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# Synthesis of bicyclic oxepanes: an enantioselective approach to the western part of Shaagrockol C

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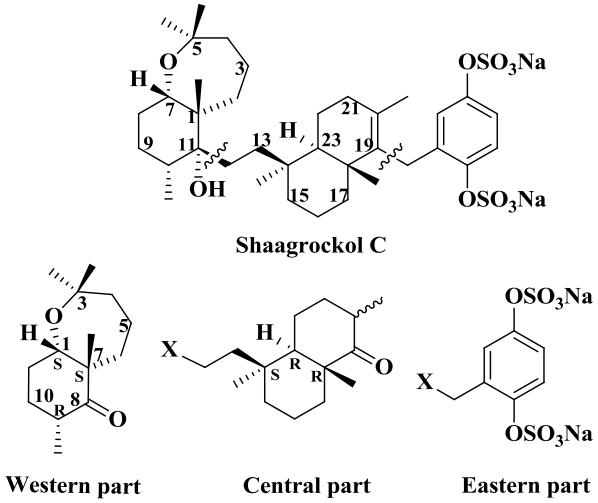
**Abstract:** In this paper, we wish to report an efficient and flexible synthetic strategy towards the synthesis of Shaagrockol C. The strategy involves the construction of a bicyclic oxepane which possess several chiral centres. Such system is present in some complex natural products.

**Keywords:** Shaagrockol C; baker's yeast; enantioselective reduction; asymmetric synthesis; bicyclic oxepane.

## Introduction

In 1992, Kashman and Isaacs reported the isolation and characterisation of Shaagrockol C from a Red Sea sponge, *Toxiclona Toxius*[1,2]. Shaagrockol C was reported to be responsible for an antifungal activity against human immunodeficiency virus type 1 (HIV-1) with an $IC_{50}$ of 6 mg/mL[3].

To the best of our knowledge, no synthesis has been reported in the literature to date. Shaagrockol C possesses two different bicyclic sesquiterpene systems linked together via an ethane bridge.

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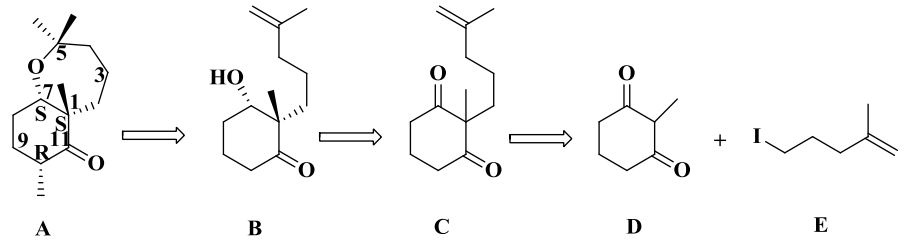
**Scheme 1:** Retrosynthetic analysis of Shaagrockol C.

The first system (western part) is a bicyclic oxepane[4-6] while the second one (central part) is an octahydronaphtalenone derivative. A *p*-hydroquinone disulfate[7-10] (eastern part) is attached to the sesquiterpene of the central part. The observation of these three molecular parts suggests a possible retrosynthetic approach for the overall molecule (Scheme 1).

In this paper, an enantioselective synthesis of the oxepane bicyclic sesquiterpene (western part) of Shaagrockol C is reported.

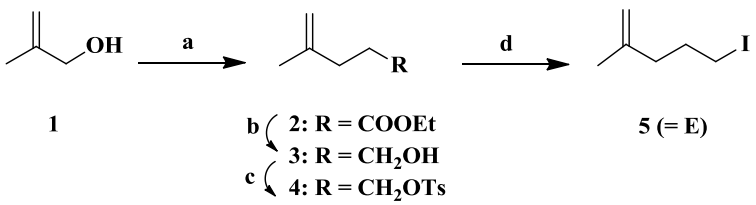
## Results and Discussion

According to the retrosynthetic pathway presented in scheme 2, the cis-oxepane bicyclic **A** would contain a carbonyl function in the C-8 position and three asymmetric centers in positions 1, 7 and 9, whose absolute configurations are 1*S*, 7*S* and 9*R*. Thus, structure **A** could be prepared by an intramolecular cyclisation of ketol **B**, followed by stereoselective alkylation to introduce the methyl group. The synthesis of compound **B** was envisaged by the enantioselective reduction of dione **C**. Compound **C** would then be synthesised by alkylation of dione **D** with iodide **E**.




**Scheme 2:** Retrosynthetic analysis of Western part **A.**

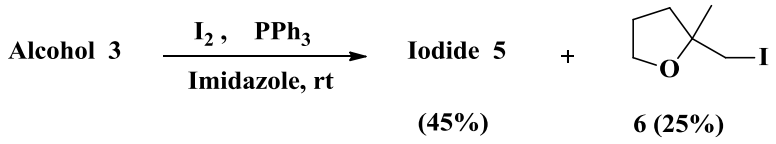
Scheme 3 summarises the synthesis of the iodide **5** needed for the alkylation reaction. This compound was accessed by a known four-steps synthesis in 75% yield from the commercially available 2-methylprop-2-en-1-ol (**1)** (trivial name: methallyl alcohol) and an orthoester. The initial condensation product gave an allyl ethyl ketene acetal which underwent a spontaneous [3,3] sigmatropic rearrangement[11]. Reduction of the ester **2** with $LiAlH_4$ in ether provided **3** in 98% yield. Tosylation of alcohol **3** (92%) followed by displacement of the tosylate gave the desired iodide **5** in 91% yield[12-14].




Reagents and conditions: **a:** triethyl orthoacetate, propionic acid, 140°C, 91%. **b:** $LiAlH_4$, ether, 0°C, 1h30, 98%. **c:** TsCl, py, 0°C, 3h, 92%. **d:** NaI, DMSO, rt, 16h, 91%.

**Scheme 3:** Synthesis of iodide **5**.

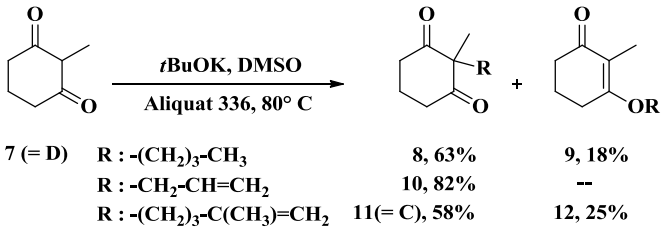
The iodide **5** could also be obtained by direct halogenation of alcohol **3** with iodine in the presence of triphenylphosphane and imidazole[15]. The expected product **5** was obtained in 45% yield, accompanied with the cyclised product **6** (25%) resulting from an intramolecular iodoetherification (Scheme 4).




**Scheme 4:** Direct halogenation of alcohol **3**.

A variety of readily accessible substrates derived from 2-methylcyclohexane-1,3-dione **7** were chosen to examine the influence of substrate modifications on the course and stereoselectivity of the alkylation in the C-2 position and the asymmetric enzymatic reduction by baker's yeast. Two examples were explored in order to indicate the generality of the procedure.

The diketones **8**, **10**, **11** and the O-alkylated products **9** and **12** were prepared by alkylation of 2-methylcyclohexane-1,3-dione **7** and various alkyl iodides, using potassium *tert*-butoxide as a base. The best conditions involved DMSO as the solvent with a catalytic amount of a quaternary ammonium salt (Aliquat 336)[16-20]. After dropwise addition of the alkylating reagent, the reaction mixture was heated to 80° C for 16 h. The desired diketone **11** was thus obtained in 58% yield accompanied by the O-alkylated product **12** in 25% yields. These results are summarised in Scheme 5.

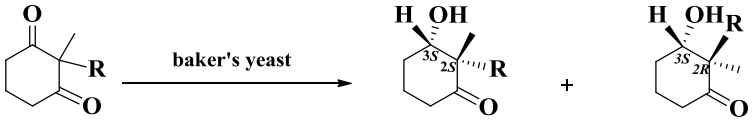



**Scheme 5:** Alkylation of 2-methylcyclohexane-1,3-dione **7**.

Numerous methods have been described for the monoreduction of 2,2-disubstituted 1,3-cyclohexanediones either chemically[21-23] or enzymatically[24,25] .

In general, the baker's yeast[26,27] mediated asymmetric reduction of diketone has shown to be an efficient stereoselective method to obtain chiral building blocks because it is inexpensive, versatile and easy to perform.

Brooks and coll[28,29], have successfully used baker's yeast in the reduction of prochiral 2,2-disubstituted 1,3-cyclohexanediones to give ketol products with two chiral centers in only one step (Scheme 6).

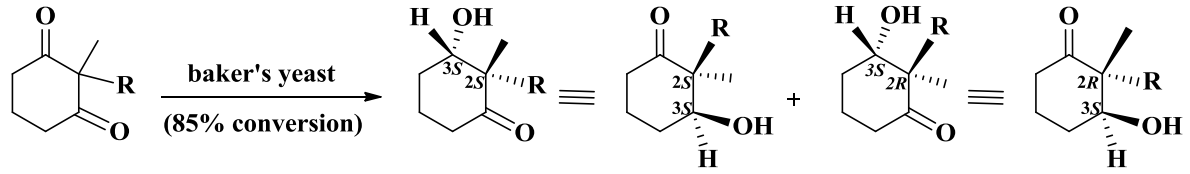



| | | |
|---|---|---|
| R= -$CH_2$-$CH_2$-$CH_3$ | 22% | 78% |
| R= -$CH_2$-CH=$CH_2$ | 45% | 55% |
| R= -$CH_2$-C≡CH | 27% | 73% |
| R= -$(CH_2)_3$-C($CH_3$)=$CH_2$ | 24% | 76% |

**Scheme 6:** Reduction of prochiral 2,2-disubstituted-1,3-cyclohexanediones with Baker's yeast.

It is interesting to note the asymmetric consistency of the yeast reduction for this series to provide only the *S* configuration in C-3 position.

Efficient yeast-mediated reductions were achieved for diones **8**, **10** and **11** with diverse side chains in the C-2 position, providing chiral intermediates for enantioselective synthesis[28,29] (Scheme 7).

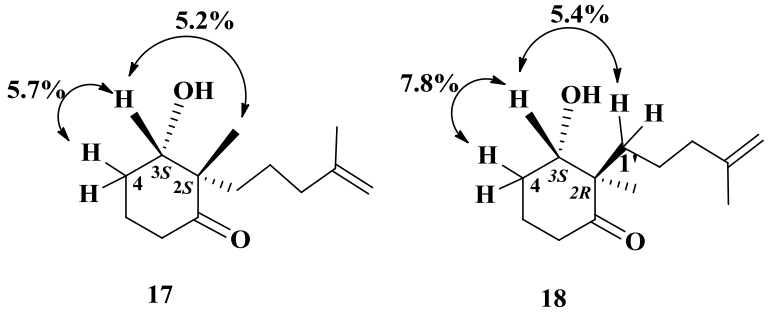



| | | |
|---|---|---|
| 8: R= -$(CH_2)_3$-$CH_3$ | 13 (2*S*, 3*S*), 40% | 14 (2*R*, 3*S*), 55% |
| 10: R= -$CH_2$-CH=$CH_2$ | 15 (2*S*, 3*S*), 45% | 16 (2*R*, 3*S*), 50% |
| 11: R= -$(CH_2)_3$-C($CH_3$)=$CH_2$ | 17(= B) (2*S*, 3*S*), 38% | 18 (2*R*, 3*S*), 57% |

**Scheme 7:** Yeast-mediated reduction of diones **8**, **10** and **11**.

Enantioselective reduction of the prochiral diketone **11** afforded the expected keto-alcohols **17** (2*S*, 3*S*) and **18** (2*R*, 3*S*) in 38% and 57% yield (85% conversion) if a second addition of saccharose and baker's yeast was performed after stirring 24 h at 30° C. The diastereomeric mixture of **17** and **18** was easily separated by column chromatography using $CH_2Cl_2$: $Et_2O$ (9:1) as eluent ($R_f$ = 0.40 and 0.35 for **17** and **18** respectively).

The stereochemistry of compounds **17** and **18** was confirmed by NOE experiments in $^1H$ NMR at 250 MHz. Several measurements have shown a positive and mutual effect (Scheme 8). For the ketol **17**, irradiation of the H-C(3) methine resulted in an enhancement of the H-$CH_3$ methyl (5.2%) and an enhancement of H-C(4) methylene protons (5.7%). With the ketol **18**, irradiation of the H-C(3) methine resulted in an enhancement (7.8%) of the H-C(1') of the methylene protons and an enhancement (5.4%) of the methylene protons at H-C(4).




**17** **18**

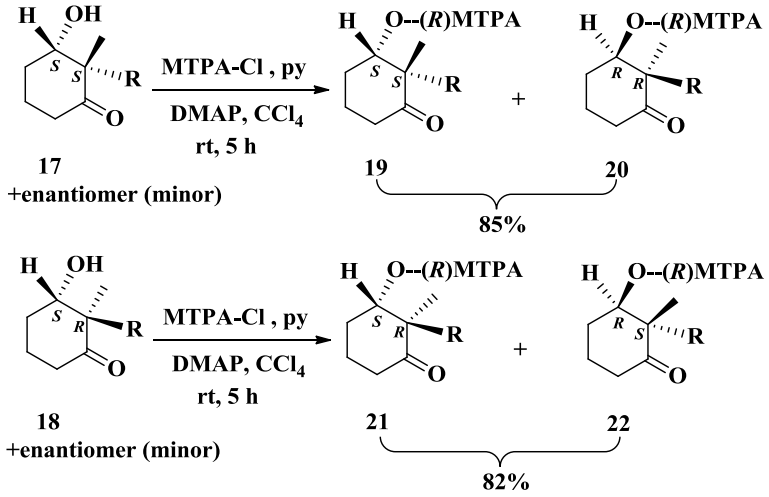
**Scheme 8:** Nuclear Overhauser studies on ketols **17** and **18**.

The relative configuration of ketols **17** and **18** was apparent by $^{13}C$ NMR spectra data. A substantial shielding was observed for the methyl signal at the C-2 position of product **17** due to a γ-steric compression effect of the *anti* hydroxyl group. A similar shielding effect was observed for the methylene signal at the C-1' position *anti* to the hydroxyl group for product **18**. The consistency of this observation is evident for each example as shown in Table 1[28,30].

**Table 1:** γ-steric Compression effect in cyclohexane ketols ($^{13}$C NMR chemical shifts, δ =)

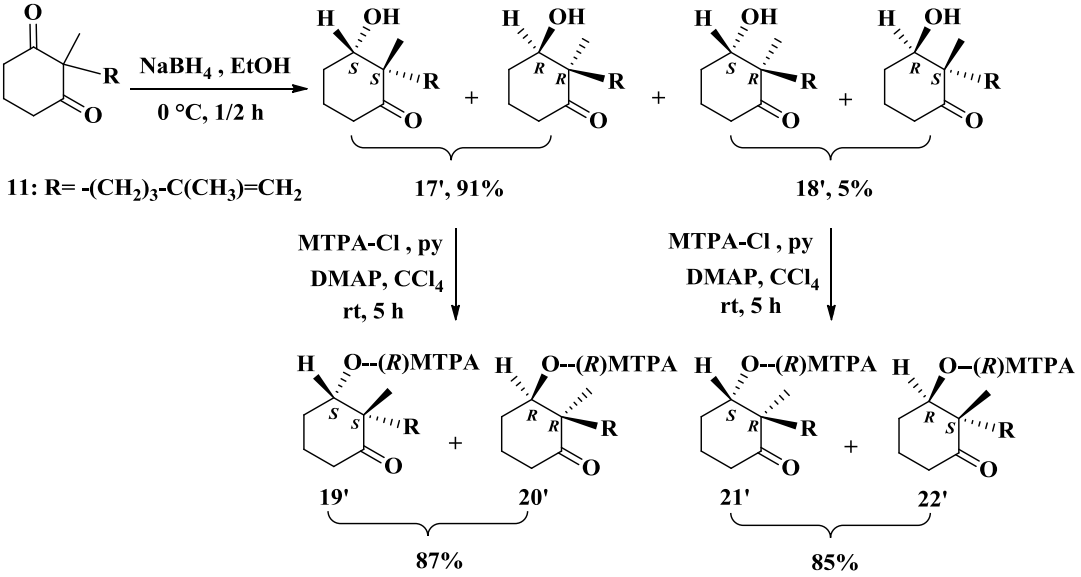
| **Ketol product** | **13 (2*S*, 3*S*)** | **14 (2*S*, 3*R*)** | **15 (2*S*, 3*S*)** | **16 (2*S*, 3*R*)** | **17 (2*S*, 3*S*)** | **18 (2*S*, 3*R*)** |
|---|---|---|---|---|---|---|
| $CH_3$ C(2) position (ppm) | 19.9 | 17.5 | 18.9 | 17.4 | 18.9 | 17.4 |
| $CH_2$ C(1') position (ppm) | 36.9 | 40.1 | 31.1 | 35.9 | 30.9 | 35.5 |

The selectivity concerning products **17** and **18** was determined by analysis of the $^{1}$H and $^{19}$F NMR spectra of (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA)[29,31,32]esters **19** to **22** (Scheme 9).




**Scheme 9:** Preparation of the (*R*)-MTPA esters **19**-**22** from the yeast products **17** and **18.**

The corresponding (*R*)-MTPA esters **19'** to **22'** of the racemic ketols **17'** and **18'** prepared from chemical reduction of dione **11** with $NaBH_4$ were studied as control standards (Scheme 10).




**Scheme 10:** Preparation of the (*R*)-MTPA esters **19'-22'** for the racemic products **17'** and **18'**.

The chemical shift of the singlet of the methyl group at C-2 position was significantly different for each diastereomeric MTPA derivative and was clearly observed in the $^{1}$H NMR spectrum. The same was true for the $CF_3$ signals for each MTPA ester which were separated in the $^{19}$F NMR spectrum. The results of the corresponding (*R*)-MTPA ester are summarised in Table 2.

**Table 2:** $^{1}$H and $^{19}$F NMR chemical shifts for methyl group in the C-2 position and the $CF_3$ group

| **(*R*)-MTPA ester** | **19 (2*S*,3*S*,*R*)** and **19' (2*S*,3*S*,*R*)** | **20 (2*R*,3*R*,*R*)** and **20' (2*R*,3*R*,*R*)** | **21 (2*R*,3*S*,*R*)** and **21' (2*R*,3*S*,*R*)** | **22 (2*S*,3*R*,*R*)** and **22' (2*S*,3*R*,*R*)** |
|---|---|---|---|---|
| $^{1}$H NMR $CH_3$ C(2) position δ (ppm) | 1.25 | 1.16 | 1.21 | 1.09 |
| **Δ δ (ppm)** | 0.09 | | 0.11 | |
| $^{19}$F NMR $CF_3$ δ (ppm) | -71.79 | -71.55 | -71.87 | -71.64 |

This significant difference for each MTPA ester was also clearly observed in the HPLC analysis as following: on the chromatogram of esters **19** and **20**, two peaks appear at 5.82 and 7.03 min like retention time in reference to the racemic mixture **19'** and **20'**. We have deducted by integration curve that the proportions were 94.8% and 5.2%. For the esters **21** and **22** by comparison with **21'** and **22'**, two peaks appear at 8.97 and 10.21 min. The corresponding proportions were 98% and 2%.

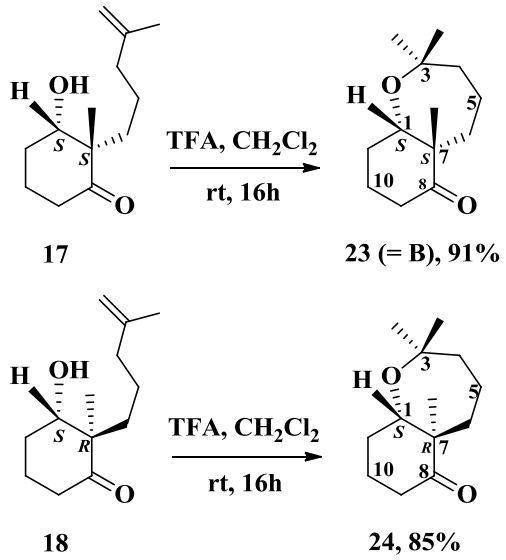
The enantiomeric excess of the yeast derived ketols **17** and **18** was determined on a chiral HPLC column with 90% and 96% respectively. These values were confirmed in $^{19}$F NMR. From the spectrum observed for esters **19** and **20** of the yeast ketol **17**, and the corresponding esters racemic **19'** and **20'**, two signals at -71.79 and -71.55 ppm, we have deducted by integration curve that the proportion was 95:5. Similarly for the esters **21**, **22**, **21'** and **22'**, two signals at -71.87 and -71.64 ppm were observed and we have deducted the proportion 98:2.

The absolute configuration of the yeast products **17** and **18** have been assigned on the basis of analysis of the $^{1}$H NMR chemical shifts of the (*R*)-MTPA esters **19**, **20**, **21** and **22** using the configuration correlation model of Mosher[32] and the (*R*)-MTPA esters **19'**, **20'**, **21'** and **22'** of the racemic ketols as controls. In each case, the methyl signal of the (*R*)-MTPA esters of the yeast products was the upfield diastereomer compared with the corresponding (*R*)-MTPA esters of the racemic ketols. According to the correlation model, this implies the (*S*)-configuration for the hydroxyl bearing chiral center of yeast products.

The stereochemistry of the C-3 position for the ketol **17** was clearly determined by $^{1}$H NMR. The doublet of doublet at 3.68 ppm ($J$ = 8.4 and 4.2 Hz) has been attributed to the proton in C-3 position. The coupling constant values indicated that the position of the proton was axial. Similarly for the ketol **18**, the coupling constant values ($J$ = 8.4 and 3.8 Hz),

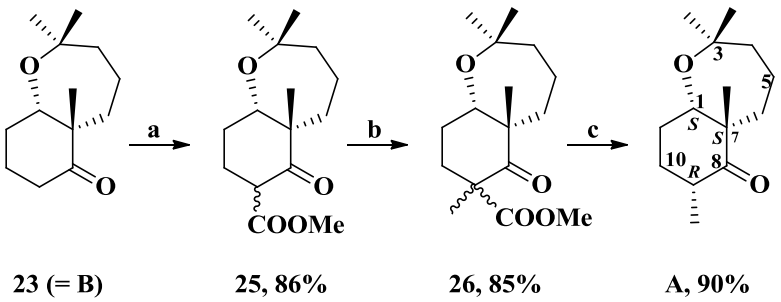
indicated that the proton at 3.89 ppm was also axial. This observation proved that the hydroxyl group in the yeast products **17** and **18** is equatorial.

We then turned our attention toward the desired intramolecular cyclisation. The optimal condition was carried out with ketol **17** and trifluoroacetic acid (TFA) in anhydrous dichloromethane as solvent under nitrogen atmosphere at room temperature for 16 h. The oxepane **23** was obtained as the only cyclised product with a yield of 91%. Applying this reaction to the ketol **18** afforded the diastereomer **24** in 85% yield (Scheme 11). The desired product **23** was easily characterised from its $^{1}$H NMR which indicated the absence of the two olefinic protons at $\delta$ = 4.65 and 4.69 ppm. The two new methyl groups were observed as a broad singlet at 1.53 ppm. Additional support from its $^{13}$C NMR spectrum and other analytical data confirmed the proposed structure of compound **23**.




**Scheme 11:** Synthesis of compounds **23** and **24**.

To finish the construction of the desired synthon **A**, it was necessary to introduce a methyl in C-9 position[33,34]. This last transformation involved the following sequence: carboxylation, methylation and decarboxylation to produce the expected compound **A** (Scheme 12).




Reagents and conditions: **a:** NaH, $Me_2CO_3$, THF, rt, 10h, 86%. **b:** NaH, $CH_3I$, THF, 0° C then rt, 16h, 85%. **c:** LiCl, HMPA, 95°C, 16h, 90%. **d:** $NaNH_2$, MeI, THF, rt, 16h.

**Scheme 12:** Synthesis of Western part **A**.

The stereochemistry of the newly formed stereogenic centre in C-9 position of compound **A** was clearly determined by $^{1}$H NMR. The doublet at 1.05 ppm ($J$ = 6.6 Hz) and the doublet of doublet of quadruplet at 2.76 ppm ($J$ = 11, 9 and 6.6 Hz) has been attributed respectively to the methyl group and the proton in C-9 position. The coupling constant values indicated that the position of the proton was axial. This observation proved that the methyl group in the C-9 position is *anti* to the methyl group in the C-7 position. Consequently, the absolute configuration of carbon 9 is *R*.

## Conclusion

The synthesis of western part A based upon catalytic asymmetric and enantioselective reduction proceeds in 9 steps and 10% yield from 2-methylcyclohexane-1,3-dione **7**.

This work has provided a general and efficient access to an optically active bicyclic oxepane and is expected to find further applications in synthesis of other related natural products. This flexible strategy should also give solutions for the preparation of other parts of Shaagrockol C.

## Acknowledgements

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## Experimental procedure

IR spectra were recorded as a KBr pellet or as a film on a spectrafile IRTF Plus MIDAC. Mass spectra were recorded on a JEOL D300 70 eV spectrometer. Microanalyses were performed by the analytical department of the UFR Sciences of the University of Reims. NMR data were recorded at 250 MHz for $^{1}$H, at 62 MHz for $^{13}$C and at 235 MHz for $^{19}$F on a Bruker AC 250 spectrometer. $CDCl_3$ was used as solvent. Chemical shifts are reported in ppm relative to TMS. Coupling constants are denoted in Hertz. HPLC column Chrompack, Lichchrosorb Si 60, 250 x 9 mm, eluent Hexane-THF (9:1), flow rate 0.9 mL/min. Optical rotations values were measured with Perkin-Elmer 241 spectrometer at 22 °C and are expressed as $[\alpha]^{22}_{D}$ (concentration in g/100 mL, solvent).

**5-Iodo-2-methylpent-1-ene (5)**
bp = 66–67 °C/18 mm (Lit[14]: 62 °C/17 mm).

**2-(Iodomethyl)-2-methyltetrahydrofuran (6)**
A solution of iodine (3.48 g, 13.68 mmol, 2.63 equiv) in $Et_2O$ (4 mL) was added to a solution of alcohol **3** (520 mg, 5.2 mmol), triphenylphosphine (1.54 g, 5.88 mmol, 1.13 equiv) and imidazole (403 mg, 5.93 mmol, 1.14 equiv) in a mixture of $CH_3CN$ and $Et_2O$ (1:3) (15 mL). The reaction was stirred under argon for 5 h at room temperature, then treated with a 5% solution $Na_2S_2O_3$ (25 mL) and extracted with a mixture of water and $Et_2O$ (1:1). The organic phase was collected and the aqueous phase was reextracted with $Et_2O$ (3x25 mL). The

combined organic layers were washed with a saturated $Na_2S_2O_3$ solution and then with brine, dried over $Na_2SO_4$ and filtered. The solvent was evaporated and the crude product was purified by silica gel column chromatography to give iodide **5** (450 mg, 41%) and compound **6** (290 mg, 25%).

**Compound (6)**

$R_f$ = 0.3 (PE-AcOEt, 9:1). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3025, 2960, 2875, 1453, 1375, 1259, 1175, 1067.

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.32 (s, 3H, $CH_3$), 1.60-2.01 (m, 4H, C$\underline{H_2}$-C$\underline{H_2}$-C), 3.20 (s, 2H, $CH_2I$), 3.84 (t, 2H, *J* = 6.5 Hz, -$CH_2$-O). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.4 ($CH_2I$), 25.9 ($CH_3$), 26.4 ($CH_2$), 36.5 ($CH_2$), 68.3 ($CH_2O$), 81.1 (C). Anal. Calcd for $C_6H_{11}I$: C, 34.28; H, 5.24; I, 60.48. Found: C, 34.52; H, 5.12; I, 60.34.

**2-Butyl-2-methylcyclohexane-1,3-dione (8) and 3-butoxy-2-methylcyclohex-2-en-1-one (9); General Procedure for compounds 10-12**.

To a solution of 2-methylcyclohexane-1.3-dione **7** (500 mg, 3.97 mmol) in DMSO (6 mL), and Aliquat 336 (139.6 mg, 0.397 mmol, 0.1 equiv) was added a *t-BuOK* (534 mg, 4.76 mmol, 1.2 equiv). The mixture was stirred for 30 min at room temperature. A solution of 1-iodobutane (810 mg, 4.40 mmol, 1.11 equiv) in DMSO (3 mL) was added dropwise. The mixture was warmed to 80 °C and stirred for 16 h, and then poured into ethyl acetate. After filtration over Florisil, the filtrate was washed with brine. The solvent was evaporated and the crude product purified by silica gel column chromatography to give **8** (447 mg, 63%) and O-alkylated compound **9** (130 mg, 18%).

**Compound (8)**

$R_f$ = 0.45 (PE-AcOEt, 4:1). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3075, 2872, 1730, 1705, 1454, 1375, 1265.

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.86 (t, 3H, *J* = 7.5 Hz, $CH_2$-C$\underline{H_3}$), 1.02-1.18 (m, 4H, C$\underline{H_2}$-$CH_3$), 1.21 (s, 3H, $CH_3$), 1.20–1.35 (m, 2H, C-$CH_2$-C$\underline{H_2}$), 1.70–2.12 (m, 4H, C$\underline{H_2}$-$CH_2$-CO and C-$CH_2$), 2.54–2.79 (m, 4H, 2$CH_2$-C=O). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 13.6 (-$CH_2$-$\underline{C}H_3$), 17.6 (-$\underline{C}H_2$-$CH_3$), 18.5 (C-$\underline{C}H_3$), 22.8 ($CH_2$-26.6 (C-$CH_2$-$\underline{C}H_2$), 37.4 (C-$\underline{C}H_2$), 37.7 (2$\underline{C}H_2$-C=O), 65.6 (C), 210.3 (2C=O). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.14; H, 10.05.

**Compound (9)**

$R_f$ = 0.35 (PE-AcOEt, 4:1). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3075, 2876, 1690, 1645, 1456, 1375, 1225, 1184, 1136, 1064, 954. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.85 (t, 3H, *J* = 7.25 Hz, $CH_2$-C$\underline{H_3}$), 1.02–1.50 (m, 2H, C$\underline{H_2}$-$CH_3$), 1.55–1.75 (m, 2H, O-$CH_2$-C$\underline{H_2}$), 1.68 (t, 3H, *J* = 1.5 Hz, $CH_3$), 1.88–2.0 (m, 2H, $CH_2$-C$\underline{H_2}$-$CH_2$), 2.23–2.29 (m, 2H, $CH_2$-C=O), 2.45–2.52 (tq, 2H, *J* = 6.1, 1.5 Hz, $CH_2$-C=), 3.94 (t, 2H, *J* = 6.5 Hz, O-$CH_2$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 7.3 ($CH_3$), 13.6 ($CH_2$-$\underline{C}H_3$), 18.9 ($\underline{C}H_2$-$CH_3$), 20.9 ($CH_2$-$\underline{C}H_2$-$CH_2$), 25.4 (O-$CH_2$-$\underline{C}H_2$-), 31.7 ($\underline{C}H_2$-C=), 36.2 ($\underline{C}H_2$-CO), 67.5 (O-$CH_2$), 114.9 (=$\underline{C}$-$CH_3$), 171.6 (=C-O), 198.8 (C=O). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: 72.62; H, 9.86.

**2-Allyl-2-methylcyclohexane-1,3-dione (10)**[28]

The compound **10** was prepared from **7** (1.26 g, 10 mmol), *t*-BuOK (1.35 g, 12 mmol) and allylbromide (2.72 g, 22.2 mmol) using the same procedure as described for the preparation of **8** and **9**. Purification by silica gel column chromatography afforded the only compound **10** (1.34 g, 82%).

**2-Methyl-2-(4-methylpent-4-enyl)cyclohexane-1,3–dione (11) and 2-methyl-3-(4-methylpent-4-enoxy)cyclohex-2-en-1-one (12)**[29]

Compounds **11** and **12** were prepared from **7** (365 mg, 2.90 mmol), *t*-BuOK (390 mg, 3.48 mmol) and iodide **5** (670 mg, 3.19 mmol) using the same procedure as described for the preparation of **8** and **9**. Purification by silica gel column chromatography afforded **11** (349 mg, 58%) and **12** (151 mg, 25%).

**Compound (11)**

$R_f$ = 0.40 (PE-AcOEt, 4:1). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3020, 2937, 2853, 1726, 1700, 1655, 1462, 1379, 1211, 1026, 893. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.22 (s, 3H, $CH_3$), 1.20–1.32 (m, 2H, C$\underline{H}_2$-$CH_2$-C=), 1.66 (br s, 3H, =C-$CH_3$), 1.72–1.79 (m, 2H, C-$CH_2$), 1.80–1.92 (m, 1H, $CH_2$-C$\underline{H}_2$-$CH_2$), 1.97 (t, 2H, *J* = 6.5 Hz, $CH_2$-C=), 2.02–2.10 (m, 1H, $CH_2$-C$\underline{H}_2$-$CH_2$), 2.54–2.76 (m, 4H, 2$CH_2$-C=O), 4.63 (m, 1H, =$CH_2$), 4.70 (m, 1H, =$CH_2$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.6 ($CH_2$-$\underline{C}H_2$-$CH_2$), 18.8 ($CH_3$), 22.0 (=C-$\underline{C}H_3$), 22.3 ($\underline{C}H_2$-$CH_2$C=), 36.8 (C-$\underline{C}H_2$), 37.6 ($\underline{C}H_2$-C=), 37.8 (2$\underline{C}H_2$-C=O), 65.5 (C), 110.5 (=$CH_2$), 144.6 ($CH_2$-$\underline{C}$=), 210.1 (2C=O). MS (EI, 70eV): m/z (%) = 208 $M^+$ (10); 126 (100); 110 (38); 96 (44), 82 (100); 67 (37); 55 (57). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.89; H, 9.72.

**Compound (12)**

$R_f$ = 0.31 (PE-AcOEt, 4:1). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3072, 2936, 2865, 1686, 1649, 1618, 1454, 1377, 1240, 1197, 1097, 1053, 995, 889. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.66 (t, 3H, *J* = 1.5 Hz, $CH_3$), 1.69 (br s, 3H, =C-$CH_3$), 1.75–1.86 (m, 2H, O-$CH_2$-C$\underline{H}_2$), 1.87–1.99 (m, 1H, $CH_2$-C$\underline{H}_2$-$CH_2$), 2.11 (t, 2H, *J* = 7.25 Hz, C$\underline{H}_2$-C($CH_3$)=), 2.28 (t, 2H, *J* = 6.5 Hz, -C$\underline{H}_2$-CO), 2.50 (tq, 2H, *J* = 6.1, 1.5 Hz, $CH_2$-C=), 3.95 (t, 2H, *J* = 6.5 Hz, OC$\underline{H}_2$), 4.65 (m, 1H, =$CH_2$), 4.71 (m, 1H, =$CH_2$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 7.4 ($CH_3$), 20.9 ($CH_2$-$\underline{C}H_2$-$CH_2$), 22.3 (=C-$\underline{C}H_3$), 25.4 ($\underline{C}H_2$-C=), 27.5 (O-$CH_2$-$\underline{C}H_2$-), 33.7 ($\underline{C}H_2$-C=), 36.2 ($\underline{C}H_2$-CO), 67.1 ($OCH_2$), 110.7 (=$CH_2$), 115.0 (=$\underline{C}$-$CH_3$), 144.4 ($CH_2$-$\underline{C}$=), 171.5 (=C-O), 198.9 (CO). MS (EI, 70eV): m/z (%) = 208 $M^+$ (100); 126 (44); 83 (50); 96 (44), 67 (23), 55 (100). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 75.05; H, 9.59.

**(2*S*,3*S*)-(+)-2-butyl-3-hydroxy-2-methylcyclohexan-1-one (13) (2*R*,3*S*)-(-)-2-butyl-3-hydroxy-2-methylcyclohexan-1-one (14); General Procedure for compounds 15-18**

Dry active baker's yeast (10 g) was added to a solution of Saccharose (15 g) in distilled water (100 mL) at 30-35 °C. The mixture was then stirred for 15 min, maintaining the temperature between 30 and 35 °C, and then the dione **8** (400 mg, 2.20 mmol) was added. The mixture was vigorously stirred at 35 °C for 24 h. Additional Saccharose (5 g) and baker's yeast (5 g) were added again.

After stirring at 35 °C for 24 h, the mixture was diluted with brine (50 mL) and $CH_2Cl_2$ (80 mL). After filtration over Celite (10 g), the two phases were separated and the aqueous layer extracted with $CH_2Cl_2$ (3x25 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The components of the mixture were purified by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) to afford recovered dione **8** (61 mg, $R_f$ = 0.42), **13** (137 mg, 40%) and **14** (190 mg, 55%). The yield was based on recovered starting material.

**Compound (13)**

$R_f$ = 0.34 ($CH_2Cl_2$-$Et_2O$, 9:1); $[\alpha]^{22}_D$ = + 68.0° (c = 0.57, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3620 (OH), 3452, 3025, 2875, 1710, 1375, 1240, 1158, 1135, 1065. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.89 (t, 3H, *J* = 7.25 Hz, $CH_2$-C$\underline{H}_3$), 0.94-1.07 (m, 1H, C$\underline{H}_2$-$CH_3$), 1.15 (s, 3H, $CH_3$), 1.17-1.39 (m, 3H, -C$\underline{H}_2$-C$\underline{H}_2$-$CH_3$), 1.51-1.79 (m, 3H, C-C$\underline{H}_2$ and $CH_2$-C$\underline{H}_2$-$CH_2$), 1.69 (br s, 1H, OH), 1.84-2.07 (m, 3H, C$\underline{H}_2$-C$\underline{H}_2$-$CH_2$), 2.32-2.40 (ddd, 2H, *J* = 11.8, 5.7, 3.0

Hz, $CH_2$-CO), 3.68 (dd, 1H, *J* = 8.4, 4.6 Hz, CH-O). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 13.9 ($CH_2$-$\underline{C}H_3$), 18.9 ($CH_3$), 20.7 ($CH_2$-$\underline{C}H_2$-$CH_2$), 23.4 ($\underline{C}H_2$-$CH_3$), 25.5 (C-$CH_2$-$\underline{C}H_2$), 28.8 ($\underline{C}H_2$-CH), 31.1 (C-$\underline{C}H_2$), 37.6 ($\underline{C}H_2$-CO), 54.7 (C), 77.5 (CH), 213.9 (CO).

**Compound (14)**

$R_f$ = 0.29 ($CH_2Cl_2$-$Et_2O$, 9:1); $[\alpha]^{22}_D$ = - 49° (c = 0.54, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3485, 3072, 2875, 1711, 1454, 1365, 1145, 1112, 1055. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, *J* = 7.25 Hz, $CH_2$-$C\underline{H}_3$), 0.98-1.09 (m, 1H, $C\underline{H}_2$-$CH_3$), 1.12 (s, 3H, $CH_3$), 1.19-1.40 (m, 3H, -$C\underline{H}_2$-$C\underline{H}_2$-$CH_3$), 1.45-1.90 (m, 4H, C-$C\underline{H}_2$ and $C\underline{H}_2$-$CH_2$-CH), 1.62 (br s, 1H, OH), 1.98-2.20 (m, 2H, $C\underline{H}_2$-CH), 2.35-2.50 (m, 2H, $CH_2$-CO), 3.90 (m, 1H, CH-O). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 13.9 ($CH_2$-$CH_3$), 17.4 ($CH_3$), 20.7 ($\underline{C}H_2$-$CH_2$-CH), 23.3 ($\underline{C}H_2$-$CH_3$), 26.1 (C-$CH_2$-$\underline{C}H_2$), 28.1 ($\underline{C}H_2$-CH), 35.9 (C-$\underline{C}H_2$), 37.8 ($\underline{C}H_2$-CO), 54.4 (C), 76.4 (CH), 214.4 (CO).

**(2*S*,3*S*)-(+)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (15) and (2*R*,3*S*)-(-)-2-allyl-3-hydroxy-2-methylcyclohexan-1-one (16)**

Compounds **15** and **16** were prepared from **10** (1.50 g, 9.04 mmol) using the same procedure as described for the preparation of **13** and **14**. Purification by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) afforded recovered dione **10** (225 mg, $R_f$ = 0.49), **15** (580 mg, 45%) and **16** (644 mg, 50%). The yield was based on recovered starting material.

**Compound (15)**

$R_f$ = 0.42 ($CH_2Cl_2$-$Et_2O$, 9:1) ; $[\alpha]^{22}_D$ = + 32.4° (c = 0.34, $CHCl_3$) ; $[\alpha]^{25}_D$ = + 32.0° (c = 0.42, $CHCl_3$)[28,31].

**Compound (16)**

$R_f$ = 0.36 ($CH_2Cl_2$-$Et_2O$, 9:1) ; $[\alpha]^{22}_D$ = - 13.9° (c = 0.78, $CHCl_3$) ; $[\alpha]^{25}_D$ = - 4.7° (c = 0.6, $CHCl_3$)[28,31].

**(2*S*,3*S*)-(+)-3-hydroxy-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (17) (2*R*,3*S*)-(-)-3-hydroxy-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (18)**

Compounds **17** and **18** were prepared from **11** (1.50 g, 7.21 mmol) using the same procedure as described for the preparation of **13** and **14**. Purification by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) afforded recovered dione **11** (225 mg, $R_f$ = 0.50), **17** (488 mg, 38%) and **18** (732 mg, 57%). The yield was based on recovered starting material.

**Compound (17)**

$R_f$ = 0.4 ($CH_2Cl_2$-$Et_2O$, 9:1); $[\alpha]^{22}_D$ = + 59.9° (c = 0.17, $CHCl_3$). HPLC: Chrompack, Lichrosorb Si 60, 250 x 9 mm, hexane-THF (9:1), flow rate 0.9 mL/min; $t_R$ = 5.82 and 7.03 min; ee = 90%. IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3626 (OH), 3481, 3082, 2957, 2872, 1703, 1649, 1462, 1379, 1236, 1159, 1134, 1060, 893. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H, $CH_3$), 1.20-1.45 (m, 2H, C-$CH_2$-$C\underline{H}_2$), 1.50-1.72 (m, 3H, C-$C\underline{H}_2$ and $CH_2$-$C\underline{H}_2$-$CH_2$), 1.68 (br s, 3H, =C-$CH_3$), 1.78 (br s, OH), 1.88-2,08 (m, 5H, $C\underline{H}_2$-C= and $C\underline{H}_2$-$C\underline{H}_2$-CH), 2.30-2.40 (ddd, 2H, *J* = 11.3, 5.7 and 1.2 Hz, $CH_2$-CO), 3.68 (dd, 1H, *J* = 8.4, 4.2 Hz, CH-O), 4.65 (m, 1H, =$CH_2$), 4.69 (m, 1H, =$CH_2$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 18.9 ($CH_3$), 20.6 ($\underline{C}H_2$-$CH_2$-CH), 21.2 (C-$CH_2$-$\underline{C}H_2$), 22.3 ($\underline{C}H_3$-C=), 28.8 ($\underline{C}H_2$-CHOH), 30.9 (C-$\underline{C}H_2$), 37.6 ($\underline{C}H_2$-CO), 38.2 ($\underline{C}H_2$-C=), 54.6 (C), 77.5 (CH), 110.2 (=$CH_2$), 145.3 (-C=), 213.9 (CO). MS (EI, 70eV): m/z (%) = 211 $M^{+1}$ (3); 210 $M^+$ (5); 128 (100); 110 (55); 95 (53), 82 (35); 69 (30); 67 (30); 55 (50). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.15; H, 10.55.

**Compound (18)**

$R_f$ = 0.35 ($CH_2Cl_2$-$Et_2O$, 9:1); $[\alpha]^{22}_D$ = - 28.9° (c = 0.56, $CHCl_3$). HPLC: Chrompack, Lichrosorb Si 60, 250 x 9 mm, hexane-THF (9:1), flow rate 0.9 mL/min; $t_R$ = 8.97 and 10.21 min; ee = 96%. IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3626 (OH), 3484, 3072, 2947, 2872, 1705, 1643, 1454, 1365, 1228, 1143, 1113, 1049, 889. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.11 (s, 3H, $CH_3$), 1.13-1.47 (m, 2H, C-$CH_2$-C$\underline{H}_2$), 1.48-1.65 (m, 2H, C-$CH_2$), 1.69 (br s, 3H, =C-$CH_3$), 1.72-1.88 (m, 2H, C$\underline{H}_2$-C$\underline{H}_2$-CH), 1.98-2.18 (m, 4H, C$\underline{H}_2$-C=, C$\underline{H}_2$-C$\underline{H}_2$-CH), 2.27-2.46 (m, 2H, C$\underline{H}_2$-CO), 3.89 (dd, 1H, *J* = 8.4, 3.8 Hz, CH), 4.64 (m, 1H, =$CH_2$), 4.69 (m, 1H, =$CH_2$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.4 ($CH_3$), 20.6 (-$\underline{C}H_2$-$CH_2$-CH), 21.7 (C-$CH_2$-$\underline{C}H_2$), 22.2 ($CH_3$-C=), 28.2 ($\underline{C}H_2$-CH), 35.5 (C-$\underline{C}H_2$), 37.8 ($\underline{C}H_2$-CO), 38.1 ($\underline{C}H_2$-C=), 54.3 (C), 76.2 (CH), 110.2 (=$CH_2$), 145.2 (-C=), 214.4 (CO). MS (EI, 70eV): m/z (%) = 211 $M^{+1}$ (2), 210 $M^+$ (7), 192 (9), 128 (100), 110 (42), 95 (36), 82 (23), 81 (22), 69 (20). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.14; H, 10.23.

**Chemical reduction of dione 11 with $NaBH_4$; Preparation of racemic ketols 17' and 18'**

A solution of compound **11** (208 mg, 1.0 mmol) in anhyd THF (5 mL) was added dropwise to a solution of $NaBH_4$ (40 mg, 1.0 mmol) in EtOH (distilled over Mg) (0.5 mL) at 0 °C for 15 min. The mixture was stirred at room temperature for 30 min and the pH was adjusted to 2 with 0.5 N HCl (2.5 mL). The mixture was then extracted with $Et_2O$ (3x10 mL). The combined organic phases were combined; washed with brine, dried ($MgSO_4$), and concentrated. The mixture was purified by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) to afford recovered dione **11** (20 mg, $R_f$ = 0.50), **17'** (172 mg, 91%, $R_f$ = 0.40) and **18'** (9 mg, 5%, $R_f$ = 0.35). The yield was based on recovered starting material.

**Compounds (17')** and **(18')**

The spectral characteristics of racemic ketols **17'** and **18'** were the same observed for **17** and **18** respectively.

**(2*S*,3*S*)-3-[(2*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy]-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (19) and (2*R*,3*R*)-3-[(2*R*)-2-methoxy-2-trifluoromethyl-2-phenylacetoxy]-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (20)**

**General Procedure for (*R*)-MTPA esters (19) and (20)**

Pyridine (0.1 mL, 1.20 mmol, 4.8 equiv), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.0 mmol, 4.0 equiv) and DMAP (5.0 mg, 0.04 mmol, 0.16 equiv) were added to a stirred solution of ketol **17** (52 mg, 0.25 mmol) in anhyd $CCl_4$ (1 mL). The mixture was stirred at room temperature for 5 h and poured into ether (10 mL) and water (10 mL). The layers were separated and the organic phase was washed with 0.1N HCl (5 mL) and aq sat $NaHCO_3$ (3x5 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product purified by silica gel column chromatography ($CH_2Cl_2$-ether, 9:1) to provide the diastereomeric products (*R*)-MTPA esters **19** and **20** (85%).

**Compound 19**

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.25 (s, 3H, $CH_3$), 1.05-1.46 (m, 2H, C-$CH_2$-C$\underline{H}_2$), 1.50-1.80 (m, 3H, C-$CH_2$, C$\underline{H}_2$-$CH_2$-CO), 1.69 (br s, 3H, =C-$CH_3$), 1.89-2.10 (m, 5H, C$\underline{H}_2$-C($CH_3$)=, C$\underline{H}_2$-CH-O(*R*)-MTPA, C$\underline{H}_2$-$CH_2$-CO), 2.28-2.45 (m, 2H, C$\underline{H}_2$-CO), 3.54 (br s, 3H, $OCH_3$), 4.65 (m, 1H, =$CH_2$), 4.69 (m, 1H, =$CH_2$), 5.06 (dd, 1H, *J* = 8.8, 4.6 Hz, C$\underline{H}$-O(*R*)-MTPA, 7.39-7.41 (m, 3H, aromatic), 7.51-7.53 (m, 2H, aromatic). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 18.9 ($CH_3$), 20.7 (-$\underline{C}H_2$-$CH_2$-CO), 21.2 (C-$CH_2$-$\underline{C}H_2$), 22.3 (-C($\underline{C}H_3$)=), 29.8 ($\underline{C}H_2$-CH), 31.0 (C-$\underline{C}H_2$), 37.6 ($\underline{C}H_2$-CO), 38.3 ($\underline{C}H_2$-C($CH_3$)=), 54.8 (C), 78.0 ($OCH_3$), 81.3

(CH-O), 84.5 (q, $J_{CCF}$ = 29.5 Hz, C-$CF_3$), 110.7 (=$CH_2$), 123.3 (q, $J_{CF}$ = 287.5 Hz, $CF_3$), 127.5-131.7 ( $C_6H_6$), 145.2 (C($CH_3$)=), 170.3 (OCO), 214.8 (CO). $^{19}$F NMR (235 MHz, $CDCl_3$+ $CFCl_3$) δ (ppm): - 71.79 ppm.

**Compound 20**

$^1$H NMR (250 MHz, $CDCl_3$): The same shielding was observed for compound **19** and only the methyl signal at C-2 position is given at 1.16 ppm.

$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 14.1 ($CH_3$), 20.7 (-$CH_2$-$CH_2$-CO), 21.1 (C-$CH_2$-$CH_2$), 22.3 (-C($CH_3$)=), 28.6 ($CH_2$-CH), 32.0 (C-$CH_2$), 37.4 ($CH_2$-CO), 38.1 ($CH_2$-C($CH_3$)=), 53.2 (C), 78.0 ($OCH_3$), 81.3 (CH-O), 84.5 (q, $J_{CCF}$ = 29.5 Hz, C-$CF_3$), 110.5 (=$CH_2$), 123.3 (q, $J_{CF}$ = 287.5 Hz, $CF_3$), 127.5-131.7 ( $C_6H_6$), 145.0 (C($CH_3$)=), 170.3 (OCO), 212.1 (CO). $^{19}$F NMR (235 MHz, $CDCl_3$+ $CFCl_3$) δ (ppm): - 71.55 ppm.

**(2*R*,3*S*)-3-[(2*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy]-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (21) and (2*S*,3*R*)-3-[(2*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy]-2-methyl-2-(4-methylpent-4-enyl)cyclohexan-1-one (22)**

Compounds **21** and **22** were prepared from **18** (55 mg, 7.63 mmol) using the same procedure as described for the preparation of **19** and **20**. Purification by silica gel column chromatography ($CH_2Cl_2$-ether, 9:1) afforded the diastereomeric products (*R*)-MTPA esters **21** and **22** (82%).

**Compound 21**

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.21 (s, 3H, $CH_3$), 1.14-1.35 (m, 2H, C-$CH_2$-C$H_2$), 1.45-1.68 (m, 2H, C-$CH_2$), 1.65 (br s, 3H, =C-$CH_3$), 1.75-2.20 (m, 6H, C$H_2$-C($CH_3$)=, C$H_2$-CH-O(*R)*-MTPA, C$H_2$-$CH_2$-CO), 2.30-2.42 (m, 2H, C$H_2$-CO), 3.49 (br s, 3H, $OCH_3$), 4.61 (m, 1H, =$CH_2$), 4.68 (m, 1H, =$CH_2$), 5.08 (dd, 1H, *J* = 8.6, 4.5 Hz, C*H*-O(*R*)-MTPA, 7.39-7.41 (m, 3H, aromatic), 7.51-7.53 (m, 2H, aromatic). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 14.4 ($CH_3$), 20.6 (-$CH_2$-$CH_2$-CO), 21.7 (C-$CH_2$-$CH_2$), 22.2 (-C($CH_3$)=), 28.9 ($CH_2$-CH), 35.8 (C-$CH_2$), 37.8 ($CH_2$-CO), 38.2 ($CH_2$-C($CH_3$)=), 54.5 (C), 78.0 ($OCH_3$), 80.9 (CH-O), 84.5 (q, $J_{CCF}$ = 29.5 Hz, C-$CF_3$), 110.2 (=$CH_2$), 123.3 (q, $J_{CF}$ = 287.5 Hz, $CF_3$), 127.4-131.6 ($C_6H_6$), 145.4 (C($CH_3$)=), 170.4 (OCO), 214.8 (CO). $^{19}$F NMR (235 MHz, $CDCl_3$+ $CFCl_3$) ) δ (ppm): - 71.87 ppm.

**Compound 22**

$^1$H NMR (250 MHz, $CDCl_3$): The same shielding was observed for compound **21** and only the methyl signal at C-2 position is given: 1.09 ppm.

$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 15.5 ($CH_3$), 20.3 (-$CH_2$-$CH_2$-CO), 21.2 (C-$CH_2$-$CH_2$), 22.2 (-C($CH_3$)=), 28.3 ($CH_2$-CH), 35.4 (C-$CH_2$), 37.8 ($CH_2$-CO), 38.2 ($CH_2$-C($CH_3$)=), 54.5 (C), 78.0 ($OCH_3$), 80.8 (CH-O), 84.4 (q, $J_{CCF}$ = 29.5 Hz, C-$CF_3$), 110.5 (=$CH_2$), 123.2 (q, $J_{CF}$ = 287.5 Hz, $CF_3$), 127.6-131.5 ( $C_6H_6$), 145.2 (C($CH_3$)=), 170.5 (OCO), 214.4 (CO). $^{19}$F NMR (235 MHz, $CDCl_3$+ $CFCl_3$) δ (ppm): - 71.64 ppm.

**Preparation of (*R*)-MTPA esters 19', 20', 21' and 22' from racemic ketols 17' and 18'**

Compounds **19'** and **20'** were prepared from **17'** using the same procedure as described for the preparation of **19** and **20**. Purification by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) afforded the diastereomeric products (*R*)-MTPA esters **19'** and **20'** (87%).

Compounds **21'** and **22'** were prepared from **18'** using the same procedure as described for preparation of **19** and **20**. Purification by silica gel column chromatography ($CH_2Cl_2$-$Et_2O$, 9:1) afforded the diastereomeric products (*R*)-MTPA esters **21'** and **22'** (85%).

**(1*S*,7*S*)-(+)-3,3,7-trimethyl-2-oxabicyclo[5,4,0]undecan-8-one (23)**

**General procedure for compound 23**

TFA (0.65 mL, 8.5 mmol, 50 equiv) was added to a solution of **17** (35 mg, 0.17 mmol) in anhydrous $CH_2Cl_2$ (1.5 mL). The mixture was stirred at room temperature for 16 h. The reaction was stopped with $NaHCO_3$ powder and filtered. The solvent was evaporated and the crude product, purified by silica gel column chromatography to provide **23** (32 mg, 91%).

$R_f$ = 0.38 (PE-AcOEt, 2:1); $[\alpha]^{22}_D$ = + 38.6° (c = 0.24, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3042, 2957, 2874, 1711, 1469, 1379, 1169, 1136, 1093. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.92−1.32 (m, 2H, -C-$CH_2$-C$\underline{H_2}$), 1.10 (s, 3H, $CH_3$), 1.45 (br s, 6H, $2CH_3$), 1.50-2.02 (m, 8H, C$\underline{H_2}$-C$\underline{H_2}$-CH-O, C-C$\underline{H_2}$-$CH_2$-C$\underline{H_2}$- C), 2.35 (t, 2H, *J* = 6.5 Hz, -$CH_2$-CO), 3.65 (dd, 1H, *J* = 6.3, 3.7 Hz, CH). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.6 ($CH_2$), 18.9 ($CH_3$), 20.6 ($CH_2$), 25.5 ($2CH_3$), 28.8 ($CH_2$), 31.6 (-C-$\underline{C}H_2$), 37.5 ($\underline{C}H_2$-C=O), 41.0 ($CH_2$), 54.5 (C), 77.4 (CH-O), 89.0 (C-O), 213.6 (C=O). MS (EI, 70eV): m/z (%) = 210 $M^+$ (3), 141 (10), 138 (12), 95 (15), 85 (66), 83 (100), 69 (10), 55 (9). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.35; H, 10.48.

**(1*S*,7*R*)-(-)-3,3,7-trimethyl-2-oxabicyclo[5,4,0]undecan-8-one (24)**

Compound **24** was prepared from **18** (50 mg, 0.24 mmol) and TFA (0.92 mL, 12.0 mmol) using the same procedure as described for the preparation of **23**. Purification by silica gel column chromatography to afford **24** (43 mg, 85%).

$R_f$ = 0.38 (PE-AcOEt, 2:1); $[\alpha]^{22}_D$ = - 16.7° (c = 0.28, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3030, 2947, 2883, 1711, 1466, 1375, 1172, 1140. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.10 (s, 3H, $CH_3$), 1.15−1.45 (m, 4H, -C-$CH_2$-C$\underline{H_2}$, C$\underline{H_2}$-$CH_2$-CO), 1.53 (br s, 6H, $2CH_3$), 1.55-2.16 (m, 6H, C-C$\underline{H_2}$-, O-C-C$\underline{H_2}$, C$\underline{H_2}$-CH-O), 2.36 (t, 2H, *J* = 6.6 Hz, -$CH_2$-CO), 3.87 (dd, 1H, *J* = 6.6, 3.7 Hz, CH). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.4 ($CH_3$), 18.3 ($CH_3$), 20.5 ($CH_2$), 25.5 ($2CH_3$), 28.5 ($CH_2$), 35.7 (-C-$\underline{C}H_2$), 37.7 ($\underline{C}H_2$-C=O), 40.9 ($CH_2$), 54.4 (C), 75.7 (CH-O), 89.1 (C-O), 213.9 (C=O). MS (EI, 70eV): m/z (%) = 210 $M^+$ (11), 193 (16), 141 (18), 128 (22), 109 (25), 95 (28), 85 (100), 83 (100), 69 (19). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.14; H, 10.39.

**(1*S*,7*S*,9*R*/1*S*,7*S*,9*S*)-methyl 3,3,7-trimethyl-8-oxo-2-oxabicyclo[5,4,0]undecane-9-carboxylate (25)**

NaH (61 mg, 1.26 mmol) was washed three times in hexane. A solution of dimethylcarbonate (0.16 mL, 1.89 mmol) in anhydrous THF (2 mL) was then added. The mixture was stirred under argon at room temperature over 10 min. A solution of **23** (45 mg, 0.21 mmol) in anhyd THF (1 mL) was added. After stirring at the same temperature for 10 h, the mixture was diluted with 5% aq $NH_4Cl$ (5 mL) and extracted in $Et_2O$ (3x5mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by silica gel column chromatography to afford **25** (48.5 mg, 86 %,).

$R_f$ = 0.37 ($CH_2Cl_2$-$Et_2O$, 9:1); $[\alpha]^{22}_D$ = + 49.3° (c = 0.25, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3030, 2957, 2820, 1745, 1712, 1462, 1375, 1160, 1136, 1055, 1030. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.11 (s, 3H, $CH_3$), 1.45 (br s, 6H, $2CH_3$), (1.03−3.11 (m, 11H, $5CH_2$, $CH_2$-CO), 3.66 (dd, 1H, *J* = 7.0, 4.0 Hz, CH-O), 3.71 (s, 3H, $OCH_3$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 17.8 ($CH_2$), 18.9 ($CH_3$), 20.8 ($CH_2$), 25.5 ($2CH_3$), 28.8 ($CH_2$), 31.8 ($CH_2$), 41.7 ($CH_2$), 45.2 (CH), 52.5 ($CH_3$), 54.5 (C), 77.3 (CH), 85.9 (C), 176.8 (CO), 213.6 (CO).

**(1*S*,7*S*,9*R*/1*S*,7*S*,9*S*)-methyl 3,3,7,9-tetramethyl-8-oxo-2-oxabicyclo[5,4,0]undecane-9-carboxylate (26)**

A solution of **25** (45 mg, 0.17 mmol) in anhydrous THF (1 mL) was added to a solution of NaH (21 mg, 0.88 mmol) in anhyd THF (1 mL) stirred under argon at 0 °C. The mixture was stirred at room temperature over 50 min. A solution of $CH_3I$ (0.11 mL, 1.70 mmol) in anhydrous THF (0.25 mL) was added dropwise for 10 min. After stirring at the same temperature for 16 h, the reaction was stopped with 5% aq $NH_4Cl$. The mixture was extracted with $Et_2O$ (3x4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by silica gel column chromatography to afford **26** (41 mg, 85%).

$R_f$ = 0.35 (PE-AcOEt, 19:1); $[\alpha]^{22}_D$ = + 37.5° (c = 0.21, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3046, 2955, 2876, 1745, 1711, 1475, 1385, 1240, 1136, 1055, 1035. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.12 (s, 3H, $CH_3$), 1.19 (s, 3H, $CH_3$), 1.45 (br s, 6H, $2CH_3$), 1.05–2.25 (m, 10H, $2CH_2$), 3.66 (dd, 1H, *J* = 6.8, 4.0 Hz, CH-O), 3.72 (s, 3H, $OCH_3$). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 16.9 ($CH_3$), 17.9 ($CH_2$), 18.8 ($CH_3$), 20.7 ($CH_2$), 25.5 ($2CH_3$), 28.7 ($CH_2$), 31.8 ($CH_2$), 41.8 ($CH_2$), 52.3 ($CH_3$), 54.5 (C), 55.2 (CH), 77.2 (CH), 85.7 (C), 174.9 (CO), 213.6 (CO).

**(1*S*,7*S*,9*R*)-(+)-3,3,7,9-tetramethyl-2-oxabicyclo[5,4,0]undecan-8-one (A)**

The mixture of **26** (40 mg, 0.14 mmol) and LiCl (40.5 mg, 0.95 mmol) in HMPA (1 mL) was stirred at 95 °C for 16 h. The mixture was cooled, diluted in water and extracted with $Et_2O$ (3x3mL). The combined organic layers was washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by silica gel column chromatography to afford **A** (27 mg, 90%).

$R_f$ = 0.4 (PE-AcOEt, 19:1); $[\alpha]^{22}_D$ = + 35.7° (c = 0.24, $CHCl_3$). IR ($CHCl_3$) $\upsilon_{max}$ ($cm^{-1}$): 3046, 2957, 2876, 1712, 1462, 1375, 1160, 1136, 1093, 1049 $cm^{-1}$. $^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.05 (d, 3H, *J* = 6.6 Hz, -CH-$CH_3$), 1.12 (s, 3H, C-$CH_3$), 1.38 (br s, 6H, $2CH_3$), 1.03-2.16 (m, 10H, 5 $CH_2$), 2.76 (ddq, 1H, *J* = 11, 9, 6.5 Hz, CH), 3.65 (dd, 1H, *J* = 7.4 Hz, CH-O). $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 16.8 ($CH_3$), 17.9 ($CH_2$), 18.9 ($CH_3$), 20.7 ($CH_2$), 25.5 ($2CH_3$), 28.8 ($CH_2$), 31.8 (C-$CH_2$), 42.3 (CH-CO), 43.2 ($CH_2$), 54.5 (C), 77.3 (CH-O), 88.9 (C-O), 213.7 (C=O). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.88; H, 10.80.

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