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Approach to the Synthesis of Diterpenes with the Bicyclo[5.3.0]decane System: (±) 10-*epi*-tormesol.

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Abstract.- The synthesis of (±) 10-*epi*-tormesol, **27**, has been achieved from (±) 1-acetyl-3a,6-dimethylhexahydroazulene **1**, by coupling of **5**, a dehydroderivative of **1**, with **23**. The same synthetic procedure afforded a series of diterpenes **24**–**26** and **28** with the same biannular system. Direct reduction of **1** with different methods does not give the desired spatial relationship (*trans/cis*) between Me-C_7/H-6/H-10 on the substrate, affording instead *trans/trans* (compounds **5** and **18**) and *cis/cis* (compound **9**). Indirect reduction: epoxydation followed by catalytic hydrogenation afforded the desired stereochemistry on the intermediate but deoxygenation caused epimerization at C-10. This synthetic achievement confirmed the original structure assigned to tormesol some years ago.

INTRODUCTION

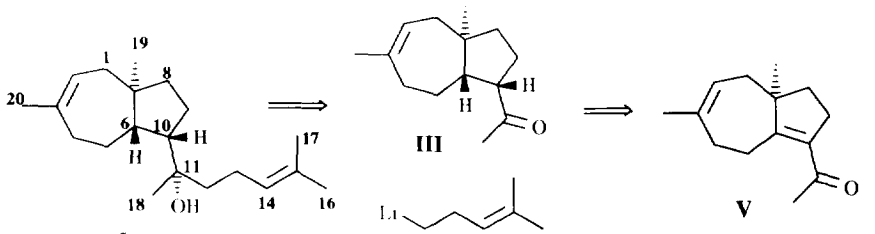
Recently, we have succesfully accomplished the synthesis of (±) 1-acetyl-3a,6-dimethylhexahydroazulene from nerolidol.[1] This synthetic achievement represents an important step towards the total synthesis of tormesane diterpenoids[2,3] and other natural products[4-6] which possess a bicyclo[5.3.0]decane system.

Tormesol,[2] whose structure was determined by chemical and spectroscopic methods, can be considered the parent compound of other tormesane diterpenoids isolated from one of the chemotypes of *Halimium viscosum*,[3] that differ from it in the functionality of either ring-A and/or the eight carbon atom side chain.

We report here the first synthetic approach to tormesol as a starting point for the asymmetric total synthesis of natural tormesol and derivatives in order to obtain their complete pharmacological spectra.

RESULTS AND DISCUSSION

The tormesol's backbone[2b] (**I**) construction requires coupling between **III** and the organometallic derivative **IV**. The former could be prepared from enone **V**, whose synthesis from nerolidol has been recently published.[1] Direct and indirect methods have been used to attempt the transformation of Enone **V** into **III** (Scheme I).

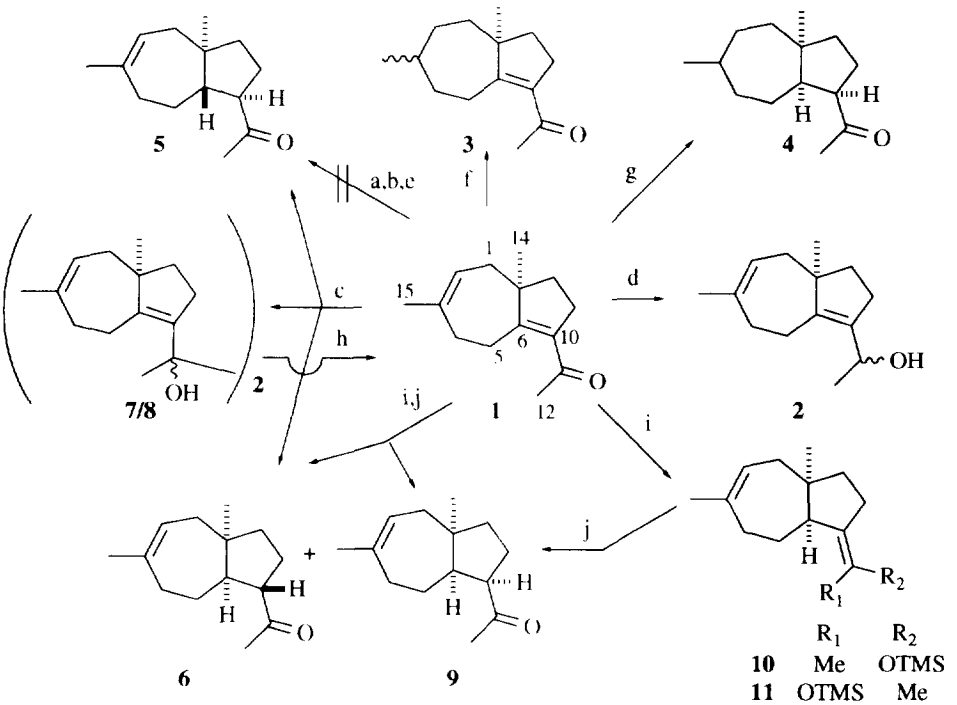


Scheme I

DIRECT METHODS. Among the direct methods used, five of them can be pointed out (Scheme II): Reduction with metals (a, b, c); Metal hydrides (d, e); Ionic hydrogenation (f); Heterogeneous catalytic hydrogenation (g) and Hydrosilylation reaction (i) (Scheme II).

Most of the reaction conditions have been successfully set up with model compounds. However, when **1** was used as starting material either with $Zn/NiCl_2$[7] or Li/HMPA[8] or with $(Ph_3PCuH)_6$[9] it was recovered unreacted while in the cases of metal hydrides (*e.g.* $NaBH_4$/MeOH,[10] $NaBH_4$/EtOH,[11] K-selectride®,[12] Bu_3SnH/AIBN[13]) an unuseful epimeric mixture of secondary hydroxy derivatives, **2**, was obtained. The Birch reduction, Li/NH_3 (l),[14] afforded –depending upon reaction conditions– different reaction products and product ratio, being the best case an unseparable CC mixture of ketones **5/6** (45% yield) together with a 21% yield of dimers **7** and **8**. The latter compounds were reconverted into **1** by Jones oxidation. The ionic hydrogenation in the presence of CF_3COOH/Et_3SiH[15] allowed the selective hydrogenation of the non-conjugated double bond leading to **3**, while the catalytic hydrogenation (Pd/C)[16] led to **4** through a chemoselective pathway. Finally, treatment of **1** with Et_3SiH in the presence of Wilkinson's catalyst (Ph_3PRhCl)[17] afforded a good yield of **6** and **9** in a 1:9 ratio, separable by CC (Scheme II). ^1H NMR spectral analysis indicated that both compounds are reduction products of the enone double bond and epimers at C-10. The ring junction has been determined as *cis* according to the nOe observed between H-6 and the angular methyl group (δ 1.02 ppm in **9** and δ 1.04 ppm in **6**). When the reaction was carried out with the isolated silylenolethers, **10** and **11**, the acid hydrolysis led to the same mixture (**6** and **9**) with a low overall yield (Scheme II). When molecular minimisation calculations are carried out for **6** and **9** (QCPE Program)[18] the results indicate that the isomer with a *cis* spatial relationship between H-6 and H-10 is the less stable one. This result is in agreement with a hydrosilylation reaction in which the intermediate is a silylenolether, moreover, in the case of an exocyclic enol ketolization in which a five-membered ring is involved, the favourable product is the less termodynamically stable compound.[19] Thus, **9**, the major compound should be the less stable compound. Thus, **6** , the epimer of **9** at C-10 should

be one of the products obtained as component of the epimeric mixture in the Birch reduction, in which the reaction afforded the most-stable conformation for the α-carbon to the carbonyl.[10]

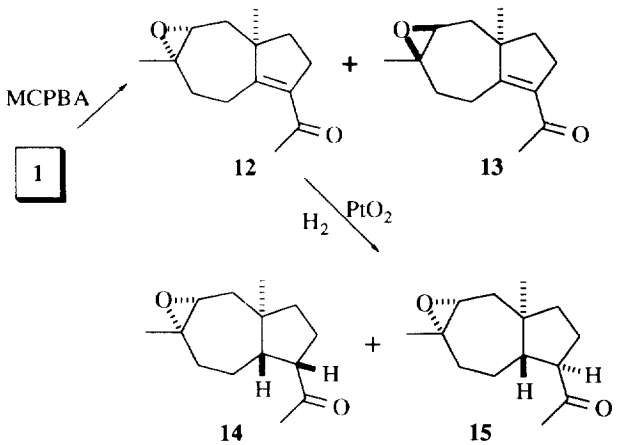


Scheme II. a. $Zn/NiCl_2$, b. Li/HMPA, c. $Li/NH_3(l)$, d. $NaBH_4$, or K-selectride® or Bu_3SnH/AIBN, e. $(Ph_3PCuH)_6$, f. CF_3COOH/Et_3SiH, g. Pd/C, h. Jones, i. Et_3SiH/Ph_3PRhCl, j. HCl

INDIRECT METHODS. The imposibility to prepare the desired product in a direct manner, required an indirect approach to its synthesis: 1. Selective protection of the trisubstituted double bond in the seven membered ring with an epoxide; 2. Catalytic hydrogenation of the enone; 3. Deoxygenation of the epoxide to go back to the double bond.

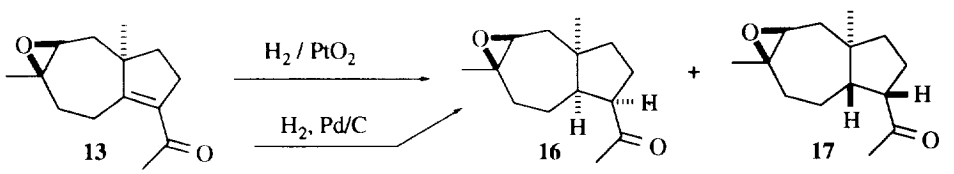
The epoxidation of **1** with MCPBA at -30°C afforded epoxides **12** and **13** in a 1:2 ratio, respectively (Scheme III). The total assignment of ^1H and ^{13}C NMR spectra for both compounds were done by 2D correlation experiments[20] and confirmed the proposed structures.

When **12** was hydrogenated in the presence of PtO_2, the desired compound **14** (62% yield) together with the minor compound **15** were obtained (Scheme III). Compound **14** corresponds to a *cis* hydrogenation product with a *trans* ring-junction, meaning that hydrogen approaches the double bond by the less-hindered face that is the opposite to both the oxiranic ring and the angular methyl-group. In fact, when the Me-14 signal is irradiated there is no nOe observed with H-6. Total assignment of **14** NMR data was done by 2D homo and heteronuclear techniques. The formation of **15** could be explained by the relative stability respect to **14** in terms of total energy according to molecular minimisations.[21]



Scheme III

When the major epoxide **13** was hydrogenated under the same reactions conditions as **12** afforded a non-separable mixture (7/3 ratio) of **16** and **17**. In this case the stereofacial selectivity is lower than in the former case as well as the overall yield (61%). This result is not surprising because in this case both faces are hindered, one by the angular methyl group and the other by the oxiranic ring (Scheme IV).

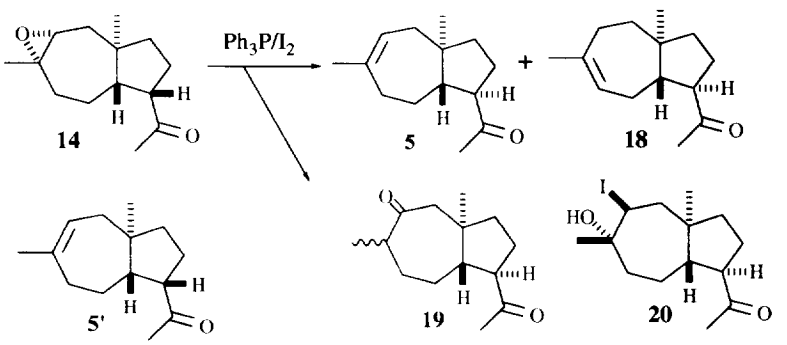


Scheme IV

However, when the reaction was carried out in the presence of Pd/C, the hydrogenation of **13** is more selective and affording only **16** (64% yield) that is the *cis* ring-junction product (Scheme IV).

Finally, deoxygenation of **14** was carried out with Ph_3P/I_2,[22] affording **5** and **18** as major products, that are positional isomers of the annular double bond (separable by CC,SiO_2-$AgNO_3$); as minor products: a diketone **19**, and a halohydrine, **20**, formed by epoxide ring-opening in the presence of HI generated *in situ*, this explains the epimerization observed at C-10 in the formation of **5** and **18** (Scheme V).

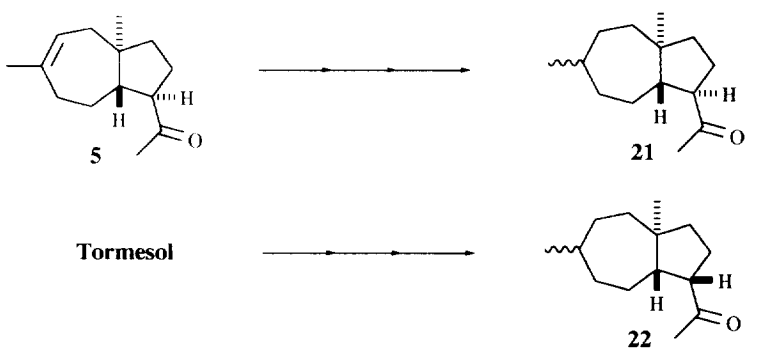
MM calculations support the absence of **5'** (Scheme IX), that is the less stable isomer (Total energy = 17.20 Kcal/mol) compare with **5** (Total energy = 13.80 Kcal/mol). As mentioned before, epimerization at C-10, either by *in situ* generation of HI and/or long reaction times, leading to **5** is favoured by its lower total energy and confirmed by the fact that it is also the major isomer formed during Birch reduction, which afforded the most stable conformation for the α-carbon to the carbonyl.



Scheme V

Deoxygenation of the mixture **16/17** afforded a complex mixture in which none of the components are useful to synthetic purposes.

When **5** was hydrogenated the methyl ketone, **21**, obtained is different to the product coming from tormesol's degradation, **22**.[2] If **5** shows a *trans* spatial relationship between H-6/H-10, this means that **21** also shows this relationship and **22** has instead a *cis* spatial relationship between H-6/H-10 as was proposed (Scheme VI).



Scheme VI

COUPLING REACTION. Even though, the desired product **5'** was not obtained, the total synthesis was continued with the norsesquiterpenoids already prepared (**5, 9**, and **18**). Each one of them was coupled with an organometallic derivative leading to the expected diterpenoid skeleton, confirming, by the differences with natural tormesol, the original structure proposed for it (Scheme VII).

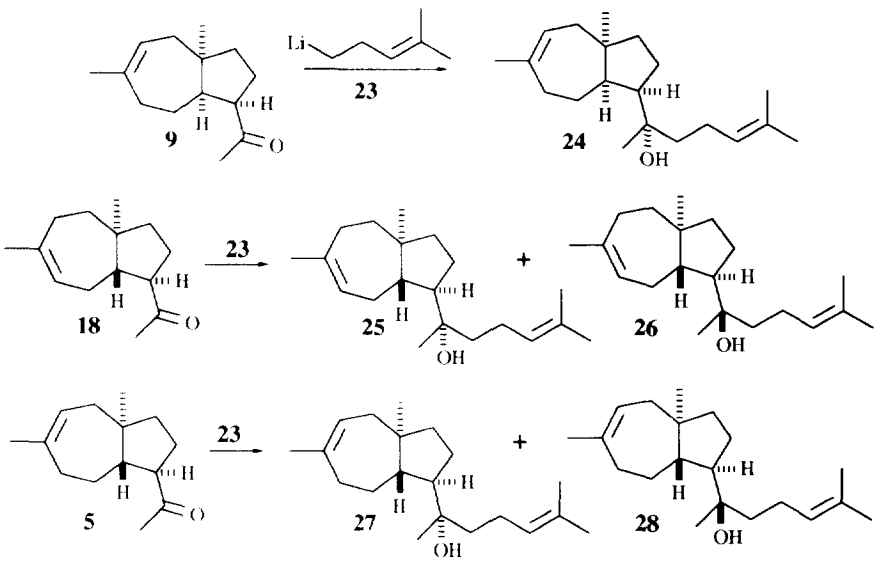
The halogenated derivative (1-bromo-4-methyl-3-pentene) prepared according to Julia's procedure from methyl-cyclopropyl-ketone,[23] was transformed into the lithium derivative **23** by direct lithiation.[24]

The reaction of **9** with **23** afforded **24**, an addition product was separated as the unique product. Compound **24** is a tertiary alcohol (M^+-18=272), in agreement with a molecular formula $C_{20}H_{34}O$.

A mixture of epimers at C-11 (**25** and **26**) was obtained in the reaction of **18** with the alkylithium. Their ^1H NMR spectra are quite similar to tormesol's and the main differences were observed in the ^{13}C

NMR spectra (Table 1), where the chemical shifts for the olefinic carbons confirmed that they are positional double bond isomers of tormesol.

Finally, when methyl ketone **5** was used another epimeric mixture (**27** and **28**) was separated. The parent ion in the mass spectra (M^+= 290) is in agreement with a $C_{20}H_{34}O$ molecular formula, and both differ from tormesol in the ratio observed for some fragments.



Scheme VII

When the Felkin-Anh model[25] was applied, it can be predicted that in the reaction of **9** with **23** , the main and even exclusive product will be **24**. When **18** is the substrate the ratio should be **26** > **25** and finally, when using **5** the ratio should be **27** ≥ **28**.

CONCLUSIONS

The structure of tormesol was determined and proposed on the basis of spectroscopic data (^1H , ^{13}C, 2D homonuclear and heteronuclear techniques, nOe and CD). The synthesis of **5** allows the determination of the relative configuration between H-6/H-10 as *cis* for natural tormesol. Moreover, in the case of **24**, the spectrum is very different from tormesol's due to the *cis* ring-junction, even though the spatial relationship between H-6/H-10 is *cis*. Compounds **27** and **28** that differ from tormesol in the spatial relationship between H-6/H-10 but show the same *trans* ring-junction are much more similar to tormesol. All these data confirmed the original structure proposed for tormesol, being **27** its epimer at C-10.

Table 1. ^{13}C NMR data ($CDCl_3$, 50.3 MHz)

C	1*	5	6	7	9	10	11	12	13*	14*	15	16	18	19	20	24	25	26	27	28
1	37.8	40.1	42.0	39.5	40.0	38.5	38.0	38.8	40.9	39.6	40.5	42.9	41.8	55.1	52.9	40.6	41.6	39.9	41.2	41.1
2	121.1	122.3	121.5	122.3	121.6	123.9	123.5	62.5	59.9	63.6	63.3	60.9	28.2	214.8	55.1	122.9	29.7	29.7	122.3	122.4
3	139.3	139.4	137.6	139.4	138.9	137.7	138.5	60.5	60.2	61.3	61.0	62.1	138.5	54.1	74.8	137.8	137.6	137.8	139.4	138.9
4	33.1	33.7	33.0	33.4	30.8	30.3	30.2	32.0	33.2	33.8	34.6	31.6	123.3	33.5	34.2	32.3	124.2	124.0	34.3	34.4
5	24.1	24.6	28.2	24.9	28.0	26.7	26.3	21.4	22.3	23.0	21.8	23.6	29.8	27.5	23.7	25.3	30.3	30.4	24.7	24.4
6	164.7	56.4	51.5	149.0	50.9	51.7	52.5	162.3	161.2	52.1	53.0	51.5	50.6	47.6	47.6	56.9	49.5	49.5	55.0	54.6
7	52.6	41.5	46.1	51.3	44.2	44.8	45.3	51.7	51.2	44.1	42.6	44.0	44.9	41.4	47.5	44.1	45.1	45.3	42.0	42.8
8	37.3	40.5	36.0	38.8	34.0	36.7	36.9	38.5	38.5	42.7	43.9	37.8	39.4	41.1	42.8	35.6	41.9	42.3	42.0	41.1
9	30.8	25.1	27.9	35.1	27.0	29.1	30.9	30.9	31.0	25.6	26.4	27.0	25.4	25.7	25.6	31.3	25.2	24.7	26.0	26.1
10	133.3	56.6	59.9	135.5	58.3	124.7	126.3	134.2	133.7	56.6	55.0	57.1	57.2	55.8	59.5	50.2	52.4	53.0	51.7	52.5
11	199.3	203.7	211.0	80.5	211.0	139.8	140.0	198.9	199.8	211.3	211.0	210.5	209.3	210.9	209.5	74.0	76.0	75.6	76.0	75.6
12	30.2	29.6	28.8	26.5	29.2	19.7	19.6	30.3	30.4	29.6	32.2	29.7	28.9	29.7	29.6	40.5	40.1	39.6	40.6	39.6
13	-	-	-	-			-	-	-	-	-	-	-	-	-	22.8	22.2	22.5	22.2	22.6
14	23.6	18.0	25.5	24.8	25.6	25.7	25.8	25.1	22.6	20.2	20.3	23.8	16.9	19.0	17.6	124.6	124.6	124.6	124.6	124.7
15	25.9	27.0	27.3	25.7	27.3	28.0	28.1	25.4	22.9	26.0	25.9	26.8	28.3	19.4	23.7	131.5	135.2	136.3	131.8	131.7
16	$Si(\mathbf{CH_2}CH_3)_3$					5.9	5.8									25.7	25.7	25.7	25.7	25.8
17	$Si(CH_2\mathbf{CH_3})_3$					6.6	6.8									17.7	17.7	17.7	17.7	17.7
18																25.3	23.2	25.3	23.1	25.8
19																25.6	17.2	17.2	18.7	18.8
20																26.4	28.3	28.3	27.1	27.2

* The assignment has been done by 2D Heteronuclear Experiments ($^1H/^{13}C$ HCCORR)

EXPERIMENTAL

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively in a Bruker WP–200 SY or AM-500 spectrometer. Chemical shifts are reported in δ, ppm and coupling constants (J) are given in Hz. MS spectra were performed on a VG–TS 250 spectrometer at 70 eV ionizing voltage. Mass Spectra are presented as m/z (% rel. int.). Diethyl ether, THF and benzene were distilled from sodium, pyridine and dichloromethane were distilled from calcium hydride under Ar atmosphere.

BIRCH REDUCTION OF **1**.

Liquid ammonia (33 ml) was added to a solution of **1** (33 mg, 0.16 mmol) in ether (5 ml) at -78ºC. Then Lithium wire (11 mg, 1.6 mmol) was added slowly. After 5-20 minutes the colour of solution turned dark blue. After 2 hours at -78ºC, some drops of saturated solution of NH_4Cl were added, after evaporation of the ammonia, water was added and extracted with ether, washed with 0.1M HCl and H_2O, dried (Na_2SO_4), filtered and evaporated to afford 33 mg of the crude product. The crude mixture was chromatographed on a silicagel column, eluted with n-hexane: EtOAc mixtures of increasing polarity, affording **5/6** (15 mg, 45 %), **1** (2 mg, 6 %), **7** (6 mg, 9 %) and **8** (8 mg, 12 %).

5/6: IR(film) ν_{max} cm^{-1}: 1713, 1450, 1350 and 1160. ^1H δ: 5.39(1H, m, H-2), 5.28(1H, s, H-2´), 2.70(2H, m, H-10 and H-10'), 2.16(3H, s, Me-12), 2.16(3H, s, Me-12´), 1.74(3H, s, Me-15), 1.63(3H, s, Me-15'), 1.04(3H, s, Me-14'), 0.74(3H, s, Me-14). **7** IR(film) ν_{max} cm^{-1}: 3340, 1460, 1370, 1150, 930 and 820. ^1H δ: 5.40(1H, m, H-2), 1.73(3H, s, Me-15), 1.38(3H, s, Me-12), 0.97(3H, s, Me-14). ^{13}C δ: see table 1. EIMS m/z (rel. int.): 205[M^+/2] (84), 187(20), 177(23), 161(100), 147(27), 137(34), 119(34), 105(47), 95(51), 81(59), 69(48), 55(82). **8** IR(film) ν_{max} cm^{-1}: 3400, 1460, 1370, 910 and 820. ^1H δ 5.41(1H, m, H-2), 1.74(3H, s, Me-15), 1.40(3H, s, Me-12), 0.94(3H, s, Me-14). EIMS m/z (rel. int.): 349(12), 256(10), 205[M^+/2] (100), 187(26), 177(20), 161(66), 137(50), 95(43), 81(40), 69(51), 55(45).

OXIDATION WITH JONES REAGENT OF **7** OR **8**: **1**

To a solution of **7** or **8** (20 mg, 0.05 mmol) in acetone (3 ml), were added 7 drops of Jones reactive. After 5 minutes the reaction mixture was chilled in an ice-water bath, and some drops of ^iPrOH were added slowly. The solvent was evaporated, extracted with ether, washed with Na_2CO_3 and H_2O, dried (Na_2SO_4), filtered and evaporated to afford **1** (15 mg, 70%).

REDUCTION OF **1** WITH $NaBH_4$: **2**

Compound **1** (11 mg, 0.05 mmol) was dissolved in 1 ml of MeOH at -10ºC. $NaBH_4$ (1.6 mg, 0.043 mmol) was added, and the mixture was stirred for 30 minutes at -10ºC. Then acetone was added, the solvent was removed and the residue extracted with EtOAc, washed with H_2O and dried over Na_2SO_4, filtered and evaporated to afford **2** (11 mg, 100%). IR(film) ν_{max} cm^{-1}: 3380, 1440, 1380, 1090, 1060, 900 and 820. ^1H δ: 5.47(1H, m, H-2), 4.72(1H, m, H-11), 1.74(3H, s, Me-15), 1.28(3H, d, J= 8.0, Me-12), 1.22(3H, d, J= 8.0, Me-12'), 0.96(3H, s, Me-14), 0.92(3H, s, Me-14'). EIMS, m/z (rel. int.): 206[M^+] (19), 193(28), 176(40), 161(100), 145(27), 133(29), 119(44), 105(48), 95(69), 69(96). Observed M^+ 206.1670; $C_{14}H_{22}O$ requires *M* 206.1671. Found C, 81.49;H, 10.75; $C_{14}H_{22}O$ requires C, 81.50; H, 10.74.

TREATMENT OF **1** WITH K-SELECTRIDE®: **2**

K-Selectride® (0.12 ml, of a 1M solution in THF, 0.12 mmol) was added to a solution of **1** (24 mg, 0.12 mmol) in 1 ml of THF at -78ºC. The reaction mixture was stirred for 3.5 hours at -78ºC. After that, 10% NaOH (2 ml) and 30% H_2O_2 (2 ml) were added. After 5 hours $NaHSO_3$ was added and stirred for 15 minutes, extracted with n-hexane, washed with water, dried and concentrated to give **2** (20 mg, 81%).

REDUCTION OF **1** WITH Bu_3SnH/AIBN: **2**

Compound **1** (29 mg, 0.14 mmol), Bu_3SnH (0.04 ml, 0.15 mmol) and AIBN (0.25 mg) were mixed and held at 80ºC, 48 hours, under argon atmosphere. The crude cool reaction mixture was cooled and poured onto a silice gel column. Elution with CH_2Cl_2 gave **2** (16 mg, 54%).

HYDROGENATION OF **1** WITH Et_3SiH/CF_3COOH: **3**

To a solution of **1** (14 mg, 0.068 mmol) and CF_3COOH (0.015 ml, 0.205 mmol) in chloroform (1 ml), was added Et_3SiH (0.010 ml, 0.068 mmol), and the mixture stirred for 7 hours at room temperature. After that 2N KOH, was added, and extracted with ether, washed with H_2O and dried over Na_2SO_4, filtered and evaporated to afford 14 mg of a mixture of **1/3**, in a 25/75 ratio, separable by CC (10% $AgNO_3$), giving **3** (10 mg, 71%) and **1** (2 mg, 14%). **3** IR(film) $\nu_{máx}$ cm^{-1}: 1676, 1607, 1454, 1358, 1267 and 1219. ^1H δ : 2.20(3H, s, Me-12), 1.04(3H, s, Me-14), 0.89(3H, d, J= 6.5, Me-15).

HYDROGENATION OF **1** WITH Pd/C: **4**

A solution of **1** (22 mg, 0.11 mmol) in absolute EtOH (2 ml) was hydrogenated in the presence of 10% Pd/C (16 mg) and K_2CO_3 (1 mg, 7.2 mmol). After 2 hours at room temperature, the mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to give **4** (22 mg, 96%). IR(film) ν_{max} cm^{-1}: 1709, 1350, 1230 and 1060. ^1H δ: 3.18(2H, m, H-10 and H-10'), 2.14(3H, s, Me-12), 2.12(2H, s, Me-12'), 1.08(3H, s, Me-14), 1.00(3H, s, Me-14'), 0.87(6H, d, J= 6.8, Me-15 and 15').

TREATMENT OF **1** WITH $Et_3SiH/(Ph_3P)_3RhCl$: **9** AND **6**

To a mixture of **1** (170 mg, 0.83 mmol) and $(Ph_3P)_3RhCl$ (103 mg, 0.11 mmol) in benzene (6 ml), was added Et_3SiH (1.3 ml, 8.3 mmol), and the reaction was heated under argon atmosphere at 70ºC for 6 hours. The mixture was cooled to room temperature, then MeOH (5 ml) was added and 4 drops of HCl and stirred for 10 minutes. After that, the mixture was extracted with ether, washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4) and concentrated *in vacuo* to afford **9** (153 mg, 90%) and **6** (16 mg, 10%).

9 IR(film) ν_{max} cm^{-1}: 1709, 1456, 1437, 1373, 1358 and 1167. ^1H δ: 5.25(1H, m, H-2), 2.70(1H, m, H-10), 2.13(3H, s, Me-12), 1.64(3H, s, Me-15), 1.02(3H, s, Me-14). ^{13}C δ: see table 1. EIMS m/z (rel. int.): 206[M^+] (69), 187(19), 177(33), 161(81), 147(27), 135(41), 119(50), 95(82), 81(100), 67(51), 55(69).

6 IR(film) ν_{max} cm^{-1}: 1709, 1456, 1437 and 1167. ^1H δ: 5.25(1H, m, H-2), 2.70(1H, m, H-10), 2.15(3H, s, Me-12), 1.64(3H, s, Me-15), 1.04(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 206[M^+] (48), 188(27), 163(51), 148(51), 121(100), 107(71), 95(89), 81(79), 55(51). Observed M^+ 206.1669; $C_{14}H_{22}O$ requires *M* 206.1671. Found C, 81.50; H, 10.72; $C_{14}H_{22}O$ requires C, 81.50; H, 10.74.

REACTION OF **1** WITH $Et_3SiH/(Ph_3P)_3RhCl$: **10** AND **11**

To a mixture of **1** (135 mg, 0.66 mmol) and $(Ph_3P)_3RhCl$ (86 mg, 0.09 mmol) in benzene (4 ml), was added Et_3SiH (1 ml, 6.6 mmol) and heated under argon at 70ºC. After 6 hours the solvent was evaporated and chromatographed on a silicagel column, eluted with dry n-hexane, affording **10** (75 mg, 35%) and **11**(60 mg, 28%).

10 IR(film) ν_{max} cm^{-1}: 1460, 1370, 1240, 1190, 1000, 850 and 740. ^1H δ: 5.39(1H, m, H-2), 1.75(3H, s, Me-12), 1.65(3H, s, Me-15), 0.99(3H, s, Me-14), 0.95(9H, t, J= 7.0, Si-(CH_2**Me**)$_3$), 0.65(6H, q, J= 7.0, Si-(**CH_2**Me)$_3$). ^{13}C δ see table 1.

11 IR(film) ν_{max} cm^{-1}: 1460, 1390, 1240, 1190, 1180, 1000, 850 and 740. ^1H & 5.39(1H, m, H-2), 1.80(3H, s, Me-12), 1.66(3H, s, Me-15), 1.00(3H, s, Me-14), 0.96(9H, t, J= 7.0, Si-(CH_2**Me**)$_3$), 0.65(6H, q, J= 7.0, Si-(**CH_2**Me)$_3$). ^{13}C δ see table 1.

HYDROLYSIS OF **10** AND **11** WITH HCl: **9** AND **6**

To a solution of **10** (75 mg, 0.23 mmol) in MeOH (4 ml), 4 drops of HClc were added and stirred for 10 minutes. Then the mixture was extracted with ether, washed with $NaHCO_3$, H_2O and dried over Na_2SO_4. After evaporation of the solvent the crude reaction product was chromatographed to afford **9** (30 mg, 63%) and **6** (10 mg, 21%).

To a solution of **11** (57 mg, 0.18 mmol) in MeOH (2 ml) 4 drops of HClc were added and stirred for 10 minutes. Usual work-up afforded **9** (25 mg, 67%) and **6** (5 mg, 13%).

EPOXIDATION OF **1** CON MCPBA: **12** and**13**.

To a solution of **1** (190 mg, 0.93 mmol) in CH_2Cl_2 (3 ml) at -30ºC, was added MCPBA (240 mg, 1.39 mmol). After 6 hours, CH_2Cl_2, H_2O and Na_2CO_3 were added at -30ºC, then the mixture was warmed up to room temperature. After separation of the organic phase and removing of the solvent, the reaction mixture was extracted with ether, washed with Na_2CO_3 and H_2O, dried over Na_2SO_4, filtered and evaporated to give 190 mg of crude product that was chromatographed to give **1** (17 mg, 9%), **12** (55 mg, 27%) and **13** (45 mg, 45%).

12 IR(film) ν_{max} cm^{-1}: 1680, 1605, 1430, 1370, 1350, 1280 and 1100. ^1H δ: 2.85(1H, dd, J= 6.5 y 2.9, H-2), 2.21(3H, s, Me-12), 1.25(3H, s, Me-15), 1.18(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 220[M^+] (10), 205(8), 192(9), 177(41), 152(37), 133(65), 119(44), 105(50), 91(100), 77(75), 65(38). Observed M^+ 220.1463; $C_{14}H_{20}O_2$ requires *M* 220.1464.

13 IR(film) ν_{max} cm^{-1}: 1680, 1600, 1440, 1350, 1260, 1190, 930 and 890. ^1H δ : 3.40(1H, m, H_A-5), 2.83(1H, dd, J= 6.4 and 4.5, H-2), 2.15(3H, s, Me-12), 1.32(3H, s, Me-15), 1.11(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 220[M^+] (5), 205(12), 192(53), 177(22), 150(74), 133(59), 119(39), 107(45), 91(100), 77(70), 65(39). Found C, 76.33; H, 9.16; $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15.

HYDROGENATION OF **12** WITH H_2/PtO_2: **14** and **15**.

Compound **12** (206 mg, 0.94 mmol) in ether (10 ml), was hydrogenated in the presence of PtO_2 (8 mg). After 30 minutes the catalyst was filtered off and the mixture was diluted with ether, dried over Na_2SO_4, filtered and the solvent was removed to give **14** (150 mg, 62%) and **15** (21 mg, 10%).

14 IR(film) ν_{max} cm^{-1}:1709, 1450, 1430, 1380, 1360, 1160, 910 and 790. ^1H (500 MHz) δ: 2.88(1H, d, J= 5.4, H-2), 2.66 (1H, dt, J=6.4 and J=11.3, H-10), 2.13 (3H, s, Me-12), 1.26(3H, s, Me-15), 1.00(3H, s, Me-14). ^1H (C_6D_6) δ: 2.60(1H, d, J=5.4, H-2), 2.30(1H, dt, J= 6.4 and 11.3, H-10), 1.93(1H, dd, J= 5.4 and 15.1), 1.73(3H, s, Me-12), 1.07(3H, s, Me-15), 1.00(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 222[M^+] (21), 207(29), 193(15), 179(54), 161(41), 151(54), 137(48), 121(76), 93(100), 79(81), 67(53), 55(76). Found C, 75.63; H, 9.94; $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

15 IR(film) ν_{max} cm^{-1}: 1709, 1450, 1430, 1160, 900 and 790. ^1H δ 3.40(1H, m, H-10), 2.86(1H, d, J= 5.4, H-2), 2.12(3H, s, Me-12), 1.26(3H, s, Me-15), 1.05(3H, s, Me-14'), 1.00(3H, s, Me-14). ^1H (C_6D_6) δ: 2.70(1H, m, H-10), 2.56(1H, d, J=5.9, H-2), 1.72(3H, s, Me-12), 1.09(3H, s, Me-15), 1.07(3H, s, Me-15), 1.00(3H, s, Me-14). ^{13}C δ see table 1. Found C, 75.61; H, 9.98; $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

CATALITYC HYDROGENATIONS OF **13**: **16** and **17**.

Compound **13** (90 mg, 0.4 mmol) in ether (4 ml), was hydrogenated in the presence of PtO_2 (6 mg). After, stirring for 4 hours at room temperature, the reaction was worked-up as usual, and CC of the crude product a mixture of **16/17** (54 mg, 61%) was obtained. IR(film) ν_{max} cm^{-1}: 1709, 1470, 1380, 1350, 1150 and 890. ^1H δ : 2.78(1H, m, H-2), 2.70(1H, m, H-10), 2.11(3H, s, Me-12), 1.27(3H, s, Me-15), 1.24(3H, s, Me-15'), 1.12(3H, s, Me-14), 0.93(3H, s, Me-14').

Compound **13** (45 mg, 0.2 mmol) in absolute EtOH (2 ml), was hydrogenated in the presence of 10% Pd/C (30 mg). After 15 minutes, usual work-up, afforded after CC, **16** (28 mg, 64%).

16 IR(film) ν_{max} cm^{-1}: 1707, 1460, 1380 and 1170. ^1H δ 2.79(1H, m, H-2), 2.65(1H, m, H-10), 2.14(3H, s, Me-12), 1.31(3H, s, Me-15), 1.15(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 222[M^+] (34), 207(35), 193(9), 179(39), 161(41), 150(32), 137(50), 124(100), 109(70), 95(76), 81(95), 67(67), 55(78). Observed M^+ 222.1618; $C_{14}H_{22}O_2$ requires *M* 222.1620. Found C, 71.15;H, 8.50; $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

DEOXYGENATION OF **14** WITH Ph_3P/I_2: **5**, **18**, **19** AND **20**

Epoxide **14** (120 mg, 0.54 mmol) was added to a stirred mixture of Ph_3P (159 mg, 0.60 mmol) and I_2 (83 mg, 0.32 mmol) in CH_3CN (9 ml) at -24°C. The reaction mixture was stirred at -24°C for 3 hours. Usual work-up afforded, after CC, **5/18** (64 mg, 58%). **19** (37 mg, 31%) and **20** (9 mg, 3%). The mixture of **5/18** was chromatographed on a silicagel column (10% $AgNO_3$) affording **5** (38 mg) and **18** (20 mg).

5 IR(film) ν_{max} cm^{-1}: 1709, 1440, 1350 and 1150. ^1H δ: 5.39(1H, m, H-2), 2.70(1H, m, H-10), 2.16(3H, s, Me-12), 1.74(3H, s, Me-15), 0.74(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 206[M^+] (4), 191(3), 178(8), 161(9), 149(10), 137(13), 123(11), 109(12), 97(21), 81(41), 69(100), 57(54). Observed M^+ 206.1670; $C_{14}H_{22}O$ requires *M* 206.1671. Found C, 81.51; H, 7.74; $C_{14}H_{22}O$ requires C, 81.50; H, 7.75.

18 IR(film) ν_{max} cm^{-1}: 1709, 1440, 1350 and 1160. ^1H δ: 5.42(1H, m, H-4), 2.14(3H, s, Me-12), 1.71(3H, s, Me-15), 0.86(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 206[M^+] (5), 191(4), 178(9), 161(10), 149(11), 137(13), 123(11), 109(12), 97(21), 81(41), 69(100), 57(54). Observed M^+ 206.1671; $C_{14}H_{22}O$ requires *M* 206.1671. Found C, 81.55; H, 7.75; $C_{14}H_{22}O$ requires C, 81.50; H, 7.75.

19 IR(film) ν_{max} cm^{-1}: 1705, 1694, 1450, 1380 and 1190. ^1H δ: 2.16(3H, s, Me-12), 1.10 (3H, d, J = 7.3, Me-15), 1.05(3H, d, J= 7.3, Me-15'), 0.88(3H, s, Me-14), 0.81(3H, s, Me-14'). ^{13}C δ see table 1. EIMS m/z (rel. int.): 222[M^+] (77), 207(14), 194(30), 179(72), 161(40), 151(64), 137(43), 123(73), 107(50), 95(100), 81(63), 67(50), 55(60). Observed M^+ 222.1618, $C_{14}H_{22}O_2$ requires *M* 222.1620.

20 IR(film) ν_{max} cm^{-1}: 3420, 1700, 1450, 1360 and 1160. ^1H & 4.70(1H, dd, J=5.5 and 11.3, H-2), 2.15(3H, s, Me-12), 1.41(3H, s, Me-15), 0.97(3H, s, Me-14). ^{13}C δ see table 1. EIMS m/z (rel. int.): 223[M^+-127] (55), 205(95), 187(39), 179(10), 161(48), 135(38), 119(29), 95(59), 81(78), 71(100).

HYDROGENATION OF **5** WITH PtO_2.

To a solution of **5** (15 mg) in dry Et_2O (2 ml) was added PtO_2 (3 mg) and the mixture was stirred for 2 h under H_2 atmosphere. When the reaction was completed, the mixture was filtered, washed with excess of Et_2O, dry over Na_2SO_4, evaporated to afford **21** (12 mg, 84% yield). IR(film) ν_{max} cm^{-1}: 1709, 1460, 1350, 1230, 1160, 1060. ^1H δ: 2.14 (3H,s, COMe), 0.87 (3H, s, Me–14), 0.87 (3H, d, J = 6.3, Me–15).

ADDITION OF ORGANO-LITHIUM TO **9**, **5** AND **18**

Formation of the organo-lithium: **23**. Lithium wire (2.5 mmol, thin strips freshly cut) and ether (1 ml) under argon were stirred while a solution of 1-bromo-4-methyl-3-pentene (2.5 mmol) in ether (3 ml) was added slowly. When the reaction began, a cooling bath (-10°C) was applied and stirred until nearly all the lithium had reacted (1 hour, aproximately) with formation of **23**.

Synthesis of **24**. To a solution, in ether, of the organo-lithium **23** (4.85 mmol) at -78°C, was added **9** (50 mg, 0.24 mmol) solved in ether (2 ml). 24 hours later NH_4Cl was added, extracted with ether, washed with H_2O and dried (Na_2SO_4) and the solvent was removed to give after CC **24** (53 mg, 76%): IR(film) ν_{max} cm^{-1}: 3430, 1450, 1370 and 1120. ^1H δ: 5.36(1H, m, H-2), 5.12(1H, t, J= 6.8, H-14), 1.69(3H, s), 1.62(6H, s), 1.17(3H, s, Me-18), 1.00(3H, s, Me-19). ^{13}C δ see table 1. EIMS m/z (rel. int.): 272[M^+-18] (54), 257(7), 229(6), 203(4), 190(21), 175(8), 161(40), 135(17), 121(31), 109(100), 95(43), 81(48), 69(87), 55(37). Observed [M^+-18] 272.2502; $C_{20}H_{34}O$ requires *M -18* 272.2504. Found C, 82.70; H, 11.83; $C_{20}H_{34}O$ requires C, 82.69; H, 11.80.

Synthesis of **25** and **26**. To a solution, in ether, of the organo-lithium **23** (2.4 mmol) at -78°C, was added **18** (19 mg, 0.093 mmol) solved in ether (1 ml), and stirred for 27 hours. The usual work-up afforded after CC **25** (10 mg, 37%) and **26** (9 mg, 34%).

25 IR(film) ν_{max} cm^{-1}: 3440, 1450 and 1390. ^1H δ: 5.43(1H, m, H-4), 5.17(1H, m, H-14), 1.69(6H, s), 1.63(3H, s), 1.13(3H, s, Me-18), 0.88(3H, s, Me-19). ^{13}C δ see table 1. EIMS m/z (rel. int.): 290[M^+] (2), 272(40), 257(4), 203(9), 190(12), 161(37), 149(14), 135(16), 121(20), 109(67), 95(42), 81(41), 69(100), 55(56). Observed M^+ 290.2609; $C_{20}H_{34}O$ requires *M* 290.2610.

26 IR(film) ν_{max} cm^{-1}: 3440, 1450 and 1390. ^1H δ : 5.43(1H, m, H-4), 5.17(1H, m, H-14), 1.69(6H, s), 1.63(3H, s), 1.15(3H, s, Me-18), 0.85(3H, s, Me-19). ^{13}C δ see table 1. EIMS m/z (rel. int.): 290[M^+] (2), 272(57), 257(5), 190(10), 161(45), 135(16), 109(68), 95(42), 81(44), 69(100). Observed M^+ 290.2608; $C_{20}H_{34}O$ requires *M* 290.2610.

Synthesis of **27** and **28**. To a solution, in ether, of the organo-lithium **23** (2.4 mmol) at -78°C, was added **5** (19 mg, 0.093 mmol) solved in ether (1 ml), and stirred for 27 hours. The usual work-up afforded after CC, **27** (11 mg, 40%) and **28** (10 mg, 37%).

27 IR(film) ν_{max} cm^{-1}: 3440, 1450, 1360.. ^1H δ: 5.39(1H, m, H-2), 5.17(1H, m, H-14), 1.74(3H, s), 1.69(3H, s), 1.63(3H, s), 1.16(3H, s, Me-18), 0.75(3H, s, Me-19). ^{13}C δ see table 1. EIMS m/z (rel. int.):

290 [M+] (2), 272(21), 203(7), 190(23), 161(25), 149(16), 127(21), 109(100), 95(43), 81(40), 69(97), 55(52). Observed M+ 290.2611; $C_{20}H_{34}O$ requires *M* 290.2610.

28 IR(film) ν_{max} cm^{-1}: 3440, 1450, 1360. ^1H δ 5.39(1H, m, H-2), 5.17(1H, m, H-14), 1.74(3H, s), 1.70(3H, s), 1.64(3H, s), 1.17(3H, s, Me-18), 0.76(3H, s, Me-19). ^{13}C δ see table 1. EIMS m/z (rel. int.): 290[M+] (8), 272(20), 190(22), 161(21), 127(19), 109(100), 95(43), 81(39), 69(97). Observed M+ 290.2610; $C_{20}H_{34}O$ requires *M* 290.2610.

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21. The presence of **15** can be explained on the basis of molecular models, which suggested that **15** was the more stable diastereoisomer. Thus, each compound was built and the conformational space available searched using the Sybyl randomsearch method (Tripos Associates, 1699 S.Hanley Road, St. Louis, Missouri, USA), with all bonds except terminal bonds and bonds in the epoxide unit defined as searchable. 1000 attempts were made to find new conformers with energies within 6 kcal/mol of the best minimum found. All the conformers were found several times, with the lowest energy conformer in each case being found at least 7 times. Using the Tripos force field, **15** (Maximin2 energy = 128.94 kcal/mol) was the more stable by ≈3.5 kcal/mol. In view of the unusual nature of the system, confirmation of this apparent energy difference was sought by performing a minimisation of the best conformers found by Sybyl using MOPAC[18] with the PM3 Hamiltonian, Eigenvector following geometry optimisation and precise convergence criteria. Once again, **15** (calcd. heat of formation −81.93 kcal/mol, Grad. <0.01) was found to be the more stable by 3.1 kcal/mol, a rank order of stability that was also observed in thermodynamic calculations (keywords THERMO(298), FORCE ROT =1) in MOPAC, albeit with a reduced preference of 0.8 kcal/mol at 298 K.
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