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Article

Preparation of (5*R*)-4,8-Dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one from (-)-Limonene oxide. A Novel Intermediate to the Synthesis of 4-5-5 Fused Tricarbocyclic Core Present in Terpenic Natural Products

Diego S. Pisoni[a], Daniel B. Silva[a], Rossana A. Schenato[b] and Marco A. Ceschi*[*,a]

[a] *Instituto de Química, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves, 9500, Campus do Vale, 91501-970 Porto Alegre - RS, Brazil*

[b] *Faculdade de Química, Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6681, 90619-900 Porto Alegre - RS, Brazil*

Este trabalho refere-se à síntese enantiosseletiva da dienona (5*R*)-4,8-dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one. Este intermediário, pode ser reconhecido como um bloco de construção versátil para a síntese de uma grande variedade de compostos com esqueleto biciclo[3.3.0]octano. A estratégia sintética empregada aqui faz uso da reatividade invertida de um precursor cianoidrina TMS-éter, como equivalente de ânion acila, para promover uma reação de alquilação intramolecular. A síntese formal do (-)-kelsoeno foi realizada pela preparação do intermediário avançado (1*R*,5*S*,8*R*)-4,8-dimethylbicyclo[3.3.0]oct-3-en-2-one, a partir da hidrogenação seletiva do composto intitulado (5*R*)-4,8-dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one.

This paper describes the conversion of the readily available (-)-limonene oxide to the new (5*R*)-4,8-dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one. This compound holds the prospect of serving as a useful chiral building block or intermediate to prepare a variety of compounds having a bicyclo[3.3.0]octane framework. The synthetic strategy made use of the umpolung reactivity of cyanohydrin TMS ether, as an acyl anion equivalent, in order to promote intramolecular alkylation. The formal synthesis of (-)-kelsoene was achieved by preparing a known advanced intermediate (1*R*,5*S*,8*R*)-4,8-dimethylbicyclo[3.3.0]oct-3-en-2-one via selective hydrogenation of the named compound (5*R*)-4,8-dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one.

Keywords: limonene oxide, bicyclo[3.3.0]octane, chiral, building block

Introduction

There is currently considerable interest in the synthesis of optically active bicyclo[3.3.0]octane containing one or more functional group(s) at suitable position(s) for synthetic purposes, as these compounds have been widely accepted as an efficient chiral building block or intermediate for preparing both natural and nonnatural biologically active compounds.[1] The tricyclo[6.2.0.0^{2,6}] decane framework **1**, constituted through the linear fusion of 4-5-5-membered carbocyclic rings, has been encountered only sporadically among natural products.[2] Among the very few known examples of terpenoid natural products based on this ring system are sulcatine G (**2**), from a *Basidiomycetes* fungus,[3,4] poduran (**3**), from the springtail *Podura aquatica*[5] and kelsoene **4**, from the marine sponge *Cymbastela hooperi*[6] as well as from the liverworts *Ptychanthus striatus*,[7] *Calypogeia muelleriana*[8] and *Tritomaria quinquedentata.*[9]

In 1999, Nabeta *et al*., on the basis of ^{1}H NMR experiments carried out on two diastereomeric substances derived from (+)-kelsoene, concluded that the natural product has the absolute configuration (-)-**4** (Figure 1).[10] However, in 2001, Schultz[11] and Mehta[12] independently demonstrated, on the basis of synthetic studies, that this conclusion was incorrect and that, in fact, the absolute configuration of natural (+)-kelsoene is as depicted in **4**. Starting from (*R*)-(+)-pulegone, Schultz proceeded with the synthesis of nonnatural (-)-kelsoene (**4**) and Mehta achieved the enantioselective synthesis of both natural (+)-**4** and nonnatural (-)-**4** kelsoene by lipase-catalyzed resolution of *endo*,*endo-cis*-bicyclo[3.3.0]octane-2,6-diol. In addition, (±)-kelsoene was constructed via a 15-step synthetic sequence starting from cyclopent-2-en-1-one and

* e-mail: mceschi@iq.ufrgs.br

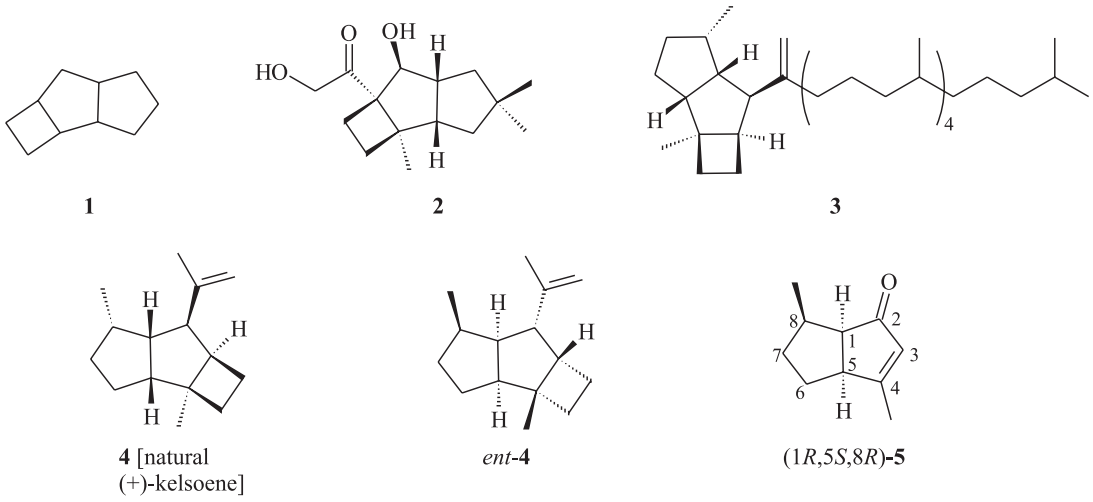
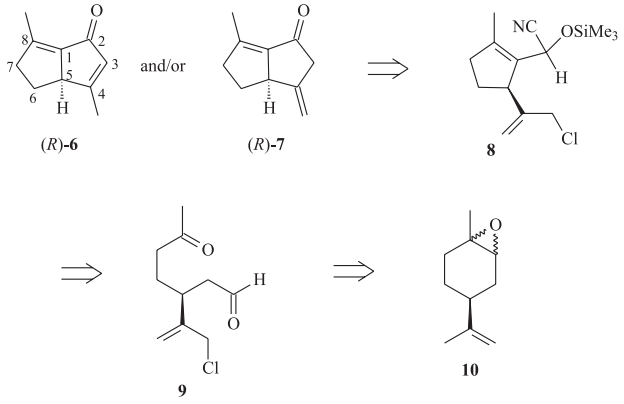


Figure 1. Natural and nonnatural products based on tricyclo[6.2.0.0^{2,6}]decane framework **1** and precursor **5**.

the bifunctional reagent lithium cyano(4-chlorobut-1-en-2-yl)cuprate by Piers.[13]

The three different strategies for the synthesis of kelsoene described so far employ the common precursor **5** in its racemic or enantiopure form at an early stage of the synthesis.

In this paper, we wish to describe the enantiospecific preparation of the new bicyclic α,β-unsaturated enone (-)-**6** from (-)-limonene oxide (**10**) (Scheme 1). We also studied the selective catalytic hydrogenations of (-)-**6** to access (-)-**5**, the intermediate for the synthesis of (-)-kelsoene (*ent*-**4**) and poduran (**3**).



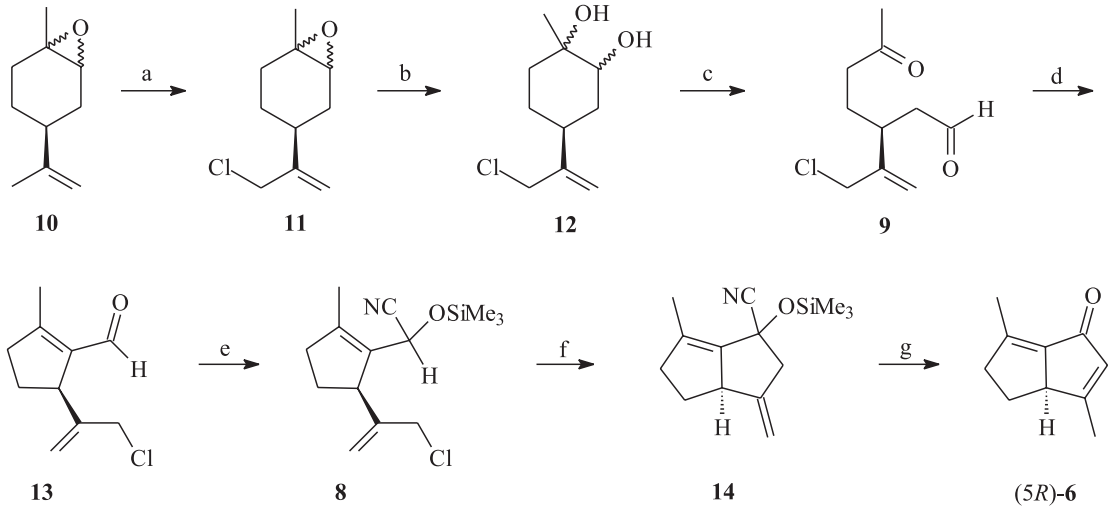
Scheme 1. Retrosynthetic analysis for (R)-**6** from (-)-limonene oxide.

From the retrosynthetic perspective, we envisioned that the pentalenone core **6** and/or **7** would be accessible from the pentacyclic cyanohydrin TMS ether **8**, by a Stork-Takahashi intramolecular alkylation, followed by decyanation.[14-16] The intermediate **8** in turn could be accessed from the acyclic keto aldehyde precursor **9** by aldol condensation and silyloxy nitrile conversion of the resulting cyclic aldehyde. The precursor **9** could be prepared from the commercially available (-)-limonene oxide (**10**), as reported in the literature.[17-20]

Results and Discussion

The synthesis of (-)-**6** started with the preparation of the enantiomerically pure keto aldehyde (-)-**9** from (-)-limonene oxide **10**, employing previously developed methodology.[18-20] (-)-Limonene epoxide **10** reacts cleanly with HOCl to afford 10-chlorolimonene oxide **11.**[18] Subsequent acid-catalyzed hydrolysis of epoxyde function to diol **12,** followed by oxidative cleavage with sodium metaperiodate, leads to the keto aldehyde (-)-**9** in 48% overall yield from (-)-**10**.[19,20]

Aldehyde **13** was obtained from (-)-**9** by aldol condensation with piperidine-acetic acid, in 44% yield.[20] The unstable conjugated aldehyde **13** thus obtained was cleanly converted to the cyanohydrin TMS ether **8** by addition of Me_3SiCN in the presence of catalytic amount of KCN/18-crown-6 complex. The intramolecular alkylation of cyanohydrin TMS ether **8** to **14** was immediately carried out without purification, based on Stork-Takahashi procedure.[14-16] In our case, we found higher yield performing the cyclization reaction at lower temperature and reduced excess of base. The crude product **14** was treated with tetra-*n*-butylammonium fluoride in aqueous THF at room temperature for 3 days to give only (-)-**6** with the endocyclic C3-C4 double bond, after chromatographic purification. Attempts to isolate thermodynamically less stable exocyclic olefin isomer **7** resulted in failure. When the decyanation of **14** was conducted at shorter reaction time and lower temperature,



a: HOCl, aq. CH_2Cl_2, rt, 1.5h; **b:** 1% H_2SO_4, 0 °C to rt, **c:** $NaIO_4$, THF/H_2O, 0 °C, 3 days (48% yield over three steps); **d:** piperidine, HOAc, benzene, reflux, 1h, 44%; **e:** Me_3SiCN, cat. KCN/18-crown-6 ether complex, 0 °C, 2h; **f:** $LiN(SiMe_3)_2$, THF, rt, 1.5h; **g:** *n*-$Bu_4N^+F^-$, 10% aqueous THF, rt, 3 days (75% based on three steps from starting aldehyde **13**).

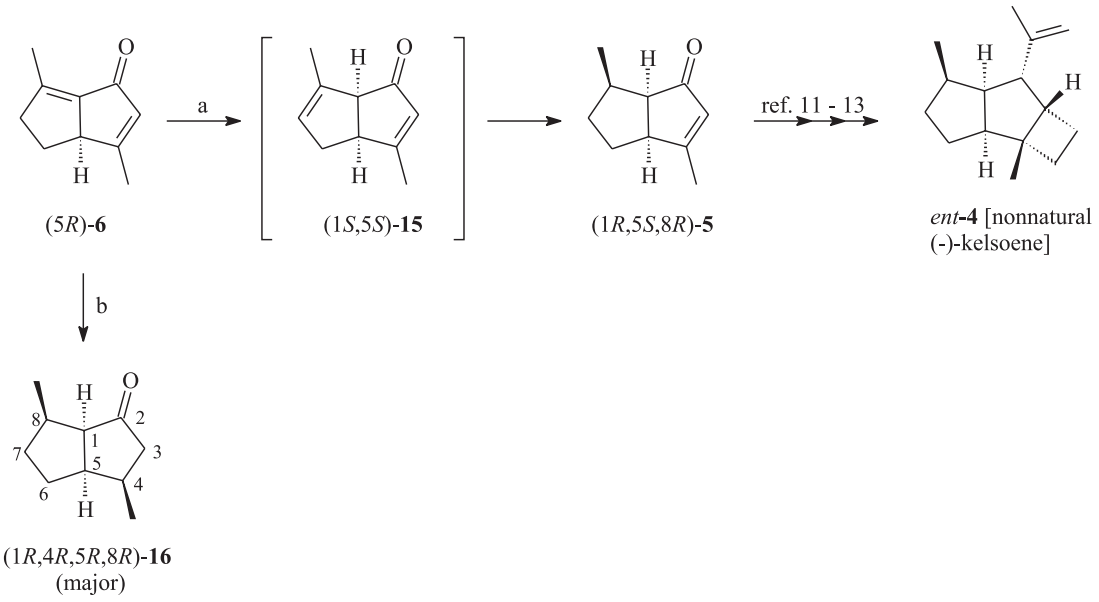
Scheme 2.

rapid isomerization took place, as observed by ^{1}H NMR spectroscopy.

Pentalenone (-)-**6** was them subjected to catalytic hydrogenation at 1 atm over 10% Pd/C in EtOH at 25 °C and the reaction course was examined by ^{1}H NMR spectroscopy and CG analysis. Running the hydrogenation reaction for 24 h, formation of **5** and **15** was observed in a ratio of approximately. 1.7:1. The rapid isomerization of **6** to **15** during the hydrogenation reaction is supported by ^{1}H NMR data comparisons between isolated **6** and the mixture containing **5** and **15**. The singlet olefinic signal H-3 in the mixture containing **5** and **15** appears at δ 5.81 and 5.68 ppm, respectively, while the corresponding resonance in **6** is at 5.88 ppm. In the ^{1}H NMR spectrum of **6**, the signals assigned to vinyl methyl hydrogens were observed at δ 2.08 (s, 3H) and 2.10 ppm (s, 3H). In the mixture of **5** and **15**, two vinyl methyl protons were observed at 2.01 and 2.04 ppm for each compound and a doublet observed at 1.02 ppm (6.8 Hz) is assigned to C-8 methyl hydrogens. After 35 h reaction, the conversion of **15** to **5** was essentially complete. At this stage, the reaction was quenched by filtration over celite to afford the crude product in 89% yield. Because of experimental difficulties, the volatile enone **5** was not purified. ^{1}H NMR spectroscopy and CG analysis of the crude product presents approximately 78% of **5**. The assignments of ^{1}H and ^{13}C in the NMR spectra of the crude product containing **5** are further supported by reported data described in the literature.[13] The addition of hydrogen to both (-)-**6** and **15** is favored by the convex upper face of the molecule; on this basis, the major hydrogenation product, which is the same in the two cases, is *endo* methyl enone **5**. In spite of this, the isomerization of the starting (-)-**6** to **15** observed in the hydrogenation reaction was not surprising in view of precedents in the literature, since it is well documented that the *cis* ring fusion stereochemistry in **15** is thermodynamically more stable than in precursor (-)-6, and a driving force of approximately 2.4 kcal/mol has been estimated for related *cis*-bicyclo[3.3.0]octan-2-ones.[21-23]

Running the hydrogenation reaction with the same catalyst at 810 kPa of hydrogen pressure in EtOH at 25 °C, for 24 h, gave a mixture of the saturated ketone **16** and a minor saturated product which was not separable by chromatography on silica gel. The structure of **16** was supported by the assignments of its ^{1}H and ^{13}C NMR data and comparison with those described in the literature[24] while the minor saturated component which was not fully characterized in this work is presumably formed by the addition of hydrogen from the more sterically encumbered face of (-)-**6**.

In summary, we have developed an efficient and stereoselective route toward dienone (-)-**6**, a versatile building block for the synthesis of natural and nonnatural chiral terpenoids bearing the bicyclo[3.3.0]octane framework. The key strategic feature is the intramolecular alkylation of cyanohydrin TMS ether **8** to **14**. In order to demonstrate the applicability of this new intermediate, we have performed the stereoselective hydrogenation of (-)-**6** to access (-)-**5,** which represents the formal total synthesis of sesquiterpene *ent*-kelsoene (**4**) and tetraterpene *ent*-



Scheme 3. *Reagents and conditions:* a: H_2 (101 kPa), 10% Pd/C, EtOH, rt, h, 90%; b H_2 (810 kPa), 10% Pd/C, EtOH, rt, 72 h, 90%.

poduran (**3**). Intermediate (-)-**6** was obtained in seven steps and 15.6% overall yield from (-)-limonene oxide (**10**). The scaffolding potential of this new building block is currently under study and will be reported in due course.

Experimental

Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. IR spectra were measured on a Mattson Galaxy Series FT-IR 3000 (model 3020). ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR-200. Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and *J* values are given in Hz. The products were analyzed by GC on a Shimadzu GC-17A Gas Chromatograph, equipped with a FID detector. GC parameters for achiral analysis: injector 230 °C; detector 300 °C; oven 80 °C for 5 min then 15 °C min^{-1} for 5 min until 300 °C; column pressure 20 kPa, column flow 6.3 mL min^{-1}; linear velocity 53.1 cm s^{-1}; total flow 138 mL min^{-1}; split ratio 1:20; column DB1 15 m × 0.53 mm (internal diameter). GC parameters for chiral analysis: injector 250 °C; detector 300 °C; oven 60 °C for 10 min then 1 °C min^{-1} until 220 °C; column pressure 100 kPa, column flow 1.1 mL min^{-1}; linear velocity 27.9 cm s^{-1}; total flow 41 mL min^{-1}; split ratio 1:27; column β-cyclodextrin 30 m × 0.25 mm (internal diameter). Optical rotations were measured in a Perkin-Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20 °C.

Purification by column chromatography was carried out on silica gel 60 (70-230 mesh). Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates with 0.2 mm of silica gel 60F-254.

*(5R)-5-chloroisopropenyl-2-methyl-1-[2-(trimethylsilyl)oxyacetonitril]-1-cyclopentene (**8**)*

To a mixture of 650 mg (3.52 mmol) of aldehyde **13**[20] and 0.62 mL (4.65 mmol) of trimethylsilyl cyanide (TMSCN) was added a catalytic amount of KCN (4.6 mg) and 18-crown-6-complex (18 mg) while stirring under nitrogen atmosphere at 0 °C. After 2 h, excess trimethylsilyl cyanide was removed *in vacuo* to give 1.02 g of the crude cyanohydrin TMS ether **8**, which was used in the next step without further purification. IR (film) ν_{max}/cm^{-1}: 3080, 2960, 2850, 2235, 1640, 1440, 1250 1090, 1060, 905, 870, 850, 750; ^{1}H NMR (200 MHz) δ 0.19 (s, 9H), 1.59 – 1.82 (m, 1H), 1.89 (s, 3H), 2.05 – 2.14 (m, 1H), 2.15 – 2.62 (m, 2H), 3.59 (bt, 1H), 3.98 – 4.19 (m, 2H), 5.05 (s, 1H), 5.09 (s, 1H), 5.27 (s, 1H); ^{13}C NMR (75 MHz) δ -0.45, 14.4, 30.0, 37.8, 47.2, 50.2, 57.6, 70.1, 116.0, 130.7, 142.7, 146.6 (for the major diastereomer).

*(5R)-4,8-dimethylbicyclo[3.3.0]oct-1(8),3-dien-2-one (**6**)*

A solution of LiN(SiMe$_3$) was prepared by adding 10.6 mL of 1mol L^{-1} BuLi in 2.60 mL (12.4 mmol) of HN(SiMe$_3$) dissolved in 60 mL of THF at 0 °C under nitrogen atmosphere. To this solution was added 1.02 g (3.52 mmol, based on the starting aldehyde **13**) of the crude cyanohydrin TMS ether **8**, in 49 mL of THF over 1 h at room temperature. The resultant mixture was stirred at the same temperature for 30 min and poured into a mixture of brine (100 mL) and *n*-hexane (78 mL) containing 50 g of ice. The organic layer was separated and extracted with *n*-hexane and ether

(5:1, 3 x 50 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent left an oil containing essentially the bicyclic cyanohydrin TMS ether **14**. Subsequently, the resulting oil was dissolved in 43 mL of 10% aqueous Et_2O, and 3.3 mL of 1mol L^{-1} *n*-$Bu_4N^+F^-$ in THF was added to this mixture. The resulting mixture was stirred at room temperature for 3 days. After this time, water (10 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 540 mg of the crude product as a yellowish foam. Purification of the residue by chromatography afforded 391 mg (2.65 mmol, 75% based over three step from starting aldehyde **13**) of (-)-**6**.

*Data for **14***. IR (film) ν_{max}/cm^{-1}: 2960, 2920, 2850, 1700, 1670, 1450, 1320, 1250, 1170, 1110, 890, 850, 755; ^{1}H NMR (200 MHz) δ 0.16 (s, 3H), 0.28 (s, 6H), 1.26 (s, 3H), 1.83 (d, *J* 0.98 Hz, 2H), 2.12 – 2.48 (m, 1H), 2.60 – 2.79 (m, 1H), 2.87 (dq, *J* 2.2 and 16.5 Hz, 1H), 3.32 (d, *J* 16.5 Hz, 1H), 3.62 (bt, 1H), 4.83 (d, *J* 2.4 Hz, 1H), 4.89 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (50 MHz) δ 1.1, 13.6, 29.7, 30.2, 42.3, 52.8, 53.0, 107.4, 120.7, 135.7, 139.5, 147.1 (signals reported for two diastereomers).

*Data for **6***. $[\alpha]_D$ -199 (c 1.19, CH_2Cl_2); mp = 50 – 52 °C; IR (film) ν_{max}/cm^{-1}: 3440, 3340, 2960, 2930, 2850, 1740, 1690, 1650, 1590, 1430, 1370, 1290, 1190, 1030, 970, 870, 670, 570; ^{1}H NMR (200 MHz) δ 1.58 (dt, 1H, *J* 8.4 and 11.5 Hz), 2.08 (s, 3H) 2.10 (s, 3H), 2.19 (dt, 1H, *J* 6.6 and 11.5 Hz), 2.42 (dd, 1H, *J* 8.4 and 16.9 Hz), 2.80 – 3.06 (m, 1H), 3.55 – 3.75 (m, 1H) and 5.88 (s, 1H); ^{13}C NMR (50 MHz) δ 15.0, 16.9, 29.3, 42.8, 55.5, 133.7, 141.0, 145.7, 171.7, 191.7.

*(1R,5S,8R)-4,8-dimethylbicyclo[3.3.0]oct-3-en-2-one (**5**)*

A mixture of **6** (100 mg, 0.67 mmol) and 10% palladium on carbon (10 mg) in ethanol (20 mL) was stirred under hydrogen (101 kPa) for 35 h. The reaction was carefully monitored by CG analysis and ^{1}H NMR spectroscopy and stopped at *ca.* 78% conversion to the ketone **5.** The crude product was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure (20 mmHg) at 38 °C to give 90 mg (89%) of the crude **5** as colorless oil.

$[\alpha]_D$ -104 (c 1.50 , CH_2Cl_2); IR (film) ν_{max}/cm^{-1}: 2957, 2872, 1699, 1622, 1456, 1379, 1273, 1190, 919, 882. ^{1}H NMR (200 MHz) δ 0.81 – 0.98 (m, 1H), 1.02 (d, *J* 6.8 Hz, 3H), 1.51 – 1.78 (m, 3H), 2.01 (s, 3H), 2.02 – 2.15 (m, 1H), 2.59 (dd, *J* 4.8 and 9.7 Hz, 1H), 3.10 (bt, 1H), 5.81 (s, 1H); ^{13}C NMR (50 MHz) δ 15.6, 17.5, 27.7, 32.2, 37.0, 50.9, 53.7, 132.4, 179.6, 210.2.

*(1R,4R,5R,8R)-4,8-dimethylbicyclo[3.3.0]octan-2-one (**16**)*

A mixture of **6** (100 mg, 0.67 mmol) and 10% palladium on carbon (10 mg) in ethanol (20 mL) was stirred under hydrogen (810 kPa) for 24 h. The crude product was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure (20 mmHg) at 38 °C to give 82 mg (80%) of a crude mixture containing **16** and a minor saturated component which was not characterized.

*Data for **16***. IR (film) ν_{max}/cm^{-1}: 2956, 1735, 1458, 1378, 1260, 1160; ^{1}H NMR (200 MHz) δ 1.02 (d, *J* 7.0 Hz, 3H), 1.11 (d, *J* 6.1 Hz, 3H), 1.58 – 2.01 (m, 5H), 2.13 – 2.46 (m, 3H), 2.53 (t, *J* 8.4 Hz, 1H), 2.73 (qui, *J* 7.6 Hz, 1H); ^{13}C NMR (50 MHz) δ 16.0, 16.6, 24.7, 31.6, 35.6, 37.9, 46.4, 47.0, 57.6, 221.1 For reported data of IR and ^{1}H NMR, see Ref.[24]

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