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Article

Synthesis of (-),6,6-(Ethylenedioxy)-1,10-Dimethyl-1(9)-Octal-2-one

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Adição de Michael assimétrica da etilvinilcetona com a imina quiral da 4,4-etilenodioxi-2-metil-cicloexanona **2c**, levando à 2,2-dissubstituída-ciclanona **(+)-5**. Esta última substância foi convertida na octalona título **(-)-1c**.

Asymmetric Michael addition of ethylvinylketone with chiral imine of 4,4-ethylenedioxy-2-methylcyclohexanone **2c** led to 2,2-disubstituted cyclanone **(+)-5**. The latter was converted into the title compound **(-)-1c**.

Keywords: *octalones, chiral imines, deracemizing alkylation*

Introduction

Chiral imines have been explored for diastereofacial differentiation in 1,4-addition reaction[1]. It provides an efficient means for generation of a quaternary asymmetric carbon[1,2], as well as annelation[3].

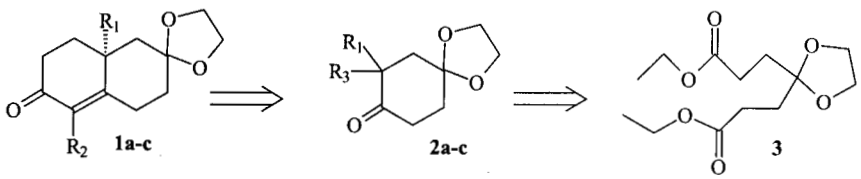
In a previous paper[4], we reported the preparation of the substituted octalones **1a** and **1b** by this method, employing optically active (S)-(-)-1-phenylethylamine as chiral auxiliary (Scheme 1).

Octalones type **1** constitute versatile building blocks for total synthesis of natural products and related ones, as they present a second carbonyl group in the B-ring, which can be further elaborated to useful synthons.

Results and Discussion

Herein, we describe the first enantioselective synthesis of (-)-6,6-(ethylenedioxy)-1,10-dimethyl-1(9)-octal-2-one **1c**, which has been used, in its racemic form, as starting compound for the preparation of terpenoids[5] such as yomogin, cuauhtemone, β-elemenone, isotelekin, plagiospirolides[6] A and B, among others.

4,4-Ethylenedioxy-2-methylcyclohexanone **2c**[4] was prepared from Dieckmann's condensation of diethyl γ,γ-ethylenedioxypimelate **3**[7] by using potassium in toluene under sonication[8] and addition (in a one pot procedure) of methyl iodide (85-80%), followed by decarboxylation with aq. KOH (10%) /ETOH (78% yield). However, running the reaction in a common cleaning bath as sonicator (Thornton T-14, 40 Khz), good yields could only be obtained as long as a mmol scale was employed (1-2 mmol)[4]. Multi-gram scale preparation of intermediate cyclanone **2b** was realized by condensation of ketal **3** with the use of Na° in toluene (reflux), and addition of CH_3I and dimethyl sulphoxide as a co-solvent (45% yield)[9].



a: R_1= CO_2Et ; R_2= H
b: R_1= CH_3 ; R_2= H
c: R_1= CH_3 ; R_2= CH_3

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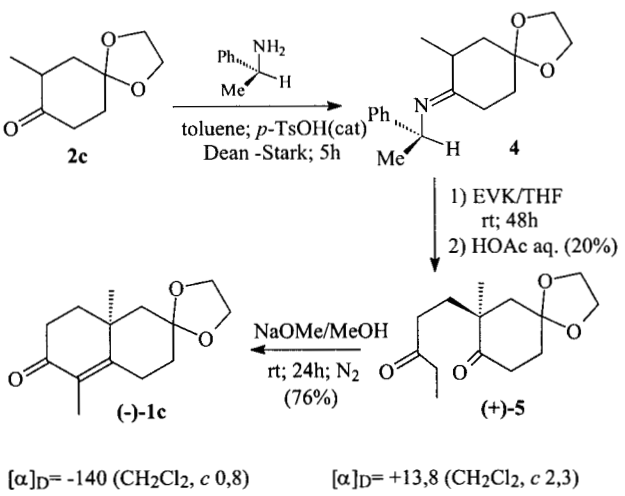
Scheme 1.



Scheme 2.

The 2-methyl-cyclanone **2c** was allowed to react with (S)-(-)-1-phenylethylamine by azeotropic removal of water (toluene, *p*-TsOH, 5h), leading to the imine **4** (Scheme 2). The crude imine was treated with ethyl-vinyketone(EVK) in the same pot, furnishing, after hydrolytic work up, the Michael adduct **(+)-5** (52% yield). The enantiomeric excess of **(+)-5** (86% ee) was established by ^{1}H-NMR spectroscopy ([Eu(hfc)$_3$]) by comparation with its racemate. Although no chemical correlation was undertaken to obtain a formal proof of the absolute configuration of **(+)-5**, the one depicted is in accordance with that which can be anticipated according to all the preceeding examples of the use of chiral imines in Michael reaction[1,2,3]. Base-induced cyclization of adduct **(+)-5** led to the desired octalone **(-)-1c**, in 76% yield.

Conclusion

In conclusion, this work , as the preceeding ones[4,10], shows that *deracemizing alkylation*[1] of imines can be used for 4,4-disubstituted cycloalkanones without lost neither in the regio, nor stereoselectivity.

Experimental

General

Solvents were purified according to the literature[11]. Column chromatography (flash) was performed with 230-400 mesh, 60 A (Merck) silica gel slurry packed in glass columns. Melting points are uncorreted. Hydrogen nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Gemini-200 (200 MHz) Varian instrument or at 200 MHz on a Brücker AC-200 instrument. The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Carbon nuclear magnetic resonance spectra (^{13}C-NMR) were obtained at Varian Gemini-200 (50 MHz) and Brücker AC-200 (50 MHz) and are reported (ppm) relative to the center line of a triplet at 77,0 ppm for $CDCl_3$. Ultrasonic irradiation were realized using a common cleaning bath (THORNTON, T14), filled with water and crushed ice was used.

Diethyl γ,γ-ethylenedioxypimelate 3[7]

A mixture of 12.37 g (54 mmol) of diethyl γ-ketopimelate[12,13], 14.2 mL (250 mmol) of redistilled ethylene glycol, 150 mL of benzene and 100 mg of *p*-toluenesulfonic acid was refluxed for 12-13h in a system equipped for azeotropic distillation of water. Ketal **3** was obtained in better yield (88%) than the ones described in literature (67%[7], 30%[14]). ^{1}H-NMR (200 MHz ,$CDCl_3$) δ 4.09(q, 4H, J = 7Hz), 3.90(s, 4H), 2.32(t, 4H, J = 8.7 Hz), 1.93(t, 4H, J = 8.7 Hz), 1.20(t, 6H, J = 7Hz).

2-Carboethoxy-4,4-ethylenedioxycyclohexanone ***2a***[14] *and 2-Carboethoxy-4,4-ethylenedioxy-2-methylcyclohexanone* ***2b***[14]

Method A

In a cylindrical tube equipped with a septum, under an argon or nitrogen atmosphere, 117 mg (3 mmol) of potassium and 5 mL of dry toluene were submitted to ultrasonic irradiation[8]. A solution of 274 mg (1 mmol) of ketal **3** and 2 mL of toluene was added dropwise by a syringe and the sonication was kept for more 25 min. The reaction mixture became viscous and yellowish. After 1 h, few drops of *tert*-butyl alcohol and solid NH_4Cl were added. The resulting mixture was partitionated between ethyl acetate and water. Addition of anhydrous Na_2SO_4 to the organic layer and removal of the solvent under reduced pressure led to 2-carboethoxy-4,4-ethylenedioxycyclohexanone[14] **2a**, as a colorless oil (193 mg, 85%). An analytical sample was obtained by bulb to bulb distillation (96 °C bath temp. / 1.0 mm). The NMR (^{1}H and ^{13}C) posses, in addition to signals of keto-tautomer form, signals attributable to the main enolic form: ^{1}H-NMR (200MHz, $CDCl_3$) δ 12.21(s, OH), 4.19(q, 2H, J = 7.5Hz), 4.00(sl, 4H), 2.50(t, 2H, J = 6.6Hz), 2.46(s, 2H), 1.85(t, 2H, J = 6.6Hz), 1.29(t, 3H, J = 7.5Hz). ^{13}C-NMR (50MHz, $CDCl_3$) δ 13.5, 27.2, 29.6, 32.1, 59.6, 63.8, 64.1, 94.6, 106.5, 169.2, 170.5.

In addition, the trapping of potassium enolate intermediate with 0.2 mL (3.2 mmol) of methyl iodide (in a one pot procedure), instead of *tert*-butyl alcohol, led to 2-carboethoxy-4,4-ethylenedioxy-2-methylcyclohexanone[14] **2b** (in this case, the mixture was allowed to stand overnight). Cyclanone **2b** was purified by flash chromatography - Hex/AcOEt, 5/1 (196 mg, 81%). ^{1}H-NMR (200MHz, $CDCl_3$) δ 4.32-3.90(several absorptions, 6H), 3.01(ddd, 1H, J = 14.7Hz, J = 10,6Hz, J = 9.8Hz), 2.74-2.63(m, 1H), 2.50(dt, 1H, J = 14,7Hz, J = 4.0Hz), 2.08-1.92(several absorptions, 2H,) 1.71(d, 1H, J = 14Hz), 1.28(s, 3H), 1.27(t,

3H, J = 7.1Hz). ^{13}C-NMR (50MHz, $CDCl_3$) δ 14.6, 22.4, 35.9, 38.1, 44.3, 55.3, 62.0, 64.9, 65.5, 107.3, 173.9, 207.9.

Method B

A 125 mL three-necked, round-bottomed flask equipped with stirrer was fitted with a pressure equalizing constant-rate dropping funnel and a condenser. A mixture of 1 g (43 mmol) of Na° in 20 mL of toluene was mantained in reflux until the metal melts. After that, 10 g (36.5 mmol) of ketal **3** in 10 mL of toluene were added dropwise (~30 min.). The reflux was kept for 5 h, with addition of more 75 mL of solvent. After that time, a Dean-Stark apparatus was connected and part of toluene/ethanol was gradually distilled off. The reaction mixture was cooled below 48 °C and dimethyl sulphoxide (20 mL) was added[9]. At room temperature, a solution of 3 mL (48 mmol) of CH_3I in 7 mL of toluene was added dropwise and the stirrer mantained for more 1 h. The mixture was allowed to stand overnight. The residue was extrated with toluene and the solvent removed under reduced pressure, leading, after bulb to bulb distillation (130-134 °C/0.5 mm), 3.93 g (45%) of **2b**[7].

4,4-Ethylenedioxy-2-methylcyclohexanone 2c[7]

The cyclanone **2c**[7] was obtained from decarboxilation of **2b** (242 mg, 1 mmol) with 3 mL of aq. KOH (10%) and 3 mL of EtOH (reflux, 16 h). Addition of solid NH_4Cl, concentration of the mixture and extration with ethyl acetate led to an oil, purified by flash chromatography - Hex/AcOEt, 5/1 (133 mg, 78% - mp: 40-42 °C). ^{1}H-NMR (200MHz, $CDCl_3$) δ 4.13-3.95(several absorptions, 4H), 2.86-2.55(several absorptions, 2H), 2.37(ddd, 1H, J = 15.3Hz, J = 5.1Hz, J = 3.1Hz), 2.18-1.85(several absorptions, 3H), 1.73(t, 1H, J = 13.6Hz), 1.03(d, 3H, J = 6.8Hz). ^{13}C-NMR (50MHz, $CDCl_3$) δ 13.9, 34.3, 37.5, 40.9, 42.4, 64.2, 64.3, 107.0, 211.2.

(+)-4,4-Ethylenedioxy-2-methyl-2-(3-oxopentil)-cyclohexanone 5

Azeotropic imination (5 h, 8 mL of toluene) of ketone **2c** (420 mg, 2.47 mmol) with (S)-1-phenylethylamine (0.8 mL, 6.22 mmol) was followed by evaporation of the solvent under reduced pressure. After removal of excess of amine and unreacted ketone (39 mg, 0.23 mmol, ~10%) by bulb to bulb distillation, ethylvinylketone (4.45 mmol) in anhydrous THF (6 mL) was added to crude imine **4**. The mixture was kept under nitrogen at room temperature, for 48 h. Hydrolysis of the imine function was performed with aq. acetic acid (20%)/THF (1/1). After concentration, the system was partitioned between ethyl acetate and water. Removal of the solvent and purification of the crude oil by flash chromatography (Hex/AcOEt, 5/1) yielded adduct **(+)-5** (52%), $[\alpha]_D$ = +13.8 (CH_2Cl_2, *c* 2.3). This compound showed an 86% optical purity measured by ^{1}H-NMR, using ((+)-[Eu(hfc)$_3$]) and comparation with its racemate (prepared by the same way from (±)-1-phenylethylamine). ^{1}H-NMR (200MHz, $CDCl_3$) δ 4.10-3.90(several absorptions, 4H), 2.70-1.65(several absorptions, 12H), 1.12(s, 3H), 1.05(t, 3H, J = 7.2Hz).

(-)-6,6-(Ethylenedioxy)-1,10-dimethyl-1(9)-octal-2-one 1c

Adduct **(+)-5** (254 mg, 1 mmol) was treated (48 h, N_2) with a mixture of 97 mg (1.8 mmol) of $CH_3O^-Na^+$ in 5 mL of dry methanol, at room temperature. After concentration, the product was extrated with ethyl acetate and purified by flash chromatography (Hex/AcOEt, 6/1). The desired octalone **(-)-1c** was obtained in 76% yield (159 mg), $[\alpha]_D$ = -140 (CH_2Cl_2, *c* 0.8). ^{1}H-NMR (200MHz, $CDCl_3$) δ 4.60-3.85 (several absorptions, 4H), 2,73(ddd, 1H, J = 16.2Hz, J = 5.0Hz, J = 3.2Hz), 2.65-1.50(several absorptions, 8H), 1.77(d, 3H, J = 1.3Hz), 1.58(d, 1H, J = 12.6Hz). ^{13}C-NMR (50MHz, $CDCl_3$) δ 11.0, 23.6, 25.5, 33.4, 34.5, 36.8, 37.9, 48.4, 63.7, 64.6, 107.7, 128.8, 160.5, 198.8.

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