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Enantioselective Synthesis of (+)-De-Isopropenyl Nootkatone†

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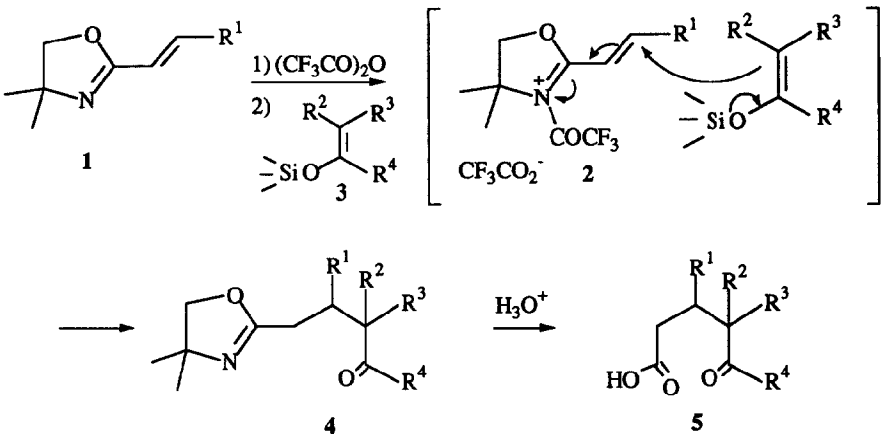
Abstract. *The absolute configuration of the δ-oxo acid* ***11****, obtained through an asymmetric Michael-type reaction involving the activated chiral α,β-unsaturated oxazoline* ***7****, was established by comparison of the CD curves of the derived (+)-octalone* ***14*** *and (+)-nootkatone* ***15****.*

The high reactivity of α,β-unsaturated *N*-trifluoroacetyloxazolinium **2** (generated *in situ* from oxazolines **1**), as Michael-type acceptors of silyl enol ethers **3**, allowed the condensation of both reactants substituted at the reactive carbon. This advantage could be turned to account in the direct preparation of polysubstituted δ-oxo acids **5** by acidic hydrolysis of the adducts **4** (Scheme 1).[1]

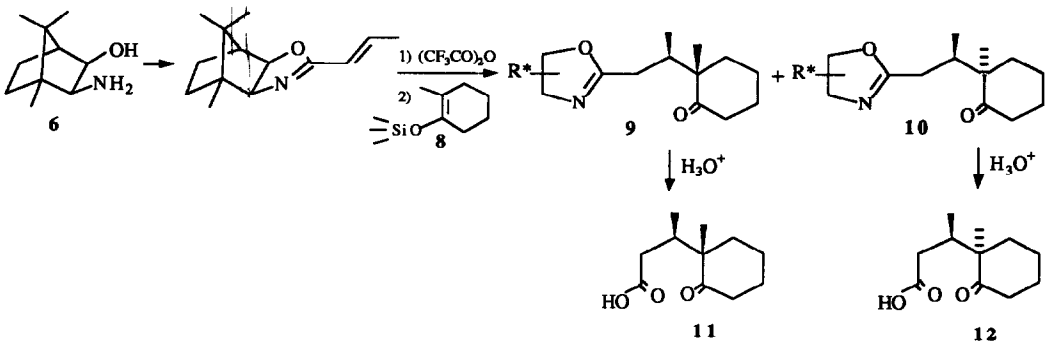


Scheme 1

In order to extend this method to asymmetric synthesis, several optically pure 2-amino alcohols were tested as chiral auxiliaries.[2] The most efficient proved to be the camphor-derived amino alcohol **6**[3] as anticipated from the proposed conformation of the reactive acyliminium intermediate.[4] Thus, the conjugate

† Dedicated to the memory of Professor Günther Snatzke.

addition of 2-methyl-1-trimethylsiloxycyclohexene **8**, prepared with good regioselectivity following Duboudin's method[5], and 2-propenyloxazoline **7** afforded two adducts **9** and **10** (Scheme 2). After acidic hydrolysis, the diastereomers **9** and **10** led respectively to the enantiomerically pure δ-oxo acids **11** and **12**, as shown by ^1H NMR spectra of their methyl esters in the presence of tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-praseodymium (III). However, the absolute configurations of the acids **11** and **12**, obtained from the chiral auxiliary **6**, remained unknown. We report here the absolute configuration assignment of **11**.



Scheme 2

The formation of the adduct **9**, precursor of the diastereomeric acid **11**, was supposed to proceed through an approach of the trimethylsilyl enol ether **8** from the less hindered face of a prefered *s-trans* trifluoroacyloxazolinium ion intermediate, as shown in Figure 1 (approach **a** favoured *versus* approach **b**). Taking account of the sterically disfavoured[4b] *s-cis* conformation of the N-trifluoroacyloxazolinium ion, the alternative approaches **c** and **d** are considered unlikely (Figure 2).

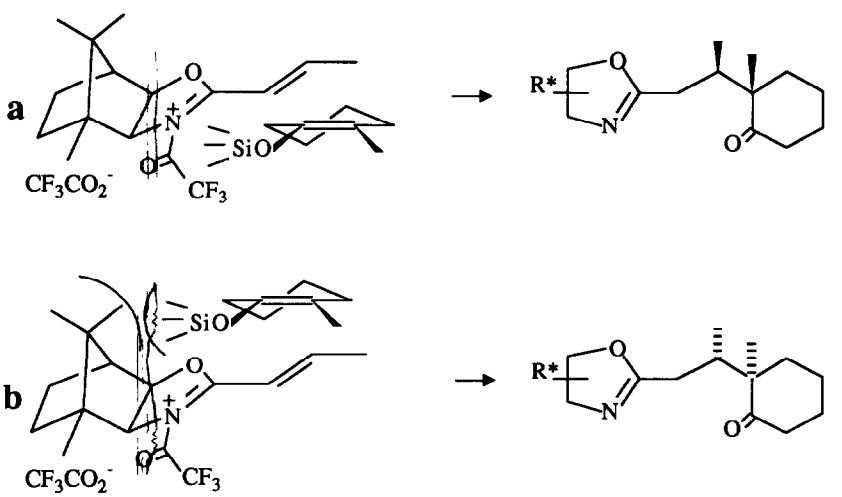


Fig 1 : *s-trans* α,β-unsaturated trifluoroacyloxazolinium approaches to **9**

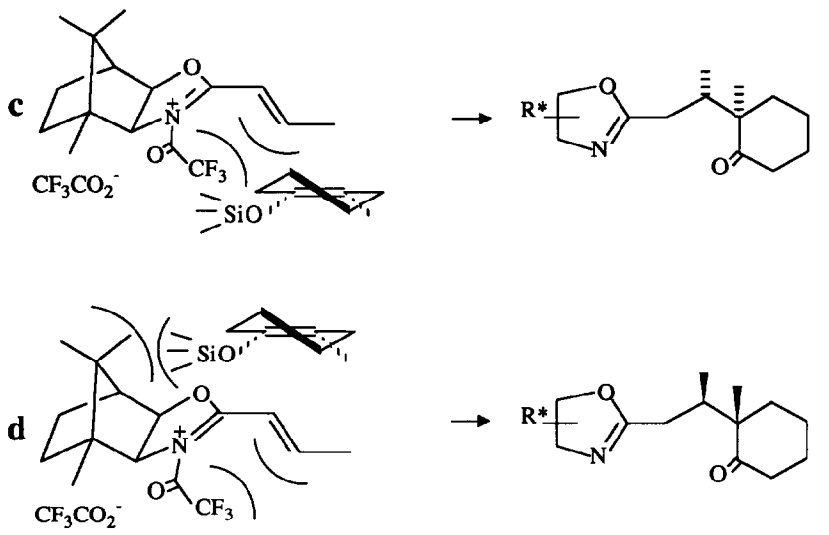
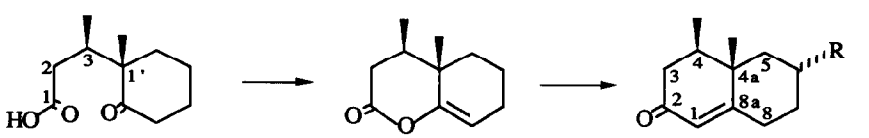


Fig 2 : *s-cis* α,β-unsaturated trifluoroacyloxazolinium approaches to **9**

According to this model, the absolute configuration of the resulting oxo acid **11** was postulated to be 3*R*, 1'*S*. In order to verify this hypothesis, a synthesis of de-isopropenyl nootkatone **14** was undertaken from the acid **6**. The (+) enantiomer of the valencane sesquiterpene nootkatone **15**[6] is one of the components of widely used grapefruit flavouring.[7] A comparison of stereomodels provides strong support for a similar conformation of the bicyclic systems in **14** and **15**. This allowed us to deduce that the asymmetrical α,β-unsaturated ketone chromophore would be identical in both molecules. The sign of the Cotton effects of this chromophore, particularly the n-π* bands, are strongly dependent on steric factors[8], and the comparison of the CD curves of **14** and **15**[9] could be used as a diagnostic method for the absolute configuration assignment in **14**.

Thus, the δ-oxo acid **11** was converted into the enol lactone **13** (85%) by heating in acetic anhydride in presence of sodium acetate[10]. Grignard reaction of the lactone **13** with methyl magnesium iodide (1.1 equiv, in ether) was followed without purification by alkali treatment with methanolic potassium hydroxide (4% w/v, 65°C, 1.5 h)[11] to afford the Robinson annulation product **14**[12] (68%) (Scheme 3).



11 **13** **14** R = H

15 R = $C(CH_3)=CH_2$

[(+)-nootkatone]

Scheme 3

The CD curves of 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2-(3*H*) naphthalenone **14** and (+)-nootkatone **15** exhibit similar maxima at *c.a.* 240 nm for the π-π^* transitions and the same negative Cotton effects with mimima at *c.a.* 317 nm for the n-π^* transitions (Figure 3).

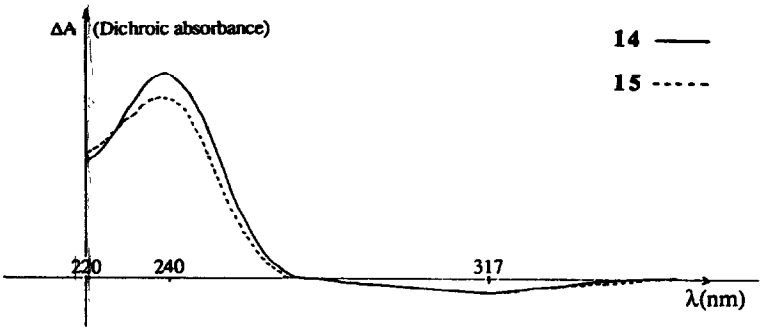


Figure 3 : CD curves of **14** and **15** in methanol

These results confirm the absolute configurations 3*R*, 1'*S* of 3-1'-methyl-2'-oxocyclohexanyl-butanoic acid **11**, precursor of **14**, and agree well with our model for the approach of the two reactants. Thus, from a synthetic point of view, this noteworthy 1,5 asymmetric induction from the chiral α,β-unsaturated oxazoline **7** could find further applications

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EXPERIMENTAL SECTION

Melting points were taken on a microscope Leitz. Optical rotations were measured on a Perkin-Elmer 241 (in $CHCl_3$ solution ; the concentrations were given in g/100 mL). IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, δ = 0 ppm) from Bruker AC200, AC250, AM300 or AM400 ; coupling constants *J* are given in Hertz (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet respectively). ^{13}C NMR spectra were recorded on AC250 (62.5 MHz) or AM300 (75 MHz). Mass spectra and high resolution mass spectra were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer. CD curves [λnm ($\Delta\varepsilon$)] were recorded on a Jobin-Yvon dichrograph V in *c.a.* 4. 10^{-4} M methanolic solution. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that organic layer was dried over magnesium sulfate, filtrated and evaporated under vacuum. (+)-Camphor was supplied by Janssen ($[\alpha]_D^{20}$ = + 44.10, c = 10, ethanol).[13] Dichloromethane was distilled from calcium hydride and trifluoroacetic anhydride was distilled from phosphorus pentoxide just before use.

Preparation of (±)-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2-(3*H*) naphthalenone 14

a) Preparation of the oxazoline 1 ($R^1 = CH_3$) : 4,4-dimethyl-2-propenyl-4,5-dihydro oxazole :
Oxazoline **1** ($R^1 = CH_3$) was prepared from N-butenoyl-2-amino-2-methyl-1-propanol by modification of the described procedure[14] : Phosphorous oxychloride (1.80 mL, 19.5 mmol) was added to a stirred solution of N-butenoyl-2-amino-2-methyl-1-propanol (2.36g, 15mmol) in dry toluene (23mL) under argon at room temperature. After 20 min, the reaction medium was evaporated under vacuum. The residu was twice dissolved in toluene and evaporated to dryness ; then it was cooled to 0°C before addition of saturated aqueous solution of Na_2CO_3 (80mL) and dichloromethane (150mL). The mixture was stirred at 0°C for 30 min and extracted with dichloromethane. After usual workup, the organic layer was evaporated under vacuum at RT to give oxazoline **1** ($R^1 = CH_3$) in 88% yield.[14]

b) Michael-type addition of 2-methyl-1-trimethylsiloxycyclohexene 8 and oxazoline 1 ($R^1 = CH_3$)
Trifluoroacetic anhydride (1.56 mL, 11.0 mmol) was added dropwise to a stirred mixture of oxazoline (1.53 g, 11.0 mmol) and $CaCO_3$ (1.10 g, 11.0 mmol) in dry dichloromethane (22mL) at -55°C under argon. After 20 min at the same temperature, a solution of 2-methyl-1-trimethylsiloxycyclohexene **8** (2.43 g, 13.2 mmol, regioselectivity 9 : 1[5]) in dry dichloromethane (11mL) was added dropwise. The mixture was stirred at -35° for 20h before successive addition of an aqueous solution of Na_2CO_3 (10%, 30mL) and methanol (20mL). The reaction medium was allowed to warm at room temperature, stirred for 5h and then extracted with dichloromethane. The crude product obtained after usual workup (2.80g) was rapidly purified by flash chromatography (heptane-ethyl acetate 1:1) to afford the mixture of diastereomers **4** ($R^1 = R^2 = CH_3$, R^3-$R^4 = (CH_2)_4$) (2.02 g, 73%) ; their ratio (**4a** : **4b** = 6:4) was determined by ^1H NMR (integration of CH-CH_3 signals). The diastereomers were separated by chromatography (eluent : heptane-ether-methanol 7:3:0.2 to 7:3:0.5).
Diastereomer (R, S*) 4a* ($R^1 = R^2 = CH_3$, R^3-$R^4 = (CH_2)_4$) :
IR : 1705, 1665 ; ^1H NMR (200MHz) : 3.90 (s, 2H, OCH_2), 1.26 (s, 6H, C-$(CH_3)_2$), 0.93 (d, J = 7, CH-CH_3), 0.91 (s, 3H, C-CH_3) ; MS (m/z) : 251 ($M^{+\cdot}$), 236, 195, 194, 180, 140 (100%), 114, 113.
Diastereomer (S, S*) 4b* ($R^1 = R^2 = CH_3$, R^3-$R^4 = (CH_2)_4$) :
IR : 1700, 1660 ; ^1H NMR (200MHz) : 3.93 (s, 2H, OCH_2), 1.29 (s, 6H, C-$(CH_3)_2$), 0.92 (d,J =7, CH-CH_3), 0.92 (s, 3H, C-CH_3), 0.79 (d, 3H, J =7, CH-CH_3) ; MS (m/z) : 251 ($M^{+\cdot}$), 236, 195, 194, 180, 140 (100%), 114.

c) Acidic hydrolysis of 4a (and esterification)
A solution of **4a** (276 mg, 1.1mmol) in 3N HCl (22mL) was heated at 100°C under argon for 5h. After cooling, dilution with water (20mL) and extraction with ether, the usual workup afforded quantitatively the oxo-acid **5a** ($R^1 = R^2 = CH_3$, R^3-$R^4 = (CH_2)_4$) [= (±)-**11**] :
IR = 3600-2300, 1700 ; ^1H NMR (400MHz) : 0.97 (d, 3H, J = 7, C-3-CH_3), 0.91 (s, 3H, C-1'-CH_3) ; MS (m/z) : 198 ($M^{+\cdot}$), 154, 112 (100%), 110, 95, 83.
To study the conditions of doubling of methoxycarbonyl ^1H NMR signal in the presence of [Pr(hfc)$_3$], the corresponding methyl ester was quantitatively prepared by treatment of an etheral solution of **5a** with an excess

of diazomethane in ether : IR : 1732, 1700 ; ^{1}H NMR (250MHz) : 3.66 (s, 3H, CO_2CH_3), 0.93 (d, 3H, J = 7, C-3-CH_3), 0.90 (s, 3H, C-1'-CH_3).

d) Acidic hydrolysis of 4b (and esterification)

A solution of the diastereomer **4b** (60mg, 0.24 mmol) in 3N HCl (4.8mL) was treated as described above to afford the oxo-acid **5b** ($R^1 = R^2 = CH_3$, R^3-$R^4 = (CH_2)_4$) [= (±)-**12**] (100%) :
IR : 3600-2300, 1700 ; ^{1}H NMR (400MHz) : 0.95 (s, 3H, C-1'-CH_3), 0.84 (d, 3H, J = 7, C-3-CH_3) ; MS (m/z) : 198 ($M^{+\cdot}$), 154, 139, 112 (100%), 110, 95, 83, 69.
The methyl ester was prepared as above : IR : 1732, 1703 ; ^{1}H NMR (250MHz) : 3.70 (s, 3H, CO_2CH_3),0.91 (s, 3H, C-1'-CH_3), 0.78 (d, 3H, J = 7, C-3-CH_3).

e) (±)-cis-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2-(3H) naphthalenone [(±)-14]

To a solution of oxo-acid **5a** (198mg, 1.0 mmol) in acetic anhydride (6mL) under argon was added anhydrous sodium acetate (15 mg). The mixture was heated at 140° for 4h. After cooling excess of acetic anhydride was evaporated under vacuum and the product was extracted with ether. The organic layer was washed with an aqueous solution of Na_2CO_3 (5%) and usual workup afforded enol lactone (±)-**13** (160 mg, 89%) :
IR : 1743, 1682 ; ^{1}H NMR (400MHz) : 5.28 (m, 1H, =CH), 2.67 (dd, 1H, J_{AB} = 18.8, J' = 6, COCH), 2.36 (dd, 1H, J_{AB} = 18.8, J' = 12.7, COCH), 1.87 (m, CH-CH_3), 1.04 (s, 3H, C-CH_3), 0.93 (d,3H, J = 7, CH-CH_3) ; MS (m/z) : 180 ($M^{+\cdot}$, 100%), 152, 111 (100%), 110, 69.
To a stirred solution of enol lactone (90 mg, 0.5mmol) in dry ether (1.5mL) was added a solution of CH_3MgI in ether (1.1 equiv) at 0°C under argon. The mixture was allowed to warm at room temperature and stirred for 16h before extraction with ether. To the crude product obtained after usual workup was added a solution of KOH in methanol (4%, 10mL) at RT under argon and the mixture was stirred at 65°C for 1,5h cooled and concentrated under vacuum. Extraction with ether followed by usual workup and preparative TLC (eluent : pentane-ether : 4 : 6) afforded the compound (±)-**14** (64mg, 72%).
mp = 66-7°C (lit 63-4°C[15a]) ; IR : 1662, 1618 ; ^{1}H NMR (300MHz) : 5.75 (bs, 1H, C-1-H), 1.08 (s, 3H, C-4a-CH_3), 0.95 (d, 3H, J = 7, C-4-CH_3, this chemical shift is characteristic of relative configurations[15]) ; MS (m/z) : 178 ($M^{+\cdot}$, 100%).

Enantioselective synthesis of (+)-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2-(3*H*) naphthalenone 14

Oxazoline 7 was prepared as previously described[4b]

a) Michael-type addition of 2-methyl-1-trimethylsiloxycyclohexene 8 and oxazoline 7

Trifluoroacetic anhydride (0.198 mL, 1.4 mmol) was added to a stirred mixture of oxazoline **7** (307 mg, 1.4 mmol) and $CaCO_3$ (154 mg, 1.54 mmol) in dry dichloromethane (2.3mL) at -70°C under argon. After 10 min at the same temperature, a solution of 2-methyl-1-trimethylsiloxycyclohexene **8** (387 mg, 2.1 mmol) in dry dichloromethane (1.2mL) was added dropwise. The mixture was stirred at -70° for 2h and at -40°C for 17h before successive addition of an aqueous solution of Na_2CO_3 (10%, 10mL) and methanol (10mL) ; it was then allowed to warm at room temperature and stirred for 6.5 h before extraction with dichloromethane. The crude product obtained after usual workup (490 mg) was purified by chromatography (eluent : pentane-ether 1:1) and

preparative TLC (eluent : pentane-ether 6:4) to afford the diastereomers **9** (170 mg, 37%) and **10** (143 mg, 31%).

Diastereomer ***9*** :

mp = 61-5°C ; $[\alpha]_D^{22}$ = -107 (c = 0.4) ; IR : 2950, 1718, 1662 ; ^{1}H NMR (250 MHz) : 4.39 (d, 1H, J = 10, C-7a-H), 3.83 (d, 1H, J = 10, C-3a-H), 1.03 (s, 3H, CH_3), 0.96 (d, 3H, J = 7, CH-C$\underline{H}_3$), 0.89 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H) ; ^{13}C NMR (62.5 MHz) : 208.9 (CO), 168.2 (C), 86.4 (CH), 80.8 (CH), 51.9 (C), 48.6 (CH), 47.9 (C), 46.6 (C), 38.4 (CH_2), 37.2 (CH_2), 34.1 (CH_2), 32.7 (CH), 31.5 (CH_2), 27.7 (CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.3 (CH_3), 17.0 (CH_3), 13.9 (CH_3), 11.6 (CH_3) ; MS (m/z) : 331 ($M^{+\cdot}$), 285, 232, 230 (100%). Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03 ; N, 4.23. Found : C, 75.82 ; H, 9.83 ; N, 4.06.

Diastereomer ***10*** :

$[\alpha]_D^{22}$ = +30 (c = 0.44) ; IR : 2938, 1707, 1664 ; ^{1}H NMR (200 MHz) : 4.42 (d, 1H, J = 10, C-7a-H), 3.84 (d, 1H, J = 10, C-3a-H), 1.06 (s, 3H, CH_3), 0.92 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H), 0.81 (d, 3H, J = 7, CH-C$\underline{H}_3$) ; ^{13}C NMR (62.5 MHz) : 209.O (CO), 168.6 (C), 86.7 (CH), 80.9 (CH), 52.1 (C), 48.8 (CH), 48.2 (C), 46.8 (C), 38.9 (CH_2), 37.0 (CH_2), 34.3 (CH_2), 32.4 (CH), 30.9 (CH_2), 27.8 (CH_2), 23.4 (CH_2), 20.5 (CH_2), 18.5 (CH_3), 17.5 (CH_3), 15.5 (CH_3), 11.7 (CH_3) ; MS (CI, isobutane, m/z) : 332 $(M+H)^+$.

Oxo-acid (3R, 1'S)-11 :

A solution of the compound **9** (120mg, 0.36 mmol)in HCl 4N (12mL) was heated under reflux for 6.5h, cooled and extracted with ether. The oxo-acid (-)-**11** was quantitatively obtained after usual work up :

$[\alpha]_D^{20}$ = - 66 (c = 1.3) ; IR : 2940, 1705 ; ^{1}H NMR (200 MHz) : 0.97 (d, 3H, J = 7, C-3-CH_3), 0.90 (s, 3H, C-1'-CH_3) ; MS (m/z) : 198 ($M^{+\cdot}$), 154, 112 (100%) ; HRMS (m/z) : $M^{+\cdot}$ $C_{11}H_{18}O_3$ calcd 198.1255, found 198.1233. Only one enantiomer was detected in the ^{1}H NMR spectrum (250 MHz) of the corresponding methyl ester in the presence of [Pr(hfc)$_3$].

The enol lactone (-)-**13** was prepared as described above for the racemic compound (Rdt. 85%). The crude product exhibited the following data : mp = 57-60°C ; $[\alpha]_D^{24}$ = - 144 (c = 0.15) ; HRMS (m/z) : $M^{+\cdot}$ $C_{11}H_{16}O_2$ calcd 180.1150, found 180.1169 ; it was treated with CH_3MgI and then methanolic solution of KOH, as described above ; 4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2-(3*H*) naphthalenone (+)-**14** was obtained in 68% yield :

$[\alpha]_D$ = + 213 (c = 0.2) ; IR : 2940, 1655, 1616 ; CD : 239 (+ 8.90), 317 (- 0.67) ; ^{1}H NMR (300MHz) : 5.75 (bs, 1H, C-1-H), 2.42 (m, 1H, C-8-Ha), 1.99 (m, C-4-H), 1.91 (m, C-7-Ha + 1H), 1.66 (m), 1.38 (m, 1H, C-7-Hb), 1.21 (m, 1H), 1.08 (s, 3H, C-4a-CH_3), 0.95 (d, 3H, J = 7, C-4-CH_3) ; ^{13}C NMR (75MHz) : 199.15 (C-2), 170.96 (C-8a), 124.07 (C-1), 41.61 (CH_2), 39.74 (CH), 38.52 (C), 38.12 (CH_2), 32.50 (CH_2), 26.21 (CH_2), 21.34 (CH_2), 15.68 (CH_3), 14.29 (CH_3) ; MS (m/z) : 178 ($M^{+\cdot}$) ; HRMS (m/z) : $M^{+\cdot}$ $C_{12}H_{18}O$ calcd 178.1357, found 178.1352.

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