When the solution turned light blue, it was flushed with nitrogen until the blue color disappeared. The cooling bath was removed and the reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 (10 mL) and hydrogenated for 4 h at 60 psi over 10% palladium on carbon (15% by weight). The reaction mixture was filtered through Celite, and the solvent removed in vacuum to give the corresponding dialdehyde (93-97% yield), which was shown to be homogeneous by TLC.

*Spectroscopic data for **15***

IR (film): ν = 2940, 2880, 2710, 1730, 1460, 1130, 1080, 1040, 850 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 1.10-2.25 (m, 3 H), 2.55-2.69 (dd, J = 15.4 Hz, 2.4 Hz, 1 H), 2.70-2.82 9dd, J = 15.3 Hz, 3.1 Hz, 1 H), 3.36 (s, 3 H), 3.48-3.72 (m, 4 H), 4.78 (AB d, J=19 Hz, 2 H), 9.70-9.86 (m, 2 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, DEPT): δ = 202.5 (CH), 201.6 (CH), 90.4 (CH_2), 85.1 (C), 71.5 , 67.0, 58.8, 50.3, 49.4, 47.2, 43.9, 34.4, 29.1, 27.8, 20.8. **MS** (70 eV): m/z (%) = 237 (2), 183 (2), 13 (4), 149 (23), 109 (8).

*Spectroscopic data for **16***

IR (film): ν = 2960, 2930, 2860, 2710, 1720, 1480, 1465, 1390, 1365, 1260, 1060, 1010, 840, 760 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 0.10 (s, 6 H), 0.85 (s, 9 H), 1.25-2.50 (m, 13 H), 2.64 (d, J = 3 Hz, 2 H), 9.76 (dd, J= 3.4 Hz, 3.2 Hz, 1 H), 9.80 (t, J= 3 Hz, 1 H), 9.89 (dd, J = 3.4 Hz, 3.5 Hz, 1 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, DEPT): δ = -2.3 (CH_3), -2.7 (CH_3), 18.2 (C), 20.8 (CH_2), 25.6 (3 CH_3), 28.3 (CH_2), 29.2 (CH_2), 34.1 (CH_2), 38.9 (CH_2), 43.9 (CH_2), 49.2 (CH), 52.9 (CH_2), 80.6 (C), 201.8 (CH), 202.5 (CH), 204.0 (CH). **MS** (70 eV): m/z (%) = 255 (21), 227 (5), 211 (28), 197 (2), 189 (18), 147 (56), 119 (14), 103 (18), 75 (100).

*Bicyclo[6.3.0]undecene **17***

(i) Preparation of C_8K[11b]

A flask containing powdered graphite (4.9 g, 411,3 mmol) and freshly cut potassium (2.0 g, 51 mmol) was immersed in a pre-heated oil bath at 140 °C and stirred vigorously under a stream of argon for 0.5 h. A finely powdered golden solid resulted, which was cooled to room temperature under dry argon.

(ii) Preparation of low-valent titanium

Into a glovebag under dry argon were combined $TiCl_3$ (2.6 g, 17 mmol) and the freshly prepared C_8K. The flask was equipped with a reflux condenser. The apparatus was removed from the glovebag and DME (145 mL) was added. The mixture was stirred under reflux with a stream of dry argon for 2 h. The resulting black suspension was cooled to room temperature.

(iii) Reductive coupling

A solution of the dialdehyde **15** (300 mg, 1 mmol) in DME (8.0 mL) was placed in a gas-tight syringe (10 mL ca-

pacity) and added at room temperature to the suspension of the low valent titanium over a 40 h period with the aid of a syringe-pump. A slight positive pressure of pure and dry Ar was kept throughout the addition. After complete addition of the dialdehyde **15** the mixture was stirred for an additional 6 h at room temperature, followed by 5 h under reflux. The reaction was quenched by the addition of MeOH (2 mL), and cooled to room temperature. The mixture was then filtered on Florisil® (3 x 8 cm) under nitrogen. The column was washed with more DME (80 mL) and EtOAc (150 mL). The combined filtrate was then concentrated in vacuum and flash-chromatographed (1.5 x 10 cm column; slurry of silica in hexane with 1% of triethyl amine; eluant gradient from hexane to EtOAc/hexane 5%-all the eluant containing 1% of triethyl amine) to provide 26.6 mg (10%) of the bicyclo[6.3.0]undecene **17**. **IR** (film): ν = 3020, 2920, 2860, 2810, 1460, 1470, 1200, 1100, 1040, 850, 770 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 0.80-2.46 (m, 1H), 2.48-2.62 (dd, J= 14.0 Hz, 7.4 Hz, 1 H), 3.40 (s, 3 H), 3.52-3.85 (m, 4 H), 4.75-4.95 (ABd, J= 22.0 Hz, 2 H), 5.53 -5.84 (m, 2 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz, APT): δ = 19.8 (CH_2), 23.1 (CH_2), 25.2 (CH_2), 26.9 (CH_2), 32.6 (CH_2), 32.8 (CH_2), 35.6 (CH_2), 48.4 (CH), 58.9 (CH_3), 67.0 (CH_2), 87.2 (C), 90.0 (CH_2), 127.1 (CH), 131.5 (CH).

MS (70 eV, expanded between m/z 140-270): m/z (%) = 254 (M^+, 6), 225 (3), 203 (2), 198 (48), 178 (72), 149 (100). **MS** (70 eV): m/z (%) = 198 (4), 178 (6), 149 (8), 89 (87), 59 (100).

Results and Discussion

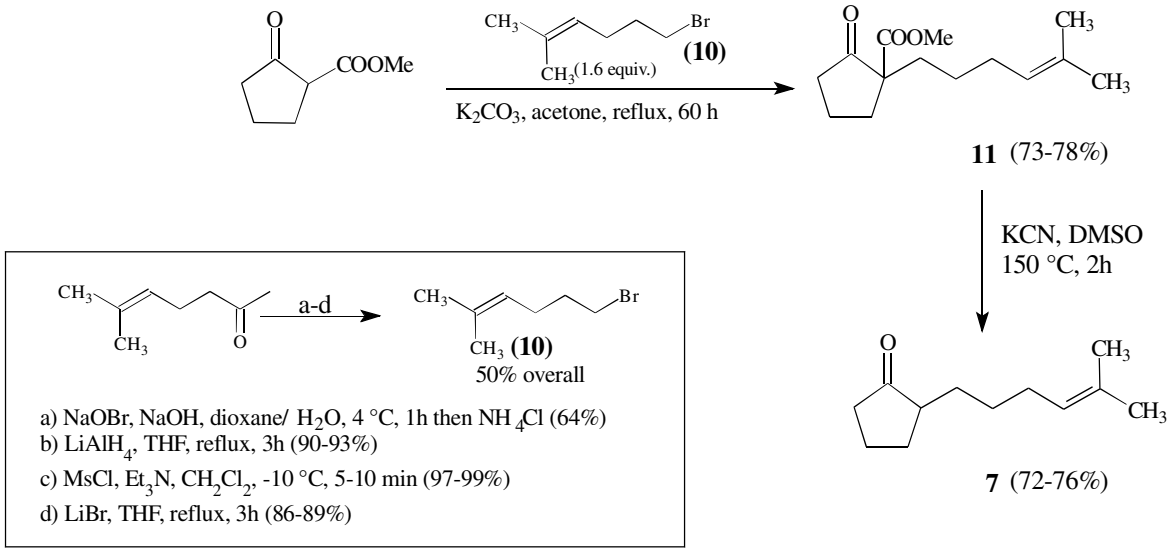
Synthesis of the dialdehyde precursor

A rather straightforward route was devised to prepare the dialdehyde intermediate **8** from 2-carbomethoxy-cyclopentanone as starting material (Schemes 3 and 4).

The bromide **10** was prepared in good overall yield from the commercially available 6-methyl-5-hepten-2-one in four steps as follows (frame inset in Scheme 3): i) bromoform oxidation[13] of 6-methyl-5-hepten-2-one to furnish the corresponding carboxylic acid (NaOBr, NaOH, dioxane/H_2O, 4 °C, 1 h, 64% yield); ii) reduction of the carboxylic acid to the primary alcohol ($LiAlH_4$, THF, reflux, 3 h, 90-93% yield); iii) formation of the corresponding mesylate[14] (MsCl, Et_3N, CH_2Cl_2, -10 °C, 5-10 min, 97-99% yield), and iv) conversion of the mesylate into the primary bromide **10** (LiBr, THF, reflux, 3 h, 86-89% yield). The overall yield for bromide **10** after these four steps was usually very good, ranging from 48% to 52% for the purified product.

Once 6-bromo-2-methyl-2-hexene was available, we turned our attention to the preparation of the 2-(5-methyl-4-hexenyl)-cyclopentanone **7**. As illustrated in Scheme 3, compound **7** was efficiently prepared by a sequence of two transformations. Alkylation of 2-carbomethoxy-cyclopentanone with unsaturated bromide **10** in the presence of K_2CO_3 as base[15] yielded the alkenyl-keto-ester **11** in 73-78%, after distillation. Surprisingly, attempted decarbomethoxylation using the standard Krapcho conditions (NaCl, DMSO, reflux)[16] did not afford the desired elimination. After some experimentation, decarbomethoxylation of **11** was finally achieved using KCN in DMSO (150 °C, 2 h)[17] to afford the expected cyclopentanone **7** in 72-76% yield.

We next turned our attention to the stereoselective installation of an allylic fragment at C-1, which after ozonolysis should produce the dicarbonyl essential for the reductive coupling. Addition of the allylic moiety was initially planned as an addition of an allylic Grignard re-



Scheme 3. Synthesis of the unsaturated cyclopentanone **7** from 2-carbomethoxy-cyclopentanone.

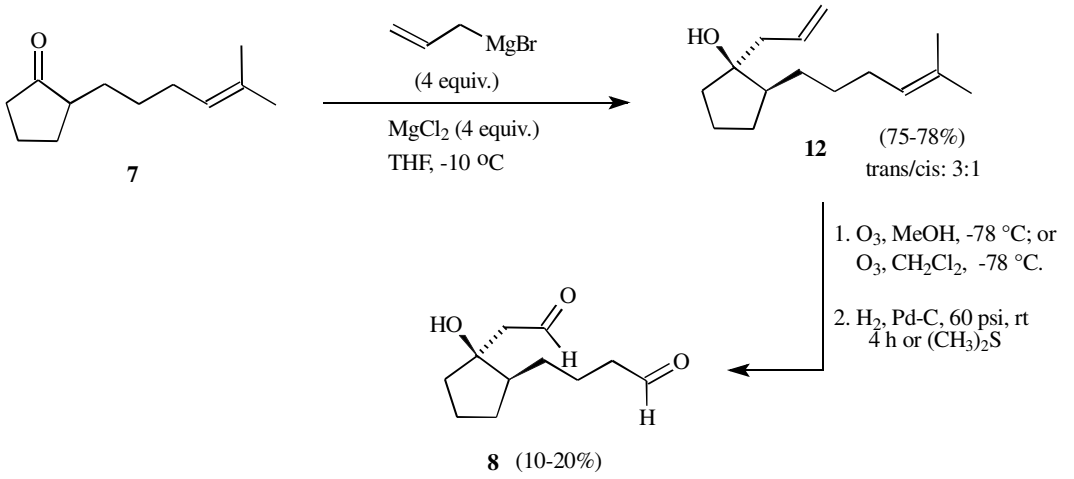
agent[18]. The *trans* stereochemistry was anticipated based on the 1,2 interaction caused by the side chain during nucleophilic attack of the Grignard reagent on the carbonyl[19].

Contrary to our initial expectations, addition of allylmagnesium bromide to cyclopentanone **7** resulted in a small conversion of the starting ketone. The expected adduct, diene-alcohol **12** was isolated from the reaction medium in low yield. Moreover, the stereoselectivity of addition was only moderate ranging from a *trans:cis* ratio of 2:1 (0 °C) to 3:1 (-10 °C) by GC analysis. The first attempts to perform this allylation step led mainly to the recovery of the starting cyclopentanone **7**, even in the presence of a large excess of allylmagnesium bromide. We reasoned that a magnesium enolate was formed during the reaction, thus preventing nucleophilic addition of the Grignard reagent to the carbonyl group.

The propensity of cyclopentanones to enolize in the presence of Grignard reagents was recognized earlier by Paquette[20]. To circumvent this problem a systematic investigation of the Grignard reaction was undertaken. The use of additives such as $CeCl_3$, $MgCl_2$ and changes in the stoichiometry of the reaction were exhaustively investigated based on the work of Paquette and Imamoto[20,21]. After much experimentation, the best conditions found to carry out nucleophilic addition of allylmagnesium bromide required four equivalents of the Grignard reagent and four equivalents of $MgCl_2$ as additives. Also, the magnesium metal had to be generated immediately before use by reduction of $MgCl_2$ with potassium metal (Rieke's magnesium) [22]. Thus, the optimum stoichiometry for conversion of cyclopentanone 7 into diene-alcohol **12** was determined as 1:4:4 ($7:CH_2{=}CHCH_2MgBr:MgCl_2$). Under these conditions cyclopentanone **7** was totally converted in the reaction medium to generate a 3:1 mixture (as determined by capillary GC) of diastereomeric tertiary diene-alcohols **12** isolated in 75-78% yield (Scheme 4). The stereochemical assignment of the *trans*-diene-alcohol as the major product was based on previous precedents in the literature[19] and on the analysis of the ^{13}C-NMR spectra (SFORD and DEPT). The *trans*-diene CH showed a signal at 48 ppm (γ-*syn*-effect) when compared to the *cis*-diene CH at 50 ppm (γ-*anti*-effect) [23].

Diastereomeric diene-alcohols **12** were not separable by flash chromatography and were used as a mixture throughout this model study (for simplicity only the major diastereomer, the *trans*, is shown in the synthetic schemes). Ozonolysis of diene **12** was performed under several different reaction conditions (Scheme 4): O_3 in MeOH or O_3 in CH_2Cl_2 and worked-up employing reductive conditions (Me_2S or H_2, Pd/C). On all occasions only small amounts (10-20% yield) of dialdehyde **8** were obtained from the reaction medium as an unstable oil. In view of the low yields and instability of dialdehyde **8**, the diene-alcohol **12** was protected in the expectation of obtaining a better yield of the corresponding dialdehyde.

Protection of tertiary alcohols is not an easy task in chemical synthesis. For this reason, protection of diene-alcohol **12** was executed using protocols based on solid literature precedents for this type of transformation. Two such protocols employ MEMCl and TBDMSOTf to form the corresponding ethers from an alcohol[24]. As expected, protection of the alcohol **12** went smoothly in both cases affording the tertiary MEM-ether **13** or silyl ethers **14** as stable compounds in high yields (Scheme 5). The protected dienes were once again submitted to ozonolysis under the conditions detailed in the experimental section. To our satisfaction dialdehydes **15** and **16** could be isolated in high yields from the reaction mixture (93-97%). These aldehydes could be stored at 4 °C, under nitrogen, for several days. However, they were shown to be unstable to silica-gel column chromatography. Thus, dialdehydes **15** and **16** were always prepared prior to use in the reductive coupling with low-valent titanium.



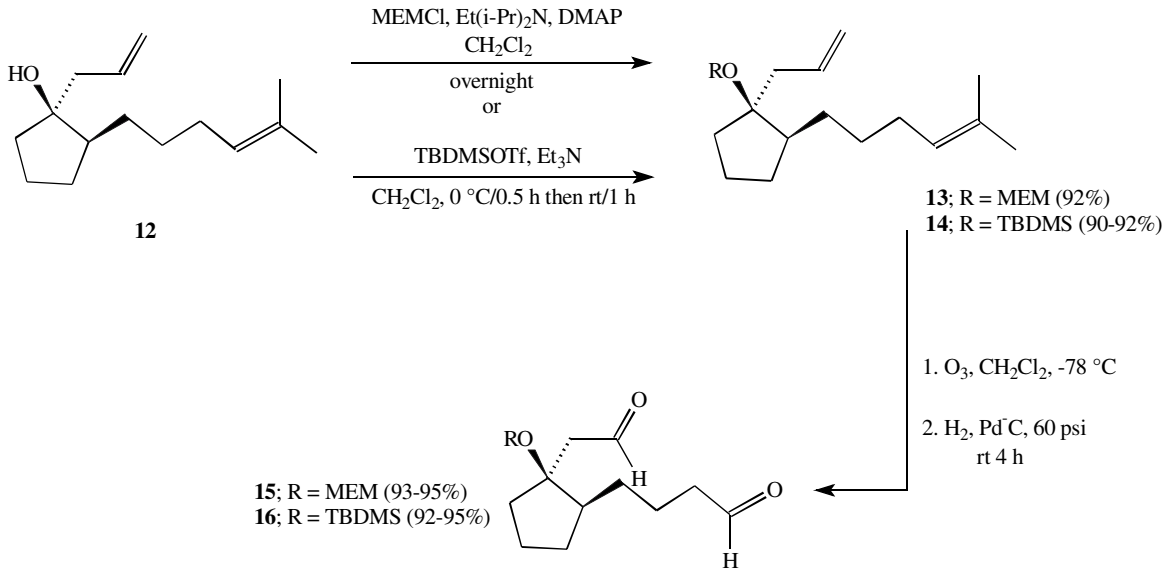
Scheme 4. Synthesis of β-hydroxy-dialdehyde **8**.

The intramolecular reductive coupling promoted by low-valent Titanium to produce the Bicyclo[6.3.0] undecene skeleton

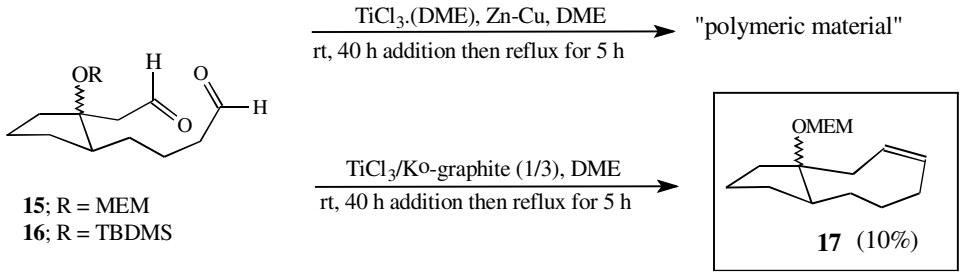
With a reliable route to the dialdehydes **15** and **16** on hand, we began to evaluate the key step for the construction of the bicyclo[6.3.0]undecene system. Initial attempts employed the traditional McMurry conditions to effect coupling, low-valent titanium being generated by reducing a $TiCl_3(DME)_{1.5}$ complex with Zn-Cu alloy under refluxing DME[25]. In our case, these conditions led invariably to complex mixtures of products. ^{1}H-NMR spectra of the crude mixtures displayed a large peak between 1 and 2 ppm, without any evidence of olefinic hydrogens. TLC of the reaction mixture displayed a complex pattern indicating the presence of a large number of products. Some modifications of the reaction conditions were examined (time of addition of substrate and temperature of reaction) with disappointing results. Aiming to prepare the intermediate pinacol, which could be later converted into the desired cyclooctene, carbonyl coupling of **15** and **16** was carried out using $TiCl_3$/Zn-Cu at room temperature[26]. These experiments resulted in complex mixtures, and no glycols could be detected by IR or ^{1}H-NMR spectroscopy. Interestingly, TLC of these reactions was very similar to that obtained for the carbonyl coupling of **15** and **16** performed under reflux conditions. Moreover, varying the time of addition of dialdehyde **15** or **16** to the Ti(0) slurry from the usual 40 h (as indicated in the literature) to 8 h (shorter reaction time), 60 h or 72 h (longer reaction times) did not significantly change the reaction outcome; in all instances a complex mixture resulted as indicated by the ^{1}H-NMR or TLC of the crude mixtures. Presumably, the $ZnCl_2$ formed during reduction of $TiCl_3(DME)_{1.5}$ complex (17 to 20 equivalents employed in each reaction) led to decomposition of the dialdehydes **15** /**16**.

Thus, we then decided to use reductive agents which would allow the reaction to be run under neutral conditions. For this purpose, C_8K (potassium on graphite) was chosen as the reducing agent to generate the low-valent titanium in the reaction medium[27].

The choice of C_8K as the reducing agent proved correct and reductive coupling was finally achieved (albeit in low yield) when the MEM-protected dialdehyde **15** was subjected to a slurry of $TiCl_3$-C_8K in DME under high dilution conditions for 40 h at room temperature (Scheme 6) to yield the bicyclo[6.3.0]undecene **17**. Although the yields obtained for **17** were low (~10%) we believe the milder reaction conditions employed in this protocol were instrumental in effecting carbonyl coupling. The use of C_8K to convert Ti(III) into



Scheme 5. Synthesis of the protected β-hydroxy-aldehyde **15** and **16**.



Scheme 6. Reductive coupling promoted by low-valent titanium of **15** and **16**.

low-valent titanium did not produce any Lewis acid in the medium (McMurry's protocol produced considerable amounts of $ZnCl_2$), and so no deleterious effects were caused to either the starting dialdehyde or the final unsaturated bicyclic ether product. The remaining material, after isolation of the bicyclic system, seemed to be polymeric by ^{1}H-NMR analysis. Attempts to improve the yields for the reductive carbonyl coupling step were fruitless.

TBDMS-protected dialdehyde 16 failed to provide any of the cyclized product even under the $TiCl_3$-C_8K protocol. Complex mixtures were obtained in all experiments carried out[28].

Conclusions

The bicyclo[6.3.0]undecene system found in a number of cyclooctanoid natural products was obtained through an intramolecular coupling of carbonyls promoted by low valent titanium from dialdehyde intermediate **15** containing a protected β-hydroxy carbonyl group. The troublesome nucleophilic addition of an allyl group to the readily enolizable cyclopentanone **7** was achieved in good yields (75-78%) by the use of an excess of the Grignard reagent in the presence of the additive $MgCl_2$, and these conditions might prove useful for other enolizable ketones. The key dialdehydes **15** and **16** for the coupling studies were prepared in a convenient and concise manner from 2-carbomethoxy-cyclopentanone in 5 steps, in an overall yield of approximately 40%.

Despite the limited success, to the best of our knowledge this is the first time a cyclooctenoid ring has been obtained by the intramolecular coupling of a protected β-hydroxy-aldehyde group with a non-conjugated aldehyde group using low-valent titanium. After completion of this study we initiated an approach to the total synthesis of the cyclooctanoid dactylol as planned in Scheme 1. Hopefully, a more extensive investigation into Clive's conditions to effect carbonyl coupling or the application of the more recent olefin metathesis approaches developed by Grubbs[29] and Nugent[30] could result in a better yield of the cyclooctenoid system, thus making it a more viable transformation for our purposes. Further results concerning these studies will be published in due course.

Acknowledgments

We thank Conselho Nacional de Pesquisas (CNPq and PADCT/CNPq), International Foundation for Science from Sweden (IFS), Fundação de Amparo a Pesquisa do Rio de Janeiro (FAPERJ), Universidade Federal do Rio de Janeiro (CEPG/UFRJ) and the Instituto de Química da Universidade Estadual de Campinas, São Paulo, for financial support of this project. The authors also thank CNPq for fellowships.

References and Notes

1. For an excellent review of the various methodologies now available for the preparation of an eight-membered ring see: Petasis, N.A.; Patane, M.A. *Tetrahedron* **1992**, *48*, 5757. For an older review emphasing more traditional methods consult: Craig, L.E. *Chem. Rev.* **1951**, *49*, 103.
2. Isolation: Schmitz; F.J.; Hollembeak; K.H.; Vanderah J.D. *Tetrahedron* **1978**, *34*, 2719. For its total synthesis see: a) Feldman, K.S.; Wu, M-J.; Rotella, D.P. *J. Am. Chem. Soc.* **1990**, *112*, 8490. b) Molander, G.A.; Eastwood, P.R. *J. Org. Chem.* **1995**, *60*, 4559.
3. Isolation: San Feliciano, A.; Barrero, A.F.; Medarde, M.; de Corral, J.M.M.; Aramburu, A.; Perales, A.; Fayo, J. *Tetrahedron Lett.* **1985**, *26*, 2369. Synthesis: Wender, P.A.; Ihle, N.C.; Correia, C.R.D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.
4. a) Kavanagh, F.; Hervey, A.; Robbins, W.J. *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 570. b) Kavanagh, F.; Hervey, A.; Robbins, W.J. *Proc. Natl. Acad. Sci. USA* **1952**, *38*, 555.
5. Barrow, K.D.; Barton, D.H.R.; Chain, E.; Ohnsorge, U.F.W.; Sharma, R.P. *J. Chem. Soc. Perkin Trans. I*, **1973**, 1590.
6. Hensens, O.D.; Willianson, J.M.; Lotti, V.J.; Chang, R.S.L.; Goetz, M.A. *J. Org. Chem.* 1991, *56*, 3399.
7. Kupchan, S.M.; Britton, R.W.; Ziegler, M.F.; Gilmore, C.J.; Restivo, R.J.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 1335.
8. a) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P.J. *J. Am. Chem. Soc.* **1977**, *99*, 2591; b) Winnik, M.A. *Chem. Rev.* **1981**, *81*, 491.
9. For reviews see: (a) McMurry, J.E. *Chem. Rev.* 1989, *89*, 1513. (b) Lenoir, D. *Synthesis* **1989**, 883.
10. See also ref. 1 for specific examples of previous preparations of eight-membered rings using the reductive carbonyl coupling process promoted by low-valent titanium. Recently the McMurry coupling process was used by Nicolaou and co-workers in one of the first total syntheses of the antitumor diterpene taxol: Nicolaou, K.C.; Yang, Z.; Liu, J.J.; Ueno, H.; Nantermet, P.G.; Guy, R.K.; Clalborne, C.F.; Renauld, J.; Couladouros, E.A.; Paulvannan, K.; Sorensen, E.J. *Nature* **1994**, *367*, 630. For an excellent account on the chemistry and biology of taxol see: Nicolaou, K.C.; Dai, W.-M.; Guy, R.K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.
11. a) Zn-Cu: Simmons, H.E; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* 1973, *20*, 1. b) C_8K: Boldrini, G.P.; Savoia, D.; Tagliavini, E; Trombini C.; Umani-Ronchi, A.U. *J. Organomet. Chem.* 1985, *280*, 307. c) Braga, D.; Ripamonti, A.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc. Chem. Commun.* **1978**, *928*.
12. Still, W.C.; Mitra, M. *J. Org. Chem.* **1978**, *43*, 2923.

13. Staunton, J.; Eisenbraun, E.J. *Org. Synth., Coll. Vol. V*, **1973**, 8 .
14. Crossland, R.K.; Servis, K.L. *J. Org. Chem.* **1970**, *35*, 3195.
15. Barco, A.; Benetti, S.; Pollini, G.P. *Synthesis*, **1973**, 316.
16. Krapcho, A.P.; Lovely, A.J. *Tetrahedron Lett.* **1973**, *14*, 957.
17. For variations in Krapcho's conditions (used originally to effect decarbethoxylation) consult: a) Muller, P.; Siegfried, B. *Tetrahedron Lett*. **1973**, *14*, 3565. b) Huang, B.-S.; Parish, E.V.; Miles, O.H. *J. Org. Chem.* **1974**, *39*, 2647. c) Miller, R.B.; Nash, R.D. *Tetrahedron* **1974**, *30*, 2961. d) Aneja, R.; Hallis, W.M.; Davies, A.P.; Eaton, G. *Tetrahedron Lett*. **1983**, *24*, 4641. e) Taber, D.F.; Amedio, J.C.; Gulino, F. *J. Org. Chem.* **1989**, *54*, 3474.
18. Bunele, W.H.; Rafferty, M.A.; Hodges, S.L. *J. Org. Chem*. **1987**, *52*, 1603.
19. For studies on the mechanism of Grignard addition to carbonyls see: Yamataka, J.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912. b) Walling, C. *J. Am. Chem. Soc*. **1988**, *110*, 6846. c) Ashby, E.C. *Pure Appl. Chem.* **1980**, *52*, 545. d) Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* **1975**, *75*, 521 and references cited therein.
20. Paquette, L.A.; Pegg, N.A.; Toops, D.; Maynard, G.D.; Roger, R.D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
21. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatagima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392.
22. Rieke, R.D.; Bales, S.E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. For other references on activation of magnesium for Grignard reactions consult: a) Lay, Y.-H. *Synthesis* **1981**, 585. b) Bonnemann, H.; Bogdanovic, B.; Brinkmann, R.; He, D.-W.; Spliethoff, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 728.
23. For application of γ-effects on stereochemical assignments using ^{13}C chemical shifts, see: Breitmaier, E. In *Structure Elucidation by NMR in Organic Chemistry. A Practical Guide;* John & Wiley Sons; Chichester, 1993, p 49-52.
24. TBDMSOTf: Corey, E.J.; Cho, H.; Rucker, C.; Hua, D.H. *Tetrahedron Lett*. **1981**, *22*, 3455. MEMCl: Williams, J.R.; Callahan, J.F. *J. Org. Chem.* **1980**, *45*, 4479.
25. McMurry, J.E.; Letcka, T.; Rico, J.G.; *J. Org. Chem.* **1989**, *54*, 3748. For more information regarding the mechanism of this reaction, see: Dams, R.; Malinowski, M.; Westdrop, I.; Giese, H.Y.; *J. Org. Chem.* **1982**, *47*, 248.
26. This approach was based on the results obtained by McMurry in which the reaction was carried out at room temperature to yield an intermediate pinacol that was then refluxed with low-valent titanium to form the corresponding olefin, see; McMurry, J.E.; Fleming, M.P.; Kess, K.L.; Krespi, L.R. *J. Org. Chem.* **1978**, *43*, 3255 and McMurry, J.E., Rico, J.G. *Tetrahedron Lett.* **1989**, *30*, 1169. For a review on pinacol formation, see: Robertson, G.M. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds; Pergamon: Oxford, 1991; Vol. 3, p 563.
27. For the use of C_8K in the preparation of active forms of metals see reference 11b. C_8K has been used previously by Clive to reduce Ti(III) to Ti(I) and effect an intramolecular carbonyl coupling during the total synthesis of compactin and mevinolin. For details consult: Clive, D.L.J.; Zhang, C.; Murthy, K.S.K.; Hayward, W.D.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 6447 and references therein. For other applications of C_8K see: Bergbreiter, D.E.; Killough, J.M. *J. Am. Chem. Soc.* **1978**, *100*, 2126.
28. A countless number of carefully planned reactions were carried out under the conditions described. The results obtained by us indicated the carbonyl coupling as a feasible transformation. However, much experimentation still remains to be done in order to find the right reaction conditions that would make the carbonyl coupling a more viable transformation.
29. a) Grubbs, R.H.; Miller, S.J.; Fu, G. *Acc. Chem. Res*. **1995**, *28*, 446. b) Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1993**, *115,* 9858. c) Grubbs, R.H.; Fu, G. *J. Am. Chem. Soc.* **1992**, *114*, 5426. d) Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
30. Nugent, W.A.; Feldman, J.; Calabrese, J.C. *J. Am. Chem. Soc.* **1995**, *117*, 8992.

* After completion of this manuscript an efficient total synthesis of dactylol was described by Alois Fürstner and Klaus Langemann (*J. Org. Chem.* **1996**, *61*, 8746) employing the olefin metathesis strategy suggested in our conclusions.

FAPESP helped in meeting the publication costs of this article